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Congress Report ASCO 2022

A GLOBAL CONGRESS DIGEST ON LUNG CANCER

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Preface

Dear Colleagues,

After 2 years of virtual meetings in the midst of the COVID-19 pandemic, the Annual Meeting of the American Society of Clinical Oncology (ASCO) returned to its live format, as oncology experts from around the world gathered again in Chicago, USA, and virtually from 3rd–7th June 2022, to discuss the most exciting updates in the field of lung cancer.

As always, "discoveries are nice, but validation is what moves science forward" – and we have seen significant forward progress in the area of resectable stage IIIA-B non-small-cell lung cancer (NSCLC), with a proof-of-concept study (NADIM I), confirmation of these findings in CheckMate 816, and data from NADIM II validating the superiority of neoadjuvant nivolumab plus chemotherapy in this setting. For unresectable stage III NSCLC, there has also been notable recent progress. After decades of failed attempts to improve on combination chemotherapy and radiation for unresectable stage III NSCLC, the incorporation of immunotherapy in the PACIFIC study has prolonged overall survival. Other strategies are also under investigation, exemplified by the encouraging results in the updated two-year follow-up of KEYNOTE-799.

An entire chapter is devoted to new ways to further improve patient outcomes by targeting $KRAS^{G12C}$, METex14, EGFR and ALK. For patients who do not harbor genomic alterations, various first-line regimens consisting of anti-PD-(L)1 antibodies with or without chemotherapy have been approved. Deeper insights into combinations of immune checkpoint inhibitors with other drug classes, e.g. the soluble LAG-3 protein eftilagimod alpha or the multikinase inhibitor cabozanitinib, are outlined due to their early clinical activity. Moreover, synergistic benefits of immunotherapy plus an anti-VEGFR-2 antibody in the immune checkpoint inhibitor-refractory setting of patients with stage IV or recurrent NSCLC who had received prior immunotherapy were explored in the S1800A substudy of Lung-MAP, which is a US-wide precision medicine master protocol. This randomized phase II study showed an impressive improvement in overall survival and will likely lead to further study.

Last but not least, this issue looks closely at patients with extensive-stage small-cell lung cancer where negative data of the SKYSCRAPER-02 trial investigating the addition of an anti-TIGIT agent to chemoimmunotherapy were presented at ASCO 2022. We did, however, see further evidence of the benefit observed with adding immunotherapy to chemotherapy. The phase III ASTRUM-005 study showed that the addition of the anti-PD-1 antibody serplulimab to standard chemotherapy improved overall survival compared to chemotherapy in the first-line setting.


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Once again, the ASCO Congress highlighted the importance of multidisciplinarity and collaborations for accelerating future cancer care – establishing new standards of care with an eye to even better outcomes in the very near future.

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Early-stage NSCLC: perioperative strategies and approaches in the unresectable

Neoadjuvant chemotherapy has been shown to significantly prolong overall survival (OS) in resectable non–small-cell lung cancer (NSCLC), although the absolute 5-year survival is improved by as little as 5 % [1]. Similarly, pathological complete responses (pCR) are infrequently achieved; 15 trials investigating preoperative chemotherapy revealed an overall median rate of 4 % [2]. A promising approach to enhance treatment success involves the addition of immunotherapy to platinum-based neoadjuvant chemotherapy. The phase III CheckMate 816 study assessing nivolumab plus chemotherapy compared to chemotherapy alone revealed significant benefits regarding pCR (24.0 % vs. 2.2 %; $p < 0.001$) and event-free survival (EFS; 31.6 vs. 20.8 months; $p = 0.005$) in patients with stage IB-IIIA NSCLC [3].

NADIM II

In the setting of potentially resectable stage IIIA-B disease, the randomized, open-label, phase II NADIM II trial confirmed the superiority of neoadjuvant nivolumab plus chemotherapy. Patients in the experimental arm (n = 57) received nivolumab 360 mg in addition to paclitaxel and carboplatin for 3 cycles, while those in the control arm (n = 29) were treated with chemotherapy alone. After surgery, adjuvant nivolumab 480 mg Q4W was administered for 6 months in the experimental arm. The control patients were observed only. At ASCO 2022, Provencio et al. reported the primary endpoint results of pCR and other outcomes [4].

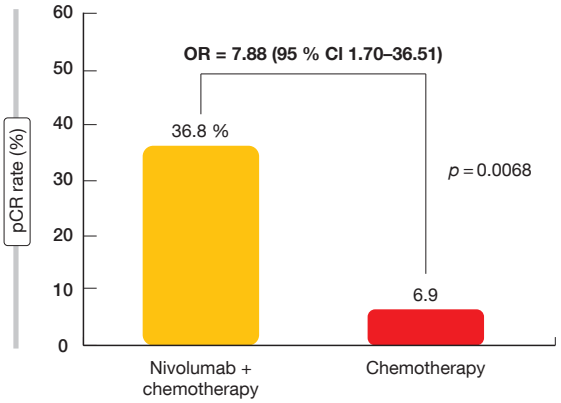

Figure 1: Superior pCR rate with neoadjuvant nivolumab plus chemotherapy vs. chemotherapy in NADIM II

Indeed, the pCR was significantly increased with immunochemotherapy (36.8 % vs. 6.9 %; OR, 7.88; p = 0.0068; **Figure 1**), which translated into a number needed to treat of 3.34. Similarly, the combined approach induced significant benefits regarding the major pathological response (MPR) rate (52.6 % vs. 13.8 %; OR, 6.94; p = 0.0012) and the overall response rate (ORR; 75.4 % vs. 48.2 %; OR, 3.29; p = 0.023). The addition of nivolumab did not impede the feasibility of surgery; on the contrary, definitive surgery was significantly more common in the experimental arm (93.0 % vs. 69.0 %; OR, 5.96; p = 0.00807).

Despite the addition of the PD-L1 inhibitor, a tolerable safety profile was maintained, with a moderate increase in grade 3/4 adverse events (AEs; 25 % vs. 10.3 %). Grade 4 events occurred only in 2 patients in the experimental arm. None of the study participants died due to AEs. The PD-L1 tumor proportion score (TPS) was shown to have a significant predictive value for pCR, with pCR rates rising across increasing TPS categories (p = 0.014).

pCR correlates with EFS in CheckMate 816

While studies have shown an association of pathological response and survival with neoadjuvant chemotherapy in resectable NSCLC and other cancers [2, 5, 6], a similar correlation with neoadjuvant immunotherapy has not been rigorously studied. At ASCO 2022, Provencio-Pulla et al. presented a post-hoc analysis on the association between pathological regression and EFS in patients who underwent surgery in CheckMate 816 and had pathologically evaluable samples (i.e., the path-evaluable population) [7]. EFS was assessed according to pCR or MPR in the primary tumor, as well as by depth of pathological regression, measured by percentage of residual viable tumor (RVT) in the primary tumor. The path-evaluable population group included 141 and 126 patients in the experimental and control arms, respectively. This analysis provides the first in-depth assessment of pathological regression and EFS in a phase III trial with neoadjuvant immunotherapy.

EFS was improved with both nivolumab/chemotherapy and chemotherapy in patients with pCR or MPR in the primary tumor relative to those without. In the combination arm, EFS improvement in patients who had pCR was achieved regardless of baseline stage of disease or tumor PD-L1 expression. No corresponding subgroup analyses were conducted for the chemotherapy-only arm due to small sample sizes. Nivolumab-treated patients with deeper pathological regression in the primary tumor appeared to have better EFS outcomes at 2 years, with the RVT reduction as a continuous variable being predictive of 2-year EFS. This did not apply to the chemotherapy-only arm.

In the path-evaluable population, the incidence of treatment-related AEs in the combination arm was similar in patients with or without pCR/MPR. This finding was consistent with the observation in all treated patients. Overall, these results from CheckMate 816, along with previously reported data, continue to support pathological response as an early indicator of EFS benefit with neoadjuvant nivolumab plus chemotherapy.

Neoadjuvant CRT compared to CT

Stage III NSCLC is a heterogeneous disease, making this subgroup of patients a challenging population. Stage III N2, which is characterized by ipsilateral mediastinal or subcarinal lymph node metastasis, represents the most advanced stage that still allows for a curative approach. If the disease is deemed resectable, neoadjuvant chemoradiotherapy (CRT) or chemotherapy (CT) precedes surgery, with the main goal of CRT being mediastinal downstaging from N2 to N1 or N0.

Several clinical trials have demonstrated no added benefit of radiotherapy to neoadjuvant CT in early-stage disease [8-12]. In view of these observations, a real-world study was conducted based on the SEER database to identify patients with stage III N2 M0 disease who had received either CRT or CT prior to surgery from 2004 to 2015 [13]. The researchers obtained data for 1,175 patients, with 799 (68.0 %) and 376 (32.0 %) having been treated with CRT and CT, respectively. OS and cancer-specific survival (CSS) constituted the primary outcomes. This is the largest retrospective cohort in this field to date and the first study to address CSS.

Overall, the findings indicated no survival benefit of adding RT to CT in the neoadjuvant setting in N2 disease. The OS rates at 1 year, 3 years, and 5 years were almost identical for CRT vs. CT, and the median OS differed only by 4 months in favor of CRT **(Table 1)**. For CSS, the results were similar despite a higher difference regarding median CSS. Nevertheless, neither endpoint showed statistically significant superiority of the combined approach. This also applied to the multivariate analysis and the inverse probability treatment weighting analysis conducted to eliminate the effect of the non-randomization bias. Significant prognostic factors for adverse OS and CSS were higher T stage, non-squamous histology, higher lymph node ratio, tumor location in the lower lobes, and pneumonectomy. The authors concluded that the combined treatment could be more harmful than useful. They recommended comparing CSS in stage IIIB disease, the assessment of different types of N2 disease, and consideration of chemoimmunotherapy modalities in neoadjuvant settings.

TABLE 1
No significant differences in overall survival and cancer-specific survival between chemoradiotherapy and chemotherapy

	Overall survival		Cancer-specific survival	
	Chemoradio-therapy	Chemo-therapy	Chemoradio-therapy	Chemo-therapy
At 1 year, %	84.7	83.2	86.6	85.5
At 3 years, %	57.3	57.3	62.3	61.8
At 5 years, %	47.1	44.1	53.8	48.9
Median, months	51	47	75	59

Three vs. 2 neoadjuvant cycles

Clinical trials investigating neoadjuvant chemoimmunotherapy generally used 2-4 cycles [3, 14-16], although there is no consensus regarding the optimal treatment duration. The phase II neoSCORE trial tested 2 cycles vs. 3 cycles of neoadjuvant treatment with the anti-PD-1 antibody sintilimab plus chemotherapy in the setting of resectable stage IB-IIIA NSCLC. Surgery was performed within the 4th week after the last dose and was followed by adjuvant chemotherapy for 1 or 2 cycles and either maintenance treatment with sintilimab for up to 1 year, or follow-up alone. The MPR rate was defined as the primary endpoint. NeoSCORE is the first randomized study comparing different treatment periods of immunochemotherapy in the neoadjuvant setting.

The analysis reported at ASCO 2022 included approximately 30 patients in each treatment arm [17]. Three cycles, as compared to 2, gave rise to a numerically higher MPR rate, translating into a 14.5 % increase (41.4 % vs. 26.9 %; p = 0.260). The absence of statistical significance is potentially due to the narrow cycle difference and the small sample size. Moreover, one additional cycle increased the pCR rate by 4.9 % (24.1 % vs. 19.2 %; p = 0.660) and the radiologically assessed ORR by 5.2 % (55.2 % vs. 50.0 %; p = 0.701). Most subgroups fared better with 3 cycles than with 2, particularly the group with clinical stage IIIA.

According to the assessment by histology, patients with squamous NSCLC achieved impressively higher MPR rates than those with the non-squamous subtype in both treatment arms; these differences were statistically significant for both 3 cycles (60 % vs. 21.4 %; p = 0.035) and 2 cycles (43.8 % vs. 0 %; p = 0.023). Across the arms, the MPR rates amounted to 51.6 % vs. 12.5 % for patients with squamous vs. non-squamous histology (p = 0.002). Similar trends were observed with respect to the pCR rate (29.0 % vs. 12.5 %; p = 0.141) and the ORR (61.3 % vs. 41.7 %; p = 0.148). The PD-L1 expression had modest predictive value for the pathological response, as patients with PD-L1 ≥ 45 % experienced improved tumor responses (p = 0.003 and 0.024 for pathological regression and change from baseline, respectively).

Planned surgery was conducted in 93.5 % vs. 89.7 % of patients in the 3-cycle vs. 2-cycle arms. No increases of surgical risk (e.g., duration of surgery, intraoperative blood loss) or postoperative complications (e.g., recurrent laryngeal nerve paresis, atrial fibrillation, pleural effusion requiring drainage) were observed with 3 treatment cycles. Treatment-related hematological and non-hematological AEs did not increase in the experimental arm. Overall, these data suggest that a higher number of cycles of neoadjuvant chemoimmunotherapy provides an improved MPR rate for patients with resectable NSCLC, especially in the squamous subtype.

Intraoperative quality metrics

Heiden et al. sought to develop a practical surgical quality score for patients who undergo definitive surgical treatment for stage I NSCLC [18]. The modifiable quality metrics used for this purpose have been identified previously and included timely surgery (i.e., surgery within 12 weeks of radiographic NSCLC diagnosis), anatomic resection via lobectomy or segmentectomy, minimally invasive approach using video-assisted thoracoscopic surgery or a robotic approach, adequate nodal sampling (i.e., ≥ 10 lymph nodes according to ACS CoC standards), and negative (R0) surgical margin. Data of 9,628 veterans with clinical stage I NSCLC from the Veterans' Health Administration Corporate Data Warehouse who underwent surgery between 2006 and 2016 were analyzed. The researchers developed a VA Lung Cancer Operative quality (VALCAN-O) score ranging from 0 to 12 points, with the highest scores representing the best surgical quality. After division of the patients into risk categories based on their scores, median OS **(Figure 2)** and recurrence-free survival were demonstrated to differ substantially. These findings were validated in an external cohort of > 100,000 patients from the National Cancer Database (2010-2016). Survival probability again differed between the score categories in a clear-cut manner.

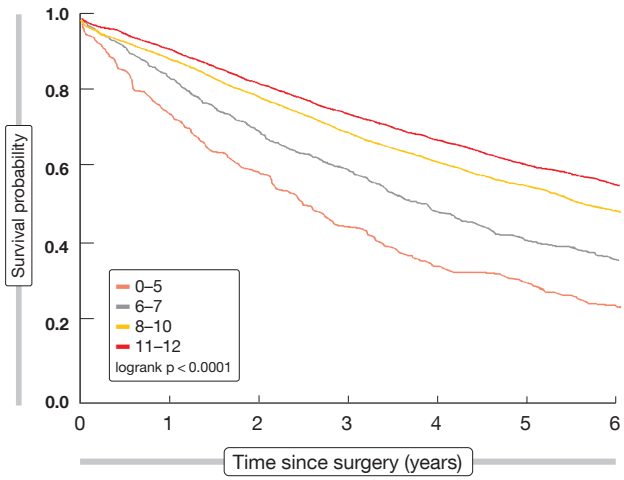

Figure 2: Overall survival outcomes after surgery according to VALCAN-O score categories

Moreover, the researchers assessed geographical trends in surgical quality across the USA from 2006 to 2019. Here, the VALCAN-O scores improved substantially over the study period in most regions; however, significant regional variation was observed even up until 2019, particularly in the Midwest and the Eastern US. Adherence to most of the quality metrics generally improved throughout the study period. Minimally invasive approaches showed a dramatic rise over time. Adequate nodal sampling also increased, while delayed surgery decreased. Conversely, the proportion of lobectomy is decreasing, whereas segmentectomy increased slightly. As the authors noted, adherence to modifiable surgical quality metrics is associated with dramatically improved long-term, cancer-specific outcomes. The VALCAN-O quality score can serve as a benchmark of surgical quality in lung cancer, thereby standardizing and improving outcomes among patients with early-stage lung cancer undergoing curative-intent resection.

Adjuvant pembrolizumab: impact of variables on DFS

The global, randomized, triple-blind, phase III PEARLS/KEYNOTE-091 trial tested pembrolizumab vs. placebo as adjuvant treatment in patients with stage IB (tumor size ≥ 4 cm) to IIIA NSCLC following complete surgical resection with negative margins and, when recommended per local guidelines, adjuvant chemotherapy for ≤ 4 cycles. At the time of the second interim analysis, pembrolizumab treatment significantly improved disease-free survival (DFS) in the overall population (53.6 vs. 42.0 months; HR, 0.76; p = 0.0014) [19]. In the group with PD-L1 TPS ≥ 50 %, the DFS difference did not reach statistical significance (HR, 0.82; p = 0.14). Immature OS data suggested a trend towards improvement in the experimental arm. The analysis of the PEARLS/KEYNOTE-091 study reported at ASCO 2022 explored the potential impact of the type of surgical resection, baseline disease burden, and use of adjuvant chemotherapy on DFS in the overall population [20].

Pembrolizumab was shown to generally improve DFS compared with placebo regardless of the type of surgical resection (bilobectomy, lobectomy or pneumonectomy), degree of lymph node involvement (pN 0, 1, or 2), tumor size (≤ 4 vs. > 4 cm), and type and extent of adjuvant chemotherapy (carboplatin- or cisplatin-based; 1-2 or 3-4 cycles). Together with the overall efficacy and safety findings, these data support the benefit of adjuvant pembrolizumab for stage IB (tumor size ≥ 4 cm) to IIIA NSCLC following complete resection and, if recommended, adjuvant chemotherapy.

Unresectable stage III tumors: KEYNOTE-799

Outcomes for unresectable stage III NSCLC patients remain poor, and new strategies are required. The open-label, non-randomized, global, phase II KEYNOTE-799 study examined the combination of pembrolizumab with concurrent CRT for 3-4 cycles followed by pembrolizumab monotherapy for up to 17 cycles in patients with stage IIIA-C, unresectable, locally advanced, previously untreated NSCLC. Cohort A included 112 patients with squamous and non-squamous NSCLC, while Cohort B contained 102 individuals with non-squamous NSCLC only. The primary analysis of the trial has shown ORRs of 71 % in both cohorts and manageable safety [21]. At ASCO 2022, Reck et al. presented updated outcomes after 1 year of additional follow-up for all enrolled patients [22].

After more than 2 years of follow-up, the treatment continued to demonstrate robust and durable responses, with additional responses observed since the last analysis. ORRs were 71.4 % and 75.5 % in Cohorts A and B, respectively **(Table 2)**. The patients responded regardless of their PD-L1 tumor proportion scores and tumor histology. Median duration of response had not been reached yet in either cohort, which also applied to OS. In Cohort A, 64.3 % of patients were alive at 24 months, and 64.0 % responded to treatment at that time; in Cohort B, 71.2 % lived, and the 24-month response rate was 68.7 %. Median PFS was 30.6 months in Cohort A and had not been reached yet in Cohort B. The 2-year PFS rates amounted to 55.3 % and 60.6 %, respectively. With respect to safety, no new signals emerged with longer follow-up. Grade ≥ 3 pneumonitis occurred in 8.0 % and 6.9 %, respectively. Discontinuation of any treatment component was due to immune-mediated AEs and infusion reactions in 18.8 % and 11.8 %, respectively.

In their summary, the authors noted that pembrolizumab plus concomitant CRT followed by pembrolizumab represents a promising strategy for patients with previously untreated, locally advanced, stage III NSCLC. The ongoing phase III KEYLYNK-012 and KEYVIBE-006 studies are further investigating pembrolizumab in addition to other compounds in unresectable, locally advanced, stage III disease.

TABLE 2
KEYNOTE-799: responses to pembrolizumab plus chemoradiotherapy in unresectable stage III NSCLC

Subgroup	Overall response rate (%)	
	Cohort A (n = 112)	Cohort B (n = 102)
Overall population	71.4	75.5
Age		
< 65 years	75.5	74.1
≥ 65 years	68.3	77.1
Sex		
Female	75.0	75.0
Male	69.7	75.8
Histology		
Squamous	72.0	Not applicable
Non-squamous	70.3	75.5
PD-L1 TPS		
< 1 %	66.7	78.6
≥ 1 %	77.3	72.5

Consolidation with nivo or nivo/ipi

The open-label, randomized, non-comparative phase II BTCRC LUN 16-081 study evaluated consolidation therapy with single-agent nivolumab 480 mg Q4W for up to 6 cycles (Arm 1; n = 54) or nivolumab 240 mg Q2W plus ipilimumab 1 mg/kg Q6W for up to 4 cycles (Arm 2; n = 51) following concurrent CRT in patients with unresectable stage IIIA or IIIB NSCLC [23]. The patients had achieved at least stable disease following chemoradiation. Improvement of the 18-month PFS rate compared to historical controls was defined as the primary endpoint.

At 18 months, PFS was obtained by 63.7 % and 67.6 % of patients in Arms 1 and 2, respectively, with median PFS amounting to 25.8 and 25.4 months, respectively. Compared to the historical controls of CRT alone (Arm A) and CRT followed by durvalumab (Arm B), the 18-month PFS rates were significantly improved. Median OS had not been reached for either arm yet. At 24 months, 77.7 % and 80.6 % of patients were alive. The authors noted that both arms demonstrated promising PFS and OS despite the limited 6-month duration of consolidation therapy. Compared to nivolumab monotherapy, nivolumab/ipilimumab gave rise to higher rates of pneumonitis (grade ≥ 2, 31.4 % vs. 22.2 %; grade 3, 17.6 % vs. 9.3 %), although no grade 4/5 events were observed. Any grade ≥ 3 treatment-related AEs occurred in 27.5 % vs. 18.5 %. ■

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Interview with Jessica Donington, MD, MSCR, Section Thoracic Surgery, The University of Chicago Medicine, Chicago, USA

The clinical care pathways in early-stage lung cancer are changing

Which agents that are currently being investigated in the neoadjuvant setting in patients with resectable NSCLC look promising from the present point of view?

Many immunotherapies are being studied in the neoadjuvant or perioperative setting, but the only one that has been reported in a phase III trial as neoadjuvant treatment to date is nivolumab. There are three prospective trials that assessed nivolumab in the resectable setting. The NADIM I trial was a groundbreaking phase II study that looked at nivolumab plus chemotherapy followed by resection and demonstrated impressive results regarding pathologic endpoints and two-year survival [1]. It was followed by the first phase III trial evaluating chemoimmunotherapy, the CheckMate 816 study. The addition of nivolumab to 3 cycles of chemotherapy led to dramatic improvements in the pathologic complete response (pCR) rate, major pathologic response rate, and event-free survival [2]. Key surgical outcome data from CheckMate 816 that were presented at last year's ASCO Congress were important, as this treatment needs to be demonstrated to be safe with respect to surgery [3]. The findings reported by Dr. Spicer gave us the impression that nivolumab plus chemotherapy can indeed be administered safely, with no increased morbidity or mortality compared to induction chemotherapy alone.

The final bit of prospective data that was presented this year at ASCO was the randomized phase II NADIM II trial. It included approximately 100 patients randomized to either 3 cycles of paclitaxel/carboplatin or paclitaxel/carboplatin plus nivolumab. The pCR rate was significantly improved with the addition of nivolumab [4]. Across these three trials, the pathologic results line up very nicely **(Figure)**. I think it is important that we now have three trials conducted in a prospective setting all of which used similar induction agents, obtained similar pathologic response rates and had similar short-term surgical outcomes. Now we are waiting for the survival data.

Another nice aspect of these trials was that PD-L1 staining in the tumor seemed to be predictive in all three trials. There was some increase in the pCR rate compared to chemotherapy alone in PD-L1–negative patients, but the rates were definitely higher in the PD-L1–positive population and even higher in the PD-L1–high expressors. It is nice to see a biomarker that behaves consistently in this setting.

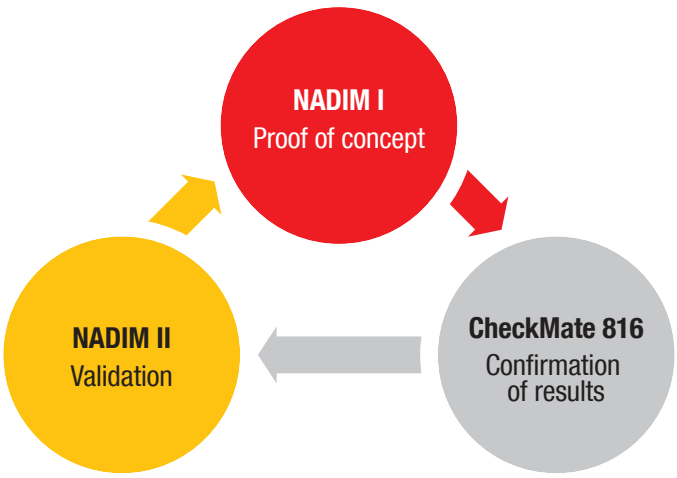

Figure: Proof-of-concept and further validation of neoadjuvant chemotherapy plus nivolumab

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How does the intensity of neoadjuvant treatment affect patient outcomes?

I do not know if "intensity" is the right word when talking about neoadjuvant treatment. We think that the effect of neoadjuvant chemotherapy or radiation therapy may depend on the number of cycles or the dose. Adding radiation to chemotherapy is known to produce higher pCR rates, which can be further increased by augmented radiation doses or additional doses of chemotherapy. In this new treatment paradigm with immunotherapy, which is a whole new class of agents, nobody actually knows how many doses need to be given.

The randomized phase III neoSCORE trial conducted at a single institution in China assessed if the number of neoadjuvant chemotherapy cycles (i.e., 2 vs. 3) matters [5]. Unfortunately, the study was closed early, but the findings indicated improved pCR rates with 3 cycles, although one can question if it is the additional dose or simply the additional time from initiation of therapy that affect the pCR rate. We believe that these medications retrain the immune system and therefore may continue to work long after the resection has been performed. Therefore, it is hard to know how many doses should be administered. While we use pathologic endpoints to guide some of our decisions, this is a new class of medications, and pCR may not be the only indicator for overall response. Nevertheless, we are starting to question how

many is enough. The upcoming series of worldwide trials evaluating perioperative chemoimmunotherapies that are administered in the neoadjuvant and adjuvant settings and will likely raise a new set of questions, including how much is enough.

Is neoadjuvant chemoimmunotherapy the new standard of care?

For N2-positive IIIA disease, I would say that neoadjuvant chemoimmunotherapy is absolutely the standard of care based on the results from CheckMate 816, and the safety data. The early pathologic responses are really impressive and are something we have never seen before. The pCR rate is one of the best predictive markers and we also now have evidence for improved event-free survival. So for N2 disease where outcomes are poor, this seems like a real improvement. Should it also be the standard of care for patients with N1 disease? I would think yes. In patients with resected N1 disease, the risk of recurrence is high, and I have always favored an induction pathway. I think having the primary tumor in place may help prime the immune system. Until we know otherwise, I think this hypothesis makes sense, because the science behind it looks good.

The more challenging question is, should it be standard of care in node-negative patients? There are node-negative patients with large primary tumors who meet the staging requirements to receive induction therapy. This is a major change in the way we deal with these patients. A patient may have a 4.5 cm peripheral tumor without nodal disease according to staging of the mediastinum. The standard approach for this patient has been upfront resection. A surgeon may see the patient on Tuesday, operate on Thursday, and the patient is home before Monday. Surgeons and patients both like this. The induction immunotherapy approach requires waiting for the biopsy results to rule out *EGFR* and *ALK* aberrations, which is followed by 9-12 weeks of therapy prior to resection. This represents a real change in the clinical care pathway and is especially difficult for surgeons with the approval of immunotherapy in the adjuvant setting. If data emerge in the next couple of years that show better survival with induction compared to an adjuvant approach, we will adapt our paradigm. But I think that changing care in patients with IB and II disease who are node-negative will be harder due to added steps than changing the care we provide for patients with IIIA or even IIB disease.

Which variables related to surgery itself are determinants of the success of curative surgery?

Twenty or 30 years ago, curative surgery meant removing the tumor with the patient staying alive. This is no longer enough, and many of the metrics that define a good operation are being refined. The increasing use of systemic therapy in earlier stages puts pressure on the surgeons to make their procedures as well tolerated as possible. In order for a patient to go on to adjuvant therapy within 4 weeks, the procedures need to go well and the patient needs to recover quickly. The Washington University group presented a great analysis at the ASCO Congress that assessed intraoperative quality metrics using very large databases [6]. Not surprisingly, the most important quality factor was R0 resection. If we leave tumor in the chest, we are doing our patients a disservice. Also, adequate nodal sampling is important. What qualifies as such is subject to constantly changing definitions, although thresholds of > 10 nodes or > 4 stations appear acceptable. Moreover, anatomic resections make a big difference.

These might be the most important metrics, next to timely and minimally invasive surgery. All of us need to work on our care pathways to make sure that patients move quickly from diagnosis to treatment. I always sit down with my patients prior to surgery and explain my priorities for each of them depending on age and fitness. Number 1 is of course not to put the patient's life at risk. The next priority is to do a good oncologic operation and other priorities include saving lung tissue and keeping the procedure minimally invasive. These are the kind of quality discussions surgeons should have all the time. I think our quality metrics are going to become more important as we move into the era of effective adjuvant and neoadjuvant therapies.

Which biomarkers to guide therapy are currently on the rise?

At present, we are still struggling with biomarkers in lung cancer. PD-L1 expression has been in use, but we just saw data from the PEARLS/KEYNOTE-091 trial showing that the PD-L1 expression was not really helpful in predicting disease-free survival [7]. This was a little disconcerting. Many resected tumors undergo full genomic analysis, and we keep looking at things like *STK-11* mutations in our attempt to identify a better biomarker out there. At the moment, tumor mutational burden does not quite appear to be the ideal marker, either. I think that new technologies like cell-free DNA are incredibly important. We have not been able to use this in early-stage lung cancer yet, because the platforms are not sensitive or reliable enough for patients without bulky stage III or stage IV disease, but this technology is advancing very quickly. I think that within the next 3 to 5 years, it will be good enough to give us an opportunity to escalate care in patients with earlier-stage lung cancer. ■

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Targeting KRAS^{G12C}, METex14, EGFR & ALK: new ways to further improve patient outcomes

KRYSTAL-1: adagrasib in *KRAS*^{G12C}-mutated tumors

KRAS^{G12C} mutations are found in approximately 14 % of patients with adenocarcinoma of the lung [1]. Adagrasib, a covalent inhibitor of KRAS^{G12C}, has been developed to show a long half-life of 23 hours, dose-dependent pharmacokinetics, and CNS penetration [2, 3]. At ASCO 2020, Spira et al. reported data from a registrational phase II cohort of 116 patients with unresectable or metastatic, *KRAS*^{G12C}-mutated NSCLC included in the multi-cohort, phase I/II KRYSTAL-1 study [4]. These patients received adagrasib 600 mg BID after pretreatment with a PD-(L)1 inhibitor in combination or in sequence with chemotherapy. Their median number of prior lines was 2, with 22 % having received ≥ 3 lines. The overall response rate (ORR) constituted the primary endpoint.

Adagrasib demonstrated promising activity. The ORR amounted to 43 %, and 80 % of patients achieved disease control. Seventeen individuals were not evaluable due to having received post-baseline scans too early or study withdrawal prior to the first scheduled assessment; after elimination of their data, the ORR was 51 %. Responses were deep, with 75 % of responders achieving tumor reductions of > 50 %. The median time to response was 1.4 months, and responses lasted for a median of 8.5 months. At the time of data cutoff, treatment was ongoing in half of responders, with 33 % still responding. Median PFS and OS were 6.5 and 12.6 months, respectively. At 12 months, 51 % of patients lived, and 29 % were progression-free.

Pre-specified correlative analyses of co-mutations showed that response rates did not vary to a noticeable degree according to the presence of *STK11*, *KEAP1*, *TP53*, or *CDKN2A* mutations. Only patients who had *STK11* wildtype plus *KEAP1* mutation in addition to their *KRAS*^{G12C} mutation showed substantially reduced responses **(Figure 1)**. The PD-L1 expression did not affect the outcomes.

Adagrasib demonstrated a manageable safety profile, with AEs being mainly grade 1 and 2. Treatment-related AEs (TRAEs) led to dose reductions and dose interruptions in 52 % and 61 %, respectively. Only 7 % of patients discontinued treatment due to TRAEs. Two grade 5 events occurred, which were cardiac failure and pulmonary hemorrhage.

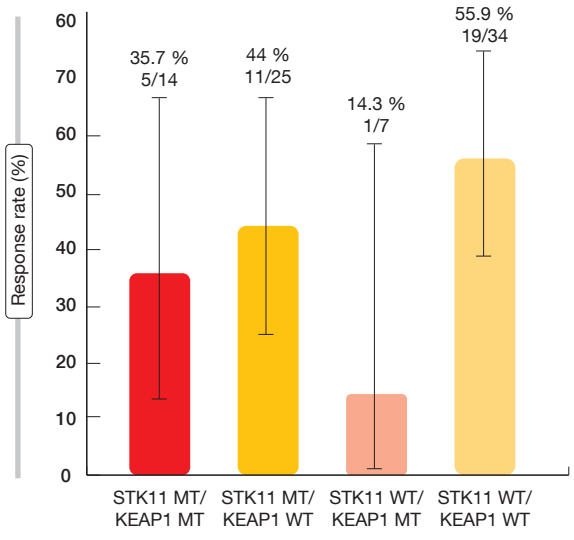

Figure 1: KRYSTAL-1: effect of the *STK11/KEAP1* mutation status on responses to adagrasib in pretreated patients with *KRAS*^{G12C}-mutant NSCLC

CNS activity of adagrasib

Brain metastases are common in the setting of *KRAS*-mutant NSCLC and are associated with poor prognosis [5]. Patients with adequately treated, stable CNS lesions were allowed to enroll in the phase II cohort of the KRYSTAL-1 trial. Among these, 19 and 13 had non-target lesions only and target lesions, respectively. Overall, the intracranial ORR amounted to 33 %; complete intracranial remission occurred in 15 %, partial remission in 18 %, and disease stabilization in 52 %, which added up to an intracranial disease control rate of 85 %. The patients showed a median intracranial duration of response of 11.2 months and a median intracranial PFS of 5.4 months. In the group with target lesions at baseline, the intracranial ORR was as high as 54 %.

The phase IB of the KRYSTAL-1 study included patients with active, untreated CNS metastases. According to the findings reported by Sabari et al., adagrasib showed encouraging and durable CNS-specific activity in a radiographically evaluable population of 19 individuals [6]. The intracranial ORR achieved in this group was 32 %, with a disease control rate of 84 %. Patients with non-target lesions only (n = 4) responded in 50 %, and those with both target lesions and non-target lesions (n = 15), in 27 %. Median intracranial duration of response had not been reached yet, and median intracranial PFS was 4.2 months. The researchers also assessed the concordance between systemic and intracranial disease control, which was 88 %.

Grade 1/2 TRAEs were observed in 60 % of patients. No grade 4/5 events occurred. Dose reduction/interruption and discontinuation resulted in 48 % and 4 %, respectively. CNS-specific

TRAEs included dizziness (20 %) and grade 1/2 aphasia and insomnia (4 %). The authors stressed that adagrasib is the first *KRAS*^{G12C} inhibitor to demonstrate clinical activity in patients with *KRAS*^{G12C}-mutant NSCLC with treated and untreated CNS metastases. At present, the confirmatory phase III KRYSTAL-12 trial is evaluating adagrasib compared to docetaxel in previously treated patients with *KRAS*^{G12C}-mutated NSCLC (NCT04685135).

Amivantamab in *MET*ex14-positive disease

Approximately 3 % of NSCLCs harbor *MET* exon 14 (*MET*ex14) skipping mutations that lead to constitutive activation of the MET pathway [7, 8]. Amivantamab, a EGFR-MET bispecific antibody, is currently being evaluated in primary MET-driven tumors. The phase I CHRYSALIS study has established amivantamab 1,050 mg and 1,400 mg in patients with < 80 kg and ≥ 80 kg body weight, respectively, as the recommended phase II dose. In the dose expansion part of the trial, the safety and efficacy of amivantamab was tested in patients with *MET*ex14 skipping mutation. Among 55 individuals whose data were presented at ASCO 2022, 9 were treatment-naïve, while no prior MET inhibitor therapy had been administered in 18 cases and 28 patients had previously received MET inhibition [9]. In the MET-inhibitor–pretreated group, the median number of prior lines was 3 (range, 1-10), and 25 % had a history of brain metastases.

A total of 46 patients were efficacy-evaluable, demonstrating an ORR of 33 %. The treatment-naïve cohort showed the highest ORR of 57 %, followed by the patients who had received no prior MET inhibitor therapy (47 %). In the MET-inhibitor–pretreated group, only 17 % responded. The clinical benefit rates were 59 % overall and 71 %, 53 % and 58 % for the treatment-naïve, MET-naïve and MET-pretreated, respectively. Over time, amivantamab therapy gave rise to durable responses. Median duration of response had not been reached yet. Eleven of the 15 responders remained on treatment, and the patient with the longest response was still receiving amivantamab at 76 weeks. Median PFS was 6.7 months in the entire group. In the treatment-naïve cohort, median PFS had not been reached yet, and for the other two groups, it was 8.3 and 4.2 months.

The safety profile of amivantamab in the *MET*ex14-positive patient cohort was consistent with the larger CHRYSALIS safety population. Most AEs were grade 1 or 2, with a low discontinuation rate of 5 %. Pneumonitis/ILD emerged in 4 %. Rash-related events were observed in 76 % and were mainly low-grade. According to the authors, these preliminary results suggest that the monotherapy activity of amivantamab in patients with primary *MET*ex14-positive NSCLC is consistent with that of approved MET tyrosine kinase inhibitors (TKIs). The findings confirmed the independent, targeting action of each arm of the bispecific agent. Enrollment in the *MET*ex14-mutated cohort of the CHRYSALIS study is ongoing.

CHRYSALIS II: amivantamab plus lazertinib

The CHRYSALIS-2 study is exploring the combination of amivantamab with the highly selective, third-generation EGFR TKI lazertinib that is CNS-active and effective against both activating *EGFR* mutations and the resistance mutation T790M [10, 11]. Shu et al. presented the data after full enrollment of Cohort A, which comprised 162 patients with *EGFR*-mutant NSCLC who had progressed on osimertinib and platinum-based chemotherapy [12]. Their median number of prior therapy lines was 3 (range, 2-14). Twenty-eight percent had received ≥ 4 lines. Most had initially been treated with a first- or second-generation EGFR TKI followed by osimertinib and platinum-based chemotherapy (42 %). Brain metastases were present at baseline in 41 %.

According to blinded independent review, 33 % of patients responded to the combined treatment, with responses lasting for a median of 9.6 months **(Table)**. The clinical benefit rate was 57 %. When viewed by prior therapy, patients who had received osimertinib followed by chemotherapy showed a 21 % ORR, while those after the EGFR TKI/osimertinib/chemotherapy sequence responded in 36 %. Heavily pretreated patients and those treated out of sequence had an ORR of 39 %. At the time of clinical cutoff, 30 of 54 responders remained on treatment; in 27 of these, the response duration was ≥ 6 months. For 69 patients with stable disease as best response, 8 remained on treatment, and disease stabilization had been present for ≥ 6 months in 15 individuals. Median OS and PFS amounted to 14.8 and 5.1 months, respectively. A retrospective, exploratory CNS analysis among 27 patients with untreated baseline brain metastasis who had com-

TABLE 1
CHRYSALIS-2: responses obtained with amivantamab plus lazertinib

Response according to blinded independent review	n = 162
ORR	33 %
Median duration of response	9.6 months
Best response, n (%)	
Complete response	2 (1)
Partial response	52 (32)
Unconfirmed partial response	1 (0.6)
Stable disease	69 (43)
Progressive disease	28 (17)
Not estimable	10 (6)
Clinical benefit rate	57 %

pleted ≥1 post-baseline brain scan yielded complete clearance in 26%. In the remaining 74%, neither clearance nor progression occurred.

The safety profile of amivantamab plus lazertinib was consistent with prior reports. Pneumonitis/ILD was observed in 7% of patients, with 4% rated as grade ≥3, although no grade 5 events occurred. Eighty percent developed cumulative rash-related AEs (grade ≥3, 10%). Most AEs were grade 1/2. AEs necessitated dose interruptions, reductions, and discontinuations of both amivantamab and lazertinib in 35%, 9%, and 7%, respectively.

As the scientists noted, the combination evoked clinically significant and durable antitumor activity without biomarker selection in a population that had exhausted the standard of care and included heavily pretreated patients. The effects were comparable to those previously reported in a post-osimertinib, chemotherapy-naïve population [13]. This suggests that intervening chemotherapy does not impact the activity of the amivantamab/lazertinib regimen. The CHRYSALIS-2 study is ongoing, as well as the randomized phase III MARIPOSA trial (amivantamab plus lazertinib in the frontline setting) and the MARIPOSA-2 trial (amivantamab, lazertinib, carboplatin and pemetrexed after osimertinib).

Inhibition of *EGFR* ex20ins mutations with CLN-081

EGFR exon 20 insertion (ex20ins) mutations are found in approximately 2-3% of all NSCLC cases [14] and are indicative of a poorer prognosis compared to tumors with more common *EGFR* mutations [15]. As the therapeutic window between wildtype *EGFR* und *EGFR* ex20ins is narrow, agents currently approved for the treatment of these patients carry significant toxicity. Safer and more effective novel therapies remain an unmet medical need.

CLN-081 is an irreversible, oral EGFR inhibitor with broad-spectrum activity against *EGFR* mutations that shows selectivity for the inhibition of *EGFR* ex20ins mutant vs. wildtype *EGFR* [16, 17]. A phase I/II, dose-escalation, dose-expansion study is currently assessing CLN-081 in patients with recurrent or metastatic, EGFR ex20ins-mutant NSCLC. Yu et al. reported the results for 73 patients who were enrolled across doses ranging from 30 to 150 mg BID [18]. This was a heavily pretreated population, with 66% having received ≥2 prior lines of therapy. Previous EGFR TKI treatment had been administered in 36%, including 3 patients (4%) who had received the EGFR ex20ins-targeting agents poziotinib and/or mobocertinib.

Enrollment at CLN-081 150 mg BID was discontinued after 11 patients based on toxicity. At doses <150 mg, the safety profile proved amenable for long-term treatment, with most AEs being grade 1/2 and an absence of grade ≥3 rash or diarrhea. Dose reductions and discontinuations were uncommon at doses <150 mg BID. Treatment-emergent pneumonitis occurred in 4 patients, but these cases were asymptomatic or confounded by comorbid medical illness. The pharmacokinetic profile was consistent with the clinical safety profile at 100 mg vs. 150 mg BID dose levels. For 8 hours post dose, a sustained pharmacokinetic exposure over GI_{50} for ex20ins *EGFR* was shown, while for wildtype *EGFR*, the exposure time over GI_{50} was limited at doses <150 mg BID.

Across dose levels, 38.4% of patients achieved confirmed partial response, with the highest rate of 41% observed in the 100 mg BID cohort. Stable disease resulted in 56.4% in this group, and the median duration of response was >21 months. Median PFS ranged from 8 months for the ≤65 mg BID dose to 12 months for the 100 mg BID dose. Three patients entered the study with CNS target lesions at baseline. One of them achieved both an intracranial and systemic response at cycle 6 and remains in partial response at cycle 16, while another continues on treatment after 1 year with stable disease both intracranially and systemically. Enrollment in the phase IIB portion of the study is planned for the second half of 2022. Moreover, studies in patients with active CNS metastases and those who have relapsed after prior EGFR ex20ins-targeted therapies are planned.

ALTA-1L: greater quality of response with brigatinib

The ALK inhibitor brigatinib has been approved for the first-line treatment of patients with locally advanced or metastatic ALK-positive NSCLC based on the open-label, randomized, phase III ALTA-1L study that compared brigatinib with crizotinib in patients after ≤1 prior systemic treatment line. An exploratory analysis of the trial data assessed the association of the depth of target lesion response to brigatinib with the outcomes [19]. This showed that the proportion of patients with the highest target lesion shrinkage of 76% to 100% was considerably larger in the brigatinib arm, where it represented the majority of patients (56%), than in the crizotinib arm (34%). The difference between brigatinib and crizotinib was significant according to Cochran-Armitage trend

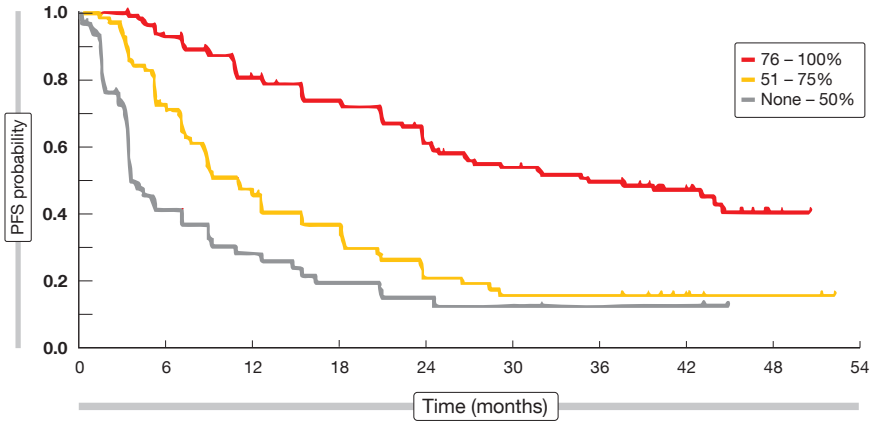

Figure 2: ALTA-L1: progression-free survival according to best target lesion shrinkage (pooled analysis for brigatinib and crizotinib)

analysis ($p < 0.0001$) and Chi-square analysis ($p = 0.0005$). Median time to the deepest target lesion regression in confirmed responders was 14.6 and 7.4 months with brigatinib and crizotinib, respectively.

The researchers established a correlation between the depth of response and PFS. Across treatments, median PFS was shortest (i.e., 3.9 months) in the group with a maximum target lesion shrinkage of 50 % and longest (i.e., 35.5 months) in those with 76 % to 100 % shrinkage **(Figure 2)**. In the group with 51 % to 75 % shrinkage, median PFS was 11.3 months. Patients with the highest degree of shrinkage had a 3-year PFS rate of 50 %, compared with 13 % and 16 % in the other groups. When viewed by treatment, the median PFS and 3-year PFS rates were numerically better in patients treated with brigatinib than in patients treated with crizotinib in the deepest response groups. Patients with > 75 % shrinkage had a significantly reduced risk of PFS or OS events compared to patients with ≤ 50 % target lesion shrinkage irrespective of treatment. The authors concluded that further evaluation of the relationship between depth of target lesion response and long-term PFS/OS and its potential as an early readout surrogate for prolonged benefit is warranted.

Subsequent therapies after lorlatinib and crizotinib

The third-generation ALK TKI lorlatinib has demonstrated significant improvement in PFS over crizotinib in patients with previously untreated, *ALK*-positive, stage IIIB/IV NSCLC in the ongoing, international, randomized, phase III CROWN study [20, 21]. Median PFS had not been reached with lorlatinib and was 9.3 months with crizotinib (HR, 0.27) [21]. At ASCO 2022, data were reported on the efficacy of subsequent therapies following discontinuation of the ALK TKIs [22]. Sixty-one percent and 8.2 % of patients were still receiving lorlatinib and crizotinib, respectively, at data cutoff.

At least 1 subsequent anticancer treatment had been administered in 22.1 % vs. 70.1 %. ALK TKIs constituted the most commonly used first subsequent anticancer drugs in both arms (63.6 % vs. 93.2 %). Chemotherapy as first subsequent treatment was used in 36.3 % vs. 2.9 %. Median duration of treatment on the first subsequent systemic anticancer therapy was 9.6 vs. 13.3 months.

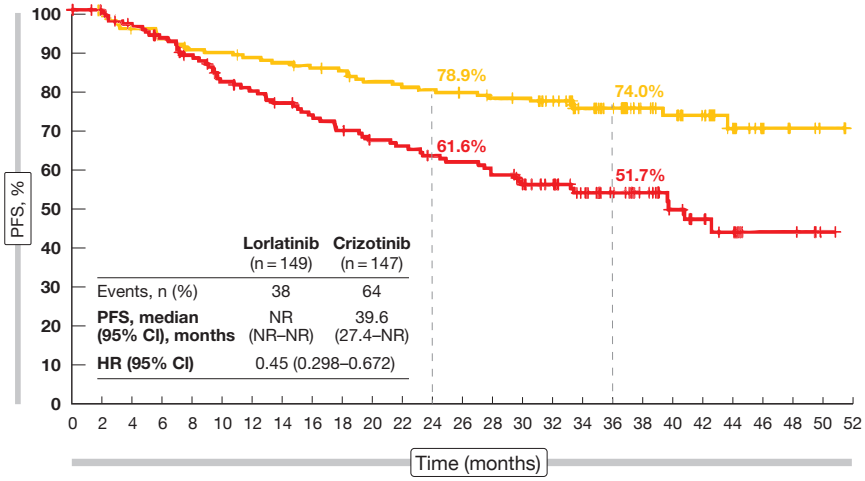

Figure 3: Prolonged PFS2 with lorlatinib compared to crizotinib on subsequent systemic treatment

Subsequent systemic anticancer treatment offered clinical benefits in both arms, with response rates of 24.2 % vs. 15.5 %. Complete responses resulted in 6.1 % vs. 1.0 %, and partial responses in 18.2 % vs. 14.6 %. Moreover, the researchers assessed PFS2, which was defined as the time from randomization to disease progression on the first subsequent systemic anticancer therapy or death due to any cause. According to the PFS2 analysis, the clinical benefit was prolonged following lorlatinib vs. crizotinib and was maintained with subsequent systemic therapies. While median PFS2 had not been reached yet in the lorlatinib arm, it was 39.6 months in the crizotinib arm (HR, 0.45; **Figure 3**). Subsequent systemic therapy is ongoing in 30.3 % and 45.6 % of patients previously treated with lorlatinib and crizotinib, respectively.

ALEK-B: alectinib plus bevacizumab

The combined administration of the ALK TKI alectinib 600 mg BID with the anti-VEGF antibody bevacizumab 15 mg/kg Q3W is being assessed in untreated patients with *ALK*-positive NSCLC in the open-label, phase II ALEK-B trial [23]. Between April 2020 and December 2021, 37 patients were enrolled. After a median follow-up of 19.9 months, median PFS had not been reached yet, and the 24-month event-free survival rate was 97.2 %. All patients were alive at that timepoint, and all had objective responses. In 3 cases (8.3 %), complete responses had occurred. The median tumor size reduction at week 6 was -52.1 %. Five patients had brain metastases at baseline. All of those with measurable disease (n = 4) responded intracranially, with 2 patients achieving complete remission. The CNS event-free rate at 12 months was 100 %. Median duration of systemic response and CNS response was 15.8 and 13.07 months, respectively.

The most commonly noted AEs included diarrhea (48.6 %), transaminase elevation (40.5 %), fatigue (37.8 %), anemia (35.1 %), and constipation (24.3 %). Grade 1/2 hypertension and proteinuria associated with bevacizumab treatment occurred in 21.6 % and 13.5 % of patients, respectively. Twelve patients (32.4 %) experienced grade ≥ 3 TRAEs, with the most frequent being ALT increases (18.9 %), AST increases (16.2 %), creatinine elevations (5.4 %), and diarrhea (5.4 %).

Overall, the combination of alectinib and bevacizumab was shown to be a safe and highly effective first-line regimen, conferring promising findings for patients with brain metastases. The authors concluded that longer follow-up will clarify the role of the combination with respect to deferment of resistance and prolongation of patient survival. These results warrant a larger confirmatory trial, ideally a randomized phase III study. ■

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Deeper insights into combinations of immune checkpoint inhibitors with other drug classes

Pooled data on chemo-IO vs. IO in PD-L1 ≥ 50 %

Various regimens consisting of anti-PD-(L)1 antibodies with or without chemotherapy have been approved for the first-line treatment of patients with advanced NSCLC that does not harbor genomic alterations. The analysis reported at ASCO 2022 by Akinboro et al. used pooled data from 12 pivotal studies to compare overall survival (OS) obtained with chemo-immunotherapy (n = 455) vs. immunotherapy (n = 1,298) in patients with *ALK*- and *EGFR*-negative tumors that showed ≥ 50 % PD-L1 expression [1]. Six randomized controlled trials each had evaluated chemoimmunotherapy and immunotherapy alone. All comparator regimens consisted of platinum-based chemotherapy.

Despite a slight numerical advantage favoring chemoimmunotherapy, the data did not suggest an OS difference compared to the immunotherapy-only treatment. Median OS was 25.0 vs. 20.9 months, which translated into a 18 % risk reduction (HR, 0.82). The Kaplan-Meier estimation suggested a marginal separation of the curves within the first 18 months. For progression-free survival (PFS), the exploratory analysis revealed superiority of chemoimmunotherapy, with a median of 9.6 vs. 7.1 months (HR, 0.69). Here, the Kaplan-Meier curves separated clearly within the first year of treatment, which might represent a potentially greater cytoreductive effect; this warrants further exploration. Also, the overall response rates (ORRs) were higher with the combined approach (61 % vs. 43 %; OR, 1.2). According to the subgroup analyses, however, patients aged ≥ 75 years appeared to derive greater benefit from immunotherapy alone with respect to both OS and PFS.

As the authors pointed out, limitations arise from the retrospective and exploratory nature of the analyses, and the results are only hypothesis-generating. No factors were examined that might explain the lack of concordance between the OS results on one hand and the PFS/ORR findings on the other. Also, potential heterogeneity across the trials including differences in PD-L1 assays need to be taken into account. Never-

theless, these findings emphasize the importance of shared decision making in selecting a therapeutic approach.

Meta-analysis according to *KRAS* status

Another pooled analysis presented by Nakajima et al. investigated the outcomes of first-line chemoimmunotherapy vs. immunotherapy according to *KRAS* mutation status and PD-L1 expression [2]. The researchers assessed the question of whether patients with *KRAS*-mutated advanced NSCLC respond differently to immunotherapy with or without chemotherapy than those with *KRAS* wildtype. To this end, data from a total of 1,430 patients included in 12 randomized trials were analyzed. Sixty-one percent of these (n = 875) had *KRAS* wildtype, while 39 % had *KRAS* mutations (n = 555). The $KRAS^{G12C}$ mutation was present in 11 % (n = 157). Roughly equal proportions within each of these groups were PD-L1–negative (TPS, < 1 %), PD-L1–low (1-49 %), and PD-L1–high (≥ 50 %). Chemoimmunotherapy had been administered in 35 % to 39 % across the groups, and immunotherapy alone had been used in 24 % to 29 % of the population.

Among patients with both *KRAS* wildtype and *KRAS*-mutant disease, ORRs were higher in the groups treated with checkpoint inhibitors plus chemotherapy than in those treated with immunotherapy alone **(Table 1)**. ORRs did not differ across patients with *KRAS* wildtype and *KRAS* mutations; this was true for chemoimmunotherapy, immunotherapy only, and chemotherapy. Likewise, OS was highest in patients treated with chemoimmunotherapy, and no notable differences emerged according to *KRAS* status for either treatment regimen. The hazard ratios were exploratory and did not have prespecified alpha.

In patients with both PD-L1–high and PD-L1–low disease, those treated with chemoimmunotherapy appeared to obtain the greatest survival benefit independent of *KRAS* status. Also, in the group with PD-L1–negative tumors, median OS was similar among patients with *KRAS* wildtype and *KRAS*-mutated disease. The numbers of patients who received immunotherapy alone were low here, which limits conclusions on the survival benefit in this group.

This analysis represents the most comprehensive assessment of patients with *KRAS*-mutated NSCLC in response to first-line therapy, although it has limitations as a retrospective, exploratory analysis. Overall, all patients appeared to benefit from the addition of chemotherapy to immunotherapy regardless of *KRAS* mutation status and PD-L1 expression. Collectively, these data suggest that the optimal comparator for studies conducted in the first-line setting in patients with *KRAS*-mutant disease might consist of immune checkpoint inhibition plus chemotherapy. Additional data are needed to determine whether there is a subset of patients with *KRAS*-mutant NSCLC who can forgo first-line immunotherapy in favor of targeted therapy that has become available for patients with $KRAS^{G12C}$-mutant disease.

TABLE 1 **Response rates and overall survival with different treatment regimens according to *KRAS* mutation status**

	***KRAS* wildtype**	***KRAS* mutation**	***KRAS*^{G12C} mutation**
	Overall response rate, %		
Immunotherapy + chemotherapy	51	46	47
Immunotherapy only	33	37	33
Chemotherapy only	32	33	44
	Overall survival, months		
Immunotherapy + chemotherapy	18.7	22.4	20.8
	HR, 1.12		
Immunotherapy only	16.4	16.2	11.8
	HR, 1.01		
Chemotherapy only	14.9	17.1	17.5
	HR, 1.02		

Eftilagimod alpha plus pembrolizumab: TACTI-002

The antitumor activity of PD-1 antagonists is synergistically enhanced in combination with the soluble LAG-3 protein eftilagimod alpha, which targets a subset of MHC class II molecules, thus activating antigen-presenting cells and leading to an increase in activated T cells. Felip et al. reported initial results from Part A of the multinational, open-label, phase II TACTI-002 trial at ASCO 2022 [3]. In this group that comprised 114 patients recruited across 6 countries, eftilagimod alpha Q2W was administered together with pembrolizumab Q3W for 8 cycles followed by eftilagimod alpha plus pembrolizumab Q3W for 9 cycles. The combined phase lasted for up to 1 year; subsequently, pembrolizumab monotherapy Q3W was administered for another year. These patients had untreated, advanced or metastatic NSCLC not amenable to targeted therapy and were unselected for PD-L1 expression. Approximately 70 % had a TPS < 50 %. ORR by iRECIST was defined as the primary endpoint.

After a median follow-up of 11.2 months, the ORR by iRECIST was 38.6 % in the ITT population, with the analysis according to RECIST 1.1 revealing a similar ORR of 37.7 %. In the evaluable population that had ≥ 1 post-baseline radiological assessment (n = 103), 42.7 % and 41.8 % of patients responded according to iRECIST and RECIST 1.1, respectively. The ORR analysis by PD-L1 status showed that those with PD-L1 expression ≥ 50 % experienced the highest ORR (52.6 % according to iRECIST), which markedly exceeded the ORR of 28.1 % in the PD-L1–negative population. Disease control rates ranged from 68.8 % to 78.9 % across all PD-L1 subgroups. No ORR difference resulted between patients with squamous and non-squamous tumors (35.0 % and 38.9 %, respectively).

Responses were deep and durable. Two thirds of patients with a post-baseline assessment had decreases in target lesions, and only 8.6 % of those with confirmed response progressed within 6 months until data cutoff. Complete remissions occurred in 2 patients. Median

duration of response had not been reached yet. The median PFS of 6.9 months was deemed promising in this PD-L1–unselected population. Again, PFS was more favorable in the PD-L1–high subgroup, with a median of 11.8 months in those with PD-L1 ≥ 50 % vs. 4.2 months in the PD-L1–negative cohort.

Eftilagimod alpha was demonstrated to be safe and well tolerated. Treatment-emergent AEs (TEAEs) included dyspnea, asthenia, decreased appetite, cough, anemia, and fatigue. Local injection site reactions were seen in 20.3 % of patients and rated as grade 1 in almost all cases; no grade ≥ 3 events were reported. Treatment-related grade ≥ 3 TEAEs occurred in 10.5 % and led to discontinuation in 9.6 %. The most common AEs with possible immune etiology were diarrhea (any grade, 15.8 %), hypothyroidism (8.8 %), hyperthyroidism (5.3 %), and pneumonitis (3.5 %). No cytokine release syndrome was observed. In their conclusion, the authors noted that eftilagimod alpha plus pembrolizumab showed encouraging efficacy in first-line, PD-L1–unselected patients and warrants late-stage clinical investigation.

COSMIC-021: cabozantinib alone and plus atezolizumab

The combination of the multikinase inhibitor cabozantinib and the anti-PD-L1 antibody atezolizumab has demonstrated encouraging clinical activity in immunotherapy-pretreated patients included in the phase IB COSMIC-021 study [4]. Outcomes for the combination in the expanded Cohort 7 and for cabozantinib alone in Cohort 20 were reported by Neal et al. [5]. COSMIC-021 enrolled a population with stage IV, non-squamous NSCLC and radiographic progression on or after one immune checkpoint inhibitor administered for metastatic disease. The patients had been treated with ≤ 2 prior lines of systemic anticancer therapy. In Cohort 7, cabozantinib 40 mg QD was administered together with atezolizumab 1,200 mg Q3W (n = 81), while Cohort 20 received cabozantinib 60 mg QD (n = 31). The PD-L1 status was not available in all patients; in those in whom it was available, approximately 70 % showed PD-L1 positivity. Platinum-based chemotherapy had been administered in > 80 % of patients in both cohorts. ORR was defined as the primary endpoint.

The combination demonstrated encouraging clinical activity, with an ORR of 19 %, a disease control rate of 80 %, median PFS of 4.5 months, and median OS of 13.8 months **(Table 2)**. Responses were observed with cabozantinib plus atezolizumab irrespective of known PD-L1 expression. There was a trend towards improved PFS and OS in the groups with PD-L1–positive tumors and unknown PD-L1 status compared to the PD-L1–negative group. Seventy-six percent of patients experienced tumor reductions. For cabozantinib alone, on the other hand, the analysis revealed only modest activity. Six percent of patients responded, with 65 % achieving disease control. Median PFS and OS amounted to 3.4 and 9.4 months, respectively.

The safety profiles of both the combination and cabozantinib monotherapy were consistent with those previously reported. Diarrhea, decreased appetite, nausea, and fatigue occurred most commonly in both cohorts. Among adverse events of special interest, rash, liver function test abnormalities, laboratory pancreatitis and thyroid abnormalities were observed. Cabozantinib dose reductions due to AEs were necessary in 40 % and 58 % in Cohorts 7 and 20, respectively, although treatment-related AEs (TRAEs) led to discontinuation of cabozantinib treatment only in 14 % and 10 %, respectively. Cabozantinib is currently tested together with nivolumab in the phase II EA5191 trial (NCT04310007) and combined with atezolizumab in the phase III CONTACT-01 study (NCT04471428).

Lung-MAP sub-study S1800A

Lung-MAP is a master protocol to evaluate biomarker-driven agents and immunotherapies in previously treated patients with stage IV or recurrent NSCLC. Those not eligible for biomarker-matched sub-studies enroll in unmatched sub-studies all of which operate independently. The unmatched sub-study S1800A was designed as a randomized phase II trial to compare pembrolizumab plus the anti-VEGFR2 antibody ramucirumab (n = 69) with standard treatment according to the in-

TABLE 2 **COSMIC-021: clinical outcomes observed with cabozantinib/atezolizumab and cabozantinib monotherapy**

	Cabozantinib + atezolizumab (n = 81)				Cabozantinib (n = 31)
	All patients (n = 81)	PD-L1 < 1 % (n = 19)	PD-L1 ≥ 1 % (n = 41)	PD-L1 unknown (n = 21)	
ORR, n (%)	15 (19)	2 (11)	8 (20)	5 (24)	2 (6)
Best overall response, n (%)					
Complete response	0	0	0	0	0
Partial response	15 (19)	2 (11)	8 (20)	5 (24)	2 (6)
Stable disease	50 (62)	12 (63)	25 (61)	13 (62)	18 (58)
Progressive disease	13 (16)	3 (16)	8 (20)	2 (10)	6 (19)
Missing/not evaluable	3 (4)	2 (11)	0	1 (5)	5 (16)
Disease control rate, n (%)	65 (80)	14 (74)	33 (80)	18 (86)	20 (65)
PFS, months	4.5	4.0	4.7	5.4	3.4
Median duration of response, months	5.8	3.4	6.5	6.2	10.6
OS, months	13.8	6.8	10.4	17.4	9.4

vestigator's choice (i.e., docetaxel plus ramucirumab; docetaxel; gemcitabine; pemetrexed; n = 67). Pembrolizumab plus ramucirumab was chosen to overcome acquired resistance to immunotherapy, which is a major area of unmet need for patients with NSCLC. Direct and indirect effects of angiogenesis-modulating factors on the tumor microenvironment have been observed [6], and pembrolizumab combined with ramucirumab has shown preliminary activity and safety in a phase I trial in patients with advanced NSCLC [7, 8]. All patients included in the sub-study S1800A had previously received both PD-(L)1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined and had experienced disease progression at least 84 days after initiation of this treatment. The majority of those enrolled in the control arm received docetaxel plus ramucirumab (n = 45), followed by gemcitabine (n = 12). Reckamp et al. presented OS data and other outcomes from S1800A at ASCO 2022 [9].

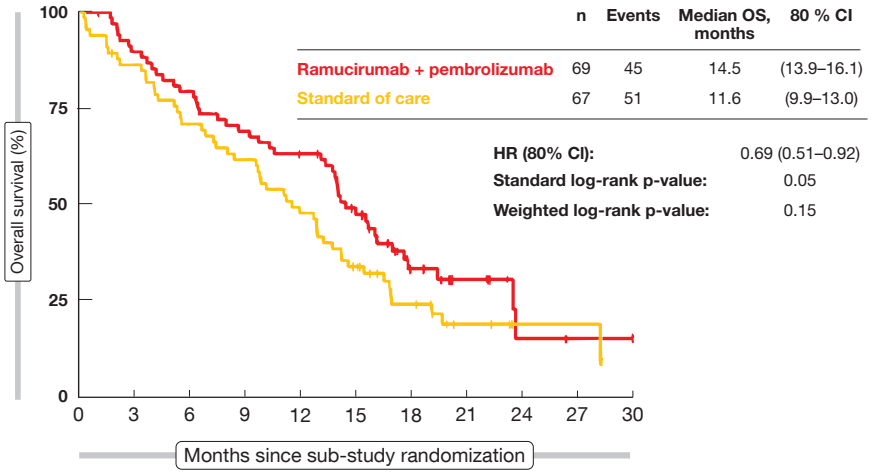

Figure 1: A: Overall survival advantage for ramucirumab plus pembrolizumab vs. standard-of-care treatment in patients after immunotherapy and platinum-based chemotherapy

Survival improvement with PFS/ORR discordance

Indeed, pembrolizumab plus ramucirumab prolonged OS compared to the standard of care (14.5 vs. 11.6 months; HR, 0.69; standard log-rank p = 0.05; **Figure**). All subgroups favored the combination. Similar reductions in mortality risk were observed independent of PD-L1 expression, and co-mutations did not affect the OS improvement. Patients with squamous/mixed histology showed a greater survival benefit (HR, 0.43) than those with non-squamous histology (HR, 0.95).

For PFS, the analysis did not reveal any superiority of the pembrolizumab-based regimen (4.5 vs. 5.2 months; HR, 0.86), which also applied to ORR (22 % vs. 28 %), although median duration of response was longer in the experimental arm (12.9 vs. 5.6 months). In both arms, > 70 % of patients experienced disease control. The authors noted that this discordance of PFS and ORR from OS has been reported in prior trials evaluating immune checkpoint inhibitors and is described as post-progression prolongation of survival.

With respect to grade 3-5 TRAEs, patients treated with pembrolizumab/ramucirumab fared better than those receiving standard therapy (42 % vs. 60 %). Nine grade 3-5 immune-related events were seen in the experimental arm (31 %). Overall, this is the first trial in the checkpoint-inhibitor–refractory setting without a chemotherapy backbone to demonstrate a survival benefit compared to standard-of-care regimens including docetaxel plus ramucirumab. Further evaluation of this approach is warranted. ■

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Extensive-stage small-cell lung cancer: successful and less successful combination strategies

In the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC), the IMpower133 and CASPIAN trials have established the anti-PD-L1 antibodies atezolizumab and durvalumab, respectively, as standard-of-care treatment in addition to platinum-etoposide [1-3]. However, PD-L1 inhibitors can only prolong overall survival by approximately 2 months and disease progression eventually develops in most cases, which still implies a significant unmet need for new therapies to improve long-term outcomes [1, 3, 4]. Moreover, the efficacy of anti-PD-1 antibodies in patients with SCLC remains unclear.

ASTRUM-005: serplulimab plus chemotherapy

The novel anti-PD-1 antibody serplulimab has shown encouraging antitumor activity in patients with previously untreated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors [5]. Cheng et al. reported interim results from the randomized, double-blind, multicenter, phase III ASTRUM-005 study evaluating serplulimab 4.5 mg/kg plus carboplatin/etoposide Q3W for up to 4 cycles as first-line treatment of 389 patients with ES-SCLC [6]. After induction, the patients received serplulimab Q3W until disease progression. Meanwhile, the control arm (n = 196) was treated with placebo plus chemotherapy followed by placebo. Approximately 70 % of patients were Asian, and the majority showed no PD-L1 expression.

Serplulimab in addition to chemotherapy elicited consistent benefits across the efficacy endpoints, which included long-term effects. Regarding the primary outcome of overall survival (OS), the treatment gave rise to a 37 % reduction in mortality risk (15.4 vs. 10.9 months; HR, 0.63; p < 0.001; **Figure**). At 24 months, 43.1 % vs. 7.9 % of patients were alive. According to the subgroup OS analysis, all patient groups benefited from the addition of serplulimab. Similarly, the progression-free survival (PFS) results favored the combined approach, with median PFS of 5.7 vs. 4.3 months (HR, 0.48) and 12-month rates of 23.8 % vs. 6.0 %. Responses occurred in 80.2 % vs. 70.4 %; 3 patients (0.8 %) in the experimental arm achieved complete remission (vs. 0 % in the control arm). The median duration of response was longer with the serplulimab-based treatment (5.6 vs. 3.2 months; HR, 0.48).

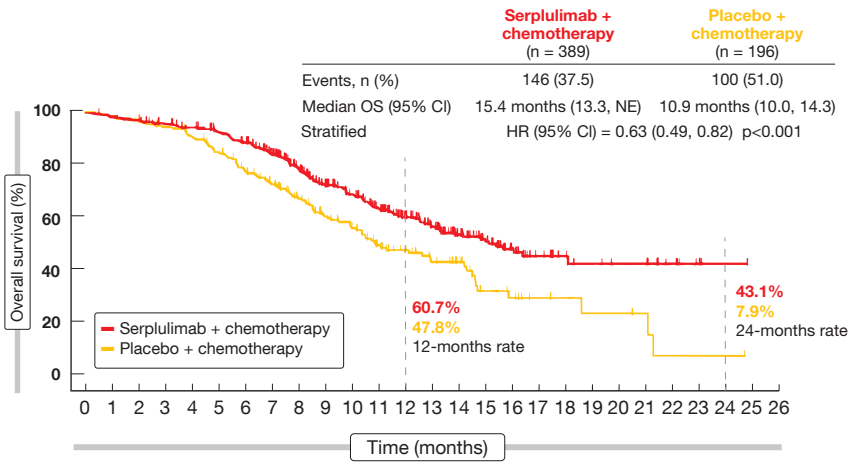

Figure 1: Survival improvement with serplulimab plus chemotherapy versus placebo plus chemotherapy

The combination demonstrated a manageable safety profile that mainly included cytopenia, alopecia, nausea, and decreased appetite. Immune-related adverse events (AEs) were observed in 37.0 % (vs. 18.4 %), with the most common being hypothyroidism (11.6 %), hyperthyroidism (9.0 %), and rash (3.1 %). Treatment-related AEs (TRAEs) led to discontinuation in 4.9 % vs. 4.1 % and patient death in 0.8 % vs. 0.5 %. Grade ≥ 3 TRAEs occurred in 33.2 % vs. 27.6 %. No new safety signals were seen during the study.

SKYSCRAPER-02: no benefit with addition of tiragolumab

The randomized, double-blind, phase III SKYSCRAPER-02 trial tested the anti-TIGIT antibody tiragolumab in combination with atezolizumab and chemotherapy as first-line treatment in patients with ES-SCLC. TIGIT is an inhibitory immune checkpoint present on immune cells in many cancers and is highly correlated with PD-1 expression [7]. Observations suggested that tiragolumab synergizes with other immunotherapies such as atezolizumab to amplify the antitumor response [8, 9].

In SKYSCRAPER-02, the experimental treatment consisted of 4 cycles tiragolumab 600 mg plus atezolizumab 1,200 mg Q3W and carboplatin/etoposide, followed by maintenance treatment with tiragolumab plus atezolizumab until progression (n = 243). Patients in the control arm received placebo in addition to atezolizumab and carboplatin/etoposide, and the maintenance regimen contained placebo plus atezolizumab (n = 247). Most of the patients were Caucasian, while those of Asian origin made up approximately one quarter. OS and PFS in the primary analysis set (i.e., all randomized patients without presence or history of brain metastases at baseline) constituted the coprimary endpoint.

After a median follow-up of 14.3 months, the addition of tiragolimab was not shown to improve PFS (5.4 vs. 5.6

months for the experimental arm vs. the control arm; HR, 1.11, p = 0.3504) or OS (13.6 months in both arms; HR, 1.04; p = 0.7963) in the primary analysis set [10]. The same was true for the full analysis set, i.e., all randomized patients, regarding both PFS (5.1 vs. 5.4 months; HR, 1.08) and OS (13.1 vs. 12.9 months; HR, 1.02). The subgroup analysis of OS in the full analysis set did not identify any population that benefited from tiragolumab-based treatment. In the group of patients with brain metastases, median OS was 11.7 vs. 10.64 months (HR, 0.92). Likewise, no differences across the arms were noted for objective responses (70.8 % vs. 65.6 %) or median duration of response (4.2 vs. 5.1 months). Tiragolumab plus atezolizumab and chemotherapy was well tolerated, with the safety profile being similar to that of atezolizumab plus chemotherapy.

The authors concluded that based on these data, targeting TIGIT in the setting of ES-SCLC does not appear to be therapeutically relevant. The PFS and OS findings observed in the control arm support the results of the IMpower133 trial, thus further confirming this combination as a standard of care for the first-line treatment of patients with ES-SCLC. SKYSCRAPER-02 will continue to the planned primary OS analysis, and biomarker analyses are ongoing. Furthermore, tiragolumab is being investigated in NSCLC and other tumor types. ■

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Expert interviews at ASCO 2022

John Varlotto summarizes the insights that have been obtained based on recent studies regarding immunotherapy plus chemoradiation in patients with unresectable, locally advanced stage III non-small cell lung cancer, explains the different effect observed with pembrolizumab and nivolumab and how these results compare to existing data. He cautions against using the impressive pathologic complete response rates with neoadjuvant chemoimmunotherapy to the unresectable setting due to the lack of long-term survival rates with neo-adjuvant chemo/immunotherapy and the impressive 47.5 median overall survival noted with concurrent chemo/radiotherapy followed by consolidative durvalumab in the Pacific Trial.

Jessica Donington highlights the most promising agents currently investigated in the neoadjuvant setting in patients with resectable NSCLC, how the "intensity" of neoadjuvant treatment affects the outcomes and discusses if neoadjuvant chemo-immunotherapy is the new standard of care. She outlines which variables related to surgery itself are determinants of the success of curative surgery and which biomarkers are on the rise to guide therapy.

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