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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the virtual World Conference on Lung Cancer, 8th–14th September 2021, and the virtual ESMO Congress, 16th–21st September, 2021

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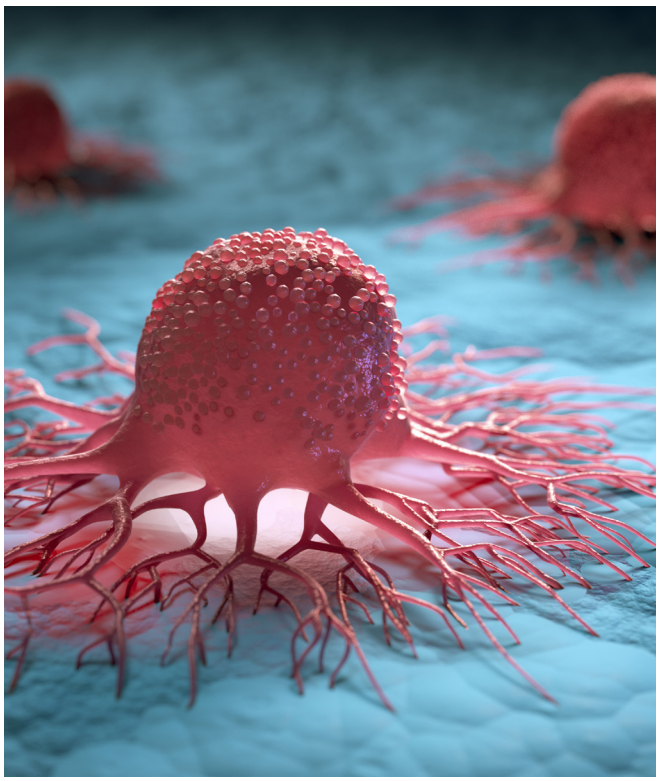

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Preface

Dear Colleagues,

With the World Conference on Lung Cancer that took place on 8th–14th September 2021 and the ESMO Congress on 16th–21st September, two prestigious cancer congresses have offered a wealth of new preclinical and clinical information in the field of lung cancer. Results from pivotal studies were updated, and fascinating novel treatment approaches were presented to large audiences around the world. More than 22,700 participants from 143 countries registered for the ESMO Congress alone.

This issue of memo inOncology summarizes important findings relating to the management of patients with lung cancer that were presented at both conferences. Among druggable targets, those belonging to the EGFR/HER2 family play an important role in the pathogenesis of lung cancer. The critical role of this pathway is mirrored by the multitude of studies investigating drugs including poziotinib, mobocertinib, amivantamab, and trastuzumab deruxtecan. The antibody-drug conjugates telisotuzumab vedotin and datopotamab deruxtecan have been developed to target c-MET and TROP2, respectively. At the same time, new data are being generated on the ideal use of long-standing EGFR inhibitors such as erlotinib and afatinib.

Checkpoint inhibition is of course a pivotal pillar of treatment that has been established across all lines of therapy and is being implemented in other entities apart from non–small-cell lung cancer, such as small-cell lung cancer and mesothelioma. The combined administration of nivolumab and ipilimumab brought about progress with respect to unresectable malignant pleural mesothelioma. In stage III NSCLC, the PACIFIC trial has set a new standard after chemoradiotherapy of unresectable stage tumors. Consolidation with durvalumab was shown to be life-prolonging under real-world conditions, and combination regimens as well as other checkpoint inhibitors are being tested in the same setting. Patients with metastatic disease who have developed brain lesions derive benefit from checkpoint inhibitor regimens, while new CNS lesions can be prevented.

Anti-cancer vaccines have been evaluated unsuccessfully in NSCLC over the last decade. Therefore, the initial promising results for another type, the anti-cancer vaccine OSE-2101 that has demonstrated a favorable benefit-risk ratio after failure of immune checkpoint inhibition, are notable. Thus, thanks to the commitment of countless researchers, clinicians and patients, the available armamentarium for lung cancer therapy is being expanded to match the requirements of cancer treatment from early-stage to late-stage disease with the aim of providing maximum benefit in each given case.

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Expansion of treatments and insights in the early-stage disease setting

The management of patients with stage I-III non–small-cell lung cancer (NSCLC) is still characterized by a high unmet medical need as up to 60 % experience disease relapse despite treatment with curative intent [1]. IMpower010 was the first phase III study of cancer immunotherapy to demonstrate a disease-free survival (DFS) benefit in the adjuvant situation after complete resection and platinum-based chemotherapy. The interim DFS analysis showed that compared to best supportive care (BSC), atezolizumab 1,200 mg Q3W for 16 cycles gave rise to significant DFS benefits in the PD-L1–positive (i.e., TC ≥ 1 %) stage II-IIIA and all-randomized stage II-IIIA populations (HRs, 0.66 and 0.79, respectively) [2]. In the intent-to-treat (ITT) population (i.e., all-randomized stage IB-IIIA patients), the significance boundary for DFS was not crossed.

At ESMO 2021, Felip et al. reported sites of disease relapse and post-relapse treatment in IMpower010 at the time of the interim DFS analysis [3]. Moreover, DFS was explored by PD-L1 expression in the all-randomized stage II-IIIA population; this demonstrated that atezolizumab-treated patients with TC ≥ 50 % experienced the greatest risk reduction (HR, 0.43), while those with TC 1-49 % did not benefit significantly (HR, 0.87).

Consistent benefits in IMpower010

Similar patterns of relapse were observed across the study arms. In the PD-L1–positive stage II-IIIA population, locoregional relapses only occurred more commonly in both arms (47.9 % and 41.2 % for atezolizumab and BSC, respectively) than distant relapses only

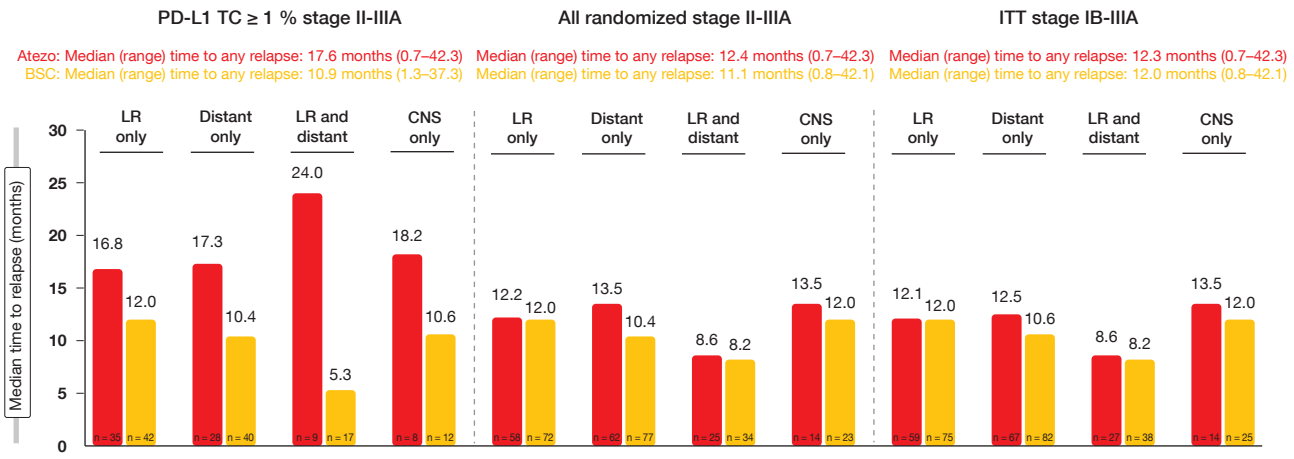

Figure 1: Time from randomization to relapse for the PD-L1 TC ≥ 1 % stage II-IIIA, all randomized stage II-IIIA, and ITT stage IB-IIIA populations included in IMpower010. LR, locoregional; CNS, central nervous system

(38.4 % and 39.2 %, respectively). Conversely, in the all-randomized stage II-IIIA and ITT stage IB-IIIA populations, distant metastases emerged slightly more often than locoregional relapses irrespective of treatment. CNS relapses only were seen in 9.0 % to 12.3 % across all groups. Time from randomization to relapse appeared to favor atezolizumab therapy in the PD-L1–positive stage II-IIIA population for all relapse categories, while the differences were small in the all-randomized stage II-IIIA and ITT stage IB-IIIA populations **(Figure 1)**.

With respect to post-relapse treatment, the analysis revealed higher rates of immunotherapy in the BSC arms of the three populations compared to the experimental arms, while no differences were observed regarding other types of subsequent treatment including chemotherapy and targeted agents. Likewise, post-relapse use of surgery and radiotherapy was similar. The authors concluded that longer follow-up is warranted and might reveal differences in relapse patterns and treatment options.

Another exploratory analysis of the IMpower010 study assessed prior therapies, including the type of surgery, and their potential impact on DFS outcome [4]. Within the randomized ITT population (n = 1,005), the majority of patients had undergone lobectomy (78.1 %) and lymph node dissection (80.7 %), and most had received 4 cycles of adjuvant chemotherapy. Median time from surgery to the first administration of atezolizumab or BSC was similar (5.2 and 5.1 months, respectively). The forest plots revealed that adjuvant atezolizumab, as compared to BSC, improved DFS in the PD-L1 TC ≥ 1 % stage II-IIIA and all-randomized stage II-IIIA populations across most disease stages, in patients with nodal involvement, and across most surgery types and chemotherapy regimens.

NADIM: neoadjuvant use of nivolumab

The single-arm, phase II NADIM trial assessed nivolumab 360 mg Q3W in addition to 3 cycles of neoadjuvant administration of paclitaxel and carboplatin in patients with resectable stage IIIA N2 or T4N0/N1 tumors. Surgery was conducted in the third or fourth week from day 21 of cycle 3. The adjuvant treatment comprised nivolumab for 1 year. In terms of the primary endpoint, which was progression-free survival (PFS) at 24 months, the primary analysis yielded a 77.1 % rate, thus supporting the addition of neoadjuvant nivolumab to platinum-based chemotherapy [5].

At WCLC 2021, the 3-year overall survival (OS) analysis was reported for the ITT (n = 46) and per-protocol populations (PP; n = 37) [6]. The latter included the patient group that received adjuvant therapy. NADIM showed promising survival results, with 36-month OS rates of 81.9 % and 91.0 % in the ITT and PP populations, respectively. This markedly exceeded the historical 3-year OS rates that have remained at approximately 30 % over the past decades. At 42 months, 78.9 % and 87.3 % of patients, respectively, were alive. The 42-month PFS rates amounted to 69.6 % and 81.1 %, respectively.

An exploratory analysis was conducted to elucidate the predictive potential of response parameters. While clinical responses based on CT scans did not predict survival outcomes, pathological complete response and circulating tumor DNA clearance (i.e., lack of detectable ctDNA at the end of neoadjuvant treatment) significantly predicted long-term survival.

The addition of nivolumab to neoadjuvant chemotherapy did not adversely affect the safety profile. For the neoadjuvant and adjuvant treatment periods alike, most treatment-related adverse events (TRAEs) were grade 1 or 2, and no fatal TRAEs occurred.

PACIFIC under real-world conditions

The phase III PACIFIC trial has established consolidation treatment with durvalumab as the standard of care in patients with unresectable stage III NSCLC who did not develop disease progression after concurrent chemoradiotherapy (CRT). Robust and long-lasting OS and PFS benefits were achieved in this study, with one third of patients remaining progression-free after 5 years of follow-up [7]. At present, the international, observational PACIFIC-R study is investigating the real-world effectiveness of the PACIFIC regimen. The analysis presented at ESMO 2021 included a total of 1,399 patients with unresectable stage III NSCLC who had been recruited into an early access program regardless of their tumor PD-L1 expression status at 290 active sites in 11 countries [8].

TABLE
COAST: anti-tumor activity of durvalumab plus oleclumab or monalizumab compared to durvalumab monotherapy

Endpoint	Durvalumab + oleclumab	Durvalumab + monalizumab	Durvalumab monotherapy
Confirmed ORR, n (%)	18 (30.0)	22 (35.5)	12 (17.9)
Confirmed + unconfirmed ORR, n (%)	23 (38.3)	23 (37.1)	17 (25.4)
Objective responses by RECIST, n (%)			
Complete response	1 (1.7)	3 (4.8)	2 (3.0)
Partial response	22 (36.7)	20 (32.3)	15 (22.4)
Stable disease	25 (41.7)	27 (43.5)	27 (40.3)
Progressive disease	7 (11.7)	7 (11.3)	15 (22.4)
Not evaluable	5 (8.3)	5 (6.5)	8 (11.9)
Disease control rate at 16 weeks, n (%)	49 (81.7)	48 (77.4)	39 (58.2)
Median duration of response, months	12.9	Not reached	Not reached
Progression-free survival, months	Not reached HR, 0.44	15.1 HR, 0.65	6.3
Progression-free survival rates at 10 months, %	64.8	72.7	39.2

After a median treatment duration of approximately 11 months, median real-world PFS with durvalumab was higher than the PFS reported in the PACIFIC trial (21.7 vs. 16.9 months). The authors pointed out that inaccuracies relating to the collection of real-world data limit this comparison; for instance, RECIST criteria are being used in a heterogeneous fashion across countries, and assessments for progression might have been impaired by the COVID-19 pandemic. Nevertheless, the efficacy of durvalumab after CRT in the analyzed subgroups was generally consistent with previous data from the PACIFIC trial [9]. Real-world PFS observed with durvalumab consolidation therapy was longer in stage IIIA disease than in stage IIIB/C disease (23.7 vs. 19.2 months), in the PD-L1–positive group compared to the PD-L1–negative group (22.4 % vs. 16.3 months), after concurrent CRT compared to sequential CRT (23.7 vs. 19.4 months), and in patients with non-squamous tumors vs. those with squamous tumors (25.3 vs. 14.7 months).

Pneumonitis/interstitial lung disease was the most common AE leading to temporary treatment interruption (5.2 %) and permanent discontinuation (9.5 %). Eighteen percent of patients developed pneumonitis that was mostly mild or moderate. Corticosteroid administration was required in 71.3 % of events. The rates of treatment discontinuation due to AEs and disease progression (16.7 % and 26.9 %, respectively) were consistent with those from PACIFIC (15.4 % and 31.3 %, respectively [7]). Overall, durvalumab consolidation therapy after CRT for approximately 11 months proved effective in a large, real-world cohort.

Combinations of durvalumab with novel agents

Combined immunomodulatory consolidation with durvalumab plus other agents in the PACIFIC setting is being explored with the aim of further improving patient outcomes. The global, open-label, randomized, phase II COAST study is testing durvalumab alone or together with either the anti-CD73 antibody oleclumab or the anti-NKG2A antibody monalizumab. Radiotherapy induces expression of CD73 and the NKG2A ligand HLA-E that inhibit antitumor immune response [10-12]. Combinations of radiotherapy and CD37/NKG2A-targeted agents with or without checkpoint inhibitors have shown increased antitumor activity in preclinical models [10, 11].

The three-arm COAST study that is being conducted at 82 sites in 9 countries is comparing durvalumab 1,500 mg plus oleclumab 3,000 mg Q4W (n = 60) with durvalumab 1,500 mg Q4W plus monalizumab 750 mg Q2W (n = 62) and durvalumab 1,500 mg Q4W monotherapy (n = 67). The objective response rate (ORR) constituted the primary endpoint. According to the interim data presented at ESMO 2021, both oleclumab and monalizumab can provide additional clinical benefit when combined with durvalumab [13]. Both combinations numerically increased ORR and gave rise to significant PFS improvement vs. durvalumab alone **(Table)**. PFS benefits with both combinations were observed across various subgroups.

The safety profiles were consistent across arms, with similar rates of AEs of special interest including pneumonitis. No new safety signals emerged in either combination arm. Overall, COAST is the first randomized phase II study to show evidence of improved outcomes with novel immunotherapy combinations in the PACIFIC setting. These data support further evaluation of the combined regimens in a registration-intent trial.

GEMSTONE-301: sugemalimab

Another study investigating consolidation treatment in the PACIFIC setting is the randomized, double-blind, placebo-controlled, phase III GEMSTONE-301 trial. The anti–PD-L1 antibody sugemalimab is being tested at a dose of 1,200 mg Q3W (n = 255) against placebo (n = 126) for up to 24 months in Chinese patients with unresectable stage III NSCLC who have not developed progression after concurrent or se-

quential CRT. GEMSTONE-301 is the first phase III study to evaluate an anti-PD-(L)1 agent after both concurrent and sequential treatment in this setting based on the observation that concurrent CRT is not accessible everywhere and can confer significant toxicity. Patient comorbidities and lack of access often limit its use in the real-world setting. Two thirds and one third of the population included in GEMSTONE-301 had received concurrent and sequential CRT, respectively.

PFS by blinded independent review was defined as the primary endpoint. According to the pre-planned interim analysis reported by Wu et al. at ESMO 2021, sugemalimab gave rise to a statistically significant and clinically meaningful PFS improvement (9.0 vs. 5.8 months; HR, 0.64; p = 0.0026; **Figure 2**) [14]. In the group after concurrent CRT, median PFS was 10.5 vs. 6.4 months (HR, 0.66), and in the patients after sequential CRT, this was 8.1 vs. 4.1 months (HR, 0.59). The OS data were immature at the time of the analysis, although a trend was obvious for a survival benefit with sugemalimab vs. placebo (not reached vs. 24.1 months in the overall population; HR, 0.44). A markedly greater proportion of patients treated in the experimental arm was alive at 24 months (78.0 % vs. 50.7 %).

Sugemalimab showed a favorable safety profile that was in keeping with the profile previously reported for sugemalimab monotherapy in NSCLC. Immune-related AEs occurred in 42.7 % in the experimental arm, with 4.7 % classified as grade 3-5 events. Treatment cycle delay and permanent drug discontinuation were due to treatment-emergent AEs in 32.2 % and 11.4 %, respectively. The authors noted in their summary that the findings obtained in the GEMSTONE-301 study suggest effectiveness of sugemalimab as consolidation therapy in unresectable stage III NSCLC after concurrent or sequential CRT.

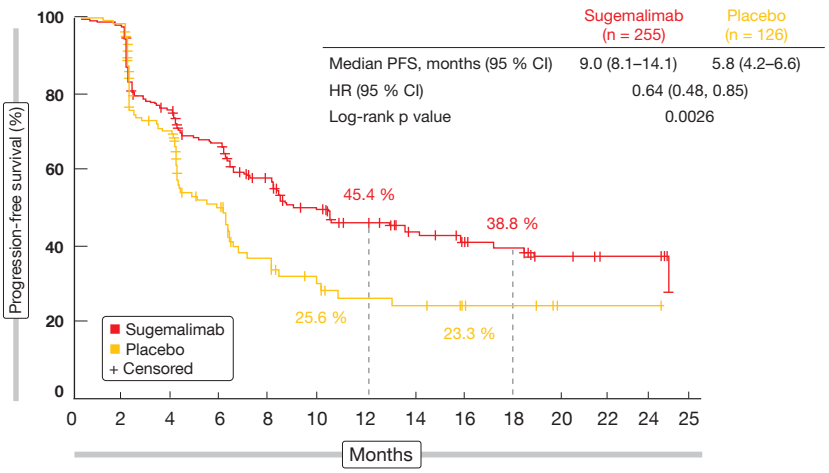

Figure 2: Progression-free survival advantage with sugemalimab vs. placebo after concurrent or sequential chemoradiotherapy for unresectable stage III lung cancer

Ancillary evaluations of the LungART data

The randomized phase III LungART trial assessed the effect of conformal postoperative radiotherapy (PORT) at a dose of 54 Gy delivered over 5.5 weeks in 252 patients with completely resected NSCLC and N2 nodal involvement after pre- and/or post-operative chemotherapy. DFS constituted the primary endpoint. According to the primary analysis presented in 2020, PORT, as compared to no PORT (n = 249), only slightly increased DFS (30.5 vs. 22.8 months; HR, 0.86; p = 0.18), with 3-year DFS rates of 47.1 % vs. 43.8 % [15]. At 3 years, 66.5 % vs. 68.5 % of patients were alive. While PORT reduced the risk of mediastinal relapse, this did not apply to distant metastatic events and the likelihood of brain metastases. In their recent analysis, Le Pechoux et al. focused on the patterns of failure observed in the study and the prognostic factors for PORT efficacy [16].

This showed that mediastinal relapse occurred mainly within initially involved lymph nodes. The 3 most frequently affected sites of mediastinal relapse were the stations 4R, 2R and 7 for right-sided tumors, and the stations 7, 4L and 4R for left-sided tumors. In terms of prognostic factors for DFS, female gender, squamous histology and absence of lymph node involvement were identified as protective. Besides age and WHO performance status, the burden of nodal disease as well as the quality of resection were relevant for DFS. Mediastinal-relapse–free survival at 3 years was significantly longer in the PORT arm irrespective of the burden of nodal disease and the presence of extracapsular extension. The authors concluded that personalized use of PORT should be based on prognostic factors of relapse and a joint assessment of toxicity and efficacy of this treatment approach. ■

REFERENCES

1 Vansteenkiste J et al., Current status of immune checkpoint inhibition in early-stage NSCLC. Ann Oncol 2019; 30(8): 1244-1253
2 Wakelee H et al., IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). J Clin Oncol 2021; 39(suppl 15): 8500
3 Felip E et al., IMPower010: sites of relapse and subsequent therapy from a phase 3 study of atezolizumab vs best supportive care after adjuvant chemotherapy in resected stage IB-IIIA NSCLC. ESMO 2021, LBA9
4 Altorki N et al., IMpower010: characterization of stage IB-IIIA NSCLC patients by type and extent of therapy prior to adjuvant atezolizumab. WCLC 2021, PL02.05
5 Provencio M et al., Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020; 21(11): 1413-1422
6 Provencio M et al., Long term survival in operable stage IIIA NSCLC patients treated with neoadjuvant nivolumab plus chemotherapy – NADIM study. WCLC 2021, OA20.01
7 Spigel DR et al., Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. J Clin Oncol 39, 2021 (suppl 15; abstr 8511)
8 Girard N et al., PACIFIC-R real-world study: treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. ESMO 2021, 1171M0
9 Antonia SJ et al., Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017; 377(20): 1919-1929

10 Wennerberg E et al., CD73 blockade promotes dendritic cell infiltration of irradiated tumors and tumor rejection. Cancer Immunol Res 2020; 8(4): 465-478
11 Tsukui H et al., CD73 blockade enhances the local and abscopal effects of radiotherapy in a murine rectal cancer model. BMC Cancer 2020; 20(1): 411
12 Nguyen AM et al., Upregulation of CD73 confers acquired radioresistance and is required for maintaining irradiation-selected pancreatic cancer cells in a mesenchymal state. Mol Cell Proteomics 2020; 19(2): 375-389
13 Martinez-Marti A et al., COAST: an open-label, phase 2, multidrug platform study of durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, stage III NSCLC. ESMO 2021, LBA42
14 W Y-L et al., GEMSTONE-301: a randomized, double-blind, placebo-controlled, phase 3 study of sugemalimab in patients with unresectable stage III non-small cell lung cancer without progression after concurrent or sequential chemoradiotherapy. ESMO 2021, LBA43
15 Le Pechoux C et al., An international randomized trial comparing post-operative radiotherapy (PORT) to no PORT, in patients with completely resected NSCLC and mediastinal N2 involvement. ESMO 2020, LBA3_PR
16 Le Pechoux C et al., An international randomized trial comparing post-operative conformal radiotherapy (PORT) to no PORT in patients with completely resected non-small cell lung cancer and mediastinal N2 involvement. ESMO 2021, 11700

Innovative and established agents across a range of targets

Anti-HER2 treatment

DESTINY-Lung01: robust effects of T-DXd

HER2 mutations constitute the predominant driver aberration in approximately 3 % of non-squamous NSCLC cases [1, 2]. While approved HER2-targeted therapies for patients with NSCLC are still lacking, the anti-HER2 antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has been licensed in various countries for use in other *HER2*-positive entities. The international, 2-cohort, phase II DESTINY-Lung01 study investigated T-DXd in patients with HER2-overexpressing and *HER2*-mutated, metastatic NSCLC who had relapsed on or were refractory to standard treatment. At ESMO 2021, Li et al. presented the primary analysis of the fully enrolled *HER2*-mutant group (i.e., Cohort 2) that contained a total of 91 patients treated with T-DXd 6.4 mg/kg Q3W [3]. Approximately 95 % of them had received platinum-based chemotherapy, 65.9 % anti-PD-(L)1 therapy, and 62.6 % both.

T-DXd showed robust and durable anticancer activity in these patients. The objective response rate (ORR) was 54.9 %, and 92.3 % achieved clinical benefit. Responses were consistently observed across subgroups, including patients with stable CNS lesions **(Figure 1)**, and lasted for a median of 9.3 months. Exploratory analyses demonstrated anticancer activity across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* gene amplification. Median progression-free survival (PFS) and overall survival (OS) amounted to 8.2 and 17.8 months, respectively.

The most common treatment-emergent AEs (TEAEs) associated with discontinuation were investigator-reported pneumonitis (13.2 %) and interstitial lung disease (ILD; 5.5 %). Seventy-five percent of adjudicated drug-related ILD/pneumonitis cases were grade 1 or 2. Nevertheless, the authors pointed out that these events remain an important identified risk that calls for effective early detection and management. TEAE-related dose reductions occurred in 34.1 % and were mainly due to nausea (11.0 %) and fatigue (8.8 %).

In their conclusion, the authors noted that DESTINY-Lung01 provides compelling evidence of positive benefit-risk balance with T-DXd in the second- and later-line settings. The data support the implementation of T-DXd as a potential new treatment standard. Meanwhile, the 5.4 mg/kg dose is being explored in the DESTINY-Lung02 trial to establish the optimal dosing regimen in patients with *HER2*-mutant NSCLC.

Poziotinib in *HER2* exon 20 insertions

The multi-cohort global ZENITH20 trial is assessing the pan-HER tyrosine kinase inhibitor (TKI) poziotinib in various settings including *EGFR* or *HER2* exon 20 insertion mutations, atypical *EGFR* or *HER2* mutations, and after failure of osimertinib. In Cohort 4 of the study, first-line poziotinib is being in-

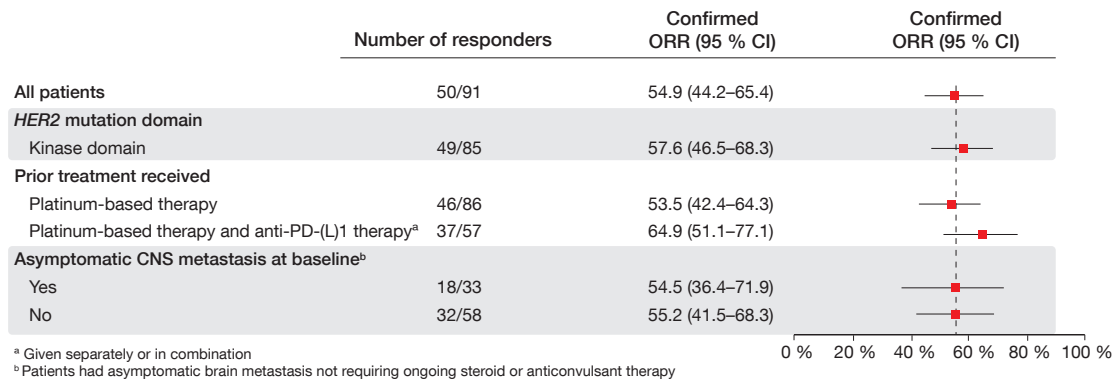

Figure 1: Consistent responses across subgroups observed with trastuzumab deruxtecan in patients with *HER2*-mutated NSCLC

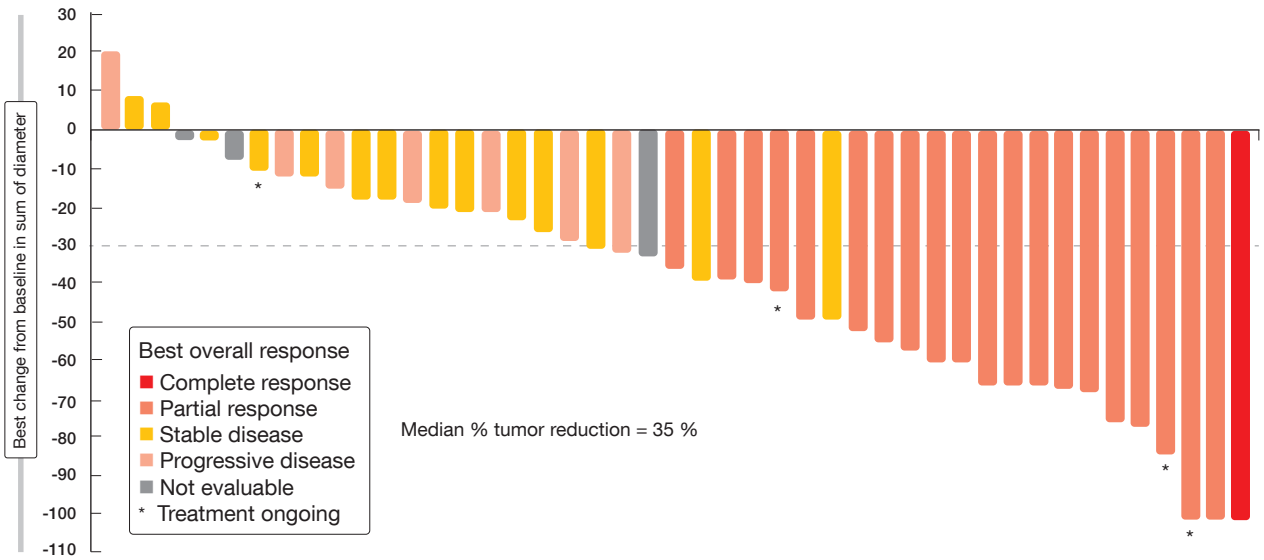

Figure 2: Reductions in target tumor size from baseline in patients with *HER2* exon 20 insertion receiving poziotinib

vestigated in patients with *HER2* exon 20 insertions; 48 of these are receiving 16 mg once daily, while enrollment is still ongoing in the group of 23 patients treated with 8 mg twice daily. Cornelissen et al. reported preliminary efficacy and safety data for the once daily dosing group within Cohort 4 at ESMO 2021 [4].

With respect to objective response, which had been defined as the primary endpoint, the treatment induced a centrally reviewed confirmed rate of 43.8 %. Disease control occurred in 75.0 %. Eighty-eight percent of patients experienced tumor reduction **(Figure 2)**. Median PFS was 5.6 months, with 26 % of patients being alive and progression-free beyond 12 months. Responses lasted for a median of 5.4 months; here, the upper range was > 19.1 months. Poziotinib showed a manageable toxicity profile that was in line with previous poziotinib studies and other second-generation EGFR TKIs. Diarrhea, rash and stomatitis were observed as the most common AEs. AEs leading to dose reductions and permanent discontinuation occurred in 77 % and 13 %, respectively. Overall, once-daily poziotinib treatment demonstrated clinically meaningful efficacy in treatment-naïve patients with NSCLC harboring *HER2* exon 20 insertion mutations.

EGFR/MET inhibition: amivantamab

Companion diagnostics & combination with lazertinib

Based on the ongoing phase I CHRYSALIS trial, the EGFR/MET bispecific antibody amivantamab has received US approval for the treatment of patients with *EGFR* exon 20 insertion-positive NSCLC who have progressed on or after platinum-based chemotherapy. CHRYSALIS is assessing amivantamab in various settings as monotherapy and combined with the third-generation EGFR TKI lazertinib. A bridging study was conducted to clinically validate two potential NGS-based companion diagnostics, the plasma-based Guardant360® CDx and the tissue-based Oncomine™ Dx Target Test, for the detection of *EGFR* exon 20 insertion variants. According to the results presented at WCLC 2021, these tests showed a high degree of concordance, and both can be used to accurately identify patients for amivantamab therapy [5].

At ESMO 2021, Leighl et al. reported CHRYSALIS data on the contribution of the addition of lazertinib to amivantamab after osimertinib failure [6]. The amivantamab plus lazertinib and amivantamab monotherapy cohorts included 45 and 121 patients, respectively **(Figure 3)**. Indeed, the combination appeared to have higher activity than the monotherapy. The addition of lazertinib resulted in a numerically higher ORR compared to amivantamab alone (36 % and 19 %, respectively) and longer duration of response (9.6 and 5.9 months, respectively). Responses for ≥ 6 months occurred in 69 % and 39 %, respectively. CNS protection was potentially improved in the combined cohort considering the even lower CNS pro-

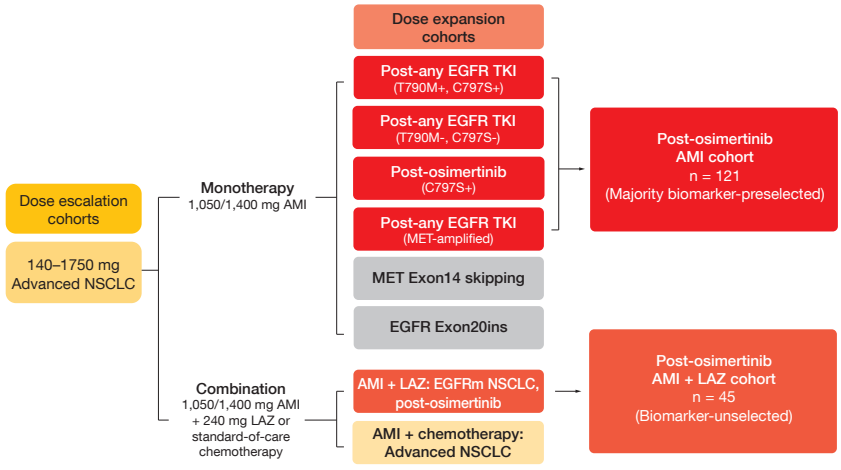

Figure 3: Design of the CHRYSALIS trial investigating amivantamab (AMI) alone and in combination with lazertinib (LAZ)

gression rate of 7 % compared to 17 % in the amivantamab monotherapy cohort.

The safety profile for both monotherapy and combination therapy was consistent with previously reported experience. Amivantamab plus lazertinib is being evaluated in multiple EGFR NSCLC populations in the CHRYSALIS-2 study and the phase III MARIPOSA trial.

Findings in *MET* exon 14 skipping mutations

Spira et al. reported the first results for amivantamab obtained in the cohort of patients enrolled in the CHRYSALIS study whose tumors harbored *MET* exon 14 skipping (*MET*ex14) mutations [7]. These mutations occur in approximately 3 % of NSCLC cases [8] and are amenable to treatment with MET TKIs, although emergence of resistance is a major concern here. The *MET*ex14 population included in CHRYSALIS is still being recruited; 19 patients with metastatic or unresectable NSCLC who had progressed after standard-of-care treatment or declined it were included in the analysis.

Among 14 response-evaluable patients, 9 (64 %) developed partial responses on amivantamab therapy, with 5 confirmed and 4 pending confirmation. Activity was observed in both treatment-naïve and previously treated patients; this included 7 individuals previously treated with MET TKIs two of whom showed potential resistance mechanisms. Median duration of response had not been reached, and 11 of the 14 response-evaluable patients remained on treatment.

The safety profile of amivantamab in this patient subgroup was consistent with the previously reported profile observed in patients with *EGFR*-mutated NSCLC. According to the authors, this first report of amivantamab in *MET*ex14-positive NSCLC confirms the bispecific targeting action of this agent, with monotherapy activity demonstrated in both EGFR-driven and MET-driven NSCLC.

Anti-c-MET ADC telisotuzumab vedotin

An ongoing single-arm, 2-stage, adaptive phase II study is evaluating the first-in-class anti-c-MET antibody drug conjugate telisotuzumab vedotin in the setting of previously treated, locally advanced or metastatic NSCLC with c-Met protein overexpression. The trial contains three cohorts based on histology and *EGFR* mutation status: a squamous cohort, a non-squamous cohort with *EGFR* mutations, and a non-squamous cohort with *EGFR* wildtype. Each of the non-squamous groups was further divided into two subgroups that show either high or intermediate c-Met expression. After this first stage, a decision is made based on ORR as to which patients to continue into the expansion stage. Telisotuzumab vedotin is administered at a dose of 1.9 mg/kg Q2W.

TABLE 1
Response rates and duration of response obtained with telisotuzumab vedotin according to independent review

NSCLC group	ORR, n/N (%)	Median duration of response, months
Non-squamous *EGFR* wildtype	13/37 (35.1)	6.9
c-Met high	7/13 (53.8)	-
c-Met intermediate	6/24 (25.0)	-
Non-squamous *EGFR* mutation	4/30 (13.3)	NA
c-Met high	4/22 (18.2)	-
c-Met intermediate	0/8 (0)	-
Squamous	3/21 (14.3)	4.4

The interim analysis reported by Camidge et al. at ESMO 2021 related to 37 and 31 patients in the non-squamous *EGFR* wildtype and *EGFR* mutation populations, respectively, and 22 patients in the squamous cohort [9]. C-Met expression based on H score was lower in the *EGFR* wildtype population (median, 225) than in the group with *EGFR* mutations (265), while the lowest score was observed in the squamous cohort (164). Among the non-squamous patients, the majority of those with *EGFR* mutation showed high c-Met expression (71 %), whereas intermediate c-Met expression prevailed in the group with *EGFR* wildtype (65 %).

Telisotuzumab vedotin demonstrated a promising ORR of 35.1 % in the non-squamous *EGFR* wildtype cohort **(Table 1)**. Patients in this cohort with high c-Met expression achieved responses in 53.8 %, thus obtaining the highest ORR of all groups, although the ORR was also clinically significant in those with intermediate c-Met expression. Based on pre-specified criteria, this cohort has expanded into stage 2 enrollment. All other groups responded to a modest extent. The most common serious TEAEs were pneumonia (5 %), malignant neoplasm progression (4 %), and pneumonitis (4 %). Grade ≥ 3 TEAEs occurred in 44 % of patients. Enrollment has been discontinued in the squamous cohort but will continue in the *EGFR*-mutated cohort until the next interim analysis.

EGFR exon 20 insertions

Mobocertinib after successful TKI treatment

The EGFR TKI mobocertinib that specifically targets *EGFR* exon 20 insertions has been granted Breakthrough Therapy designation for the treatment of NSCLC patients with *EGFR* exon 20 insertion mutations after progression on platinum-based chemotherapy (in the United States) or after prior chemotherapy (in China) based on preliminary phase I/II results [10]. At ESMO 2021, Spira et al. presented efficacy and safety data from an expansion cohort of patients who had progressed after an objective response or stable disease for ≥ 6 months on any prior EGFR TKI therapy in the phase I/II study [11]. Twenty patients received mobocertinib 160 mg once daily. Prior TKI therapies included poziotinib, osimertinib, afatinib, and erlotinib. In 55 %, EGFR TKIs had been administered as the most recent prior treatment, including poziotinib (n = 7), osimertinib (n = 3), and an investigational TKI (n = 1). Median time on prior TKI therapy was 7.8 months.

The treatment with mobocertinib provided a clinically meaningful benefit

in this patient group. After a median follow-up of 14.2 months, confirmed ORR and disease control rate were 40 % and 90%, respectively. Responses lasted for a median of 13.0 months. Median PFS was 7.3 months, and median OS had not been reached yet. At 12 months, 78.6 % of patients were alive. The analysis further demonstrated that the safety profile resembled that in other patient cohorts from the phase I/II trial and was consistent with the broader class of EGFR TKIs. Among all-grade treatment-related AEs, diarrhea occurred most commonly (90 %), although grade ≥ 3 diarrhea emerged only in one patient. AEs led to dose reductions in 4 patients (20 %), and 2 (10 %) discontinued treatment due to AEs. The authors concluded that mobocertinib represents a potentially promising treatment option in patients with *EGFR* exon 20 insertion-positive metastatic NSCLC including those who experienced objective responses on prior EGFR TKI therapy.

Novel inhibitor DZD9008

The selective, irreversible EGFR/HER2 inhibitor DZD9008 is being developed for the treatment of patients with NSCLC and *EGFR* or *HER2* mutations. DZD9008 demonstrated encouraging anti-tumor activity in heavily pretreated patients with different subtypes of *EGFR* exon 20 insertion mutations in the two ongoing phase I studies WU-KONG1 and WU-KONG2 [12]. Both of these trials contain several dose escalation and dose expansion cohorts; in addition, WU-KONG1 has a food effect cohort. Overall, the safety set included 102 patients treated with at least one dose of DZD9008 50 mg to 400 mg once daily in either study. The efficacy set included 56 patients with *EGFR* exon 20 insertions who received DZD9008 50 mg to 400 mg once daily followed by at least one post-treatment RECIST assessment. Here, 18 and 38 patients were derived from the dose escalation and dose expansion cohorts, respectively.

The novel agent showed favorable pharmacokinetic properties with a half-life of approximately 50 hours and no apparent effect of high-fat food on exposure, among others. Regarding anti-tumor efficacy, the confirmed ORRs were 22.2 % and 44.7 % across all dose levels in the dose escalation and dose expansion cohorts, respectively. Efficacy was observed at doses ≥ 100 mg, in patients with and without baseline brain metastases, and across different *EGFR* exon 20 insertion subtypes. The longest treatment duration was more than 17 months. Median PFS had not been reached yet at the time of the analysis. DZD9008 was well tolerated, with a manageable AE profile. Across all dose levels, grade ≥ 3 drug-related AEs occurred in 33.3 %. AEs leading to dose reduction or discontinuation were observed in 15.7 % and 5.9 %, respectively. A phase II study evaluating DZD9008 in pretreated patients with NSCLC harboring *EGFR* exon 20 insertions is ongoing.

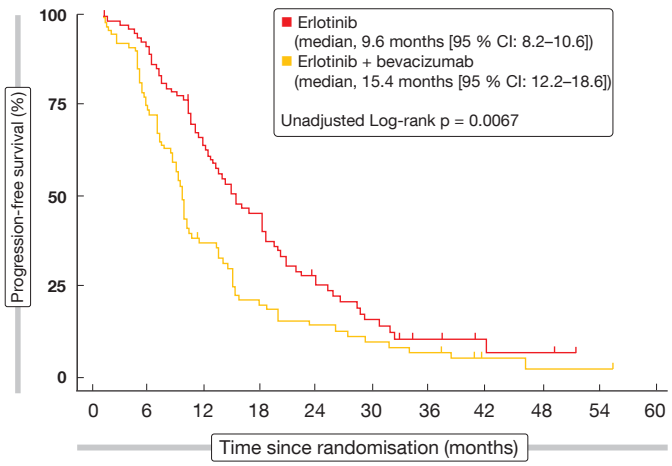

Figure 4: Progression-free survival achieved with the addition of bevacizumab to erlotinib in the BEVERLY trial

Combinations of EGFR TKIs with bevacizumab

BEVERLY: erlotinib

Studies have shown that the addition of VEGF inhibitors to first-generation EGFR TKIs can prolong PFS in *EGFR*-mutated, non-squamous NSCLC [13-15]. The multicenter, randomized, phase III BEVERLY trial tested the combination of the anti-VEGF antibody bevacizumab with erlotinib in the first-line treatment of patients with stage IIIB or IV, *EGFR*-positive NSCLC. A total of 160 individuals were randomized in a 1:1 fashion to either erlotinib 150 mg once daily plus bevacizumab 15 mg/kg Q3W or single-agent erlotinib.

Compared to erlotinib only, the combined administration of bevacizumab plus erlotinib significantly improved PFS (15.4 vs. 9.6 months; HR, 0.66; p = 0.015; **Figure 4**) and ORR (70 % vs. 50 %; p = 0.01), whereas OS was prolonged in a non-significant manner (33.3 vs. 22.8 months; HR, 0.72; p = 0.132) [16]. Exploratory subgroup analyses of PFS and OS suggested that the benefit of the combination might be particularly pronounced in former and current smokers.

A quality-of-life analysis revealed no significant difference across the treatment arms in any of the items of the EORTC C30-LC13 questionnaire. With respect to time to deterioration of global health status/quality of life, patients in the experimental arm showed slightly better outcomes, although this difference was not significant. No unexpected safety signals occurred. The combination gave rise to higher rates of severe hypertension and rash. As the authors stated, bevacizumab plus erlotinib might be considered as a first-line option in patients who cannot receive osimertinib, and this regimen warrants further investigation.

WJOG9717L: osimertinib

No benefit from the addition of bevacizumab to another EGFR-targeted agent was found in the WJOG9717L study [17]. Osimertinib 80 mg once daily (n = 61) plus bevacizumab 15 mg/kg Q3W was compared with osimertinib alone (n = 61). The combination did not show superiority in terms of PFS (22.1 vs. 20.2 months; p = 0.213), ORR (82 % vs. 86 %), or OS (HR, 0.970), although the subgroup analysis indicated that ever-smokers or patients with exon 19 dele-

TABLE 2
Clinical outcomes of the UpSwinG study that investigated sequential afatinib and osimertinib

	Median time to treatment failure, months	Median overall survival, months	Overall response rate afatinib, %	Overall response rate osimertinib, %
All patients	27.7	36.5	73.6	45.2
Mutation type				
Deletion 19	28.6	38.0	74.0	47.1
L858R	22.1	33.1	72.7	40.4
Ethnicity				
Asian	28.8	42.3	79.3	48.0
Non-Asian	25.5	31.3	67.3	36.0
Brain metastases				
No	28.4	37.6	71.2	45.8
Yes	21.4	29.6	91.3	41.7
ECOG performance status				
< 2	28.5	39.8	77.9	47.9
≥ 2	29.6	33.1	70.6	40.0
Asian and deletion 19	29.7	43.8		

tion might derive PFS benefits from the addition of bevacizumab (HRs, 0.481 and 0.622, respectively). According to the AE analysis, the combination might reduce the osimertinib-associated risk of pneumonitis, although hypertension, epistaxis and proteinuria occurred considerably more often in the experimental arm.

Real-world experience relating to afatinib use

UpSwinG: sequential treatment

In patients with *EGFR*-mutant NSCLC, survival outcomes substantially depend on the availability and implementation of subsequent therapy following acquired resistance to first-line therapy. As the T790M mutation is the cause of resistance to afatinib in up to 50-70 % of cases [18] and is highly sensitive to osimertinib, the sequential use of afatinib and osimertinib might help to maximize the duration of targeted treatment. In the non-interventional, global UpSwinG study, health records were analyzed to assess patient outcomes on first-line afatinib followed by second-line osimertinib after the acquisition of the T790M mutation in regular clinical practice. The analysis reported at WCLC 2021 included 191 patients who were predominantly Asian and female [19]. Approximately 14 % had brain metastases.

The median duration of treatment with afatinib and osimertinib was 15.1 and 9.5 months, respectively. Nearly half of the patients had at least one further treatment line after osimertinib, which mostly consisted of chemotherapy (84.5 %). Time to treatment failure, which was defined as the primary endpoint, was 27.7 months, and median OS amounted to 36.5 months **(Table 2)**. These outcomes were consistent across subgroups including those with ECOG PS ≥ 2 and brain metastases. Median OS was longest in Asian patients (42.3 months) and Asian patients with deletion 19 mutation (43.8 months). The authors pointed out that these data are of special interest as osimertinib, as compared to first-line EGFR TKIs, has been shown not to confer significant OS benefit in Asians [20].

Overall, the results from the UpSwinG study substantiate previous studies such as GioTag that demonstrated encouraging OS of > 3 years in patients with acquired T790M who received sequential afatinib and osimertinib [21]. However, the majority of patients included in UpSwinG underwent tissue biopsy, and mutations were mainly detected based on PCR-based techniques. The authors noted that greater implementation of next-generation sequencing and liquid biopsies might increase the number of patients who are likely to benefit from targeted treatment.

REFERENCES

1 Stephens P et al., Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature 2004; 431(7008): 525-526
2 Mazières J et al., Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013; 31(16): 1997-2003
3 Li BT et al., Primary data from DESTINY-Lung01: a phase 2 trial of trastuzumab deruxtecan in patients with *HER2*-mutated metastatic non-small cell lung cancer. ESMO 2021, LBA45
4 Cornelissen R et al., Efficacy and safety of poziotinib in treatment-naïve NSCLC harboring HER2 exon 20 mutations: a multinational phase 2 study (ZENITH20-4). ESMO 2021, LBA46
5 Jatkoe T et al., Validation of companion diagnostics for the identification of patients with EGFR exon20ins NSCLC for amivantamab therapy. WCLC 2021, P24.14
6 Leighl N et al., Amivantamab monotherapy and in combination with lazertinib in post-osimertinib EGFR-mutant NSCLC: analysis from the CHRYSALIS study. ESMO 2021, 1192M0
7 Spira AI et al., Amivantamab in non-small cell lung cancer with MET exon 14 skipping mutation: initial results from CHRYSALIS. WCLC 2021, OA15.03
8 Frampton GM et al., Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015; 5(8): 850-859
9 Camidge DR et al., Telisotuzumab vedotin monotherapy in patients with previously treated c-Met+ advanced non-small cell lung cancer. WCLC, OA 15.04
10 Riely GR et al., Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with *EGFR* exon 20 insertion mutations from a phase I/II trial. Cancer Discov 2021; 11(7): 1688-1699
11 Spira AI et al., Mobocertinib in *EGFR* exon 20 insertion-positive metastatic NSCLC patients with disease control on prior EGFR TKI therapy. ESMO 2021, OA15.01
12 Jänne P et al., Phase 1 studies of DZD9008, an oral, selective EGFR/HER2 inhibitor in advanced NSCLC with *EGFR* exon20 insertion mutation. WCLC 2021, OA15.02
13 Seto T et al., Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014; 15(11): 1236-1244
14 Saito H et al., Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-pos-

Elderly patients and uncommon mutations

Brückl et al. presented the final results of a post-hoc analysis of elderly patients included in the prospective, non-interventional GIDEON study that investigated first-line afatinib treatment in routine clinical practice in Germany [22]. Forty-three percent (n = 66) of the patients treated in GIDEON were aged ≥ 70 years. Compared to those younger than 70 years, this group tended to have worse ECOG performance status and a greater number of comorbidities (Charlson Comorbidity Index ≥ 1, 36 % vs. 9 %). Nevertheless, the efficacy of treatment did not appear to be compromised. PFS outcomes were comparable in the groups aged ≥ 70 years and > 70 years, with 12-month PFS rates of 58.9 % and 43.9 %, respectively. Median OS was 30.4 and 27.4 months, respectively. Moreover, elderly patients showed a similar safety profile and incidence of grade ≥3 AEs. Dose reductions and discontinuations due to AEs were required in similar percentages.

There is a lack of clinical data on the activity of EGFR TKIs in NSCLC patients with uncommon *EGFR* mutations (i.e., non-deletion 19/L858R). An updated analysis of a database of patients with NSCLC and uncommon *EGFR* mutations treated with afatinib in randomized controlled trials and real-world practice was reported at ESMO 2021 [23]. Overall, 1,023 patients were identified; most of them were treated in clinical studies or compassionate use programs.

Afatinib demonstrated pronounced activity against major uncommon, compound, and other uncommon mutations including E709X and L747X mutations with respect to time to treatment failure and ORR. Encouraging results were observed for time to treatment failure irrespective of ethnicity (11.5 and 10.3 months in Asian and non-Asian TKI-naïve patients, respectively) and the presence of brain metastases (8.2 months). The analysis also showed activity against certain exon 20 insertions at residues A763, M766, N771, and V769, and against the osimertinib resistance mutations G724S, L718Q, L718V, and C797S. In the 15 patients who received afatinib after osimertinib, ORR and disease control rate were 36 % and 100 %, respectively.

TROP2-targeted therapy

Update of TROPION-PanTumor01

The antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) has been developed to target the transmembrane glycoprotein TROP2 that is highly expressed in NSCLC regardless of genomic mutation status and has been associated with poor prognosis [24-26]. Dato-DXd was tested in the dose-escalation/dose-expansion phase I TROPION-PanTumor01 study in various tumor types. In the NSCLC cohort, 50 patients each received Dato-DXd 4 mg/kg and 6 mg/kg, while 80 were treated with 8 mg/kg.

Previous analyses of the TROPION-PanTumor01 study have demonstrated promising antitumor activity with a manageable safety profile in this heavily pretreated NSCLC cohort [27, 28]. At WCLC 2021, Garon et al. presented updated results according to which Dato-DXd continued to demonstrate highly encouraging efficacy and a manageable safety profile at all three doses [29]. The 6 mg/kg dose, which had been selected for further development, gave rise to an ORR of 28 % and median duration of response of 10.5 months. Most responses were durable over time. TEAEs were primarily non-hematologic (i.e., nausea, stomatitis, alopecia, fatigue), and were mostly classified as mild or moderate. ILD that was adjudicated as drug-related occurred in 6 % in the 6 mg/kg cohort. The phase III TROPION-Lung01 trial is currently evaluating Dato-DXd for the treatment of NSCLC.

Dato-DXd in patients with actionable aberrations

The TROPION-PanTumor01 subset analysis presented at ESMO 2021 related to patients with actionable genomic alterations (AGAs) [30]. As is

REFERENCES

itive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 2019; 20(5): 625-635
15 Nakagawa K et al., Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20(12): 1655-1669
16 Piccirillo MC et al., Bevacizumab + erlotinib vs erlotinib alone as first-line treatment of patients with EGFR mutated advanced non squamous NSCLC. Final analysis of the multicenter, randomized, phase III BEVERLY trial. ESMO 2021, 12070
17 Kenmotsu H et al., Primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small-cell lung cancer harboring *EGFR* mutations; WJOG9717L study. ESMO 2021, LBA44
18 Girard N et al., Optimizing outcomes and treatment sequences in EGFR mutation-positive non-small-cell lung cancer: recent updates. Future Oncol 2019; 15(25): 2983-2997
19 Popat S et al., Sequential afatinib and osimertinib in patients with advanced *EGFR*m+ NSCLC and acquired T790M: the real-world UpSwinG study. WCLC 2021, P51.05
20 Kim ES et al., EGFR tyrosine kinase inhibitors for EGFR mutation-positive non-small-cell lung cancer: outcomes in Asian populations. Future Oncol 2021; 17(18): 2395-2408
21 Hochmair MJ et al., Sequential afatinib and osimertinib in patients with *EGFR* mutation-positive non-small-cell lung cancer: final analysis of the GioTag study. Future Oncol 2020; 16(34): 2799-2808
22 Brueckl WM et al., Elderly patients treated with afatinib in clinical practice – final results of the GIDEON study in *EGFR* mutated NSCLC in Germany. ESMO 2021, 1230P
23 Yang JCH et al., Afatinib for the treatment of NSCLC with uncommon EGFR mutations: an updated database of 1023 cases. ESMO 2021, 1212P
24 Mito R et al., Clinical impact of TROP2 in non-small lung cancers and its correlation with abnormal p53 nuclear accumulation. Pathol Int 2020; 70(5): 287-294
25 Inamura K et al., Association of tumor TROP2 expression with prognosis varies among lung cancer subtypes. Oncotarget 2017; 8(17): 28725-28735
26 Jiang A et al., Expression and clinical significance of the Trop-2 gene in advanced non-small cell lung carcinoma. Oncol Lett 2013; 6(2): 375-380
27 Meric-Bernstam F et al., TROPION-PanTumor 01: dose analysis of the TROP2-directed antibody-drug conjugate datopotamab deruxtecan for the treatment of advanced or metastatic non-small cell lung cancer. J Clin Oncol 39, 2021 (suppl 15; abstr 9058)
28 Spira A et al., Datopotamab deruxtecan (Dato-DXd; DS-1062), a TROP2 ADC, in patients with advanced NSCLC: updated results of TROPION-PanTumor01 phase 1 study. WCLC 2020, OA03.03
29 Garon EB et al., TROPION-PanTumor01: updated results from the NSCLC cohort of the phase 1 study of datopotamab deruxtecan in solid tumors. WCLC 2021, MA03.02
30 Garon EB et al., Efficacy of datopotamab deruxtecan in patients with advanced/metastatic non-small cell lung cancer and actionable genomic alterations: preliminary results from the phase 1 TROPION-PanTumor01 study. ESMO 2021, LBA49
31 Scagliotti GV et al., Addressing the unmet need in lung cancer: The potential of immuno-oncology. Cancer Treat Rev 2015; 41(6): 465-475
32 Maione P et al., Overcoming resistance to targeted therapies in NSCLC: current approaches and clinical application. Ther Adv Med Oncol 2015; 7(5): 263-273

known, this group derives limited benefit from existing therapies once TKIs and platinum-based chemotherapy have failed [31, 32]. The AGA subset included in the NSCLC cohort of TROPION-PanTumor01 comprised 34 patients with *EGFR* mutations (85 %), *ALK* fusions (9 %), *ROS1* fusions (3 %), and *RET* fusions (3 %). Eighty-two percent had already been treated with ≥ 3 prior lines.

Highly encouraging anti-tumor activity of Dato-DXd was observed in this heavily pretreated population. The ORR was 35 %, and responses lasted for a median of 9.5 months; this was consistent with the overall NSCLC population of the study [29]. Clinical activity emerged in the *EGFR*-mutated setting even after osimertinib failure. AEs were generally grade 1 and 2, with nausea and stomatitis being the most common events. The safety profile proved manageable and consistent with that observed in the overall NSCLC group [29]. Dato-DXd is being further evaluated in the TROPION-Lung05 trial in NSCLC patients with actionable genomic alterations after exhaustion of targeted agents and platinum-based chemotherapy options. ■

Immunotherapy: boosting efficacy and overcoming resistance

POSEIDON: durvalumab ± tremelimumab

The global, randomized, open-label, phase III POSEIDON trial evaluated the PD-L1 inhibitor durvalumab with or without the anti-CTLA-4 antibody tremelimumab in addition to chemotherapy as a first-line strategy in the setting of metastatic NSCLC. At 153 sites in 19 countries, 1,013 patients with squamous or non-squamous, stage IV NSCLC were randomized into three arms. One experimental arm received durvalumab 1,500 mg plus chemotherapy according to investigator's choice Q3W for 4 cycles, which was followed by durvalumab 1,500 Q4W plus pemetrexed until progression (D+CT; n = 338). In the other experimental arm, the regimen consisted of durvalumab plus tremelimumab 75 mg and chemotherapy Q3W for 4 cycles, followed by durvalumab Q4W, tremelimumab (week 16 only) and pemetrexed until progression (D+T+CT; n = 338). Patients in the control arm received platinum-based chemotherapy Q3W for up to 6 cycles followed by pemetrexed (CT; n = 337). Johnson et al. presented the results of the study at WCLC 2021 [1].

The primary endpoints were progression-free survival (PFS) and overall survival (OS) for D+CT vs. CT. Indeed, D+CT led to significant improvement of PFS compared to CT (5.5 vs. 4.8 months; HR, 0.74; p = 0.00093), while for OS, a trend favored the combination (13.3 vs. 11.7 months; HR, 0.86; p = 0.07581). The analysis of the key secondary endpoints showed that D+T+CT, as compared to CT, demonstrated statistically significant and clinically meaningful improvements in both PFS (6.2 vs. 4.8 months; HR, 0.72; p = 0.00031) and OS (14.0 vs. 11.7 months; HR, 0.77; p = 0.00304). Patients with non-squamous histology derived more prominent benefits from the triple combination than those with squamous tumors **(Table 1)**. In the non-squamous group, the hazard ratios for PFS and OS with D+T+CT vs. CT were 0.66 and 0.70, respectively, while in the squamous group, this was 0.77 and 0.88, respectively.

Overall, the safety profile was similar across all three arms. The addition of tremelimumab to durvalumab plus CT did not give rise to a meaningful increase in the treatment discontinuation rates (15.5 % and 14.1 % with D+T+CT and D+CT, respectively). According to the authors' conclusion, durvalumab plus tremelimumab and chemotherapy represents a potential new first-line treatment option for patients with metastatic NSCLC.

TABLE 1
Outcomes with durvalumab ± tremelimumab plus chemotherapy vs. chemotherapy according to histology

Endpoint	D + T + CT	D + CT	CT
Non-squamous histology			
Progression-free survival, months	6.8 HR, 0.66	6.4 HR, 0.77	5.5
Overall survival, months	17.2 HR, 0.70	14.8 HR, 0.82	13.1
Confirmed objective response rate, %	45.5	44.3	23.7
Duration of response, months	16.4	10.6	6.0
Squamous histology			
Progression-free survival, months	4.6 HR, 0.77	4.7 HR, 0.68	4.6
Overall survival, months	10.4 HR, 0.88	11.5 HR, 0.84	10.5
Confirmed objective response rate, %	27.4	37.3	25.6
Duration of response, months	5.6	5.5	4.8

Cemiplimab plus chemotherapy: EMPOWER-Lung 3

The anti-PD-1 antibody cemiplimab has been approved as first-line monotherapy for the treatment of patients with advanced NSCLC and PD-L1 ≥ 50 % based on the EMPOWER-Lung 1 study

[2]. At ESMO 2021, Gogishvili et al. reported the second interim analysis of the double-blind, randomized, phase III EMPOWER-Lung 3 trial that assessed first-line treatment with cemiplimab 350 mg plus platinum-doublet chemotherapy Q3W for 4 cycles [3]. Patients with non-squamous or squamous advanced NSCLC were randomized either to the experimental arm (n = 312) or the control arm that received placebo plus chemotherapy (n = 154). The treatment continued for up to 108 weeks or disease progression in both arms. Any PD-L1 expression was permitted.

The addition of cemiplimab to chemotherapy gave rise to clinically meaningful and statistically significant improvements in OS (21.9 vs. 13.0 months; HR, 0.71; p = 0.014), PFS (8.2 vs. 5.0 months; HR, 0.56; p < 0.0001), and objective response rate (ORR; 43.3 % vs. 22.7 %; odds ratio, 2.68; p < 0.0001). Complete remissions occurred in 2.6 % in the experimental arm, whereas there were none in the control arm. Median duration of response amounted to 15.6 vs. 7.3 months.

The combination demonstrated an acceptable benefit-risk profile with a low discontinuation rate (3 % vs. 1 %) due to treatment-related AEs (TRAEs). Any-grade immune-related AEs (irAEs) occurred in 19 %. The safety profile was generally consistent with the profiles known for cemiplimab and platinum-based chemotherapy. Patient-reported outcomes indicated delays in the time to definitive clinically meaningful deterioration in global health status/quality of life (HR, 0.78) and pain symptoms (HR, 0.39). Also, overall change from baseline in global health status/quality of life and pain symptoms improved. In their summary, the authors noted that cemiplimab in combination with platinum-doublet chemotherapy is a new first-line option for patients with advanced NSCLC without targetable mutations irrespective of histology and PD-L1 expression levels.

Post-hoc analysis of nivo/ipi in patients with brain lesions

Brain metastases are diagnosed in 10 % of patients with NSCLC and typically confer poor prognosis [4, 5]. Nivolumab in combination with ipilimumab has shown promising efficacy in patients with CNS lesions across multiple tumor types including advanced NSCLC [6-9]. The randomized phase III CheckMate 9LA trial has evaluated nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W in addition to 2 cycles of chemotherapy *versus* 4 cycles of chemotherapy with optional pemetrexed maintenance as first-line treatment of patients with stage IV or recurrent NSCLC. According to the 2-year update, the combination provided durable survival benefit vs. chemotherapy alone, with OS rates of 38 % vs. 26 % [10].

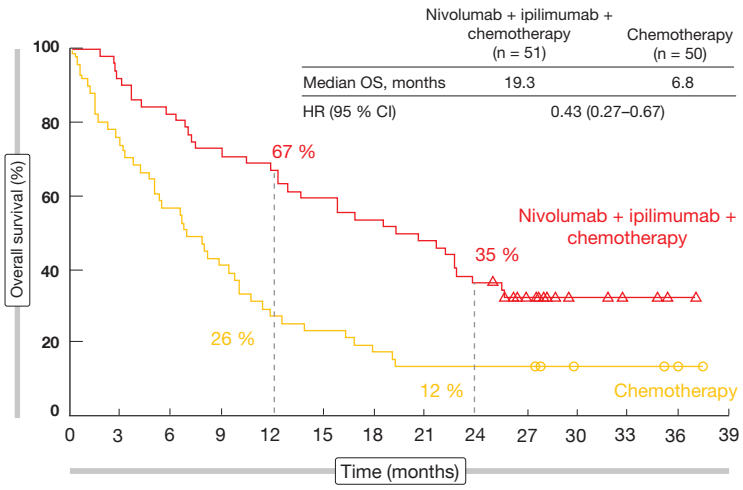

Figure 1: CheckMate 9LA: overall survival with nivolumab plus ipilimumab and chemotherapy vs. chemotherapy only in patients with baseline brain metastases

Patients with brain metastases that were adequately treated and asymptomatic for ≥ 2 weeks prior to the first dose were allowed to participate. In the experimental and control arms, this group included 51 and 50 individuals, respectively, while 310 and 308, respectively, had no brain lesions at baseline. At WCLC 2021, Carbone et al. reported a post-hoc analysis of patients with and without brain metastases after a minimum follow-up of 2 years [11].

The findings showed that nivolumab plus ipilimumab in addition to chemotherapy induced significant survival benefit compared to chemotherapy alone independent of the presence of baseline brain metastases. Patients with CNS lesions achieved an even more pronounced mortality reduction (median OS, 19.3 vs. 6.8 months; HR, 0.43; **Figure 1**) than those without (15.6 vs. 12.1 months; HR, 0.79). Likewise, regarding systemic response, the HRs were 0.40 and 0.74 for the two cohorts. The ORRs were 43 % and 37 % in the experimental arms of the groups with and without brain lesions, respectively, and median duration of response was 15.5 and 13.0 months, respectively.

Among the patients with CNS metastases, nivolumab plus ipilimumab and chemotherapy improved intracranial efficacy in terms of PFS (13.5 vs. 4.6 months; HR, 0.36), ORR (39 % vs. 20 %), and duration of response (22.3 vs. 18.9 months), which was consistent with systemic efficacy. Complete intracranial responses resulted in 10 % vs. 8 %. Fewer patients developed new brain metastases with the immunotherapy-based approach, both in the group with baseline CNS lesions (16 % vs. 30 %) and those without (2 % vs. 4 %). Median time to development of new brain metastases was 9.0 vs. 4.6 months in the patients who had baseline brain lesions. In their summary, the authors noted that these data further support the use of nivolumab plus ipilimumab in addition to chemotherapy as an efficacious first-line treatment option in patients with advanced NSCLC, including those with brain metastases.

ATEZO-BRAIN

The single-arm, phase II, Bayesian ATEZO-BRAIN trial aimed to determine the activity and safety of atezolizumab in patients with stage IV non-squamous NSCLC and untreated brain metastases based on the observation that this patient group is underrepresented in clinical trials evaluating chemotherapy plus immunotherapy in the first-line setting.

Forty patients received carboplatin (5 AUC) plus pemetrexed 500 mg/m² and atezolizumab 1,200 mg Q3W for 4-6 cycles followed by pemetrexed plus atezolizumab Q3W for a maximum of 2 years. Anticonvulsants and dexamethasone at ≤ 4 mg daily doses were permitted. Safety and PFS constituted the co-primary endpoint.

Atezolizumab plus carboplatin and pemetrexed demonstrated a favorable safety profile and efficacy in these patients, including those receiving corticosteroids [12]. The trial was completed as the boundaries for futility or unacceptable toxicity were not reached, with a 12-week PFS rate of 60 % and a grade 3-4 toxicity rate of 27.5 %. Most TRAEs were grade 1 and 2, and no fatal TRAEs occurred. Three patients had grade 4 TRAEs including thrombocytopenia, neutropenia, and hallucinations. Among AEs in general, fatigue (any grade, 60 %) and anemia (45 %) were observed most commonly. Selected immune-related AEs mainly comprised skin rash (20 %) and increases of the transaminases (13 %). One case of grade 3 pneumonitis was reported (3 %).

Median systemic PFS was 8.9 months, and 24.9 % of patients were progression-free at 18 months. Median intracranial PFS amounted to 6.9 months, which is similar to the PFS reported in the KEYNOTE-189 trial in patients with brain metastases [13]. Most responses in body and brain were concordant **(Table 2)**. Forty and 47.5 % of patients achieved intracranial and systemic responses, respectively. Median OS was 13.6 months, and at 2 years, 32 % were alive. Correlative studies based on brain imaging and blood samples are ongoing.

TABLE 2
Intracranial and systemic responses with atezolizumab plus chemotherapy in ATEZO-BRAIN

Outcome, n (%)	Best intracranial response	Best systemic response
Complete response	4 (10)	0
Partial response	12 (30)	19 (47.5)
Stable disease	19 (47.5)	16 (40)
Progressive disease	4 (10)	3 (7.5)
Not evaluable	1 (2.5)	2 (5)
Objective response rate	16 (40)	19 (47.5)

MRTX-500: sitravatinib plus nivolumab

Although checkpoint inhibitor therapy has changed the treatment landscape for NSCLC, resistance through various mechanisms including the development of an immunosuppressive tumor microenvironment is common, and treatment options are limited in the setting of disease refractory/resistant to anti-PD-(L)1 therapies. It was hypothesized that the combination of nivolumab with the tyrosine kinase inhibitor sitravatinib is a rational approach to augmenting the anti-tumor immune response and extending long-term patient benefit. Sitravatinib targets the TAM receptors TYRO3, AXL, MERTK, as well as VEGFR2 and KIT that have been shown to reduce myeloid-derived suppressor cells and enhance anti-tumor immune responses, among others [14]. The open-label, single-arm, phase II MRTX-500 trial tested sitravatinib 120 mg once daily plus nivolumab in patients with non-squamous, advanced NSCLC who had benefited from anti-PD-(L)1 therapy (i. e., complete or partial response or stable disease ≥ 12 weeks). Checkpoint inhibitors had been administered as the most recent line of treatment.

At ESMO 2021, Leal et al. reported updated efficacy and safety of sitravatinib plus nivolumab in the second- or third-line settings [15]. This analysis comprised 68 patients. The ORR, which constituted the primary endpoint, was 18 %, including complete remissions in 3 %. Seventy-eight percent of patients obtained disease control, and responses lasted for a median of 12.8 months. Median PFS and OS were 5.7 and 14.9 months, respectively. The 24-month OS rate was 32 %.

Among TRAEs, diarrhea (all grades, 62 %), fatigue (52 %) and nausea (44 %) were reported most commonly. The most frequent immune-related TRAEs included hypothyroidism, diarrhea, transaminase elevations, TSH increase, maculopapular rash, and pancreatitis. No grade 5 events occurred. TRAEs prompted treatment discontinuation in 22 %. In 81 %, at least one dose interruption of sitravatinib had to be performed due to AEs. These results support the ongoing randomized, open-label phase III SAPPHIRE trial assessing second-/third-line sitravatinib plus nivolumab *versus* docetaxel after progression on or following checkpoint inhibition in patients with advanced NSCLC.

Tislelizumab as combination partner of sitravatinib

The anti-PD-1 antibody tislelizumab has been designed to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, which is a mechanism of T cell clearance and anti-PD-1 resistance [16, 17]. Tislelizumab is being investigated in combination with sitravatinib in several solid tumor types with the aim of enhancing anti-tumor activity beyond that provided by either agent alone. An open-label, multicenter, non-randomized phase Ib trial tested sitravatinib 120 mg once daily plus tislelizumab 200 mg Q3W. Zhou et al. presented the results for Cohorts A, B and F that contained patients with squamous or non-squamous metastatic NSCLC who had received 1–3 prior lines of systemic therapy with or without an anti-PD-(L)1 inhibitor (n = 75) [18]. Any PD-L1 expression level was permitted.

The findings suggested efficacy of the combination irrespective of checkpoint inhibitor pretreatment. The overall ORR was 16.9 %, with a numerically higher proportion of anti-PD-(L)1-naïve patients responding compared to the relapsed/refractory cohort (22.2 % and 13.6 %, respectively). Likewise, anti-PD-(L)1-naïve patients experienced numerically longer PFS (7.0 months) and OS (15.3 months) than the pretreated group (PFS, 5.2 months; OS, 10.1 months). In the total cohort, median PFS and OS were 5.5 months and 11.9 months, respectively. Disease control was achieved in 84.5 %. Tislelizumab plus sitravatinib demonstrated a manageable safety profile consistent with what had previously

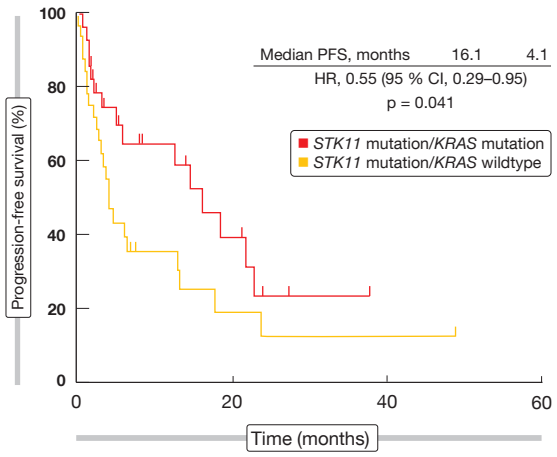

Figure 2: Significantly prolonged progression-free survival on immune checkpoint inhibition in the presence of *STK11/KRAS* co-mutations

been reported. Hypertension was the most commonly reported grade ≥ 3 treatment-emergent AE and TRAE, although no cases of hypertension led to treatment discontinuation.

Gao et al. presented a separate analysis of Cohorts A and F that included 47 patients with squamous and non-squamous metastatic NSCLC refractory or resistant to anti-PD-(L)1 therapy [19]. Disease control resulted in 86.4 % in this group, with median duration of response of 6.9 months. According to the authors, the promising anti-tumor activity observed in this study supports sitravatinib plus tislelizumab as a potential treatment option for patients with metastatic NSCLC that is relapsed or refractory to prior anti-PD-(L)1 therapy. Further investigation is warranted.

Results according to smoking status in RATIONALE 304 & 307

In the RATIONALE 304 study, tislelizumab plus chemotherapy gave rise to significantly improved PFS compared to chemotherapy alone as first-line treatment of patients with advanced non-squamous NSCLC [20]. According to the sub-analysis presented by Lu et al. at ESMO 2021, the efficacy and safety of tislelizumab plus chemotherapy in smokers (63.8 % of the population) was consistent with the findings observed in the overall population [21]. Median PFS for the two treatment arms was 9.7 vs. 4.6 months (HR, 0.466) in smokers, while these results did not differ in non-smokers (8.5 vs. 7.7 months; HR, 1.075). Tislelizumab in addition to chemotherapy induced higher ORR regardless of smoking status.

A similar sub-analysis of the RATIONALE 307 study that investigated first-line tislelizumab plus chemotherapy in NSCLC patients with squamous histology suggested consistent PFS and ORR independent of smoking status [22]. The primary analysis of RATIONALE 307 had revealed a significant PFS benefit and manageable safety compared with chemotherapy alone [23]. In this study, 83.7 % of patients were smokers. This group showed a median PFS of 7.6 months with both chemotherapy regimens (i.e., paclitaxel or nab-paclitaxel plus carboplatin) vs. 5.5 months with chemotherapy alone. Non-smokers equally benefited from the addition of tislelizumab in terms of PFS, with HRs of 0.475 and 0.119 for the two treatment regimens. ORR was higher in the experimental arm regardless of smoking status. In both RATIONALE 304 and 307, the safety profile recorded in smokers and non-smokers was consistent with that observed in the overall population.

STK11/KRAS co-mutations: predictive significance

Basher et al. elucidated the predictive role of *STK11/KRAS* co-mutations identified by next-generation sequencing and the incidence of irAEs in the setting of immune checkpoint inhibitor treatment [24]. Overall, 703 patients with stage IIIB/IV NSCLC from three centers in Florida were retrospectively analyzed.

Indeed, concomitant *STK11* and *KRAS* mutation was associated with significantly improved PFS compared to *STK11* mutation/*KRAS* wildtype (16.1 vs. 4.1 months; HR, 0.55; p = 0.041; **Figure 2**). For OS, the analysis showed a trend favoring the co-mutation (32.3 vs. 21.8 months; HR, 0.61; p = 0.21). irAEs were shown to predict OS improvement with the treatment: patients who developed irAEs lived for a median of 46.3 months compared to 29.7 months in the cohort without immune-related side effects (HR, 0.59; p = 0.022). While Hispanic patients experienced irAEs more frequently than their non-Hispanic white counterparts, they did not derive a significant survival benefit. Further studies might identify unique aspects of this population that can account for these observations. ■

REFERENCES

1 Johnson ML et al., Durvalumab ± tremelimumab + chemotherapy as first-line treatment for mNSCLC: results from the phase 3 POSEIDON study. WCLC 2021, PL02.01
2 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
3 Gogishvili M et al., EMPOWER-Lung 3: cemiplimab in combination with platinum-doublet chemotherapy for first-line treatment of advanced non-small cell lung cancer. ESMO 2021, LBA51
4 Waqar NS et al., Non-small-cell lung cancer with brain metastasis at presentation. Clin Lung Cancer 2018; 19(4): e373-e379
5 Sperduto PW et al., Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol 2017; 3(6): 827-831
6 Di Giacomo AM et al., Immunotherapy of brain metastases: breaking a "dogma". J Exp Clin Cancer Res 2019; 38(1): 419
7 Tawbi HA et al., Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018; 379(8): 722-730
8 Emamekhoo H et al., Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: Interim analysis of CheckMate 920. J Clin Oncol 37, 2019 (suppl; abstr 4517)
9 Borghaei H et al., Nivolumab + ipilimumab as first-line treatment for patients with advanced non-small cell lung cancer with brain metastases: results from Checkmate 227. Cancer Research 2020; 80(Suppl. 16): Abstract CT221
10 Reck M et al., First-line nivolumab plus ipilimumab plus two cycles of chemotherapy versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer: Two-year update from

CheckMate 9LA. J Clin Oncol 39, 2021 (suppl 15; abstr 9000)
11 Carbone DP et al., First-line nivolumab + ipilimumab + chemotherapy in patients with advanced NSCLC and brain metastases: results from CheckMate 9LA. WCLC 2021, OA09.01
12 Nadal E et al., ATEZO-BRAIN (GECP 17/05): non-randomized phase II clinical trial of atezolizumab combined with carboplatin plus pemetrexed in chemotherapy-naïve patients with advanced non-squamous NSCLC with untreated brain metastases. WCLC 2021, OA09.02
13 Garassino MC et al., Outcomes among patients with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab plus pemetrexed-platinum: Results from the KEYNOTE-189 study. AACR Annual Meeting 2019, CT043
14 Du W et al., Sitravatinib potentiates immune checkpoint blockade in refractory cancer model. JCI Insight 2018; 3: e124184
15 Leal TA et al., MRTX-500: phase 2 trial of sitravatinib + nivolumab in patients with nonsquamous non-small-cell lung cancer progressing on or after prior checkpoint inhibitor therapy. ESMO 2021, 1191O
16 Qin S et al., RATIONALE 301 study: tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma. Future Oncol 2019; 15: 1811-1822
17 Zhang T et al., The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother 2018; 67(7): 1079-1090
18 Zhou Q et al., Sitravatinib + tislelizumab in patients with metastatic non-small cell lung cancer. ESMO 2021, 1280P
19 Gao B et al., Sitravatinib + tislelizumab in patients with anti-PD-(L)1 refractory/resistant metastatic non-small cell lung cancer. ESMO 2021, 1284P
20 Lu S et al., Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): a randomized phase 3 trial. J Thorac Oncol 2021; 16(9): 1512-1522
21 Lu S et al., RATIONALE 304: tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for non-squamous non-small cell lung cancer in patients who are smokers vs non-smokers. ESMO 2021, 1290P
22 Yu X et al., RATIONALE 307: tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small cell lung cancer in patients who were smokers vs non-smokers. ESMO 2021, 1297P
23 Wang J et al., Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021; 7(5): 709-717
24 Basher F et al., Prognostic value of STK11 & KRAS mutations and irAE incidence in response to immunotherapy in Hispanics: a multicenter analysis. WCLC 2021, MA01.07

Small-cell lung cancer: on the road to improved efficacy and tolerability

ATLANTIS

Lurbinectedin, a selective inhibitor of oncogenic transcription, has been approved at a dose of 3.2 mg/m^2 Q3W for the treatment of patients with small-cell lung cancer (SCLC) showing disease progression on or after platinum-based chemotherapy in the US. The randomized, phase III ATLANTIS trial tested the combination of lurbinectedin 2 mg/m^2 and doxorubicin 40 mg/m^2 Q3W for a maximum of 10 cycles followed by lurbinectedin 3.2 mg/m^2 Q3W in 307 patients with relapsed SCLC after one prior chemotherapy line. Patients in the control arm (n = 306) received either topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) Q3W. Enrollment required a chemotherapy-free interval (CTFI) after first-line treatment of ≥ 30 days. Primary prophylaxis with G-CSF was mandatory in the whole study population. In both arms, approximately one third of patients each had a CTFI of < 90, 90-179, and ≥ 180 days. CNS involvement was present in 15.0 % and 16.0 %, respectively.

ATLANTIS did not meet its primary endpoint, as the overall survival (OS) curves for the two regimens were superimposable, with median OS of 8.6 and 7.6 months for lurbinectedin/doxorubicin and topotecan or CAV, respectively (HR, 0.967; p = 0.7032) [1]. None of the subgroups according to the stratification factors (i. e., CTFI, ECOG PS, baseline brain involvement, prior immunotherapy) derived significant benefit from lurbinectedin/doxorubicin compared to topotecan or CAV. Median progression-free survival was significantly improved in the experimental arm (HR, 0.831; p = 0.0437). Here, patients with a CTFI of ≥ 180 days and those after prior PD-(L)1 inhibitor treatment were more likely to benefit from the lurbinectedin combination, whereas those with a short CTFI interval of < 90 days and CNS metastases appeared to fare better with the comparator regimens. Overall response rates were similar across the arms (31.6 % vs. 29.7 %), although responses lasted longer in the lurbinectedin-treated group (median

TABLE
Adverse events observed on second-line treatment with lurbinectedin/doxorubicin vs. topotecan or cyclophosphamide/doxorubicin/vincristine (CAV)

	Lurbinectedin + doxorubicin (n = 303) n (%)	Topotecan or CAV (n = 289) n (%)
Any treatment-related AE	268 (88.4)	266 (92.0)
Any grade ≥ 3 AE	143 (47.2)	218 (75.4)
Any grade 4 AE	49 (16.2)	158 (54.7)
Any grade ≥ 3 serious AE	38 (12.5)	83 (28.7)
Death associated with AEs	1 (0.3)	10 (3.5)
Treatment discontinuation associated with AEs	23 (7.6)	45 (15.6)
Delays associated with AEs	79 (26.1)	99 (34.3)
Reductions associated with AEs	66 (21.8)	138 (47.8)

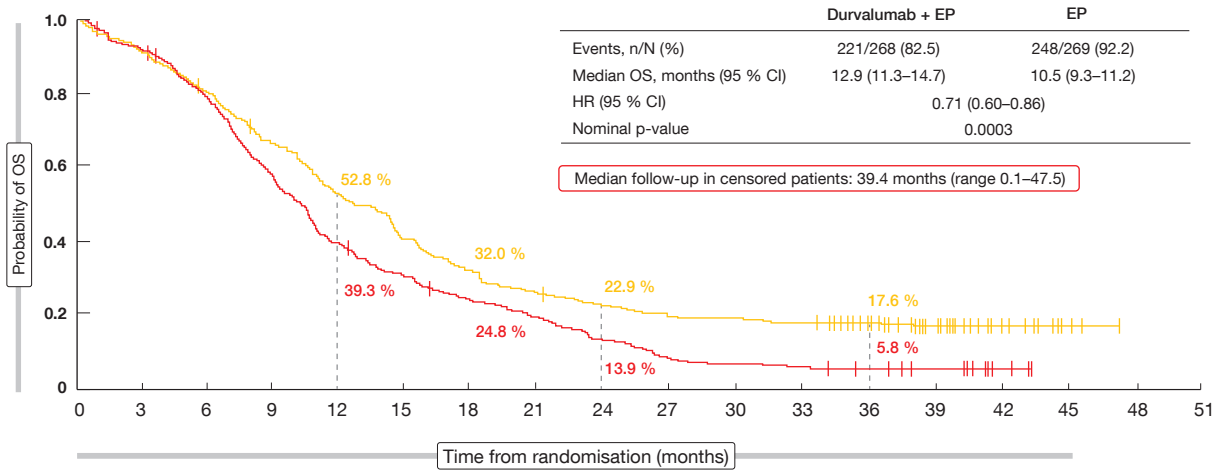

Figure: Overall survival update after 3 years for durvalumab plus EP vs. EP alone in the CASPIAN trial

duration of response, 5.7 vs. 3.8 months; HR, 0.581; p = 0.0012).

Significantly lower cytopenia rates

As the safety analysis demonstrated, higher-grade adverse events (AEs) and fatalities due to AEs occurred less frequently with lurbinectedin/doxorubicin, which also applied to dose reductions, dose delays, and treatment discontinuations **(Table)**. These differences were mainly based on significantly lower rates of grade ≥ 3 cytopenias in the experimental arm. Anemia occurred in 14.5 % vs. 31.1 % (p < 0.0001), neutropenia in 37.0 % vs. 69.2 % (p < 0.0001), febrile neutropenia in 4.0 % vs. 8.3 % (p = 0.0377), and thrombocytopenia in 13.9 % vs. 31.1 % (p < 0.0001).

With respect to non-hematological toxicity, no major differences were observed. Overall, these results support the clinical benefit of lurbinectedin for patients with SCLC who are being treated in the second line. Also, ATLANTIS confirmed CFTI as the most important prognostic factor in the second-line setting. New combinations of lurbinectedin with other cytotoxic agents such as irinotecan as well as immune checkpoint inhibitors are being explored.

CASPIAN trial: 3-year OS

The global, randomized, open-label, three-arm, phase III CASPIAN trial was conducted to assess the first-line administration of the PD-L1 inhibitor durvalumab with or without the anti-CTLA-4 antibody tremelimumab in addition to platinum-etoposide (EP) in patients with extensive-stage (ES) SCLC. In both experimental arms, the combinations were administered Q3W for 4 cycles and were followed by durvalumab maintenance Q4W until progression. The control arm received EP alone Q3W for up to 6 cycles followed by optional prophylactic cranial irradiation.

Durvalumab plus EP, as compared to EP, has been shown to significantly improve OS (HR, 0.73; p = 0.0047) [2]. This benefit was sustained after more than 2 years of median follow-up, while the combination of durvalumab plus tremelimumab and EP gave rise to a numerical OS improvement over EP, although this did not fulfill the requirements of statistical significance [3]. At ESMO 2021, Paz-Ares et al. reported a planned exploratory analysis of OS after a median follow-up of more than 3 years [4]. Progression-free survival and objective response data had not been collected since the previous data cutoff. Similarly, in terms of safety, only serious AEs including death were analyzed. Among phase III trials of EP with a PD-(L)1 inhibitor in the setting of ES-SCLC, this updated OS analysis shows the longest median follow-up reported to date.

Tripling of the survivor rate

Durvalumab plus EP demonstrated a sustained OS benefit over EP. Median OS was 12.9 vs. 10.5 months, which translated into a 29 % mortality reduction (HR, 0.71; p = 0.0003; **Figure**). At 36 months, the proportion of survivors was 3 times higher in the experimental arm than in the control arm (17.6 % vs. 5.8 %). The addition of the checkpoint inhibitor to chemotherapy induced OS benefits of similar magnitude in all subgroups.

Also, patients who received the durvalumab-tremelimumab combination plus EP experienced a sustained numerical OS advantage compared to EP alone, with a 19 % mortality reduction. The 36-month OS rates amounted to 15.3 % vs. 5.8 %. Most patients in the experimental arms remained on durvalumab treatment at data cutoff. Exposure to tremelimumab and chemotherapy had not changed compared to the previous analysis [3].

REFERENCES

1 Paz-Ares L et al., Lurbinectedin/doxorubicin versus CAV or topotecan in relapsed SCLC patients: phase III randomized ATLANTIS trial. WCLC 2021, PL02.03
2 Paz-Ares L et al., Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394 (10212): 1929-1939
3 Goldman JW et al., Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021; 22(1): 51-65
4 Paz-Ares L et al., Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: 3-year overall survival update from the phase 3 CASPIAN study. ESMO 2021, LBA61

Likewise, the safety profile was consistent with the known profile of this treatment. Serious AEs occurred in similar percentages across the durvalumab plus EP and EP arms (32.5 % and 36.5 %, respectively), while this rate was higher for durvalumab plus tremelimumab and EP (47.4 %), as previously reported [3]. Regarding treatment-related AEs leading to death, the rates were 2.3 %, 4.5 % and 0.8 % for durvalumab plus EP, durvalumab plus tremelimumab and EP, and EP alone, respectively. The authors concluded that these data further establish durvalumab plus EP as standard of care for the first-line treatment of patients with ES-SCLC. ■

Malignant pleural mesothelioma: immunotherapy-based approaches across all treatment lines

Long-term results from CheckMate 743

The randomized phase III CheckMate 743 trial evaluated nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W for up to 2 years compared with cisplatin or carboplatin plus pemetrexed Q3W for 6 cycles as first-line treatment of patients with unresectable malignant pleural mesothelioma (MPM). More than 300 patients were randomized into each study arm. Overall survival (OS) constituted the primary endpoint. Indeed, the dual checkpoint inhibition significantly prolonged OS [1] and was approved as first-line treatment of unresectable MPM in many countries.

Peters et al. reported the 3-year update from CheckMate 743 at ESMO 2021 [2]. In addition to the clinical assessments, the researchers conducted exploratory biomarker analyses using a 4-gene inflammatory signature score, tumor mutational burden (TMB), and the lung immune prognostic index (LIPI). The 4-gene inflammatory signature score included the *CD8A*, *STAT1*, *LAG3*, and *CD274* (*PD-L1*) genes and was established via RNA sequencing of tumor samples, while the LIPI score was based on LDH levels and neutrophil-to-lymphocyte ratio from peripheral blood.

According to the 3-year update, nivolumab plus ipilimumab continued to provide durable benefit compared to chemotherapy. OS in all randomized patients was 18.1 vs. 14.1 months, translating into a 27 % risk reduction (HR, 0.73). At 3 years, 23 % vs. 15 % of patients were alive. All subgroups benefited from

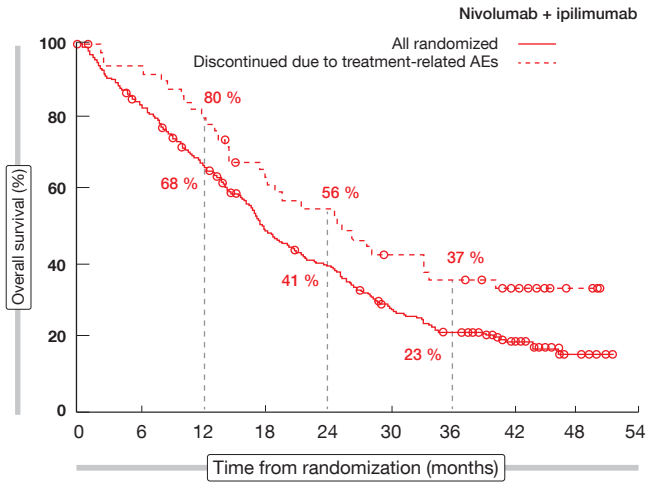

Figure 1: CheckMate 743: overall survival in patients who discontinued first-line nivolumab plus ipilimumab compared to the total randomized population in the experimental arm

immunotherapy compared to chemotherapy. Progression-free survival (PFS) remained unchanged (6.8 vs. 7.2 months; HR, 0.92), although a delayed benefit became apparent at 24 months (PFS rates, 18 % vs. 7 %) and 36 months (14 % vs. 1 %). Median duration of response was longer in the experimental arm (11.6 vs. 6.7 months) despite patients being off therapy for one year at the time of the analysis. At 36 months, 28% of responders in the immunotherapy arm had ongoing responses (vs. 0 % in the control arm).

No disadvantage after treatment discontinuation

The exploratory biomarker analysis indicated a correlation of high 4-gene inflammatory signature scores with improved survival on immunotherapeutic treatment. In the experimental arm, median OS was 21.8 vs. 16.8 months for high and low scores (HR, 0.57), and 35 % vs. 15 % of these patients were alive at 36 months. On the other hand, survival did not differ according to the 4-gene inflammatory signature score in the chemotherapy arm. Neither LIPI scores nor TMB tertiles showed a correlation with OS. After 12 additional months of follow-up, safety was consistent with the previous report. The overall rate of treatment-related AEs (TRAEs) had not changed.

A post-hoc analysis revealed no adverse impact of discontinuation of all components of nivolumab plus ipilimumab in patients who stopped treatment due to TRAEs **(Figure 1)**. After discontinuation, 34 % had ongoing re-

sponses for ≥ 3 years, and 37 % were alive at 36 months. In their summary, the authors pointed out that these data from CheckMate 743 confirm nivolumab plus ipilimumab as a standard of care for unresectable MPM regardless of histology.

Pembrolizumab plus nintedanib in r/r disease

The phase I PEMBIB trial investigated the combined strategy of pembrolizumab and the triple angiokinase inhibitor nintedanib in patients with unresectable MPM relapsing on or refractory to platinum-based chemotherapy. Pembrolizumab 200 mg was administered Q3W, while nintedanib 150 mg was taken twice daily with a 7-day monotherapy lead-in. Ancillary analyses were performed based on blood and tumor samples. Danlos et al. reported results for 30 patients at ESMO 2021 [3]. Most patients had received one previous systemic anticancer treatment line (77 %), while 2 and ≥ 3 lines had been administered in 17 % and 6.7 %, respectively.

The combined treatment gave rise to a 12-week disease control rate of 68.4 % **(Figure 2)**. Median PFS was 6.2 months. AEs proved generally manageable, with diarrhea, fatigue, and dyspnea occurring most commonly. Pembrolizumab plus nintedanib showed similar pharmacodynamic effects according to cytokine measurements. PD-L1 expression on tumor cells and tumor-infiltrating CD8+ T lymphocytes at baseline appeared to be predictive of anti-angiogenic and anti-PD-1 efficacy as these were more prevalent in patients who benefited from treatment. Furthermore, higher IL-6 concentrations showed an association with primary resistance to treatment and correlated with the global somatic copy-number alteration (SCNA) score. The authors concluded that SCNAs due to accumulation of oncogenic mutations lead to IL-6–mediated immunosuppression and resistance to anti-angiogenic and anti-PD1 therapy.

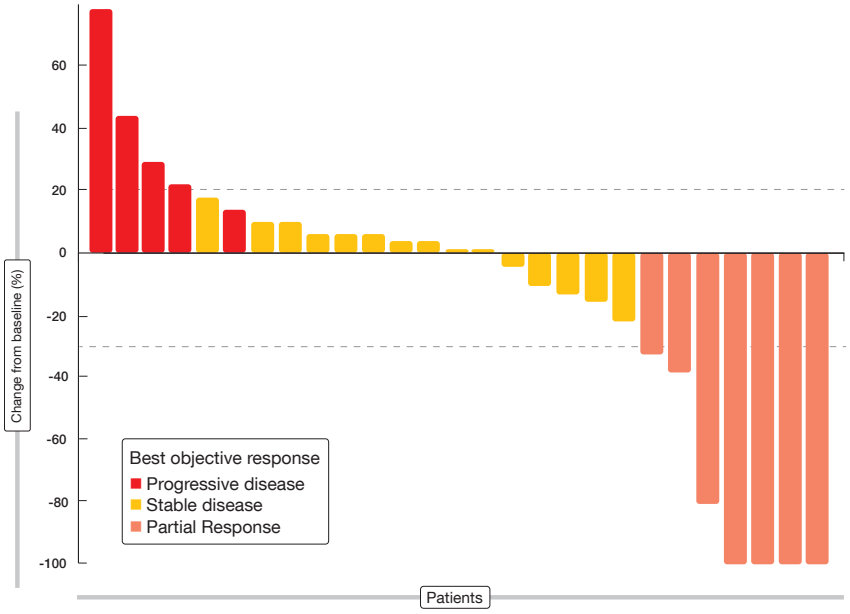

Figure 2: Responses observed with pembrolizumab plus nintedanib in patients relapsed on or refractory to previous platinum-based chemotherapy

Neoadjuvant use of atezolizumab

The S1619 study was designed based on the assumption that adding an PD-L1 inhibitor to neoadjuvant chemotherapy followed by maintenance immunotherapy after surgical resection and adjuvant radiation might increase survival outcomes [4]. Chemotherapy-naïve patients with resectable MPM received atezolizumab 1,200 mg Q3W in addition to cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for 4 cycles. Surgery, i.e., extrapleural pneumonectomy (EPP) or pleurectomy and decortication surgery (P/D) was performed in the absence of progression. This was followed by optional radiotherapy and maintenance atezolizumab with 1,200 mg Q3W for one year. The primary endpoint was safety, tolerability, and feasibility of this approach in 24 evaluable patients.

Among 28 eligible patients, 21 completed neoadjuvant therapy. Eighteen patients with stable disease or partial response underwent surgery; P/D and EPP were performed in 17 patients and one patient, respectively. Fifteen individuals received maintenance atezolizumab. At the time of the analysis, three patients remained on this treatment. No new safety signals arose in the context of the triple regimen or the atezolizumab maintenance therapy, and no delayed treatment-related grade > 3 AEs were reported. Additional efficacy data will be updated at a future congress. ■

REFERENCES

1 Baas P et al., First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021; 397: 375-386
2 Peters S et al., First-line nivolumab + ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year update from CheckMate 743. ESMO 2021, LBA65
3 Danlos FX et al., Pembrolizumab and nintedanib for patients with advanced pleural mesothelioma. ESMO 2021, 1732M0
4 Tsao A et al., S1619 A trial of neoadjuvant cisplatin-pemetrexed with atezolizumab in combination and maintenance for resectable pleural mesothelioma. WCLC 2021, OA13.01

Interview: Oliver Gautschi, MD, Luzerner Kantonsspital, Lucerne, Switzerland

Gradual progress in the management of mesothelioma and thymoma

Which innovative strategies for the treatment of patients with unresectable malignant pleural mesothelioma you do deem promising?

This is an important field where little progress has been made in the past. At ESMO 2021, updated results of the randomized CheckMate-743 trial of nivolumab plus ipilimumab *versus* chemotherapy were presented by Prof. Peters [1]. The overall survival benefit was pronounced in patients with PD-L1–positive or non-epithelioid mesotheliomas, although there was an OS benefit in the total population. In Switzerland, the nivolumab/ipilimumab combination is now approved for the treatment of PD-L1–positive or non-epithelioid mesotheliomas. Chemotherapy still plays a role for other patients. Ongoing trials will tell if we should treat other patients with immunotherapy plus chemotherapy in the future.

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What can presently be said about immunotherapeutic approaches in the setting of thymoma and thymic carcinoma?

We are speaking about orphan diseases. Most thymic tumors are resectable or respond to chemotherapy. Patients with non-resectable thymic tumors are usually treated with several lines of systemic therapy including chemotherapy, corticosteroids, or tyrosine kinase inhibitors. Dr. Girard presented the results of the NIVOTHYM trial, a European trial assessing nivolumab in pretreated patients [2]. NIVOTHYM confirmed the activity of PD-L1 checkpoint inhibition in thymic tumors, with a response rate of 12 %. However, there is considerable toxicity because patients can develop autoimmune complications. Currently, I recommend immunotherapy for thymic tumors only in the setting of a clinical trial. The NIVOTHYM trial remains open for enrolment, the second cohort is currently ongoing to assess the combination of nivolumab plus ipilimumab. ■

REFERENCES

1 Peters S et al., First-line nivolumab plus ipilimumab vs chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year update from CheckMate 743. ESMO 2021, LBA65
2 Girard N et al., Efficacy and safety of nivolumab for patients with pre-treated type B3 thymoma and thymic carcinoma: Results from the EORTC-ETOP NIVOTHYM phase II trial. ESMO 2021, LBA66

ATALANTE-1: anti-cancer vaccination after IO failure

OSE-2101 is an anti-cancer vaccine with modified neoepitopes restricted to HLA-A2+ targeting the tumor-associated antigens CEA, p53, HER2, MAGE-2 and MAGE-3 that are frequently expressed in lung cancer [1]. HLA-A2 is assessed in the serum and is positive in approximately half of patients. The randomized, phase III ATALANTE-1 trial tested OSE-2101 in patients with HLA-A2–positive, advanced or metastatic NSCLC who had experienced failure to combined or sequential platinum-based chemotherapy and immunotherapy. Immunotherapy had been administered in the most recent line and had failed due to primary or secondary resistance. Six subcutaneous injections of OSE-2101 were given Q3W followed by Q8W injections for up to year 1 and then 12-weekly injections until progression, while treatment in the control arm consisted of single-agent docetaxel or pemetrexed Q3W until progression. OSE-2101 gave rise to an OS benefit in 103 patients, with 1-year rates of 46 % vs. 36 % (HR, 0.71) [2]. However, due to the COVID-19 pandemic, the study was stopped in April 2020, and a population of interest was identified for further analyses. This comprised 118 patients who had secondary resistance to immunotherapy after sequential chemo-immunotherapy. At ESMO 2021, Besse et al. presented the results of the final primary analysis performed in this group [3].

Indeed, the cancer vaccine gave rise to statistical OS improvement with a meaningful median survival gain of 3.6 months (11.1 vs. 7.5 months; HR, 0.59; p = 0.017). Moreover, OSE-2101 treatment resulted in significantly longer post-progression survival (7.7 vs. 4.6 months; HR, 0.46; p = 0.004). The disease control rates at 6 months were similar across the two arms (25 % vs. 24 %; p = 0.87), which also applied to median PFS (2.7 vs. 3.2 months; p = 0.40). OSE-2101 was well tolerated, with a lower rate of treatment-related grade 3-5 AEs (11 % vs. 35 %). Administration site reactions occurred most commonly in the experimental arm (all grades, 39 %). Cytokine release syndrome was observed in 8 %, including one grade 3 event (1 %). The vaccine induced significant improvements in time

to worsening to ECOG performance status ≥ 2 (8.6 vs. 3.3 months; HR, 0.45; p = 0.0005) and quality of life according to the EORTC QLQ-C30 questionnaire (p = 0.04). In their conclusion, the authors noted that OSE-2101 demonstrated a favorable benefit-risk ratio vs. chemotherapy in a setting that is characterized by a lack of therapeutic alternatives.

REFERENCES

1 Beebe M et al., Formulation and characterization of a ten-peptide single-vial vaccine, EP-2101, designed to induce cytotoxic T-lymphocyte responses for cancer immunotherapy. Hum Vaccin 2008; 4(3): 210-218

2 Giaconne G et al., Activity of OSE-2101 in HLA-A2+ non-small cell lung cancer patients after failure to immune checkpoint inhibitors: Step 1 results of phase III ATALANTE-1 randomised trial. ESMO 2020 1260M0

3 Besse B et al., Activity of OSE-2101 in HLA-A2+ non-small cell lung cancer patients after failure to immune checkpoint inhibitors: final results of phase 3 Atalante-1 randomised trial. ESMO 2021, LBA47

DUBLIN-3: microtubule-binding agent plinabulin in later lines

TABLE
Landmark analyses for overall survival with plinabulin plus docetaxel vs. placebo plus docetaxel

Time of analysis (month)	Plinabulin + docetaxel	Placebo + docetaxel	p value
12	43.48	40.47	0.4862
18	31.11	23.75	0.0645
24	22.13	12.51	0.0072
36	11.73	5.27	0.0393
48	10.6	0	

Patients with *EGFR*-wildtype, advanced NSCLC in the second or third treatment line represent a large population with limited treatment options. A novel approach is the first-in-class selective immunomodulating microtubule-binding agent (SIMBA) plinabulin that releases the immune defense protein GEF-H1, thus inducing dendritic cell maturation, which is a key step in the initiation of durable anticancer response [1, 2]. The global, randomized phase III DUBLIN-3 trial tested plinabulin 30 mg/m^2 in addition to docetaxel Q3W (n = 278) versus docetaxel plus placebo (n = 281) in patients with non-squamous or squamous, stage IIIb/IV NSCLC who had progressed during or after one or two platinum-based regimens. Overall survival constituted the primary endpoint.

According to the results presented by Feinstein et al. at ESMO 2021, the DUBLIN-3 study met its primary objective [3]. Median OS was 10.5 vs. 9.4 months for plinabulin plus docetaxel vs. docetaxel alone (HR, 0.82; p = 0.0399). The combination gave rise to doubling of the OS rates at 24 and 36 months (**Table**). Likewise, the key secondary endpoints of DUBLIN-3 were met: median PFS was 3.6 vs. 3.0 months (HR, 0.76; p = 0.0082), with significantly higher PFS rates at 6 months (30.3 % vs. 17.8 %) and 12 months (17.1 % vs. 4.7 %). ORR was doubled with the addition of plinabulin (12.23 % vs. 6.76 %; p = 0.0275).

Durable activity and decreased grade 4 neutropenia

As the exploratory analysis demonstrated, the OS advantage was larger in the group that received ≥ 8 cycles (28.2 vs. 19.3 months; HR, 0.453; p = 0.0121) than in those treated with ≥ 4 cycles (18.3 vs. 13.5 months; HR, 0.634; p = 0.0022). Moreover, the analysis revealed a favorable long-term OS trend for the experimental regimen in the cohort that had been exposed to PD-(L)1-targeted therapy prior to study inclusion (i.e., 23 % of the total population), with 48-month OS rates of 12.5 % vs. 0 %. Pooled data from the phase IB/II 101 study and DUBLIN-3 suggested long-term survival benefit with the combination in Western patients.

Grade 3/4 AEs adjusted for cycle number per patient per year occurred less commonly in the experimental arm than in the control arm (estimated event rate, 9.88 vs. 11.04; p = 0.0253). Grade 4 neutropenia on day 8 in all cycles was significantly reduced with the combination (5.13 % vs. 33.58 %; p < 0.0001). Among non-hematological grade 3/4 AEs, diarrhea was reported more commonly for plinabulin plus docetaxel (8.4 % vs. 0.7 %), as was hypertension (17.2 % vs. 1.1 %) that transiently occurred after the infusion. According to the Q-TWiST analysis integrating efficacy, safety and quality of life, patients treated with the combination derived a > 18 % improvement, which is clinically meaningful. The authors concluded that plinabulin plus docetaxel shows a favorable risk-benefit ratio and has the potential of a preferred second/third-line treatment option in the setting of NSCLC with *EGFR* wildtype.

REFERENCES

1 Kashyap AS et al., GEF-H1 signaling upon microtubule destabilization is required for dendritic cell activation and specific anti-tumor responses. Cell Rep 2019; 28(13): 3367-3380

2 Singh AV et al., A novel vascular disrupting agent plinabulin triggers JNK-mediated apoptosis and inhibits angiogenesis in multiple myeloma cells. Blood 2011; 117(21): 5692-700

3 Feinstein T et al., DUBLIN-3 (BPI-2358-103): a global phase 3 trial with the plinabulin/docetaxel combination vs. doc in 2nd/3rd line NSCLC patients with EGFR-wild type progressing on a prior platinum-based regimen. ESMO 2021, LBA48

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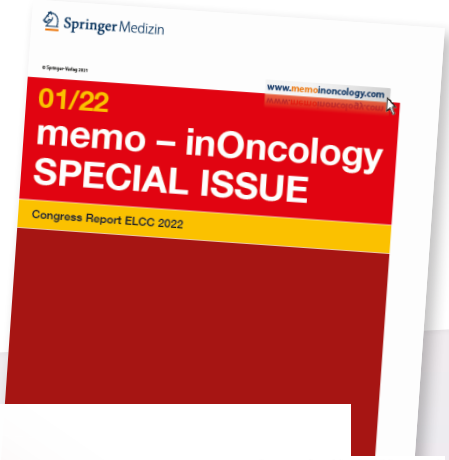
Expert interviews at ESMO 2021 Lung Cancer

Robin Cornelissen discusses new agents developed for the treatment of NSCLC patients with EGFR or HER2 exon 20 insertion mutations, the role of next-generation sequencing in clinical practice, rare drivers of lung cancer with potential interest in the future, targeted approaches in the management of lung cancer as well as prognostic markers for survival or clinical decision making before extended pleurectomy and decortication surgery in malignant pleural mesothelioma.

Edward B. Garon relates to anticancer vaccines, an area full of promises for lung cancer patients, their potential caveats compared to other novel treatment approaches, depicts the most interesting trial results from the phase I trial of intratumoral administration of CCL21-gene modified dendritic cells combined with intravenous pembrolizumab for advanced NSCLC and explains how antibody drug conjugates like datopotamab deruxtecan, a novel TROP2-directed ADC, fit in the therapeutic landscape in the future.

Natasha B. Leighl outlines recent insights gained in terms of circulating tumor DNA in patients with advanced NSCLC, the impact of liquid biopsy on the time to treatment, advantages of complementary testing, the clinical utility of plasma ctDNA testing in the context of treatment monitoring and future first-line treatment options for patients with advanced NSCLC.

Oliver Gautschi highlights the most relevant findings presented at ESMO 2021 in terms of lung cancer, innovative treatment approaches currently tested for use in patients with unresectable malignant pleural mesothelioma, immunotherapeutic approaches in the setting of thymoma and thymic carcinoma and summarizes potential strategies for the management of RET-positive NSCLC.



Forthcoming Special Issue

This special issue will be offering a synopsis from the ELCC 2022 that will be held in March 2022. 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 multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.