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Preface

Dear Colleagues,

The International Association for the Study of Lung Cancer (IASLC) 2022 World Conference of Lung Cancer (WCLC) was held in Vienna, Austria, and virtually from 6th to 9th August and saw leading scientists, researchers and patient advocates from around the world gather again to discuss the most exciting updates in the field of lung cancer and thoracic oncology with key updates summarized in 380 invited lectures, 60 oral and 84 mini oral presentations, as well as almost 1,000 posters and ePosters.

This issue of memo inOncology summarizes content presented in various fields, starting with promising findings across the highly investigated oncogenic targets *EGFR, MET*ex14 and *KRAS*. Here, the summaries offer a look at data from CHRYSALIS, CHRYSALIS-2, VISION, CodeBreaK 100/101, and TROPION-Lung02.

In early-stage lung cancer, sublobar resection appears to be a new standard of care for patients with NSCLC cT1a N0 sized ≤ 2 cm. In the setting of resectable stage IIIA-B NSCLC, NADIM II demonstrated superiority of neoadjuvant nivolumab plus chemotherapy. While the updated findings of the IMpower010 trial supported the favorable benefit-risk profile of adjuvant atezolizumab and thus the use as standard-of-care in PD-L1–positive, resected NSCLC, the DOLPHIN study focused on PD-L1–positive, unresectable NSCLC. In this patient population, the data obtained for durvalumab plus radiotherapy warrant phase III assessment.

The article on small-cell tumors focuses on the power of immune-based strategies. After frontline chemoimmunotherapy, the bispecific T cell engager tarlatamab showed promising efficacy in relapsed/refractory SCLC. Also, follow-up data from KEYNOTE-604 that investigated the addition of pembrolizumab to first-line chemotherapy continued to show improved outcomes.

In the field of checkpoint inhibition, durvalumab plus tremelimumab in addition to chemotherapy was highlighted as a potential first-line option in harder-to-treat patient groups such as those with *STK11, KEAP1* or *KRAS* mutations. Further research is required to assess the possible role of combination therapy with durvalumab and olaparib in metastatic NSCLC. According to an exploratory pooled analysis of 5 phase III trials, a second course of pembrolizumab monotherapy is feasible and clinically meaningful.

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Overall, the IASLC 2022 WCLC offered an exceptional educational experience that provided a platform for sharing extraordinary progress in the field of lung cancer diagnosis and treatment to further improve patient outcomes and quality of life.

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Promising findings across oncogenic targets

Amivantamab plus lazertinib in *EGFR*-positive lung cancer

The EGFR-MET bispecific antibody amivantamab is being assessed in combination with the third-generation EGFR tyrosine kinase inhibitor lazertinib in the multicohort CHRYSALIS-2 trial in patients with *EGFR*-mutant non–small-cell lung cancer (NSCLC). Results from the cohort receiving amivantamab/lazertinib in addition to carboplatin/pemetrexed (n = 20) were presented at WCLC 2022 by Marmarelis et al. [1]. These patients had progressed on prior EGFR TKI treatment; 45 % and 70 % had received first/second-generation EGFR TKIs and osimertinib, respectively. In 25 %, platinum-based therapy had been administered. Safety constituted the primary endpoint.

The safety profile of the regimen was consistent with the profiles of the individual agents. Adverse events (AEs) were mostly grade 1 and 2. No cases of pneumonitis/interstitial lung disease (ILD) occurred. With respect to efficacy, the analysis yielded an overall response rate (ORR) of 50 % and a clinical benefit rate of 80 %. These results were identical in patients with baseline brain metastases (n = 10). Responses proved durable; after a median follow-up of 7.1 months, 15 patients remained on treatment. This included the 10 responders 3 of whom showed response duration of ≥ 6 months. Median duration of response, progression-free survival (PFS) and overall survival (OS) were not estimable at the time of the analysis. Amivantamab/lazertinib plus chemotherapy is currently being evaluated in the randomized, phase III MARIPOSA-2 trial in post-osimertinib settings (NCT04988295).

Likewise, amivantamab/lazertinib demonstrated clinically significant and durable antitumor activity in the untreated setting. In the CHRYSALIS study,

TABLE
Clinical outcomes obtained with tepotinib in *MET*ex14-positive lung cancer diagnosed by tissue biopsy

Endpoint	First-line population (n = 69)	Second- and later-lines population (n = 51)
Best overall response, n (%)		
Complete response	0	0
Partial response	43 (62.3)	26 (51.0)
Stable disease	17 (24.6)	16 (31.4)
Progressive disease	7 (10.1)	4 (7.8)
Not estimable	2 (2.9)	5 (9.8)
Overall response rate, %	62.3	51.0
Disease control rate, %	87.0	82.4
Median duration of response, months	Not estimable	12.6
Median progression-free survival, months	15.9	13.8
Median overall survival, months	22.7	19.6

all analyzed patients (n = 20) with advanced *EGFR*-mutated NSCLC (i.e., deletion 19 or L858R mutation) had partial responses after a median follow-up of 22.3 months [2]. Median duration of response and median PFS were not estimable. Seventy percent of patients were progression-free; in 2 additional cases, the treatment was ongoing beyond RECIST progression. No new safety signals occurred, and most AEs were graded as 1 or 2. One patient developed grade 3 pneumonitis/ILD (5 %). Cumulative grouped rash-related AEs (i.e., acneiform dermatitis, rash, folliculitis, erythematous rash, maculopapular rash) emerged in the entire group, with 2 grade ≥ 3 events (10 %).

The assessment included a ctDNA analysis according to which half of patients showed *TP53* co-mutations. Activating *EGFR* mutations were found in 15 of 18 patients at baseline but were undetectable by day 1 of cycle 3. The ongoing phase III MARIPOSA trial is investigating frontline amivantamab/lazertinib compared to osimertinib in patients with *EGFR*-mutated NSCLC (NCT04487080).

VISION: analysis of Cohort C

The approval of the MET inhibitor tepotinib for the treatment of advanced lung cancer with *MET* exon 14 (*MET*ex14) skipping mutations was mainly based on the results obtained in Cohort A of the phase II VISION study [3]. At WCLC 2022, the primary analysis of the independent confirmatory Cohort C (n = 161) was reported [4]. Like Cohort A, these patients had received tepotinib 500 mg/d in the first, second, or third lines after central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy.

The data provided independent confirmation of the robust and durable efficacy of tepotinib, with comparable or improved outcomes across endpoints compared to Cohort A. ORR by independent review, which was defined as the primary endpoint, was 54.7 %, and disease control was achieved in 80.1 %. Median duration of response and median PFS were 20.8 and 13.8 months, thus exceeding the respective results observed in Cohort A (11.1 and 8.5 months). Median OS was 18.8 months. Treatment-naïve patients enrolled by tissue biopsy experienced particularly pronounced benefits, although the efficacy was also robust and durable in previously treated patients enrolled based on tissue biopsy **(Table)**. For both Cohorts A and C, robust and durable clinical outcomes were observed in the first line as well as in later lines.

Moreover, the analyses revealed promising intracranial activity in patients with brain metastases. Across Cohorts A and C, 43 patients with brain lesions were evaluable. Fifteen had target lesions; here, the intracranial ORR was 66.7 %, and the intracranial median duration of response had not been reached yet. Tepotinib was generally well tolerated, with most AEs being mild to moderate. Peripheral edema was the most common AE (any grade, 66.5 %, grade ≥ 3, 10.9 %). Treatment-related AEs (TRAEs) led to permanent discontinuation in 14.7 %. They necessitated dose reductions and interruptions in 33.5 % and 42.5 %, respectively, although these patients were able to remain on treatment and continued to benefit.

First data from CodeBreaK 100/101

The first-in-class KRAS^{G12C} inhibitor sotorasib is being used as monotherapy for patients with pretreated *KRAS*^{G12C}-mutated advanced NSCLC. In the animal model, sotorasib was shown to synergize with immune checkpoint inhibitors, inhibiting tumor growth and enhancing CD8+ T cell infiltration [5]. Therefore, the phase IB, multicenter, open-label CodeBreaK 100/101 study was designed to explore the combinations of sotorasib with either atezolizumab or pembrolizumab. Oral daily sotorasib doses of 120 mg, 240 mg, 360 mg, 720 mg, and 960 mg were tested. In one patient group, a lead-in regimen of sotorasib was administered for 21 or 42 days followed by the combination with atezolizumab (n = 10) or pembrolizumab (n = 19) Q3W. The concurrent treatment group, on the other hand, received sotorasib plus atezolizumab (n = 10) or pembrolizumab (n = 19) from the beginning. All patients had advanced *KRAS*^{G12C}-mutated NSCLC and had received or refused prior standard therapies. Prior anti-PD-(L)1 treatment had been administered in two thirds of patients. The primary endpoint was safety.

At WCLC 2022, Li et al. reported the first data for the lead-in and concurrent treatment groups after a median follow-up of 12.8 months [6]. Sotorasib plus atezolizumab or pembrolizumab gave rise to higher incidences of grade 3/4 TRAEs compared to the rates observed with either monotherapy [7-9]. Grade 3/4 TRAEs were mainly liver enzyme elevations. These showed an onset after a median of 50-73 days, which meant that 88 % occurred outside the dose-limiting toxicity window (i.e., 21 days following the initiation of combination treatment). Ninety-seven percent of grade 3/4 hepatotoxicity events resolved with corticosteroids, treatment modification, and/or discontinuation. The lead-in co-

horts experienced lower incidences of grade 3/4 TRAEs and TRAEs prompting discontinuation than the concurrently treated cohorts; likewise, lower doses of sotorasib were associated with a trend towards less liver enzyme elevation. No fatal TRAEs occurred.

Across all cohorts, deep and durable responses were noted, which included treatment at low doses. Also, immunotherapy pretreatment did not affect clinical responses. The ORR was 29 %, and disease control was achieved in 83 %. Median duration of response was 17.9 months. In particular, lead-in sotorasib plus pembrolizumab induced deep responses. Median OS was 15.7 months for sotorasib plus any checkpoint inhibitor. Based on these observations, low-dose sotorasib as a lead-in regimen followed by the combination with pembrolizumab will be further studied as first-line treatment in patients with advanced NSCLC.

Doublet and triplet therapy with Dato-DXd: TROPION-Lung02

Initial results for the TROP2-targeting antibody drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd) in addition to pembrolizumab with or without platinum chemotherapy were presented by Levy et al. [10]. This was the first reported clinical experience of a TROP2 ADC combined with a checkpoint inhibitor ± platinum-based chemotherapy. Patients with advanced or metastatic NSCLC participated in the phase IB TROPION-Lung02 study that contained 6 cohorts. Cohorts 1 and 2 tested the doublet approach, which was Dato-DXd 4 mg/kg or 6 mg/kg plus pembrolizumab Q3W, while Cohorts 3 to 6 were dedicated to the triplet regimens consisting of Dato-DXd 4 mg/kg or 6 mg/kg plus pembrolizumab and either carboplatin AUC5 (Cohorts 3 and 4) or carboplatin 75 mg/m² (Cohorts 5 and 6). Overall, 40 and 48 patients received the doublet and triplet approaches, respectively. Pretreatment was allowed in the doublet group (median, 1 prior line), while the triplet group was treatment-naïve. Safety and tolerability represented the first endpoint.

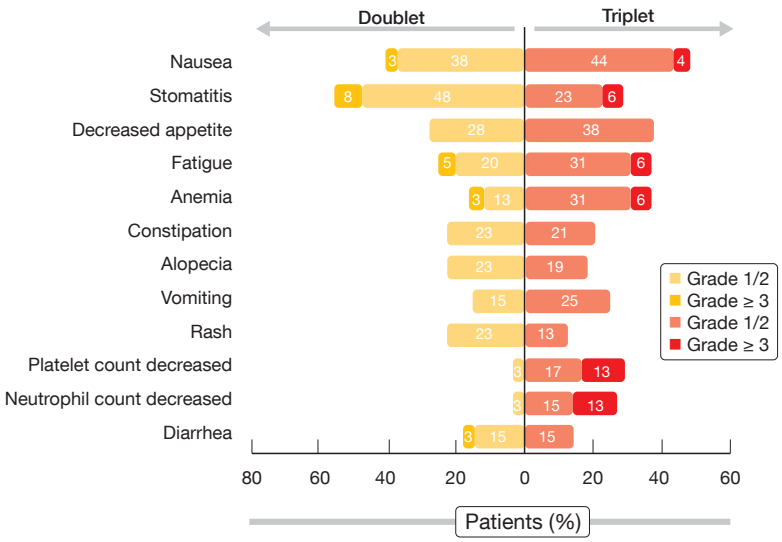

Figure: Common adverse events with Dato-DXd plus pembrolizumab (doublet) and Dato-DXd plus pembrolizumab and platinum chemotherapy (triplet)

After a median follow-up of 6.5 and 4.4 months for the doublet and triplet groups, respectively, the regimens showed a tolerable safety profile. The most frequent treatment-emergent AEs (TEAEs) were stomatitis with the doublets (any grade, 56 %) and nausea (any grade, 48 %) with the triplets **(Figure)**. Most of the events were graded as 1 and 2. Grade ≥ 3 study treatment-related TEAEs occurred in 35 % and 54 %, respectively. TEAEs due to Dato-DXd led to discontinuation in 15 % and 10 %, respectively. Five percent of patients in the doublet group developed drug-related ILD grade 1/2; grade 3 events emerged in 3 % and 2 %, respectively.

Preliminary efficacy findings were encouraging. In the overall population, ORRs were 37 % and 41 % for the doublet and triplet therapy, respectively. Both groups had a 84 % disease control rate. In the first-line setting, doublets and triplets gave rise to ORRs of 62 % and 50 %, respectively, while 100 % and 90 % of patients, respectively, achieved disease control. Responses were obtained across all PD-L1 expression levels. As the authors noted in their summary, these results support further evaluation of Dato-DXd 6 mg/kg plus immunotherapy combination regimens. The phase III TROPION-Lung08 trial is evaluating Dato-DXd plus pembrolizumab vs. pembrolizumab alone as first-line therapy in patients with advanced or metastatic NSCLC and PD-L1 TPS > 50 % (NCT05215340). ■

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Stage I-III disease: surgical and systemic options

SLR as new standard of care in cT1a N0 (≤ 2 cm)

Lobar resection has been the surgical standard of care for cT1 N0 non–small-cell lung cancer (NSCLC) for decades, while sublobar resection (SLR) was reserved for a subset of patients with marginal pulmonary reserve. However, the recently published JCOG0802/WJOG4607L study showed that in fit patients with cT1a N0 tumors sized ≤ 2 cm, segmentectomy was not inferior to lobectomy regarding overall survival (OS) [1]. The randomized, international, non-inferiority, phase III CALGB 140503 (Alliance) trial compared lobectomy with SLR (i.e., segment or wedge resection) in patients with peripheral NSCLC cT1a N0 ≤ 2 cm. Preoperatively, node negativity at level 10 and ≥ 2 mediastinal nodal stations had to be confirmed. Approximately 350 patients were randomly allocated to each arm. In the SLR group, 58.8 % underwent wedge resection.

Indeed, the two approaches were demonstrated to be equal [2]. Regarding the primary endpoint of disease-free survival (DFS), the 5-year rates were 64.1 % vs. 63.6 % for the lobar resection and SLR groups, respectively, after a median follow-up of 7 years (HR, 1.01; p = 0.0176 for non-inferiority). SLR was not inferior to lobectomy across major demographic and clinical features according to a post-hoc exploratory subgroup analysis. Moreover, no differences emerged in terms of lung cancer-related recurrences/deaths (HR, 0.99; p = 0.9521) or competing deaths (HR, 1.12; p = 0.5897). The 5-year OS rates amounted to 78.9 % vs. 80.3 % (p = 0.014 for non-inferiority).

Disease recurrence was observed in approximately 30 % of patients without significant differences between arms in the incidence of isolated locoregional or systemic relapses. Regarding pulmonary function, SLR, as compared to lobectomy, induced less pronounced reductions in FEV_1 and FVC, although the authors noted that this might not be clinically meaningful. Overall, the results of the Alliance study and the JCOG0802/WJOG4607L trial establish SLR as the standard of care for patients with NSCLC cT1a N0 sized ≤ 2 cm.

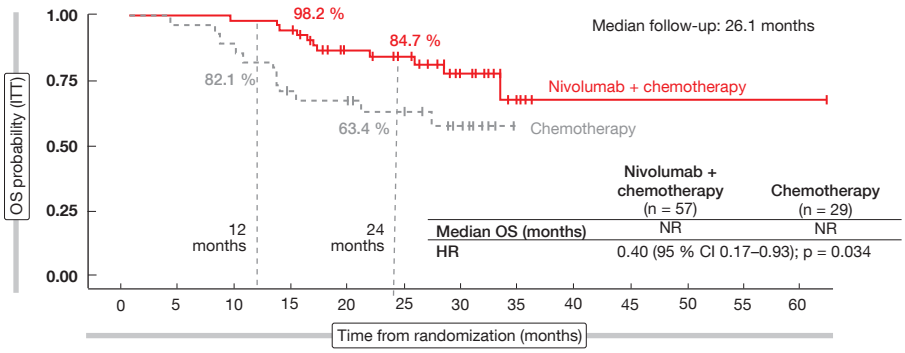

Figure 1: NADIM II: overall survival with neoadjuvant nivolumab plus chemotherapy vs. chemotherapy alone

NADIM II: secondary endpoints

In the randomized phase II NADIM II study, neoadjuvant nivolumab plus chemotherapy has been shown to significantly improve pathological complete response (pCR) rates compared to chemotherapy alone in patients with resectable stage IIIA-B lung cancer (36.8 % vs. 6.9 %; OR, 7.88; p = 0.0068) [3]. Patients who had R0 surgery went on to receive adjuvant treatment with nivolumab Q4W for 6 months in the experimental arm (n = 57) or observation in the control arm (n = 29). At WCLC 2022, Provencio et al. presented the results for the secondary endpoints of the trial [4].

In the total group, lobectomy constituted the most frequently performed surgical procedure (78.1 %). Definitive surgery was achieved in 93.0 % vs. 69.0 % with the immunotherapy-based treatment vs. chemotherapy alone (OR, 5.96; p = 0.00807). Also, the results for R0 resection favored the combined regimen (92.5 % vs. 65.0 %; OR, 6.60; p = 0.007), as did the downstaging rates (69.8 % vs. 40.0 %; OR, 3.47; p = 0.04). Median progression-free survival (PFS) had not been reached yet in the experimental arm after a median follow-up of 26.1 months, while it was 18.3 months in the control arm (HR, 0.48; p = 0.025). At 24 months, 66.6 % vs. 42.3 % of patients were progression-free. The PFS analysis by pCR status showed that patients with pCR in both arms remained progression-free over time, whereas those with pathological incomplete responses had drastically lower PFS probability.

Median OS had not been reached in either arm yet, although the 24-month rates significantly favored the nivolumab-based strategy (84.7 % vs. 63.4 %; HR, 0.40; p = 0.034; **Figure 1**). Again, patients who obtained pCR did not experience any event irrespective of the type of treatment; the groups with incomplete responses, on the other hand, fared considerably worse. Overall, the addition of nivolumab did not impede the feasibility of surgery, and the combination maintained a tolerable safety profile. As the authors emphasized, NADIM II is the first clinical trial with a neoadjuvant immunotherapy-based combination for resectable stage IIIA-B NSCLC to show improved OS.

According to a biomarker analysis of the NADIM II data, pre-treatment circulating tumor DNA (ctDNA) levels significantly predicted OS and PFS [5]. This was true regardless of the cut-off used. The authors concluded that baseline ctDNA levels clearly identified patients at high risk of progression and death, thus adding a significant degree of prognostic information to the clinical stage.

First OS analysis of IMpower010

Adjuvant atezolizumab has been demonstrated to significantly prolong DFS compared to best supportive care

in the phase III IMpower010 trial that included patients with completely resected stage IB-IIIA (IB tumors ≥ 4 cm) NSCLC who had received 1–4 cycles of platinum-based chemotherapy [6]. Felip et al. reported the first pre-specified interim analysis of OS and a safety analysis at a median follow-up of 45.3 months [7]. According to the hierarchical testing protocol of IMpower010, the stage II-IIIA subpopulation with PD-L1 ≥ 1 % was analyzed first.

In this group, a trend for OS was seen favoring atezolizumab. Median OS had not been reached yet in either arm, with 60-month OS rates of 76.8 % vs. 67.5 % (HR, 0.71). Regarding other subpopulations, the PD-L1 ≥ 50 % stage II-IIIA cohort experienced a clinically meaningful OS trend (HR, 0.43), while the all-randomized stage II-IIIA cohort and the ITT population (stage IB-IIIA) did not derive any survival benefit from the checkpoint inhibitor treatment. Patients with PD-L1 ≥ 50 % stage II-IIIA disease in whom *EGFR*/*ALK* aberrations had been excluded exhibited 60-month OS rates of 84.8 % vs. 67.5 % (HR, 0.42).

After 13 months of additional follow-up, the safety profile remained broadly unchanged, and no new safety signals emerged. All-grade and grade 3/4 AEs of special interest for atezolizumab occurred in 52.1 % and 7.9 %, respectively. These numbers matched the rates reported at the time of the DFS interim analysis [6]. In their entirety, the updated findings support the favorable benefit-risk profile of adjuvant atezolizumab in PD-L1–positive, resected NSCLC and contribute to evidence supporting the use of this standard-of-care regimen. IMpower010 will continue on to the final DFS analysis.

DOLPHIN: durvalumab plus radiotherapy

Based on the PACIFIC study, consolidation therapy with durvalumab after definitive chemoradiotherapy has been established as the standard of care for locally advanced, unresectable NSCLC [8]. However, approximately 25 % of these patients are unable to receive durvalumab due to AEs of chemoradiotherapy or poor performance status [9]. The multicenter, single-arm, phase II DOLPHIN study evaluated a chemotherapy-free approach consisting of durvalumab 10 mg/kg Q2W plus concurrent curative radiation therapy (60 Gy) for up to 1 year until disease progression in patients with PD-L1–positive, unresectable stage III or postoperatively recurrent NSCLC. Tachihara et al. presented the findings for 35 patients with ECOG performance status of 0 or 1 after a median follow-up of 18.7 months [10].

The PFS rate at 12 months by independent central review, which was defined as the primary endpoint, was 72.1 %, thus exceeding the expected 50 % rate. Overall, 90.9 % of patients responded to treatment, with 36.4 % and 54.5 % achieving complete and partial remissions, respectively **(Figure 2)**. All of the participants obtained disease control. Grade 3/4 AEs occurred in 47.1 %, and 2 patients (5.9 %) died due to AEs. In 17.6 %, AEs led to the discontinuation of durvalumab, although all patients completed radiotherapy. Any-grade pneumonitis or radiation pneumonitis were reported in 61.8 %, with grade 3/4 events in 11.8 %. No patient died because of pneumonitis or radiation pneumonitis. The authors concluded that durvalumab plus radiotherapy is promising and warrants phase III assessment.

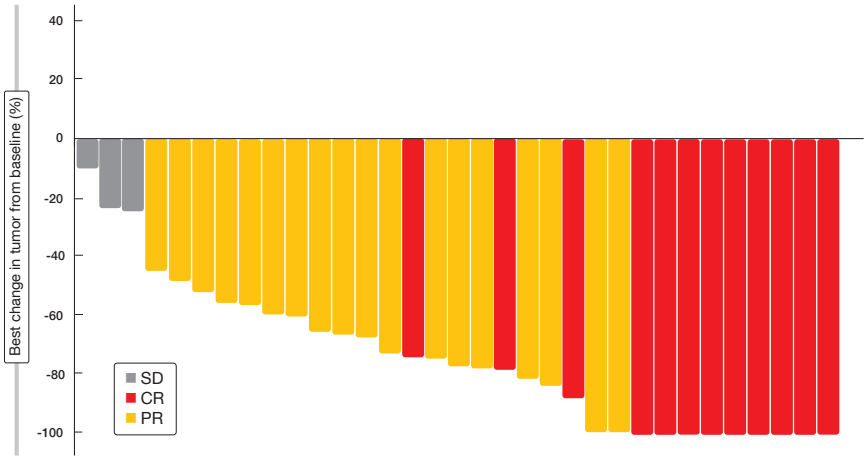

Figure 2: Responses achieved with durvalumab and concurrent radiotherapy in the DOLPHIN study

Surgery vs. chemoradiation in T4 N2 disease

No clear treatment guidelines exist for T4 N2 NSCLC with additional intrapulmonary nodules. Using data entered into the National Cancer Database between 2010 and 2015, Kumar et al. evaluated long-term OS in the setting of T4 N2 M0 lung cancer with additional nodules in a different ipsilateral lobe [11]. The retrospective analysis compared 196 patients after multimodal therapy including primary site resection (thoracic surgery group) with 277 patients who had received concurrent chemoradiation without surgery (chemoradiation group). Patients in the thoracic surgery group were somewhat younger than those in the chemoradiation group (65.5 vs. 67 years), and higher percentages were female (60.2 % vs. 45.8 %) and had adenocarcinoma histology (68.1 % vs. 47.6 %).

The analysis yielded improved survival in the thoracic surgery group, with 5-year rates of 40.3 % vs. 26.8 % ($p < 0.001$). The propensity score matched analysis showed 5-year survival rates of 45.8 % vs. 20.4 % ($p < 0.001$); after adjustment for factors including age, sex, comorbidity score, median census-tract household education level and tumor location, the mortality risk was reduced by 45 % (HR, 0.55; $p < 0.001$). Adjusted hazard ratios for thoracic surgery vs. chemoradiation were 0.54 for patients with tumors sized ≤ 3 cm ($p = 0.030$) and 0.47 for patients aged ≤ 65 years without comorbidities ($p = 0.048$). Within the thoracic surgery cohort, 51 and 145 patients had received induction chemotherapy prior to surgery and adjuvant chemotherapy after surgery, respectively, each with or without radiation. No significant difference resulted in 5-year OS between these two groups (41.6 % vs. 36.4 %; $p = 0.23$). This also applied after adjustment for patient and disease characteristics ($p = 0.37$).

In their summary, the authors point out that these findings further highlight the heterogeneity of stage IIIB disease and support consideration of NSCLC with additional nodules as a unique subcategory of T4 N2 disease. Further prospective studies could evaluate surgery as part of a multimodal treatment regimen in patients with T4 N2 NSCLC who have additional intrapulmonary nodules in a different ipsilateral lobe. ■

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Immune-based strategies are raising hope in small-cell tumors

DeLLphi-300: tarlatamab

Especially after frontline chemoimmunotherapy, treatment options are limited in patients with small-cell lung cancer (SCLC). Notch ligand delta-like ligand 3 (DLL3) represents a potential therapeutic target as it is aberrantly expressed on the surface of SCLC cells [1, 2]. By binding both DLL3 and CD3, the bispecific T cell engager (BiTE©) tarlatamab induces T-cell–mediated tumor lysis [3]. Tarlatamab is the first DLL3-targeted immunotherapy to undergo clinical evaluation.

In the first-in-human DeLLphi-300 study, tarlatamab was tested in the setting of relapsed/refractory SCLC with the aim to assess safety and tolerability, determine the maximum tolerated dose or recommended phase II dose, characterize pharmacokinetics, and to investigate preliminary antitumor activity. The patients had progressed or recurred following ≥ 1 platinum-based chemotherapy (including a PD-L1 inhibitor, if standard of care) and had ≥ 2 measurable lesions. Tarlatamab doses of 0.003-100 mg and 100 mg Q2W were used in the dose exploration and expansion phases, respectively.

At WCLC 2022, Borghaei et al. presented exploration and first expansion data of the DeLLphi-300 study for a total of 106 patients [4]. One third of these had received ≥ 3 prior lines of therapy, and half had previously been treated with anti-PD-(L)1 agents. In almost all cases, extensive-stage disease was present at the initial diagnosis.

Low-grade AEs and promising efficacy

Tarlatamab showed a manageable safety profile across the evaluated doses. Cytokine release syndrome (CRS) was the most common treatment-related AE (all grades, 53 %) but was almost exclusively restricted to mild and moderate events (grade ≥ 3, 1 %). CRS occurred mainly in cycle 1 and was generally manageable. No grade 4/5 CRS events were reported. Eight percent of patients required tocilizumab treatment for the management of this complication.

Similarly, higher-grade events were rare among the other common AEs including pyrexia (all grades, 38 %; grade ≥ 3, 2 %), dysgeusia (23 % and 0 %, respectively), fatigue (22 % and 3 %, respectively), and nausea (20 % and 0 %, respectively). Treatment-related neurologic events, which occurred in 50 %, were predominantly grade 1 and mainly comprised dysgeusia and headache. Confusion constituted the most common grade ≥ 3 and the only grade 4 neurologic event in the study. All-grade and grade 4 treatment-related neutropenia emerged in 16 % and 4 %, respectively. No patient developed febrile neutropenia. Only 4 % of the study population discontinued tarlatamab therapy due to treatment-related AEs.

In this heavily pretreated patient group, tarlatamab demonstrated promising antitumor activity with encouraging response durability. The confirmed overall response rate (ORR) was 23 % and included 2 cases of complete response. Thirty-seven percent of patients experienced target lesion shrinkage ≥ 30 %. Responses lasted for a median of 13.0 months. Median progression-free survival (PFS) and median overall survival (OS) were 3.7 and 13.2 months, respectively. Based on these results, the registrational phase II DeLLphi-301 study is assessing tarlatamab in SCLC patients after ≥ 2 lines of treatment (NCT05060016).

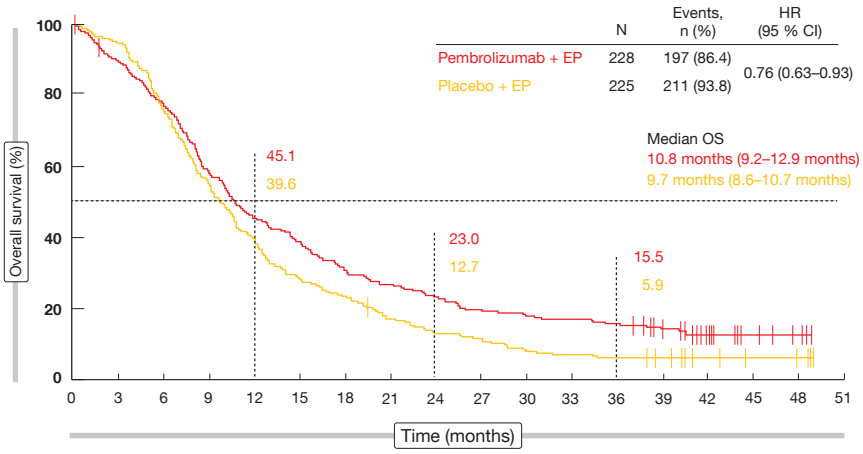

Figure: Updated overall survival with pembrolizumab plus chemotherapy vs. placebo plus chemotherapy in the KEYNOTE-604 study

Long-term survivors in KEYNOTE-604

In the setting of previously untreated stage IV SCLC, pembrolizumab plus etoposide/platinum (EP) Q3W for 4 cycles followed by pembrolizumab for up to 31 cycles significantly improved PFS compared to placebo plus EP followed by placebo in the phase III KEYNOTE-604 study [5]. The experimental and control arms included 228 and 225 patients, respectively. Rudin et al. presented long-term results after approximately 3.5 years of follow-up, as well as outcomes in patients who completed 35 cycles of pembrolizumab [6].

Pembrolizumab plus chemotherapy continued to elicit clinically meaningful OS and PFS improvement. The OS analysis in the ITT population revealed a 24 % mortality reduction with the pembrolizumab-based treatment (median, 10.8 vs. 9.7 months; HR, 0.76) even though 15 % of patients in the control arm had subsequently received immune checkpoint inhibitor therapy **(Figure)**. At 36 months, the OS rates were approximately 3 times higher in the experimental arm (15.5 % vs. 5.9 %). The risk of progression or death was reduced by 30 %, with median PFS of 4.8 vs. 4.3 months (HR, 0.70) and 36-month PFS rates of 6.9 % vs. 0.5 %. All subgroups except for patients with baseline brain metastases benefited from the immunotherapy-based approach with respect to both OS and PFS. Ten percent of the total group responded for ≥ 42 months. As previously reported, the safety profile of pembrolizumab plus EP was generally manageable. Immune-mediated AEs occurred in 27.4 % vs. 12.1 %, with grade 3-5 rates of 8.1 % vs. 1.3 %.

Eighteen patients had completed 35 cycles of pembrolizumab. At the time of the last assessment, 14 remained alive. Median OS had not been reached yet; the 2-year OS rate after completing the 35 cycles was 72.2 %. All patients were responders, with 11.1 % and 88.9 % achieving complete and partial remissions, respectively. In 83.3 %, responses lasted for ≥ 24 months. Among the control patients, on the other hand, only 2 of 225 individuals (0.9 %) had completed 35 cycles and were alive at data cutoff.

These results support the continued assessment of pembrolizumab-based combinations for the treatment of extensive-stage SCLC. The phase III KEYVIBE-008 trial is investigating MK-7684A, a co-formulation of vibostolimab, and pembrolizumab plus EP vs. atezolizumab plus EP in the first-line setting (NCT05224141). ■

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Checkpoint inhibition: subgroups, combination maintenance and retreatment

POSEIDON: impact of mutational status

The global, randomized, open-label, phase III POSEIDON trial was conducted to test the PD-L1 antibody durvalumab with or without the CTLA-4 inhibitor tremelimumab in addition to chemotherapy Q3W for 4 cycles compared to platinum-based chemotherapy Q3W for up to 6 cycles. Patients with stage IV NSCLC and *EGFR*/*ALK* wildtype who were treatment-naïve in the metastatic setting participated in POSEIDON. The combination regimens

TABLE
Clinical outcomes for durvalumab/tremelimumab plus chemotherapy (D/T + CT) vs. chemotherapy (CT) alone in patients with *STK11*, *KEAP1* and *KRAS* mutations

Endpoint	D/T + CT	CT	D/T + CT	CT	D/T + CT	CT
	***STK11* mutation**		***KEAP1* mutation**		***KRAS* mutation**	
Overall survival, months	15.0	10.7	13.7	8.7	25.7	10.4
	HR, 0.56		HR, 0.43		HR, 0.56	
24-month OS rates, %	32.3	4.5	35.0	0.0	51.7	25.6
Progression-free survival, months	6.4	4.6	5.0	5.1	8.5	4.7
	HR, 0.47		HR, 0.94		HR, 0.57	
24-month PFS rates, %	34.6	0.0	30.6	0.0	40.0	20.0
Overall response rates, %	45.2	27.3	45.5	33.3	55.0	21.2
Median duration of response, months	13.6	3.3	16.4	4.6	Not reached	5.4

were followed by durvalumab Q4W until progression, with one additional tremelimumab dose in week 16 in the triple combination arm. Indeed, the combined administration of durvalumab, tremelimumab and chemotherapy gave rise to statistically significant and clinically meaningful improvements in both progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone [1].

According to growing insights into the prognostic and predictive significance of certain molecular aberrations, *STK11*- and *KEAP1*-mutated tumors convey poor prognosis, while the *KRAS*-mutant subgroup is heterogeneous and generally responsive to checkpoint inhibitor therapy, unless associated with co-mutations such as *STK11* and *KEAP1* [2, 3]. Therefore, Peters et al. performed an exploratory analysis of outcomes obtained in the POSEIDON study by *STK11*, *KEAP1* and *KRAS* mutational status [4].

In the mutation-evaluable group with non-squamous histology included in the trial (n = 612), 14 %, 6 % and 30 % of patients had *STK11, KEAP1* and *KRAS* mutations, respectively. Durvalumab/tremelimumab plus chemotherapy, as compared to chemotherapy alone, induced favorable trends for OS and PFS with generally longer median findings and higher 24-month rates across the molecularly defined groups, as well as higher overall response rates (ORRs) **(Table)**. Responses obtained in the triple combination arm included complete remissions and were deeper and more durable than those in the control arm. Overall, these data suggested the use of durvalumab plus tremelimumab in addition to chemotherapy as a potential first-line option in harder-to-treat patient subgroups such as those with *STK11*, *KEAP1* or *KRAS* mutations.

Durvalumab/olaparib maintenance: ORION

In light of the need to further improve outcomes obtained with immunotherapy in metastatic NSCLC, the multicenter, double-blind, international, phase II ORION study evaluated durvalumab in combination with the PARP inhibitor olaparib as maintenance therapy. After first-line treatment with durvalumab Q3W plus platinum-based chemotherapy for 4 cycles, patients were randomized to either durvalumab Q4W plus olaparib (n = 134) or durvalumab plus placebo (n = 135) until progression.

The rationale of the study was based on the observation that increased DNA damage triggered through PARP inhibition might modify tumor immunogenicity and sensitize tumors to PD-(L)1 blockade, thus possibly promoting more durable responses than checkpoint inhibition alone [5, 6]. Investigator-assessed PFS was defined as the primary endpoint of the ORION trial.

According to the analysis reported at WCLC 2022, median PFS was numerically longer with the olaparib-based treatment than with durvalumab alone (7.2 vs. 5.3 months; HR, 0.76; p = 0.074) [7]. The results for the subgroups were generally consistent with the ITT analysis. Median OS was immature; the 12-month rates amounted to 65.6 % vs. 60.4 % (HR, 0.90; p = 0.604). Durvalumab plus olaparib was generally well tolerated, with no new safety concerns identified. The experimental arm experienced numerically higher rates of grade 3/4 AEs (34.3 % vs. 17.9 %), serious AEs (18.7 % vs. 14.2 %), and AEs leading to discontinuation of either study treatment (10.4 % vs. 4.5 %). Treatment-related deaths were reported in 0 % vs. 0.7 %.

The biomarker analyses demonstrated that the presence of homologous recombination repair (HRR) mutations did not enrich for activity in the experimental arm; median PFS with durvalumab plus olaparib was shorter in these patients compared to those with HRR wildtype tumors (3.9 vs. 7.4 months). Among patients with HRR wildtype, PFS favored the combination vs. durvalumab monotherapy. Moreover, PFS was improved in the experimental arm compared to the control arm in the subgroups without PD-L1 expression (< 1 %) and with PD-L1 expression of 1-49 %. PFS in the cohort with PD-L1 ≥ 50 % did not differ across the arms; compared with the < 50 % subgroups, median PFS was numerically higher in both treatment groups.

However, the small sample sizes and numbers of events preclude definitive conclusions. As the authors noted, further research is required to assess the possible role of combination therapy with durvalumab and olaparib in metastatic NSCLC.

Pembrolizumab retreatment in 5 phase III trials

Single-agent pembrolizumab and pembrolizumab plus chemotherapy as first-line treatment substantially prolong OS and PFS compared to chemotherapy in advanced NSCLC without *EGFR*/*ALK* alterations [8-11]. In the clinical trial setting, patients whose disease progresses after the completion of 35 cycles of pembrolizumab have the potential to receive a second course for up to 17 additional cycles. An exploratory pooled analysis assessed the outcomes of patients who received second-course pembrolizumab after pembrolizumab monotherapy (Cohort 1) or pembrolizumab plus chemotherapy (Cohort 2). Cohort 1 included a total of 57 patients from the KEYNOTE-024, KEYNOTE-042 and KEYNOTE-598 trials, while Cohort 2 consisted of 14 patients from KEYNOTE-189 and KEYNOTE-407.

Rodríguez-Abreu et al. presented the results according to which a second course of pembrolizumab monotherapy is feasible and elicits clinically meaningful benefit [12]. Disease control during the second-course treatment was achieved in 73.7 % and 50.0 % in Cohorts 1 and 2, respectively. Cohort 1 contained only PD-L1–positive patients with PD-L1 expression ≥ 1 %. Here, the ORR was higher in the group with TPS 1-49 % (27.3 %) than in patients with TPS ≥ 50 % (17.4 %; **Figure**). Median duration of response had not been reached in Cohort 1 yet, and 78.8 % of patients responded for ≥ 6 months. Median OS was 27.5 months in Cohort 1 and had not been reached in Cohort 2. In both cohorts, 85.1 % of patients were alive at 6 months. Median PFS was 10.3 and 7.7 months, respectively, with 6-month rates of 60.8 % and 54.5 %, respectively.

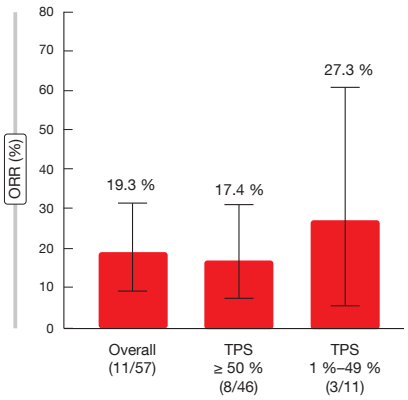

Figure: Overall response rates by PD-L1 expression during second-course pembrolizumab

The safety of the treatment proved manageable during the second course, with low rates of grade 3/4 treatment-related AEs (5 % and 7 %, respectively). Immune-mediated events were observed in Cohort 1 only; grade 1/2 and 3 AEs occurred in 9 % and 2 %, respectively. No treatment-related grade 5 events were reported in either cohort. These data support pembrolizumab retreatment upon disease progression in patients with advanced or metastatic NSCLC after completion of 35 cycles of first-course pembrolizumab with or without chemotherapy. ■

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WCLC CONGRESS

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Expert interviews at WCLC 2022

Julia Rotow summarizes the achievements of EGFR tyrosine kinase inhibitors in the neoadjuvant therapy of lung cancer regarding multiple clinical outcomes, discusses if modification of the disease biology will be a feasible treatment goal in the setting of EGFR-directed neoadjuvant treatment sometime and talks about the individualization of neoadjuvant treatment of oncogene-driven lung cancer.

Alexander Louie explains which modes of imaging can be particularly helpful when clinicians face unique diagnostic challenges in lung cancer patients with pneumonitis after chemoradiotherapy and immunotherapy. Moreover, he summarizes what needs to be considered regarding pneumonitis treatment and highlights current and future pneumonitis research areas.

Federico Cappuzzo discusses the effectiveness and limitations of minimal residual disease (MRD) assessment in the detection of patients with early-stage lung cancer at low risk of relapse and highlights which clinical investigations regarding the clinical impact of MRD assessments in solid tumors are ongoing and what we can expect from them in the future.

Filiz Oezkan depicts the most important factors influencing the choice of treatment in patients with PD-L1-positive NSCLC, explains how the 50 % PD-L1 threshold affects the treatment selection and explains which treatment options appear favorable in the setting of PD-L1 levels below 1 % while also taking into account possible challenges associated with biomarker testing for PD-L1 in NSCLC.

Maximilian Hochmair highlights relevant study data in the field of *EGFR*-mutated advanced lung cancer, novel therapies in the management of *KRAS* p.G12C mutation as well as *MET* exon 14 skipping mutations in NSCLC. He draws attention to antibody drug conjugates in the management of NSCLC patients as well as the optimal treatment sequence in the ALK-positive setting.

Helmut Popper talks about the characteristics of the recently defined molecular subtypes of small-cell lung cancer (SCLC), outlines if this subtyping is suitable for therapeutic decision-making and gives an overview about potential new therapeutic targets in the field of SCLC.

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