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A GLOBAL CONGRESS DIGEST ON LUNG CANCER

Report from the virtual European Lung Cancer Congress, 30th March–2nd April 2022

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Preface

Dear Colleagues,

The European Lung Cancer Congress (ELCC) that took place virtually on 30th March–2nd April 2022 effectively disseminated the latest advances in lung and thoracic malignancies and gave 131 speakers from all around the world the chance to present promising new research avenues as well as the opportunity for discussions and new perspectives. By clearly highlighting the importance of a multidisciplinary team in the management of patients with lung cancer, this congress once more enabled to advance science, spread education, and improve the practice of lung cancer specialists worldwide.

This issue of memo inOncology looks closely at upcoming and established immunotherapy standards as novel adjuvant strategies are needed to optimize outcomes after complete surgical resection in patients with early-stage non–small-cell lung cancer (NSCLC). Data presented at ELCC support the use of atezolizumab in PD-L1–expressing NSCLC, underscore pembrolizumab as standard-of-care therapy for patients with metastatic NSCLC without targetable *EGFR* or *ALK* aberrations, highlight camrelizumab plus carboplatin/paclitaxel as a standard first-line option for patients with advanced squamous NSCLC, and show that tislelizumab plus chemotherapy has a tolerable safety profile in this patient group.

Moreover, the potential of targeted therapies in oncogene-driven lung cancer including *EGFR*-, *MET*ex14-, *ROS1*- and *RET*-mutated tumors is illustrated, with several first-line strategies emerging for patients harboring these mutations. Promising candidates included in this report are osimertinib, furmonertinib, oritinib, savolitinib, unecritinib and selpercatinib, all of which are currently investigated in phase I/II-III studies.

Last but not least, prognostic determinants and new treatment modalities including the combination of an anti-PD-L1 antibody and a CTLA-4 inhibitor or thoracic consolidative radiotherapy during immunotherapy in the setting of extensive-stage small-cell lung cancer are presented while also shedding light on dual targeting with anti-TIGIT and anti-PD-1 monoclonal antibodies in untreated limited-stage SCLC.

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Although we all hope to meet again in person at future conferences to hear about breakthroughs that will further advance daily clinical practice, it requires dedicated meetings like ELCC that even enabled discussions of clinical cases in interactive sessions to move the field even further in such a way as to not only provide the optimal management of patients with thoracic malignancies but also to use personalized strategies to ensure even better care for patients.

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Looking more closely at upcoming and established immunotherapy standards

IMpower010: adjuvant atezolizumab

Adjuvant treatment using immune checkpoint inhibition after complete resection of early-stage lung cancer is being investigated considering the modest survival benefit conferred by platinum-based combination chemotherapy in this setting [1, 2]. IMpower010 was the first phase III immunotherapy study to demonstrate a significant disease-free survival (DFS) improvement in the adjuvant setting after platinum-based chemotherapy [3]. Patients included in this trial had undergone complete resection of stage IB-IIIA NSCLC and subsequently received 1–4 cycles of cisplatin-based chemotherapy. Three to 8 weeks after the last dose, 1,005 patients were randomized to either atezolizumab 1,200 mg 3-weekly for 16 cycles or best supportive care (BSC). DFS was tested hierarchically in the PD-L1 TC ≥ 1 % stage II-IIIA population followed by the all-randomized stage II-IIIA group and the ITT (i.e., stage IB-IIIA) population.

At the time of the interim analysis, atezolizumab gave rise to a significant DFS benefit in the PD-L1 TC ≥ 1 % stage II-IIIA group, leading to a 34 % risk reduction (median DFS, not estimable vs. 35.3 months; HR, 0.66; p = 0.0039) [3]. DFS rates at 36 months were 60.0 % vs. 48.2 %. The greatest magnitude of DFS improvement, however, occurred in the stage II-IIIA subpopulation with high PD-L1 expression (TC ≥ 50 %). Felip et al. presented further analyses for this cohort at the ELCC 2022 [4].

TABLE
Patterns of disease relapse for adjuvant atezolizumab vs. best supportive care in the PD-L1 TC ≥ 50 % stage II-IIIA population

Site of relapse, n (%)	Atezolizumab (n = 115)	BSC (n = 114)
Locoregional only	15 (13)	17 (15)
Distant	10 (9)	30 (26)
Distant only	6 (5)	21 (18)
CNS only	1 (1)	7 (6)
Locoregional + distant	4 (4)	9 (8)
Second primary of the lung	0	3 (3)

Reduction of distant relapses

Median DFS in the group with PD-L1 TC ≥ 50 % stage II-IIIA disease had not been reached yet with atezolizumab and was 35.7 months with BSC, translating into a 57 % reduction in the risk of disease recurrence or death (HR, 0.43). At 36 months, 73.8 % vs. 48.6 % of patients were disease-free. Similar results emerged after the exclusion of patients with *EGFR* and *ALK* alterations (median DFS, not estimable vs. 37.3 months; HR, 0.43). Exploratory overall survival (OS) data for these groups were immature, and further follow-up is required. Most key subgroups within the PD-L1 TC ≥ 50 % stage II-IIIA population fared better with adjuvant atezolizumab than with BSC regarding DFS. The risk reductions achieved by these subgroups were similar after the exclusion of *EGFR*- and *ALK*-positive patients.

The percentage of patients experiencing relapse as their earliest DFS event was halved in the PD-L1 TC ≥ 50 % stage II-IIIA population for atezolizumab vs. BSC (22 % vs. 44 %). Moreover, the relapse patterns differed by site. While locoregional progression as a sole event occurred in comparable proportions of patients across the two arms (13 % vs. 15 %), distant relapses were markedly less frequent with atezolizumab. Five percent vs. 18 % of patients treated with atezolizumab and BSC, respectively, only experienced distant recurrence. In addition, lower rates emerged in the experimental arm with respect to CNS recurrence, locoregional plus distant relapse, and second primaries of the lung **(Table)**. Time to relapse was 18.1 vs. 10.1 months for atezolizumab vs. BSC. Any systemic post-relapse treatment was administered in 76 % and 60 % of patients, respectively, with 16 % and 38 % receiving immunotherapy.

The safety results observed in the PD-L1 TC ≥ 50 % stage II-IIIA group were consistent with those for the stage IB-IIIA population. No patient died due to treatment-related AEs (TRAEs; vs. 0.8 % for atezolizumab in the overall population), and AEs leading to discontinuation of atezolizumab emerged in 19 % (vs. 18.2 %). According to the authors, these findings build on the positive benefit-risk profile for atezolizumab in PD-L1–expressing NSCLC and support its use as adjuvant treatment.

3-year follow-up for KEYNOTE-598

In the randomized, double-blind, phase III KEYNOTE-598 trial, the first-line regimen of pembrolizumab plus ipilimumab did not improve efficacy compared to single-agent pembrolizumab while increasing toxicity in stage IV NSCLC with PD-L1 TPS ≥ 50 % [5]. This led to discontinuation of both ipilimumab and placebo per external data monitoring committee recommendation. Pembrolizumab monotherapy continued in both arms. Each arm contained approximately 280 patients; 33.8 % and 38.7 % received subsequent anticancer treatment in the experimental and control arms, respectively.

Long-term outcomes presented by Rodríguez-Abreu et al. at the ELCC after 13 additional months of follow-up confirmed the absence of clinical benefits with the combination [6]. Both OS and PFS curves were superimposable across the treatment regimens, with HRs of 1.05 and 0.99, respectively. At 24 months, 48.0 % and 48.5 % of patients, respectively, were alive, with 27.2 % and 25.1 %, respectively, being progression-free. Likewise, ORRs did not differ (46.5 % vs. 46.1 %). Even with the prolonged follow-up, the incidence of TRAEs was higher in the combination arm (any grade, 75.5 % vs. 68.7 %; grade 3-5, 35.1 % vs. 20.3 %), leading more often to treatment discontinuation. Patients treated with pembrolizumab/ipilimumab received 10 cycles on average, while those in the pembrolizumab monotherapy arm received 15 cycles.

Furthermore, the scientists investigated clinical outcomes in patients who completed 35 cycles, i.e., approximately 2 years of pembrolizumab treatment. This applied to more patients in the monotherapy arm (n = 71) than in the combination arm (n = 52). Most of these had durable responses, including patients who discontinued ipilimumab after the first interim analysis. Compared to the overall population, both groups showed higher ORRs of approximately 88 %. Median duration of response had not been reached yet in either arm. Two patients in the combination arm and 9 in the monotherapy arm started a second course of pembrolizumab. At data cutoff, 8 of them were still alive. Overall, these findings underscore the significance of single-agent pembrolizumab as a standard-of-care therapy for patients with metastatic NSCLC and PD-L1 TPS ≥ 50 % who do not harbor targetable *EGFR* or *ALK* aberrations.

Camrelizumab in squamous tumors: CameL-sq

The anti-PD-1 checkpoint inhibitor camrelizumab was evaluated as first-line treatment in the randomized, phase III CameL-sq trial conducted in Chinese patients with stage IIIB-IV squamous NSCLC. Patients were randomized to either camrelizumab 200 mg plus carboplatin/paclitaxel (n = 193) or placebo plus carboplatin/paclitaxel (n = 196) 3-weekly for 4–6 cycles. This was followed by maintenance treatment with camrelizumab 200 mg 3-weekly in the experimental arm, while the control arm received placebo. Cross-over to the active treatment was permitted upon progression. At the time of the primary analysis, the camrelizumab-based regimen, as compared to chemotherapy alone, gave rise to a significant PFS improvement (8.5 vs. 4.9 months; HR, 0.37; $p < 0.0001$) [7]. OS results were immature.

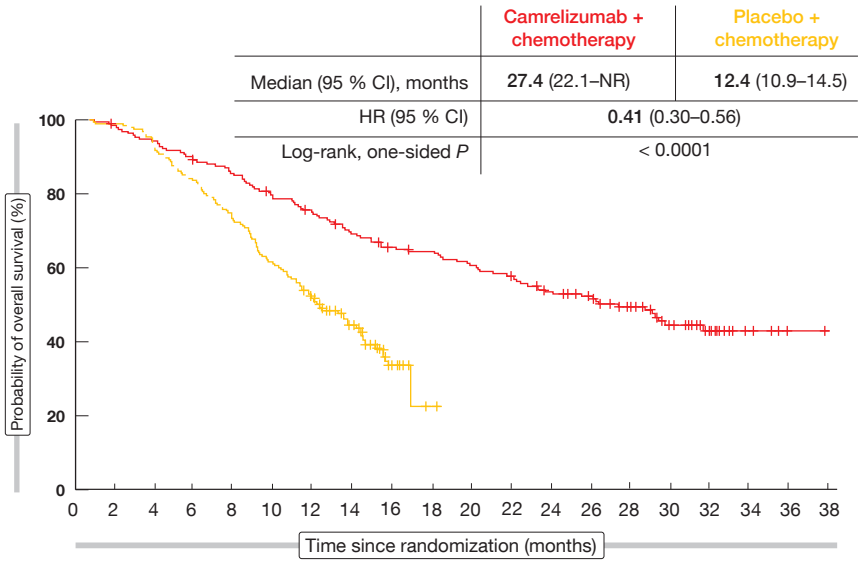

Figure: CameL-sq trial: overall survival with camrelizumab plus chemotherapy vs. chemotherapy alone after adjustment for cross-over

According to the update reported at the ELCC by Zhou et al., the addition of camrelizumab to chemotherapy continued to demonstrate survival benefits after > 1 year of additional follow-up [8]. Despite a cross-over rate of 55.8 %, median OS was almost double in the experimental arm, translating into a 43 % reduction in mortality risk (27.4 vs. 15.5 months; HR, 0.57; p < 0.0001). At 36 months, 42.8 % vs. 23.7 % of patients were alive. A rank-preserving structural failure time model was used to estimate the cross-over–adjusted OS, resulting in a 59 % mortality reduction with camrelizumab plus chemotherapy (27.4 vs. 12.4 months; HR, 0.41; p < 0.0001; **Figure**). No new safety signals emerged over time. The authors concluded that these data further support camrelizumab plus carboplatin/paclitaxel as a standard first-line option for patients with advanced squamous NSCLC.

Tislelizumab: safety data from RATIONALE-307

Tislelizumab is a new PD-1 inhibitor that was designed to minimize binding to Fcγ receptors on macrophages to abrogate antibody-dependent phagocytosis, which is a potential mechanism of resistance to anti-PD-1 therapy [9, 10]. The open-label, randomized, phase III RATIONALE-307 trial compared tislelizumab plus paclitaxel/carboplatin (Arm A) with tislelizumab plus nab-paclitaxel/carboplatin (Arm B) and paclitaxel/carboplatin alone (Arm C) as first-line treatment for patients with locally advanced or metastatic squamous NSCLC. Tislelizumab plus chemotherapy significantly prolonged PFS (7.6 months in both Arm A and B) vs. chemotherapy (Arm C: 5.5 months; p < 0.001 for both comparisons), which translated into risk reductions of 48 % and 52 %, respectively (HRs, 0.524 and 0.478, respectively) [11]. Also, a manageable safety and tolerability profile was observed. At ELCC 2022, Yu et al. presented results from a post-hoc safety analysis of the RATIONALE-307 study that included a total of 355 patients [12].

These data showed that in patients with advanced squamous NSCLC, tislelizumab plus chemotherapy had a tolerable safety profile which was consistent with that of other checkpoint inhibitors including PD-1 inhibitors. Endocrine disorders were more common in Arms A and B (12.5 % and 6.8 %) than in Arm C (0 %), as were hypersensitivity reactions (25.8 % and 30.5 % vs. 12.0 %) and hypothyroidism (13.3 % and 14.4 % vs. 2.6 %). Regarding the most commonly reported treatment-emergent AEs by system organ class, comparable rates resulted for tislelizumab plus chemotherapy vs. chemotherapy alone, indicating that tislelizumab did not compound chemotherapy-specific toxicity. ■

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Oncogene-driven lung cancer: EGFR, METex14, ROS1, RET

NEOS: neoadjuvant osimertinib

The neoadjuvant potential of the third-generation EGFR TKI osimertinib was assessed in the multicenter, single-arm, phase II NEOS study that included patients with resectable, stage II-IIIB N2, *EGFR*-mutant (ex19del/L858R) adenocarcinoma of the lung. Forty patients received osimertinib 80 mg QD for 6 weeks prior to surgery. Among these, 38 completed treatment, and 32 underwent surgical resection. The interim analysis presented at the ASCO 2021 Congress already indicated that neoadjuvant osimertinib is effective and safe [1]. At ELCC 2022, Lyu et al. reported updated findings of the NEOS trial [2].

The objective response rate (ORR), which was defined as the primary endpoint, was 71.1 %. Disease control had been achieved by all patients. Three out of 28 pathologically evaluable individuals (11 %) experienced major pathological responses, which included one case of complete response (4 %). Almost half of all patients showed pathological responses of ≥ 50 %. R0 resections were performed in 94 %. Overall, the safety profile of neoadjuvant osimertinib remained consistent with previous reports. The most common adverse events (AEs) included rash (any grade, 50 %), diarrhea (30 %), and oral ulceration (30 %). Grade 3 treatment-related AEs (i.e., rash, hypertension, renal disease) were observed in 3 patients (7.5 %). No event led to treatment discontinuation.

As the authors noted in their conclusion, the NEOS study demonstrated promising efficacy and good tolerability of neoadjuvant osimertinib. Phase III trials enrolling larger numbers of patients are warranted to further validate this strategy. At present, the three-arm, randomized, NeoADAURA trial is assessing neoadjuvant osimertinib alone or together with chemotherapy vs. standard-of-care chemotherapy (NCT04351555).

First-line furmonertinib: FURLONG

Furmonertinib is a selective third-generation EGFR TKI that irreversibly inhibits both *EGFR*-sensitizing and T790M resistance mutations. The randomized, double-blind, multicenter, phase III FURLONG study investigated first-line treatment with furmonertinib 80 mg QD compared to gefitinib 250 mg QD in Chinese patients with locally advanced or metastatic, *EGFR*-mutated (ex19del/L858R) lung cancer [3]. Asymptomatic CNS metastases were allowed. The furmonertinib and gefitinib arms included 178 and 179 evaluable patients, respectively.

The primary endpoint was met, with patients treated in the experimental arm deriving significant PFS improvement compared to those in the control arm (20.8 vs. 11.1 months; HR, 0.44; p < 0.0001; **Figure**). Across subgroups, the PFS findings favored furmonertinib. No differences emerged between the study arms in terms of ORR (89 % vs. 84 %; p = 0.2078) or disease control rate (96 % vs. 93 %; p = 0.3551), although furmonertinib-treated patients experienced significantly longer duration of response (19.7 vs. 10.5 months; p < 0.0001) and time to progression (20.9 vs. 11.2 months; p < 0.0001). Median overall survival (OS) had not been reached yet.

Despite longer median duration of exposure in the experimental arm (18.3 vs. 11.2 months), furmonertinib showed a favorable safety profile, with relatively lower rates of grade ≥ 3 treatment-related AEs (TRAEs; 11 % vs. 18 %) as well as lower rates of abnormal liver function readings, diarrhea, and rash. Overall, these results suggest that furmonertinib, as compared to gefitinib, is a potentially preferred first-line regimen in patients with *EGFR*-mutant NSCLC.

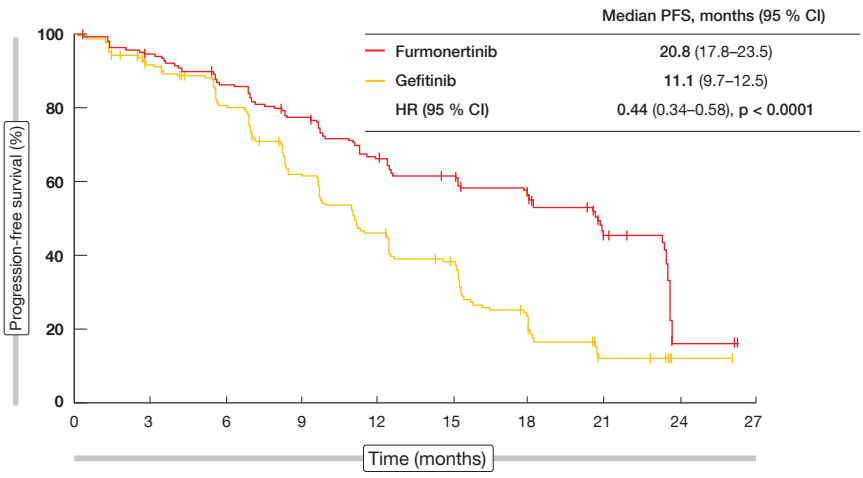

Figure: Superior progression-free survival with furmonertinib vs. gefitinib in *EGFR*-mutated advanced lung cancer

Oritinib after progression

Oritinib, which is another selective, irreversible third-generation EGFR TKI, was tested in Chinese patients with locally advanced or metastatic NSCLC who had progressed on ≥ 1 first- and/or second-generation EGFR TKI [4]. This group was shown to harbor the *EGFR* T790M resistance mutation prior to inclusion. In this single-arm phase II study, 227 individuals received oritinib 200 mg OD. The ORR was defined as the primary endpoint.

Indeed, oritinib demonstrated potential clinical benefit, with an ORR of 60.4 % and a disease control rate of 92.5 %. Most patients experienced decreases in target lesion size. Responses lasted for a median of 12.5 months, and median PFS was 12.6 months. The new

EGFR TKI showed a favorable safety profile. Diarrhea represented the most common TRAE (any grade, 41.9 %), followed by increases in blood creatine phosphokinase levels (23.8 %). Among grade ≥ 3 AEs, creatine phosphokinase elevations were observed most frequently (4.0 %). The rates of TRAEs leading to dose reduction or discontinuation were low at 1.3 % and 1.8 %, respectively. Four patients died due to TRAEs (1.8 %). A randomized, controlled, double-blind, phase III trial is currently comparing oritinib with gefitinib in the first-line treatment of patients with advanced NSCLC harboring *EGFR*-sensitizing mutations (NCT04239833).

Savolitinib in *MET*ex14-mutated tumors

The highly selective oral MET TKI savolitinib has demonstrated clinically meaningful ORR in patients with unresectable or metastatic, *MET*ex14-mutated pulmonary sarcomatoid carcinoma (PSC) and other NSCLCs in a single-arm, phase II study [5]. Within the full analysis set of 70 patients, 28 were treatment-naïve but unfit for chemotherapy, while 42 were chemotherapy-pretreated. Twenty-five had been diagnosed as PSC and 45 as other NSCLCs. Savolitinib was administered according to body weight, with patients ≥ 50 kg receiving 600 mg and those < 50 kg receiving 400 mg OD. Fifteen individuals had CNS metastases. Lu et al. presented the final OS results of the study as well as subgroup analyses at the ELCC 2022 [6].

In the full analysis set, median PFS was 6.9 months, with a 15-month PFS rate of 25 %. Both treatment-naïve and previously treated patients showed a median PFS of 6.9 months; likewise, the PFS results did not differ for the PSC vs. other NSCLCs cohorts (5.5 and 7.0 months, respectively) and groups with and without brain metastases (7.0 and 6.2 months, respectively). Median OS in the full analysis set amounted to 12.5 months; at 24 months, 31 % of patients were alive. Pretreated patients fared better regarding OS than the treatment-naïve population (19.4 vs. 10.9 months), although this should be interpreted with caution due to differences in patient characteristics. The group with PSC had shorter OS than the one with other NSCLCs (10.6 vs. 17.3 months), which was presumably due to the poor prognosis of this lung cancer type. Median OS in patients with brain metastases was 17.7 months; this further confirms the efficacy of savolitinib with respect to CNS affliction.

With prolonged follow-up, the AE rates were similar to previously reported data. Peripheral edema, nausea, and hypoalbuminemia were noted as the most common any-grade AEs. Grade ≥ 3 AEs primarily included transaminase elevations. According to the authors, the updated findings of this phase II trial corroborate the benefit and acceptable safety profile of savolitinib in patients with *MET*ex14-mutated NSCLC.

ROS1-positive disease: unecritinib

Unecritinib (TQ-B3101) has been designed to target receptor tyrosine kinases including ALK, ROS1, and MET. Phase I data have revealed favorable tolerability and preliminary antitumor activity of this agent in pretreated patients with advanced *ALK*-positive, *ROS1*-positive, or *MET*-amplified tumors [7]. In the phase II trial conducted at 29 sites in China, unecritinib was assessed at a dose of 300 mg BID in 111 patients with locally advanced or metastatic, *ROS1*-positive NSCLC after ≤ 2 chemotherapy regimens [8]. Fifty-nine percent were treatment-naïve, while 31 % and 10 % had received 1 and 2 prior treatment lines, respectively. Almost 30 % showed brain metastases at baseline.

Objective responses, which constituted the primary outcome, occurred in 78.4 %. The disease control rate was 87.4 % and the median duration of response 20.3 months. Almost all subgroups benefited from the treatment. Median PFS was 15.6 months, and median OS had not been reached yet at the time of the analysis. At 24 months, 88.1 % of patients were alive.

TRAEs mainly comprised transaminase elevations, vomiting, neutrophil and leukocyte count decreases, sinus bradycardia, diarrhea, and elevated serum creatine phosphokinase levels. Grade ≥ 3 TRAEs occurred in 45.1 %. Among AEs of interest, any-grade ocular organ diseases were observed in 26.1 % but were restricted to grade 1 and 2. Overall, TRAEs led to dose disruption and discontinuation in 35.1 % and 16.2 %, respectively. The authors noted that unecritinib exhibited promising efficacy with a manageable safety profile, thus offering a new first-line strategy for patients with locally advanced or metastatic *ROS1*-positive NSCLC.

Lasting effects of selpercatinib in LIBRETTO-001

The first-in-class, highly selective and potent RET inhibitor selpercatinib has shown durable responses in patients with *RET*-fusion–positive NSCLC in the ongoing, global, phase I/II LIBRETTO-001 study [9]. At ELCC 2022, Drilon et al. reported an update for 316 patients 69 of whom were treatment-naïve while 247 had previously been

TABLE
LIBRETTO-001: CNS response to selpercatinib in patients with *RET*-fusion–positive NSCLC (n = 26)

Objective CNS response by independent review committee, %	84.6
Best CNS response, n (%)	
Complete response	7 (26.9)
Partial response	15 (57.7)
Stable disease	4 (15.4)
Progressive disease	0
Not evaluable	0
Duration of CNS response	
Median, months	9.4
1-year rate, %	36.1
2-year rate, %	20.6

treated with platinum-based chemotherapy [10]. Selpercatinib continued to demonstrate robust and durable efficacy. ORRs were 84.1 % and 61.1 % for the treatment-naïve and pretreated groups, respectively, and median PFS was 22.0 and 24.9 months, respectively. The 3-year OS rates amounted to 57.1 % and 58.5 %, respectively.

Moreover, selpercatinib showed considerable CNS activity. Measurable CNS metastases had been present at baseline in 26 patients. In this group, 22 (84.6 %) experienced complete or partial remission in the CNS (**Table**). The median CNS PFS was 19.4 months at a median follow-up of 22.1 months. No new safety signals occurred during the extended follow-up.

While LIBRETTO-001 is still enrolling patients with *RET*-altered solid tumors, recruitment has started for the global, randomized, phase III LIBRETTO-431 trial that will compare selpercatinib to standard frontline chemotherapy in treatment-naïve patients with *RET*-fusion–positive advanced or metastatic NSCLC (NCT04194944). ■

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SCLC: prognostic determinants and new treatment modalities

Long-term survival in CASPIAN

The global, randomized, open-label, phase III CASPIAN trial was initiated to test the anti-PD-L1 antibody durvalumab with or without the CTLA-4 inhibitor tremelimumab in addition to etoposide-platinum chemotherapy (EP) as first-line treatment in patients with extensive-stage small-cell lung cancer (ES-SCLC). Compared to EP only, this three-arm study revealed a significant benefit of durvalumab plus EP regarding overall survival (OS) that was sustained after more than 3 years of follow-up (12.9 vs. 10.5 months; HR, 0.71; p = 0.0003) [1, 2]. Durvalumab plus tremelimumab in addition to EP led to numerical OS improvement vs. chemotherapy alone, with 36-month OS rates of 15.3 % vs. 5.8 % (HR, 0.81) [2, 3]. Considering the lack of well-characterized biomarkers that predict the efficacy of immune checkpoint inhibitors, Paz-Ares et al. presented an analysis of long-term survivors (LTS) at ELCC 2022 [4]. Characteristics were assessed in patients who were still alive at the 22 March 2021 data cut-off after a median follow-up for OS of 39.4 months.

The analysis showed that the CASPIAN trial population contained more than 3 times as many LTS in the durvalumab plus EP arm than in the EP arm (16 % vs. 5 %). Those in the durvalumab/tremelimumab plus EP arm were almost 3 times as many (14 %). Overall, 81 patients in the two immunotherapy arms constituted LTS. At the data cut-off, 46 of them were still receiving durvalumab (n = 27) or both checkpoint inhibitors (n = 19) in addition to chemotherapy. In terms of baseline characteristics, LTS, as compared to the ITT populations, had a higher incidence of favorable prognostic markers such as female gender and good performance status. Although the proportions of patients with brain and liver metastases were lower than in the ITT arms, they were not zero, indicating that some patients achieved long-term survival despite the presence of these lesions.

Clinical and molecular differences

LTS in both checkpoint-inhibitor–based treatment arms were more likely to have completed EP induction and to have achieved objective responses than the ITT population **(Figure)**. Their PFS rates at 12 and 24 months were markedly higher across all arms. No evidence of cumulative toxicity emerged despite longer exposure in LTS, who did not experience increases in serious adverse events (AEs). The distribution of serious AEs across system organ classes was similar for LTS and ITT patients.

With respect to molecular characteristics, the investigators assessed PD-L1 expression, tissue tumor mutational burden (tTMB), and the presence of the HLA-DQB1*03:01 allele. For the dur-

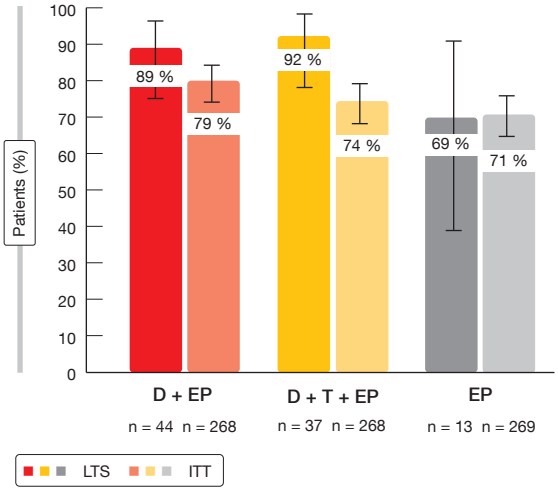

Figure: Objective response rates in long-term survivors (LTS) and the ITT population with durvalumab plus EP (D+EP), durvalumab/tremelimumab plus EP (D+T+EP), and EP alone

valumab plus EP arm, the molecular assessments yielded no association of any of these markers with OS ≥ 18 or ≥ 36 months. At the same time, PD-L1 expression ≥ 1 % and the presence of the HLA-DQB1*03:01 allele were enriched in the durvalumab/tremelimumab plus chemotherapy arm in patients with median OS ≥ 18 months vs. those with OS < 18 months. This held true even after 36 months, although the patient numbers grew small over time. The authors noted that further investigation is warranted to understand the potential role of these and other biomarkers in SCLC.

Consolidative radiotherapy

The safety and efficacy of thoracic consolidative radiotherapy during immunotherapy in the setting of ES-SCLC has not been reported to date. Daher et al. therefore performed a multicenter, retrospective study that investigated consolidative radiotherapy (defined as radiation given at the end of chemotherapy to responders) in consecutive patients with ES-SCLC who were treated with platinum-based chemotherapy plus durvalumab or atezolizumab [5]. Twenty-five individuals treated at 4 centers in Israel were compared to a group of 101 patients who did not receive consolidative radiotherapy.

Indeed, consolidative radiotherapy was shown to be safe and feasible for patients with ES-SCLC undergoing chemoimmunotherapy. The rates of immune-related AEs were similar across the irradiated and not irradiated groups (12.0 % vs. 14.9 %). No pneumonitis cases were reported as related to consolidative radiotherapy. Grade 3 AEs occurred in 20 % vs. 14.9 %, and no grade 4 or 5 events were identified. In addition, patients receiving consolidative radiotherapy showed longer median PFS (8.5 vs. 5.6 months; HR, 0.48; p < 0.003) and OS (27.7 vs. 13.2 months; HR 0.33; p < 0.007). Prospective studies are required to assess the potential role of consolidative radiotherapy in the treatment of ES-SCLC.

Trial in progress: AdvanTIG-204

In the setting of limited-stage SCLC, no novel therapeutic agents improving clinical outcomes beyond concurrent chemoradiotherapy (cCRT), which represents the standard of care, have been established to date. The randomized, multicenter, open-label, phase II AdvanTIG-204 study is assessing first-line treatment with the anti-TIGIT antibody ociperlimab 900 mg Q3W in addition to the PD-1 inhibitor tislelizumab 200 mg Q3W plus cCRT (Arm A) vs. tislelizumab 200 mg Q3W plus cCRT (Arm B) and cCRT alone (Arm C) [6]. After 4 cycles of treatment, patients in Arms A and B go on to receive ociperlimab plus tislelizumab and tislelizumab monotherapy, respectively.

TIGIT is a co-inhibitory immune checkpoint receptor that is upregulated on T cells and natural killer cells in multiple solid tumors, giving rise to escape from immune surveillance [7, 8]. Dual targeting of tumors with anti-TIGIT and anti-PD-1 monoclonal antibodies has shown synergistic immune activation and enhanced antitumor activity in the phase I AdvanTIG-105 trial [9]. Approximately 120 patients with untreated limited-stage SCLC will be included in AdvanTIG-204. Progression-free survival in the ITT analysis set is defined as the primary endpoint. The first patient was enrolled in July 2021, and the study is ongoing. ■

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Interview: Jordi Remon, MD, PhD, Department of Medical Oncology, Centro Integral Oncológico Clara Campal, Hospital HM Nou Delfos, HM Hospitales, Barcelona, Spain

"PD-L1 expression remains the gold standard"

What needs to be considered in the context of neoadjuvant and adjuvant immunotherapy in patients with resectable lung cancer?

Today we know that immunotherapy works in the perioperative therapeutic strategy of patients with early-stage NSCLC, both in the neoadjuvant setting in combination with chemotherapy and in the adjuvant setting. However, data from the metastatic setting show that patients with oncogenic-driven NSCLC do not benefit from checkpoint inhibition, at least when the treatment is administered as monotherapy. This does not completely translate to the adjuvant setting where data are somewhat conflicting, with IMpower010 showing no benefit of adjuvant atezolizumab in *EGFR*-mutant and *ALK*-positive tumors, while the KEYNOTE-091 trial conducted with pembrolizumab demonstrated an advantage in patients with *EGFR* mutations [1, 2]. However, this is a very small number of patients. From my point of view, most important before starting immunotherapy either in the neoadjuvant or adjuvant setting is the assessment of at least the most common genomic alterations including *EGFR*, *ALK*, *ROS1*, and *BRAF*. Taking into account the data from metastatic disease, especially for *EGFR*-, *ALK*-, and *ROS1*-positive tumors, these should be more or less excluded from treatment with adjuvant checkpoint inhibitors. In the neoadjuvant setting, this is less clear as patients with *EGFR*- and *ALK*-positive tumors were not eligible for the CheckMate 816 study [3].

In which ways can tyrosine kinase inhibitors contribute to effective perioperative treatment?

Many trials clearly established that TKIs, at least EGFR TKIs, improve disease-free survival as compared to placebo in patients with *EGFR*-mutant, completely resected stage II and IIIA NSCLC. However, with respect to overall survival, the data are still immature. Obviously, we would like to convey this benefit to other oncogenic drivers in the adjuvant setting, which is complicated due to their low incidences. We would also like to have more early data on the efficacy of TKIs in the neoadjuvant setting, as the evidence is still very limited here. Although third-generation EGFR TKIs provide high response rates of approximately 70 % in *EGFR*-mutant tumors according to the RECIST criteria, the pathological complete response (pCR) rates with neoadjuvant TKI monotherapy are below 10-15 %. We know that pCR with chemotherapy alone or plus immunotherapy is associated with disease-free survival benefit. Therefore, I am not completely sure that TKI monotherapy in the neoadjuvant setting will be strong enough to achieve high pCR rates.

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What can we achieve today with targeted agents in patients with oncogene-driven lung cancer who develop brain metastases?

This a very relevant clinical question, because we know that oncogenic-driven NSCLCs have a higher incidence of brain metastases than the wildtype tumors, and approximately 30 % of patients with oncogenic-driven NSCLC show brain metastases at baseline. Very potent next-generation TKIs with good brain penetration are available today. For patients with baseline brain metastasis, even for those that are minimally symptomatic, these targeted agents should be the standard of care. With this strategy, we can defer the use of radiotherapy that may have delayed cognitive side effects. Indeed, starting with a next-generation TKI, especially in *EGFR*- or *ALK*-positive tumors, does not negatively impact the outcome of these patients, allowing to defer the radiotherapy strategy in case of progression.

Which other treatment approaches are deemed promising in patients with CNS affliction whose tumors do not harbor genetic drivers?

Patients with baseline brain metastases and without oncogenic drivers have mostly been excluded from trials testing checkpoint inhibitors as monotherapy or in combination with chemotherapy. However, today we have data from different clinical trials, especially with combinations of chemotherapy and immunotherapy, showing that patients with previously treated and asymptomatic brain metastases who receive immunotherapy and chemotherapy obtain the same magnitude of benefit as those without brain metastases. In the phase II Atezo-Brain trial conducted by the Spanish Lung Cancer Group, atezolizumab plus chemotherapy showed high intracranial activity in patients with asymptomatic and untreated brain metastases, resulting in an intracranial response rate of 40 % [4]. Thirty-two percent of these patients were alive at 2 years, meaning that even patients with minimally symptomatic and untreated brain metastases may achieve long-term survival benefit when receiving the combination of chemotherapy and immunotherapy. This data must be validated in larger prospective trials.

What are the current challenges in selecting the best immunotherapeutic approach for the individual patient with metastatic NSCLC, and how do you handle them?

One of the most challenging questions is why we do not obtain the same results in daily clinical practice as are reported in clinical trials. The answer is that the population is completely different, with just 30 % of the patients we see in our daily practice mirroring those included in studies. I think that today the best strategy for patient selection is the assessment of the PD-L1 expression in tu-

mors. PD-L1 is the most reliable predictive biomarker. For patients with high PD-L1 expression, immunotherapy as monotherapy is the standard of care. There is a debate if some of these tumors might benefit from the addition of chemotherapy. Perhaps those patients with high tumor volume, even if their tumors highly express PD-L1, could be more suitable to be treated with a combination strategy. The ongoing INSIGNA and PERSEE trials may help to answer this question. However, indirect comparisons of clinical trials testing immunotherapy as monotherapy (KEYNOTE-024) or in combination with chemotherapy (KEYNOTE-189) in tumors with high PD-L1 expression have reported the same median OS of 27 months and the same 3-year OS of 43.7 % [5, 6]. For the other group of tumors with PD-L1 expression below 50 %, any combination strategy regardless of the PD-L1 expression status or histological subtype could be suitable.

What are potential predictive biomarkers for checkpoint inhibitor therapy, as well as pitfalls encountered with their use and ways to optimize their implementation in clinical routine?

Although several predictive biomarkers have been assessed in NSCLC, the PD-L1 expression remains the gold standard. The association between tumor mutational burden in the blood and the efficacy of atezolizumab was tested prospectively in the BFAST trial. However, high tumor mutational burden was not a strong predictive biomarker for the selection of patients who benefited from atezolizumab compared with chemotherapy [7]. Today, we can only say that PD-L1 remains the standard of care. Probably the most important point for which predictive biomarkers could be relevant is the identification of patients who might develop more pronounced toxicity or a higher risk of early progressive disease on immunotherapy. To my mind, this is the more relevant challenge in our daily clinical practice, as well as the best therapeutic approach at progression under immunotherapy. ■

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Expert interviews at ELCC 2022

Jarushka Naidoo depicts recent developments in the first-line therapy of limited-stage small cell lung cancer (SCLC), treatment options for patients with newly diagnosed extensive-stage SCLC, agents emerging for the management of patients with platinum-refractory disease, the molecular types of SCLC and how they respond to targeted therapies and ICIs and gives an overview of the greatest difficulties in the field of irAEs.

Jordi Remón outlines what needs to be considered in the context of neoadjuvant and adjuvant immunotherapy in patients with resectable lung cancer, how TKIs can contribute to effective perioperative treatment and talks about treatment approaches in patients with or without oncogene-driven lung cancer who develop brain metastases. Current challenges in selecting the best immunotherapeutic approach for the individual patient with mNSCLC and promising potential predictive biomarkers of ICI in patients with NSCLC are highlighted, too.

Lizza Hendriks discusses how clinical trials should be adapted considering the increasing use of brain metastasis screening in lung cancer patients, the immune micro-environment of CNS metastases, the role of the treatment sequence in the management of patients with brain lesions and summarizes how patients with low PD-L1 expression, frail/elderly patients and those with actionable mutations can be addressed, followed by depicting novel biomarkers for precision immunotherapy.

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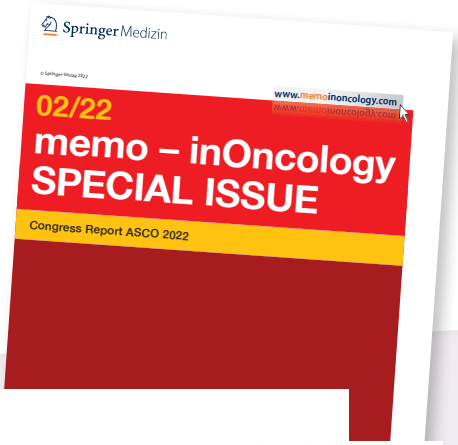

Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2022 that will be held in June 2022. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to lung cancer treatment and care. Stay tuned for the latest news in oncology and its subspecialties.

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