PW PHYSICIAN'S WEEKLY

ASCO 2020 ANNUAL MEETING CONFERENCE REPORT

LUNG CANCER

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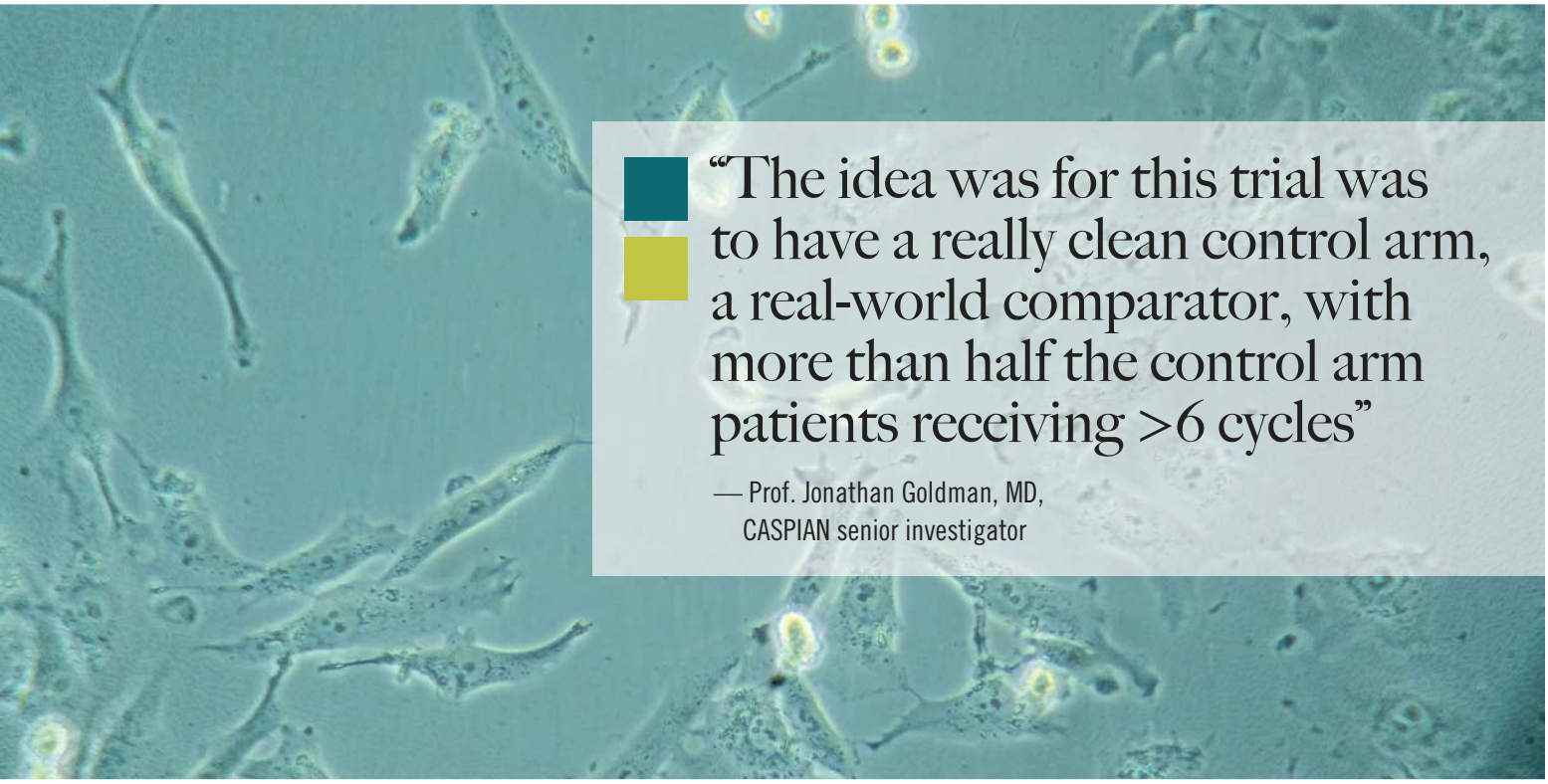
CASPIAN Trial Update:
Phase 3 Results & Perspectives



> "The idea was for this trial was to have a really clean control arm, a real-world comparator, with more than half the control arm patients receiving >6 cycles"
>
> — Prof. Jonathan Goldman, MD, CASPIAN senior investigator

Updated findings from the phase 3 CASPIAN trial presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program showed maintained overall survival (OS) benefit of durvalumab treatment in combination with platinum etoposide chemotherapy vs chemotherapy alone, in newly diagnosed patients with extensive-stage small cell lung cancer (ES-SCLC) after more than 2 years of follow-up.

ASCO data showed that more than 10% of patients on durvalumab plus chemotherapy had not progressed and remained on treatment at two years vs 2.9% on chemotherapy alone.

The CASPIAN trial met the primary endpoint of OS in June 2019, reducing the risk of death by 27% (based on a hazard ratio [HR] of 0.73; 95% confidence interval [CI] 0.59-0.91; p=0.0047) which formed the basis of the US FDA approval in March 2020.

Adding an Anti-CTLA4 Antibody to the Mix

At the Virtual ASCO Annual Meeting held 29-31 May 2020, Prof. Luis Paz-Ares (Hospital 12 de Octubre, Madrid, Spain) presented the first report of the third study arm of CASPIAN, in which investigational CTLA-4 inhibitor tremelimumab was added to PD-L1 checkpoint inhibitor durvalumab on top of standard of care chemotherapy.

CASPIAN randomized 805 patients to 3 treatment arms: durvalumab + tremelimumab + etoposide cisplatin/carboplatin (EP) (n=268), EP alone (n=269), or durvalumab + EP (n=268). The primary endpoint of the study was OS; secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety and tolerability. Findings from CASPIAN reported previously in the *Lancet* that, after a median follow-up of 14.2 months, the addition of the durvalumab improved the median OS to 13.0 months versus 10.3 months with EP alone (HR 0.73; 95% CI 0.59-0.91; P=0.0047) [2]. Consequently, in March 2020, the FDA approved durvalumab in combination with EP as first-line therapy for ES-SCLC.

In the current presentation, after a median follow-up of 25.1 months, the median OS was 12.9 months among patients who received durvalumab + EP compared with 10.5 months for those who received EP alone (HR 0.75; 95% CI 0.62-0.91;

P=0.0032), fully supporting the initial report. Of note, the study design allowed the use of either backbone carboplatin or cisplatin; the OS data favored durvalumab regardless of whether carboplatin (HR 0.79; 95% CI 0.63-0.98) or cisplatin (HR 0.67; 95% CI 0.46-0.97) was the backbone chemotherapy agent used.

"Importantly, the separation among the curves seems to be observed over time and, indeed, survival at 2 years improves from 14% [of participants] in the control arm to 22% on the experimental arm. The magnitude of the benefit is very similar and very consistent across all the prespecified subgroups of patients analysed, including those treated with cisplatin or those patients with liver or brain metastases," said Prof. Paz-Ares.

However, the study's third arm testing dual checkpoint blockade with tremelimumab + durvalumab + EP did not meet the prespecified threshold for statistical significance (P≤0.0418). The median OS for this combination was 10.4 months versus 10.5 months for EP alone (HR 0.82; 95% CI 0.68-1.00; P=0.0451). The OS survival rates at 18 months were 32.0% in the durvalumab + EP arm, 30.7% in the tremelimumab + durvalumab + EP group, and 24.8% in the EP cohort; at 24 months, those rates were 22.2%, 23.4%, and 14.4%, respectively.

The median PFS was 4.9 months for the tremelimumab + durvalumab + EP arm compared with 5.4 months for the EP arm (HR 0.84; 95% CI 0.70-1.01). The confirmed ORR and median duration of response were 58.4% and 5.2 months, respectively, in the tremelimumab + durvalumab + EP group compared with 58.0% and 5.1 months for the EP arm.

Safety events were consistent with the known adverse events (AEs) associated with the medicines. The rates of grade 3/4 and serious AEs were, respectively, 70.3% and 45.5% in the tremelimumab + durvalumab + EP arm, 62.3% and 32.1% in the durvalumab + EP arm, and 62.8% and 36.5% in the EP group. AEs leading to treatment discontinuation occurred in 21.4% of patients in the tremelimumab + durvalumab + EP arm, 10.2% in the durvalumab + EP group, and 9.4% in the EP cohort. Treatment-related deaths were 12 in the tremelimumab + durvalumab + EP arm, 6 in the durvalumab + EP arm, and 2 in the EP arm. In conclusion, the benefit-to-risk ratio favored treatment with durvalumab + EP, without tremelimumab, for treatment-naïve ES-SCLC.

Ongoing Survival Benefit With Durvalumab in ES-SCLC

While the third arm of the study missed the co-primary endpoint of the phase 3 CASPIAN study, the ongoing data constitute robust support for accumulating evidence that anti-PD-1L therapy boosts results when added to a platinum backbone.

Physician's Weekly asked CASPIAN senior investigator Prof. Jonathan Goldman, MD, oncologist at the Ronald Reagan UCLA Medical Center, for his perspective:

"The idea was for this trial was to have a really clean control arm, a real-world comparator, with more than half the control arm patients receiving >6 cycles. The patients did really well for that regimen too, so I think we can be confident in the result and the meaningful additional element of durvalumab," says Dr. Goldman.

"Unfortunately, adding tremilimumab to durvulumab did not have benefit, and I think now that that data will call into question CTLA-4's role in small-cell lung cancer. There are other agents in other trials that have shown an improved response rate with adding to CTLA-4 to PD-1/ PD-L1 inhibitors and while there's definitely an increase in toxicity at this point it is not clear that that is met with improved long-term outcomes."

"The PD-L1 inhibitor, durvulumab, in chemotherapy has meaningfully improved survival in an area where there have been no changes for decades, and now to improve on that new standard, I think we have to become more creative," Dr. Goldman says. It may be adding in other agents to the maintenance phase."

Dr. Goldman says that they are looking at adding temozolomide and a PARP inhibitor to the maintenance phase of the PD-L1 inhibitor and notes that there are some potential benefits, including evidence of synergy between each of those different components, which was reported in *Clinical Cancer Research* as well as by us. "There's been some excitement already about PARP inhibitors and immunotherapy drugs."

"We really should also be focusing on the tail of the curve – the patients who received the most durable response in this study. On the durvalumab arm, there are 10-20% of patients who are still doing well, 18 and 24 months into treatment which is, without durvalumab, a rare event. I think our ability to select those patients up front right now is limited. PD-L1 expression does not appear to be a useful biomarker. Tumor mutational burden studies remain to be done; that analysis is underway. There is some thought that there are different histologic and genetically distinct subgroups of small cell lung cancer, and some of them do seem to be more inflamed and perhaps more susceptible to immunotherapy benefit, but at this point that is a hypothesis that requires prospective confirmation."

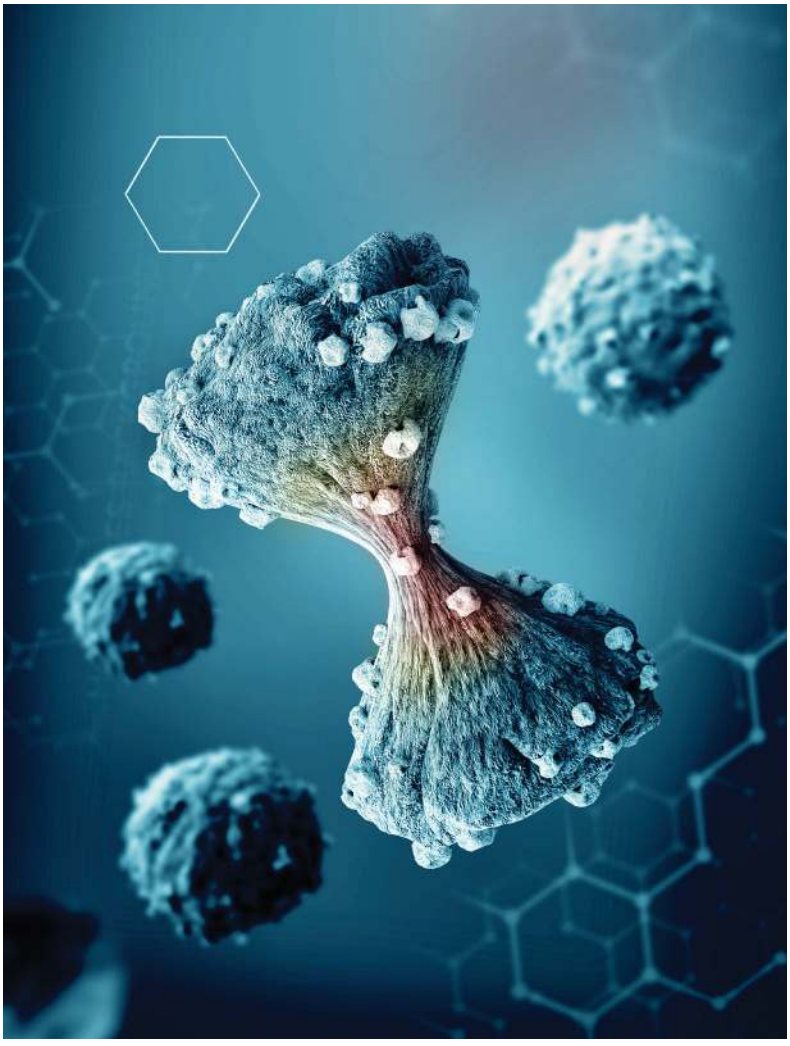
SOURCE:

Paz-Ares LG,et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated Results from the phase III CASPIAN study. ASCO Virtual Meeting, 29-31 May 2020, Abstract 9002.

Paz-Ares LG, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. 2019;394(10212): 1929-1939.

Phase III ADAURA Trial: **Practice Changing Results for NSCLC**

Physician's Weekly interviewed the study's principle investigator and presenter at ASCO, Prof. Roy Herbst, Yale Cancer Center, USA



Adjuvant osimertinib demonstrated a statistically significant and clinically meaningful benefit for patients with stage IB, II, or IIIA EGFR-mutant non-small cell lung cancer (NSCLC) with complete tumor resection in the phase 3 ADAURA trial, presented at the Virtual ASCO Annual Meeting held 29-31 May 2020 [1].

Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, with demonstrated efficacy as a frontline agent for metastatic NSCLC with confirmed *EGFR*-mutation, which was published in the *New England Journal of Medicine* [2]. The phase 3 ADAURA clinical trial attempted to assess whether this agent is also effective in earlier stages of metastatic disease characterized by *EGFR* mutation, namely as an adjuvant therapy after complete surgical resection of stage IB, II, or IIIA disease.

Briefly, oral osimertinib (80 mg, once daily) was compared with placebo for a treatment duration of up to 3 years or until disease recurrence; median duration of exposure was 22.3 months (range 0-43). The primary endpoint was disease-free survival (DFS), and the key secondary endpoint was overall survival (OS).

The study was unblinded early under the recommendation from an Independent Data Monitoring Committee due to efficacy. At the time of the unblinding, randomized patients (n=682) had been followed up for at least 1 year. For the primary endpoint in stage II-III patients, the DFS curves separated early on and showed an 83% reduced risk of disease recurrence for the osimertinib arm (HR 0.17; 95% CI 0.12-0.23; P<0.0001). Adding in the early-stage IB patients to the overall population did not change this trend (HR 0.21; 95% CI 0.16-0.28; P<0.0001), indicating that osimertinib benefits early-stage patients as well. Osimertinib was well tolerated. Overall, there was a 79% reduction in the risk of disease recurrence or death with osimertinib. Osimertinib versus placebo DFS rates at 2 years were 89% vs 53%, respectively.

The main conclusion of ADAURA was that adjuvant osimertinib provides a highly effective, practice-changing treatment for patients with stage IB/II/IIIA *EGFR*-mutant NSCLC after complete tumor resection.

Physician's Weekly asked ADAURA senior investigator Roy Herbst, MD, PhD, for some additional information:

What about the overall survival, will you be able to get that data from ADAURA?

"Overall survival is, of course, critical. However, I think that the PFS measure here is so strong, that there is no discussion that patients still benefit by time before their cancer comes back. Waiting for the survival data will take a few more years. I think we'll still be able to file based on the clinical evidence to date. Patients will have access to osimertinib anyhow when they fail the control arm; we'll make sure the study provides that for them. The OS data could be hard to obtain for those patients on the control arm, if they end up switching to osimertinib. But they have all been at least one year on the trial, so why would someone switch? They've had surgery, they've had actual therapy with chemo, that was at 24 weeks, now they're 72 weeks or so post-enrollment. Are they going to now switch with no measurable disease and start on osimertinib? I think if I were in that position I'd wait, and just be followed. And whether or not we should continue giving them a placebo every day or not—we're still discussing that with regulatory—we will still follow the trial for survival. Sure, there will be some crossover that could pull the survival curves a little closer together, but I would predict we'll still see a survival benefit. Even in the absence of that, it's such a high magnitude of disease-free survival benefit, I think it will change practice."

Speaking of practice-changing, will we start sequencing for *EGFR* mutations in every early-stage disease patient?

"For every non-squamous lung cancer, you can make the case for sequencing at some point. Yes, I think to sequence *EGFR* in early-disease patients can be useful, but we should start off in Asia, where *EGFR* mutation is about 30%. This practice might be slower to catch on in the US where *EGFR* mutation is only 10-15%. I expect soon that at the time of the initial pathology, we'll probably get an immune profile, including PD-L1 expression, and some data on EGFR status, and you can even make a case that the paradigm might include some of the other targeted alterations like *MET, ALK*, or *RAS*."

Do you anticipate resistance to develop?

"Preexisting or acquired, we know that there are these dormant persister cells, which are resistant. We also know that with treatment, resistant populations will emerge. Yes, I do anticipate we'll see resistance develop, and when patients fail on osimertiniib, either early or late. Because osimertinib selectively targets activating *EGFR* mutations, as well as the T790M-resistance mutation, through the formation of a covalent bond to the C797 residue in the ATP-binding site of mutant *EGFR*, we will need to screen patients for *EGFR* C797X/S alterations. If C797 is mutated, we have other trials and combinations that we're looking at to treat those patients. I would not avoid using osimertinib because I'm worried about resistance developing; hopefully, there will be less resistance because we have an early-stage setting, therefore fewer cells will become resistant leading to less heterogeneity."

What about the patients on the tail of the curve?

"Why do some patients respond better than others? Every time someone got a pharmacokinetic timepoint, or every time they came in for one of their 12- or 24-week visits, we gathered blood, to allow us to analyze cell-free DNA. Therefore, we will be able to look at liquid biopsies and we'll get a sense for any other mutations present. In addition, we should be able to gain insight from these samples as to how quickly resistance may be developing. What triggers this change, when does this occur? I think we'll begin to learn about how resistance emerges. There's a lot of science to be gained from this trial too, from the longitudinal follow-up."

Next steps?

"We next get to do some of the science end of the trial, while continuing to keep the trial running and moving forward. To expand this knowledge base, the LAURA trial will look at osimertinib after chemoradiation in the locally advanced unresectable stage IIIA-3B setting, and the FLAURA2 trial will combine with chemotherapy in the metastatic setting. Furthermore, there will be the neo-ADAURA trial, which is going to look at osimertinib in patients before they had any therapy, before they even had surgery, which will provide good data on response rates as opposed to progression, or disease-free-survival, because you are starting with a tumor that is intact. One can actually imagine a trial where you cut out the whole tumor to determine whether it might be resistant to a given agent, so you can know what to do next. You might even think about combining it with chemotherapy in some instances. For the time being, we can be satisfied that the ADAURA trial results give another 30% of lung cancer patients, albeit only 10-15% of those in the US but 2-3 times that number in Asia, another sliver of a win. A good number of patients, in fact 5-10%, now have the ability to get a targeted agent to prevent reoccurrence."

SOURCE:

Herbst RS, et al. Phase III study assessing the efficacy of adjuvant use of targeted agent osimertinib in patients with localized non-small-cell lung cancer and *EGFR*mutation after complete tumor resection and adjuvant chemotherapy. ASCO Virtual Meeting, 29-31 May 2020, Abstract

Soria JC, et al. Osimertinib in Untreated *EGFR*-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;378(2):113-125.

MET Mutation Inhibitor Associated with Tumor Reductions in NSCLC

Targeting tumor driver appears effective in half of NSCLC patients

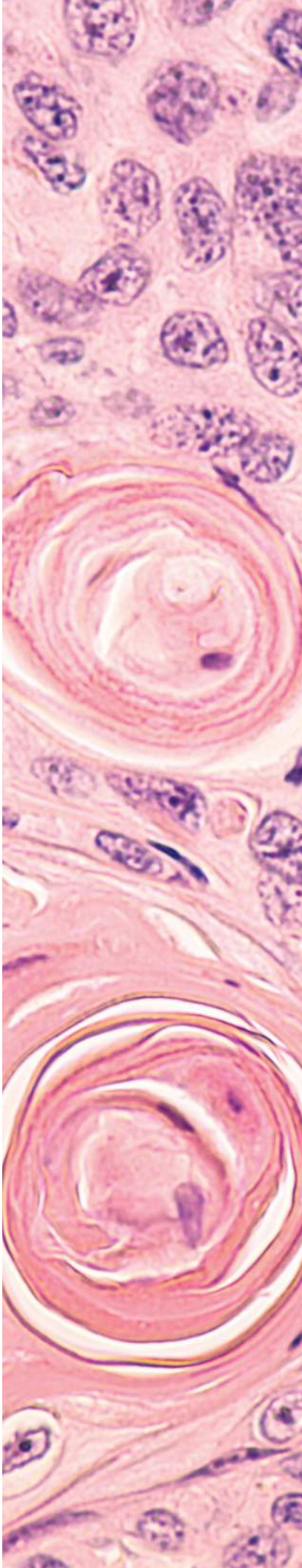
Treatment with the investigative agent tepotinib — an oral MET inhibitor — appears to produce a response in about half of patients diagnosed with metastatic or relapsed non-small cell lung cancers, according to a presentation at the virtual annual meeting of the American Society of Clinical Oncology 2020 (ASCO), as well as reported in the *New England Journal of Medicine*.

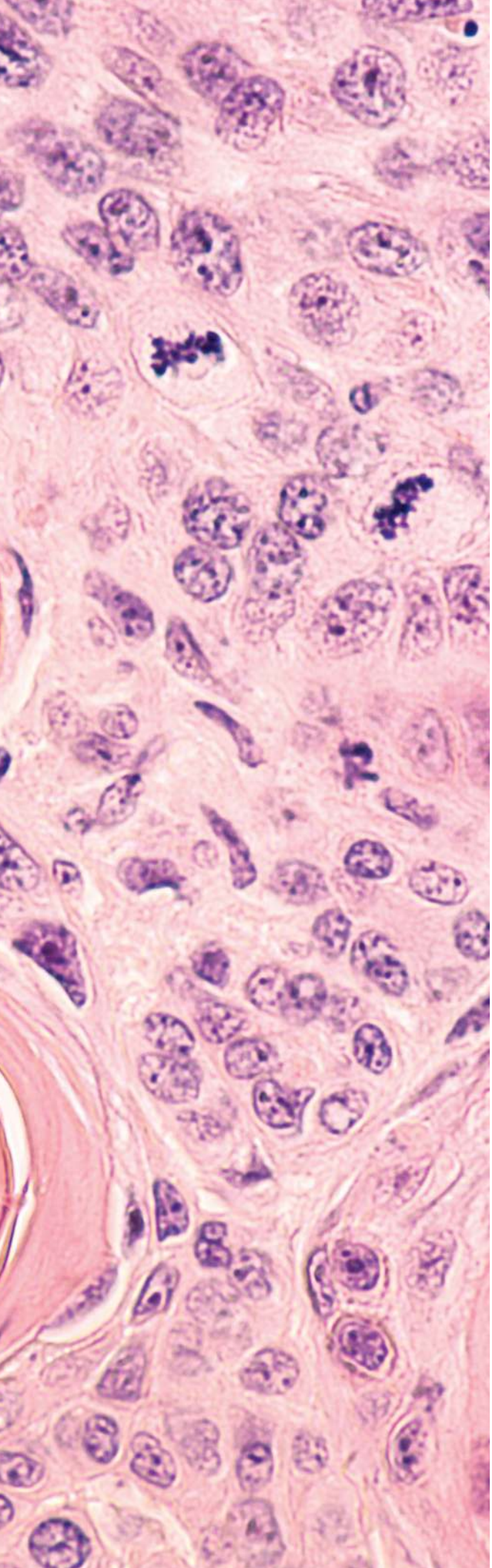
Among 99 patients treated for 9 months with tepotinib, the response rate by independent review was 46%, with a median duration of response of 11.1 months in the combined-biopsy group of patients, reported Paul Paik, MD, clinical director of the thoracic oncology service at Memorial Sloan-Kettering Cancer Center, New York.

"The VISION study showed that the selective MET inhibitor tepotinib had durable clinical activity in patients with non-small cell lung cancer with MET mutations associated with exon 14 skipping," Dr. Paik reported. "These findings validate MET exon 14 skipping mutations as bona fide therapeutic targets and underscore the importance of routine testing for these MET alterations by means of liquid or tissue biopsy."

In the study, the patients' tumors were biopsied by both methods, he reported. The response rate was 48% among 66 patients in the liquid-biopsy group and 50% among 60 patients in the tissue-biopsy group; 27 patients had positive results according to both methods. The investigator-assessed response rate was 56% and was similar regardless of the previous therapy received for advanced or metastatic disease, Dr. Paik and colleagues reported.

A splice-site mutation that results in a loss of transcription of exon 14 in the oncogenic driver MET occurs in 3 to 4% of patients with non-small cell lung cancer, the researchers noted. They explained that in the molecular cascade, the MET proto-oncogene encodes a receptor tyrosine kinase, and binding to its ligand induces downstream signaling through the RAS–RAF and phosphoinositide 3-kinase pathways. Aberrant MET signaling drives tumor growth through increased cell proliferation, survival, invasion, and metastasis. MET dysregulation through splice-site alterations that cause a loss of trans-cription of exon 14 in MET can result from point mutations, insertions or deletions, or large-scale whole-exon deletions. These alterations spatially disrupt distinct splicing sites at the acceptor or donor site flanking MET exon 14. As a result of MET exon 14 skipping mutations, the MET juxtamembrane domain, which contains a binding site for Y1003 CBL, is deleted; this leads to impaired MET ubiquitination, decreased MET turnover, and increased signaling.





Tepotinib is designed to inhibit the oncogenic MET receptor signaling caused by MET alterations, including both MET exon 14 skipping alterations and MET amplifications, or MET protein overexpression.

"The 50% response rate in this study is meaningful," said Wasif Saif, MD, deputy physician-in-chief and medical director of the Northwell Health Cancer Institute, Lake Success, New York. "However, caution is required as this was an open-label, phase 2 study and not validated in a phase III study yet. The most assuring fact is that this 50% response rate is not short of the responses seen in other drugs tested for lung cancer in the recent years, such as pembrolizumab."

Asked about the implications of the VISION trial findings, Dr. Saif said, "It is clear to us now that non-small cell lung cancer is not just 1 disease, but many types of disease with specific genetic differences. Certain people may have non-inherited gene mutations that can cause their cancer cells to grow and multiply.

"Hence, this agent, a selective MET inhibitor, offers a new treatment option with favorable safety profile and without the toxicities of chemotherapy agents. However, we know tumor is smart to develop resistance to agents, therefore, we are required to now focus on drug switching and/or combination therapy to overcome target resistance," he said.

In the open-label, phase II study, Dr. Paik administered tepotinib at a dose of 500 mg once daily in patients with advanced or metastatic non-small cell lung cancer with a confirmed MET exon 14 skipping mutation. As of Jan. 1, the researchers had enrolled 152 patients into the study and had administered tepotinib.

The median age of the patients in the efficacy population was 74 years; 46% of the patients had a history of smoking, and almost all (97%) had metastatic disease at study entry.

Adverse events of grade 3 or higher that were considered by investigators to be related to tepotinib therapy were reported in 28% of the patients, including peripheral edema in 7%. Adverse events led to permanent discontinuation of tepotinib in 11% of the patients.

Dr. Saif said that the pursuit of a MET-targeted agent has had disappointing results when Phase III trials have been conducted. "One of the possible explanations for their failure is due to the inclusion of patients with MET aberrations that are dispensable for tumor growth and thus insensitive to MET inhibition," he suggested.

"On the other hand, MET exon 14 mutations have been identified as primary oncogenic drivers, offering a potential target that will be sensitive to MET inhibitors," he said. "In other words, if MET activity is a primary driver of MET exon 14 mutation-positive tumor growth, there is good reason to suppose that selective MET inhibitors have the potential to deliver better efficacy with a favorable safety profile. This study provided the proof of the hypothesis.

"This agent further strengthens ' precision oncology' to treat the patient according to genetic makeup of the tumor," Saif said.

Among Small Cell Lung Cancer Patients Treating Metastatic Breast Cancer Survivors

Programmed death ligand 1 (PD-L1) interacts with PD-1 to inhibit T-cells and the immune system. This pathway is often hijacked by tumors, and antibodies to PD-1 and PD-L1 have therefore been investigated for SCLC treatment. Clinical trials that have tested the combination of chemotherapy and immunotherapy for the treatment of SCLC have not shown notable differences in the efficacy of PD-1 compared with PD-L1 antibodies when combined with chemotherapy.

The efficacy of the anti-PD-1 drug, pembrolizumab, in combination with chemotherapy for the treatment of SCLC was investigated in the KEYNOTE-604 clinical trial.

"In my opinion, this trial, although negative for its primary endpoint by statistical design, was important. The relative impact that was seen, terms of progression-free survival (PFS) and overall survival (OS), was in the same ballpark as what we saw with the anti-PD-L1 durvalumab and atezolizumab

"The overall take home message from the Virtual ASCO Annual Meeting this year is that chemoimmunotherapy is effective and beneficial for patients with SCLC," says Taofeek Owonikoko, MD, PhD, MSCR, who was a session discussant in chemoimmunotherapy at ASCO 2020. Dr. Owonikoko is a Professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine.

trials combined with chemotherapy, published in the *Lancet* and the *New England Journal of Medicine*, respectively," says Dr. Owonikoko. "More importantly, the ECOG-ACRIN EA5161 trial was presented this year and showed both PFS and OS advantage with nivolumab combined with chemotherapy. As a result, I do not think the data we have supports a claim that anti-PD-L1 drugs are better than or act differently to anti-PD-1 drugs. Could there be unique differences between anti-PD-L1 and anti-PD-1 drugs? Possibly, however I don't think we can claim that such unique differences are significant enough to impact the efficacy of each in SCLC.

While chemoimmunotherapy does not help every patient, the positive impact seen in the subset of patients is evident, even in a clinical trial design that does not select patients based on specific biomarkers. According to Dr. Owonikoko, going forward, it is important to determine which SCLC patients benefit from chemoimmunotherapy in order to optimize its benefits. This is the key question in the field right now. "It is going to be hard, but I don't think it is impossible to define these patients. Many different groups around the world are looking at biomarkers, or exposure to previous therapies in the subset of patients who relapse, or looking at PD-L1 expression and tumor mutational burden," Dr. Owonikoko notes. "These avenues have shown promise in research but have not held up well when applied to patients being treated in the frontline with chemoimmunotherapy."

Traditional Chemo Treatment Often Not Effective

A major obstacle facing the field right now, Dr. Owonikoko explains, is that there is still a large proportion of SCLC lung cancer patients that are not treated; 30% of newly diagnosed cases never receive any treatment. That subset of patients has a significant impact on overall prognosis for this disease when compared with population-based theories. "Another major obstacle is that, although frontline treatment can be effective, the efficacy may not be durable. And once this frontline treatment fails, the treatment options for managing the disease dwindles very quickly," he says. "Chemotherapy is only effective for a vanishingly small subset of patients, if it even works at all. Furthermore, the duration of that efficacy is such that after maybe one or two restaging scans, the efficacy has worn off and you need to start looking for new ways of managing their disease."

Future Perspectives on SCLC Phenotyping and Treatment

One of the most promising ideas going forward is the emergence of SCLC stratification in different phenotypes of SCLC. "We have to stop treating SCLC as one uniform disease and recognize that there are likely biologically unique subsets that may or may not respond to different interventions, be it chemotherapy, immunotherapy, or a combination of the two," says Dr. Owonikoko. "Of course, the first thing that needs to be done is to phenotypically define the distinct subsets in SCLC. These subsets are not necessarily distinguishable by the typical somatic mutations like we have seen in other tumor types, but by more dominant transcriptional activation pathways."

The early work to tease apart the subset phenotypes would require RNA sequencing, to generate hypotheses, and then prospectively validate the subtypes. RNA sequencing may be impractical as a tool to identify patients for unique treatment approaches given the technical sophistication and time it requires to interpret the data. Therefore, in order to operationalize it, the correlation with protein expression must first be examined, and then traditional immunohistochemistry for patient selection should be trusted.

"There are currently quite a few studies that are being eagerly awaited, especially in limited-stage SCLC. Lots of the research has been conducted in extensive stage disease, but 30% of patients do not fall into this category. There are at least two major trials ongoing in limited stage disease: a national US study (NRG Oncology LU005), the STIMULI trial in Europe which is looking more at a post-chemotherapy maintenance strategy, and the ADRIATIC trial looking at the durvalumab and tremelimumab strategy both as concurrent and consolidation treatment," says Dr. Owonikoko. "With limited stage disease we begin with the same treatment regime that we have been using for the past 25 years of chemotherapy and radiation. Whether adding immunotherapy to that regime will result in better outcomes is what we are eagerly waiting to find out."

ASCO 2020 ANNUAL MEETING CONFERENCE REPORT

CHECKMATE-227: 3+ Years Follow-up Shows Long-Term NSCLC Benefit of Nivolumab and Ipilimumab

■ Updated results from part 1 of the phase 3 CHECKMATE-227 trial with > 3 years of follow-up in patients with advanced non-small cell lung cancer (NSCLC) reported long-term efficacy data from first-line treatment with nivolumab and ipilimumab compared with platinum doublet chemotherapy.

Suresh Ramalingam, MD, FASCO, Professor of hematology and medical oncology at the Winship Cancer Institute, Emory University in Georgia, presented CHECKMATE-227. The trial had a total of 1,739 stage IV NSCLC patients enrolled; the co-primary endpoints were overall survival (OS) and progression-free survival (PFS). The trial met both endpoints, which were published last year in the New England J of Medicine. This presentation looked at the long-term benefits of this combination.

In part 1, the investigators randomized 1,189 patients whose tumors scored ≥ 1% for PD-L1 to 3 treatment arms: 3 mg/kg nivolumab every 2 weeks plus 1 mg/kg ipilimumab every 6 weeks (n = 396); 240 mg nivolumab every 2 weeks (n = 396); or histology-based chemotherapy (n = 397).

With a median follow-up of 43.1 months, patients with PD-L1 ≥ 1% had a 21% reduced risk for death when treated with nivolumab plus ipilimumab when compared with chemotherapy (median 17.1 months vs 14.9 months; HR: 0.79; 95% CI: 0.67–0.93). Nivolumab monotherapy was somewhat lower, granting a 10% reduced risk of death (HR: 0.90; 95% CI: 0.77-1.06). Patients in the nivolumab monotherapy arm had a median OS of 15.7 months (HR: 0.9; 95% CI, 0.77-1.06). OS rates at 3 years were 33% for nivolumab plus ipilimumab, 29% for nivolumab monotherapy, and 22% for platinum doublet chemotherapy.

Higher 3-year PFS rates with nivolumab plus ipilimumab versus chemotherapy (18% vs 4%) were also reported in patients with PD-L1 ≥ 1%.; the median PFS with nivolumab plus ipilimumab was 5.1 months (HR: 0.81; 95% CI: 0.69-0.96).

Overall response rates were also superior with nivolumab plus ipilimumab (36.4%), compared with nivolumab monotherapy (27.5%) and chemotherapy (30.2%) in patients with PD-L1 ≥ 1.

No new safety signals were observed in any of the arms with the extended follow-up.

Ramalingam SS, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. ASCO Virtual Meeting, 29-31 May 2020, Abstract 9500.

Durvalumab plus Standard Therapy Prolonged OS in Malignant Pleural Mesothelioma

■ Patients with treatment-naïve and unresectable malignant pleural mesothelioma may respond to treatment with durvalumab given alongside cisplatin and pemetrexed, according to phase 2 results presented this year.

Patrick Forde, MD, Associate Professor of Oncology at Johns Hopkins University, the phase 2 PrE0505 study enrolled 55 patients with newly diagnosed unresectable alignant pleural mesothelioma. The trial had a single arm, namely chemotherapy with durvulumab 1120 mg, cisplatin 75 mg/m2, and pemetrexed 500 mg/m2 every 3 weeks, for a maximum of 6 cycles, followed by a year of maintenance durvalumab alone. The comparator was a pemetrexed-cisplatin historical control.

Histological characterization revealed that 75% of patients had epithelioid histology, while 13% had sarcomatoid, 11% biphasic, and/or 2% desmoplastic histologies.

The pre-specified criteria for clinically meaningful benefit was set at 19.0 months, corresponding to a 58% improved median overall survival (OS) associated with the historical control group (12.0 months). The primary endpoint was met; the median OS in this trial with the addition of durvulumab was 20.4 months. The 6-, 12-, and 24-month OS rates were 87.2%, 70.4%, and 44.2%, respectively, while corresponding progression-free survival (PFS) rates were 69.1%, 16.4%, and 10.9%. The median PFS was 6.7 months.

At the data cut-off on April 24, 2020, 56.4% of patients had a partial response, 40.0% had stable disease, and 1.8% had progressive disease.

Durvalumab combined with platinum-based chemotherapy was well tolerated, with no new safety signals. Grade 3 or higher adverse events occurred in 36 patients, probably immunotherapy related. Grade 1-2 adverse events were hypothyroidism (n=7), rash (n=5), pruritus (n=3), aspartate aminotransferase AST elevation (n=3), hyperthyroidism (n=3), dermatitis (n=2), neuropathy (n=2), alanine aminotransferase elevation (n=1), lipase increase (n=1), and pneumonitis (n=1).

Tumor mutational burden (TMB) and PD-L1 expression were also examined. Although not significant, median OS among patients was numerically higher in patients with a TMB of 24 or higher, at (27.9 months versus 14.2 months for those with TMB <24).

Forde P, et al. PrE0505: Phase II multicenter study of anti-PD-L1, durvalumab, in combination with cisplatin and pemetrexed for the first-line treatment of unresectable malignant pleural mesothelioma (MPM)—A PrECOG LLC study. ASCO Virtual Meeting, 29-31 May 2020, Abstract 9003.

TERAVOLT Registry Outcomes: Thoracic Cancers Versus COVID-19

■ In a global registry of 428 thoracic cancer patients infected with COVID-19, 169 patients have recovered, 119 are still infected with COVID-19, but 141 have died.

Leora Horn, MD, MS, Clinical Director of the Thoracic Oncology Program at Vanderbilt Ingram Cancer Center, presented the results of the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry. "Patients with thoracic malignancies are considered high-risk given their age, pre-existing comorbidities, smoking, and pre-existing lung damage in addition to therapies administered to treat their illness. We launched a global consortium to collect data on patients with thoracic malignancies diagnosed with COVID-19 infection to understand the impact on this patient population," she said.

The median age of recovered patients was 63.3; this age was a year older for those still being treated. Median age of patients with fatal cases was 70.2. Most patients were male. Patients had ECOG performance status of 0-1. Non-small cell lung cancer was the predominant subtype; 60-75% of patients had stage IV disease.

A total of 141 patients in the 428-patient registry have died (33%), suggesting considerable mortality risk. The cause of death in this cohort was mainly determined to be due to COVID-19 (79.4%), although 10.6% was ascribed to progressive cancer, and 8.5% to the combination of cancer and COVID-19. Of those who died, 5% had been on a ventilator. Alarmingly, 78% of patients with the combination of COVID-19 and thoracic cancer were admitted to the hospital.

Data collection is ongoing, but 1 publication has already been published from this registry, published in Cancer Cell.

Horn L, et al. Thoracic Cancers International COVID-19 Collaboration (TERAVOLT): Impact of type of cancer therapy and COVID therapy on survival. ASCO Virtual Meeting, 29-31 May 2020, Abstract LBA111.

Whisenant JG, et al. TERAVOLT: Thoracic Cancers International COVID-19 Collaboration [published online ahead of print, 2020 May 16]. Cancer Cell. 2020;10.1016/j.ccell.2020.05.008.

ES-SCLC: Pembrolizumab KEYNOTE-604 Data

■ Data from the phase 3 KEYNOTE-604 trial showed that patients with extensive-stage small cell lung cancer (ES-SCLC) who received pembrolizumab with backbone chemotherapy etoposide/platinum (EP) compared with patients who received EP and placebo did not benefit from improved overall survival (OS). However, progression-free survival (PFS) rates did reach the threshold for significance.

Charles M. Rudin, MD, PhD, Medical Oncologist at Memorial Sloan Kettering Cancer Center in New York, presented the findings. The KEYNOTE-604 study aimed to improve upon the efficacy of immunotherapy in newly diagnosed ES-SCLC with the combination of pembrolizumab and EP.

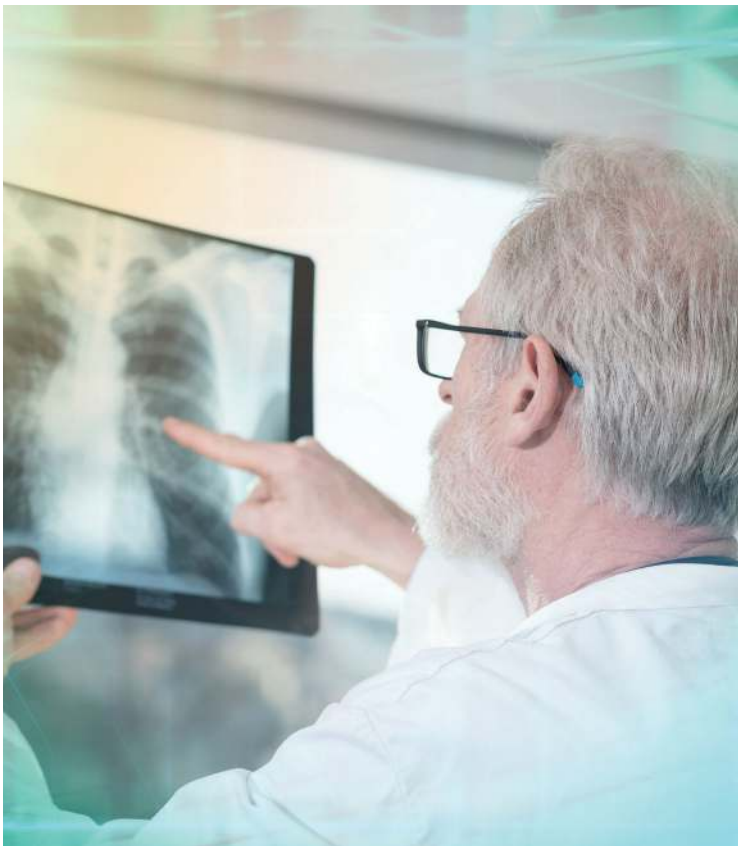
The study randomized 453 patients; pembrolizumab 220 mg on day 1 plus EP 100 mg/m2 on days 1 and 2 and carboplatin AUC 5 on day 1 or cisplatin 75 mg/m2 on day 1 (n=228) or placebo, matching EP, and carboplatin or cisplatin (n=225) for up to 31 cycles. The co-primary endpoints were PFS per RECIST v1.1 by blinded independent central review and OS. Secondary endpoints were overall response rate (ORR) and duration of response (DOR) per RECIST v1.1 by independent review as well as safety.

The final PFS analysis was significant (4.8 vs 4.3 months; HR: 0.73; 95% CI: 0.60-0.88). The 12-month PFS rate observed with the pembrolizumab combination was 15.9% versus 5.0% with the placebo combination. Even at 18 months, the PFS rate in the pembrolizumab arm was higher than the placebo arm at 10.8% versus 2.1%. In terms of OS, pembrolizumab/EP prolonged OS compared with the control combination (10.8 vs 9.7 months; HR: 0.80; 95% CI: 0.64-0.98; $P = 0.0164$), but it did not reach the superiority threshold, which was $P \leq 0.0128$. The 12-month OS rate was 45.1% in the pembrolizumab arm compared with 39.6% in the placebo arm. At 24 months, the OS rate was 22.5% in the pembrolizumab arm compared with 11.2% in the placebo arm.

The safety analysis showed that adverse events (AEs) of any-grade occurred in 100% of patients in the pembrolizumab arm and 99.6% of patients in the placebo arm, in the as-treated population. AEs were grade 3/4 in 76.7% of subjects who received pembrolizumab/EP compared with 74.9% of those who received the placebo combination. Grade 5 AEs/death occurred in 6.3% of patients in the pembrolizumab arm versus 5.4% in the control arm.

Placing these results in context, other trials looking at immunotherapy in this setting like the phase 3 IMpower 133 study, as well as the CASPIAN trial significantly improved OS compared with EP alone. However, both of these other trials provided stronger responses, raising the question of whether there may be a distinction in targeting PD-L1 as opposed to PD-1.

Rudin CM, et al. KEYNOTE-604: Pembrolizumab or placebo plus etopiside and platinum as first-line therapy for extensive-stage small cell lung cancer. ASCO Virtual Meeting, 29-31 May 2020, Abstract 9001.



Tiragolumab and Atezolizumab Shows Clinical Improvements in ORR in NSCLC

■ Tiragolumab and atezolizumab showed improved objective response rate over tiragolumab and placebo in chemotherapy-naïve locally advanced or metastatic non-small cell lung cancer (NSCLC).

Delvys Rodriguez-Abreu, MD, from the NYU Perlmutter Cancer Center, presented the phase 2 CITYSCAPE trial, which tested patients with chemotherapy-naïve PD-L1-positive locally advanced or metastatic NSCLC. Participants were randomized to the combination of tiragolumab and atezolizumab (n=67) versus placebo plus atezolizumab (n = 68). Co-primary endpoints were investigator-assessed objective response rate (ORR) and progression-free survival (PFS).

The primary analysis indicated that tiragolumab/atezolizumab improved ORR and median PFS compared with tiragolumab/placebo. The ORR was 31.3% in the tiragolumab arm versus 16.2% in the placebo arm. The median PFS was 5.4 months and 3.6 months in the tiragolumab and placebo arms, respectively (HR: 0.57).

According to the updated analysis, the ORR was 37.3% versus 20.6% in the tiragolumab and placebo arms, respectively. Investigators also stratified patients according to PD-L1 tumor proportion score (TPS, between 1- 49% versus > 50%). Patients with a PD-L1 TPS of at least 50% derived even more benefit from tiragolumab/atezolizumab with an ORR of 66% versus 24% with atezolizumab alone, whereas there was no difference between the treatment arms in the group whose tumors had a TPS between 1-49% PD-L1 positive cells.

Rodriguez-Abreu, D et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE) ASCO Virtual Meeting, 29-31 May 2020, Abstract 9503.

Phase 3 CheckMate 9LA: Nivolumab/ Ipilimumab Plus Chemotherapy Improves Overall Survival

■ In the CheckMate 9LA trial, a statistically significant improvement in overall survival (OS) was observed with nivolumab/ipilimumab plus 2 cycles of chemo versus 4 cycles of chemo in first-line advanced or metastatic non-small cell lung cancer (NSCLC), researchers reported.

CheckMate 9LA randomized 719 patients with stage IV or recurrent NSCLC who had no prior systemic therapy either to nivolumab (360 mg Q3W) plus ipilimumab (1 mg/kg Q6W) plus chemotherapy (2 cycles), or chemotherapy (4 cycles) alone. Patients in the experimental arm were treated with immunotherapy for up to two years or until disease progression or unacceptable toxicity. Patients in the control arm were treated with up to four cycles of chemotherapy and optional pemetrexed maintenance (if eligible) until disease progression or unacceptable toxicity.

At a pre-planned interim analysis, OS was significantly prolonged with nivolumab/ipilimumab plus chemotherapy versus chemotherapy alone, reported Martin Reck, MD, PhD, Head of Thoracic Oncology at the Lung Clinic Grosshansdorf in Germany. Median OS was 15.6 versus 10.9 months (HR 0.69; 95% CI: 0.55–0.80; P = 0.0006) and a one year overall survival rate of 63% compared with 47%. "The benefit in overall survival was seen in the majority of investigated subgroups and was consistent across the various levels of PD-L1 expression," said Dr. Reck in his presentation. In addition, progression-free survival was also improved in favor of the nivolumab/ipilimumab/chemo arm, with a hazard ratio of 0.68 and a 1-year progression-free survival rate of 33%, compared to 18% in the chemotherapy alone arm. No new safety signals were reported.

"The CheckMate-9LA study demonstrated that the combination of nivolumab and ipilimumab, together with a limited course of chemotherapy, should be considered as a new first line treatment opportunity for patients with advanced non-small cell lung cancer," he concluded.

Reck M, et al. ASCO 2020 virtual meeting, abstract 9501

First-line Durvalumab With or Without Tremelimumab in MYSTIC Study

■ In the phase 3 CCTG BR.34 trial, there was no additional effect on overall survival (OS) was observed by adding platinum-based chemotherapy to dual checkpoint inhibition in first-line advanced or metastatic con-small cell lung cancer (NSCLC).

The international, open-label, randomized CCTG BR.34 trial accrued 301 participants from Canada and Australia, with stage IV NSCLC, EGFR/ALK wildtype, ECOG PS 0/1. Patients were randomized to receive either durvalumab (1500 mg IV) plus tremelimumab (75 mg IV) for four cycles followed by durvalumab maintenance until disease progression or the same plus chemotherapy. Patients with squamous carcinoma received gemcitabine-based treatment, patients with non-squamous received pemetrexed-based therapy, including pemetrexed maintenance in addition to immunotherapy.

"At a median follow up of 16.6 months, no significant difference in OS was seen between the two treatment arms," reported Natasha Leighl, MD, Clinician Investigator at the Princess Margaret Cancer Centre in Toronto, Canada. Median OS was16.6 months with durvalumab/tremelimumab/chemo versus 14.1 months with durvalumab/tremelimumab (HR 0.88, 90% CI: 0.67-1.16; P=0.46). "There were some interesting trends, including [subgroups stratified] by sex, the presence of brain metastases, and pathologic subtype, but none of these were significant."

Median progression-free survival (PFS), however, was significantly improved in the durvalumab/tremelimumab/chemotherapy arm at 7.7 versus 3.2 months (HR 0.67; 95% CI: 0.52-0.88; P=0.0035), as was the objective response rate at 28% versus 14%, (odds ratio 2.51; 95% CI: 1.36-4.63; P=0.003). The addition of chemotherapy significantly increased toxicity, in particular for classically recognized side effects such as myelosuppression, nausea and vomiting, fever, both neutropenic and non-neutropenic, neuropathy, and alopecia. Grade 3 or higher adverse events were reported in 82% and 70% of patients, in the durvalumab/tremelimumab/chemotherapy arm and the durvalumab/tremelimumab arms, respectively.

Leighl NB, et al. ASCO 2020 virtual meeting, abstract 9502.

Addition of Nivolumab to Chemotherapy Significantly Improves Survival in ES-SCLC

■ In the phase 2 ECOG-ACRIN EA5161 trial, a significant improvement in both progression-free and overall survival was observed from adding the checkpoint inhibitor nivolumab to chemotherapy (cisplatin/carboplatin with etoposide) as frontline therapy for extensive-stage small cell lung cancer (ES-SLC), researchers reported in an oral presentation this year.

The ECOG-ACRIN EA5161 trial enrolled 160 patients with measurable (RECIST v1.1) ES-SCLC, who had not received prior systemic treatment for ES-SCL. Patients were randomized 1:1 to nivolumab 360 mg plus a platinum-based backbone (either cis/carboplatin) with etoposide every 21 days for 4 cycles followed by maintenance nivolumab 240 mg every 2 weeks until progression or up to 2 years, or to cis/carboplatin and etoposide every 21 days for 4 cycles followed by observation. The primary endpoint of this trial was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety assessments.

"In the nivolumab-plus-chemotherapy arm, the median progression-free survival was 5.5 months versus 4.7 months in the chemotherapy-alone arm. The hazard ratio is 0.68 with a P-value of 0.047," reported Ticiana Leal, MD, Assistant Professor at University of Wisconsin Carbone Cancer Center in Maddison. In the intention-to-treat population, the PFS in the nivolumab-plus-chemotherapy arm, is 5.5 months versus 4.6 months in the chemotherapy-alone arm (HR: 0.65; 95% CI: 0.46-0.91; P=0.012).

In addition, the median OS was improved by adding nivolumab to chemotherapy: 11.3 months versus 8.5 months (HR: 0.67; 95% CI: 0.46-0.98, P=0.038), as was the ORR (52% versus 47%) and the duration of response (5.6 months versus 3.3 months). The combination of nivolumab and chemotherapy was well tolerated with manageable toxicities.

"In conclusion, this trial confirms the efficacy of the combination of nivolumab and platinum-based chemotherapy in extensive-stage small cell lung cancer," said Dr. Leal.

Leal T, et al. ASCO 2020 virtual meeting, abstract 9000

Stereotactic Ablative Radiotherapy Plus Atezolizumab for Medically Inoperable Lung Cancer

■ Results from a randomized Phase 1 trial showed feasibility and safety of neoadjuvant and adjuvant atezolizumab with stereotactic ablative radiotherapy (SABR) for early stage, inoperable non-small cell lung cancer (NSCLC) patients

SABR is the standard-of-care for medically inoperable, early stage NSCLC, but regional and distant failures remain problematic. Preclinical data have suggested synergy between radiotherapy and checkpoint inhibition, and suggest that neoadjuvant delivery of checkpoint blockade may be superior to adjuvant-only delivery.

In a poster presentation, researches from the University of California Davis Comprehensive Cancer Center in Sacramento, reported the results of a phase 1 trial exploring the feasibility and safety of neoadjuvant atezolizumab plus SABR. Primary endpoint of the trial was to determine the maximum tolerated dose of atezolizumab plus SARB and the recommended phase 2 dose (RP2D).

In total, 20 patients with inoperable, T1-3 NSCLC were enrolled: 15 patients in the dose-finding phase and 5 patients at the recommended phase 2 dose. Patients received 6 cycles of atezolizumab. A 3+3 dose finding design was employed with 3 dose levels: 3 mg/kg, 10 mg/kg, and 1200 mg flat dosing. SABR was delivered starting cycle 3 to 50 Gy over 4-5 fractions. Dose limiting toxicity (DLT) was assessed during the first 9 weeks.

Atezolizumab 1200 mg flat dosing was the RP2D. Grade 3 pneumonitis was not observed. 15/20 patients completed all 6 cycles. Median progression-free survival was 25.5 months.

The researchers concluded that tezolizumab administrated before, during, and after SABR is feasible, and well tolerated in inoperable early-stage NSCLC. Antitumor activity was observed with 2 doses of atezolizumab. RP2D is 1200 mg. This combination will be tested in a randomized phase 3 trial SWOG/NRG S1914.

Kelly K, et al. ASCO 2020 virtual meeting, abstract 9011.

Trastuzumab Deruxtecan Demonstrates Durable Efficacy for HER2-Mutated NSCLC

■ DESTINY-Lung01 trial, trastuzumab deruxtecan (T-DXd) demonstrated clinical activity with a high objective response rate and durable response rate in patients with HER2-mutated non-small cell lung cancer (NSCLC), according to researchers.

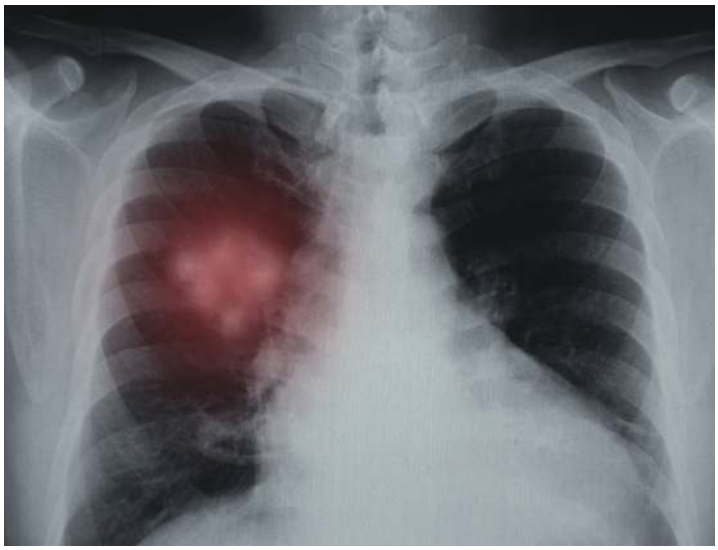
T-DXd is a novel antibody-drug conjugate. It consists of three components: a humanized, anti-HER2 monoclonal antibody, a topoisomerase I inhibitor payload, and an exatecan derivative, linked by a tetrapeptide-based cleavable linker. T-DXd has a high drug-to-antibody ratio of approximately 8; that is, there are eight molecules attached to one monoclonal antibody.

DESTINY-Lung01 is an ongoing, multicenter, phase 2 trial of T-DXd in patients with unresectable, metastatic non-squamous NSCLC who have relapsed or are refractory to standard treatments and whose tumors overexpress HER2 or contain a HER2-activating mutation. At data cut-off, 42 patients with HER2-mutation had received T-DXd. Median treatment duration was 7.75 month (range, 0.7-14.3 months); 45.2% of the patients remained on treatment.

"Confirmed objective response rate among these 42 patients was 61.9%; one patient had a complete response, 25 patients had a partial response," reported Egbert Smit, MD, Professor of Pulmonary Medicine at the Netherlands Cancer Institute in Amsterdam. Median duration of response was not reached at data cut-off. Estimated median progression-free survival was 14.0 months (95% CI: 6.4-14.0 months), median overall survival was not yet reached. Drug-related treatment-emergent adverse events (TEAE) grade ≥3 were observed in 22 patients (52.4%), and drug-related serious TEAE in 7 patients (16.7%). There were 5 cases (11.9%) of low-grade drug-related interstitial lung disease.

"These data demonstrate the potential of T-DXd as a new treatment option for patients with HER2-mutated non-small cell lung cancer," Dr. Smit concluded.

Smit EF, et al. ASCO 2020 virtual meeting, abstract 9504



A Trial of Pembrolizumab in Combination With Chemotherapy and Radiotherapy in Stage III NSCLC

■ Results from the phase 2 Keynote-799 trial show that addition of pembrolizumab to concurrent chemoradiation in patients with unresectable, stage IIIA-C NSCLC leads to objective response rates (ORR) that exceeded 50%, researchers reported.

Concurrent platinum doublet chemotherapy with radiotherapy is the first-line standard of care for patients with unresectable, stage III NSCLC. However, this approach provides a low five-year overall survival rate. The Keynote-799 trial, therefore, evaluated the addition of pembrolizumab to this first-line therapy. Patients in cohort A (n=112) received 1 cycle of pembrolizumab plus chemotherapy (paclitaxel/carboplatin), 2 cycles of immunochemotherapy plus concurrent radiotherapy, followed by up to 14 cycles pembrolizumab. Patients in cohort B (n=73, still recruiting) received 1 cycle of pembrolizumab plus chemotherapy (pemetrexed/cisplatin), 2 cycles of immunochemotherapy plus concurrent radiotherapy followed by up to 14 cycles pembrolizumab.

"Objective response rate, the primary endpoint of the trial, was 67.0% in cohort A and 56.6% in cohort B, predominantly partial responses," reported Salma Jabbour, MD, Professor of Radiation Oncology at Rutgers Cancer Institute in New Brunswick. Median duration of response has not yet been reached in both cohorts. Progression-free survival rate at 6 months was 81.4% in Cohort A and 85.2% in Cohort B. Overall survival rates at 6 months were 87.2% and 94.8% in Cohort A and Cohort B, respectively.

"The study's second primary objective was the incidence of grade 3 or higher pneumonitis. In both cohorts the rate of grade 3 or higher pneumonitis was less than 10%. One patient in Cohort B had interstitial lung disease. Four patients in Cohort A and none in Cohort B had treatment related grade 5 pneumonitis," said Dr. Jabbour. The incidence of other adverse events was consistent with the toxicity profiles of pembrolizumab monotherapy and advanced NSCLC and concurrent chemoradiotherapy in stage III NSCLC.

"Pembrolizumab plus concurrent chemoradiation shows promising anti-tumor activity in patients with unresectable locally advanced stage III NSCLC with an acceptable toxicity profile," he concluded.

Jabbour SK et al. ASCO 2020 virtual meeting, abstract 9008.

Emerging Treatment for Malignant Pleural Mesothelioma Improves Overall Survival

■ To date, second-line chemotherapy is not the standard of care in patients with malignant pleural mesothelioma (MPM). The multicenter, double-blind, randomized phase 2 RAMES Study explored the efficacy and the safety of the addition of the antibody targeting the vascular endothelial growth factor receptor 2 (VEGFR2/KDR) ramucirumab to gemcitabine as the second-line treatment in MPM patients after platinum/pemetrexed regimens. The primary endpoint of the trial was overall survival (OS). Second endpoints are progression-free survival (PFS), response rate, safety and quality of life.

The RAMES Study enrolled 161 patients with progressive disease after first-line treatment with platinum/pemetrexed. Patients were randomized to gemcitabine (1000 mg/m2 IV on days 1 and 8 every 21 days) plus placebo or gemcitabine plus ramucirumab (10 mg/kg IV on day 1, of a 21-day cycle), until tolerability or progressive disease. Median number of courses was 3.50 in the gemcitabine/placebo arm and 7.50 in the gemcitabine/ramucirumab arm.

"Addition of ramucirumab to gemcitabine significantly improved median OS," reported Maria Pagano, MD oncologist at General Hospital Arcispedale Santa Maria Nuova, in Reggio Emilia, Italy. "Median OS in the gemcitabine/ramucirumab arm was 13.8 months and 7.5 months in the gemcitabine/placebo arm. OS at 6 and 12 months were 74.7% and 56.5% in the gemcitabine/ramucirumab arm and 63.9% and 33.9% in the gemcitabine/placebo arm, respectively. The beneficial effect of ramucirumab was observed regardless of age, tumor histological type and time-to-progression from the first-line treatment."

A key secondary endpoint was PFS, which was 6.2 months in the gemcitabine/ramucirumab arm and 3.3 months in the gemcitabine/placebo arm (P=0.26) and disease control rates (complete response, partial response, stable disease, respectively) were 72.50% (0%, 6.25%. 66.25%) in the gemcitabine/ramucirumab arm and 42% (0%, 9.88%, 41.98%) in the gemcitabine/placebo arm. Addition of ramucirumab to gemcitabine did not result in an increase of toxicity. The safety profile was comparable to other anti-angiogenic agents, particularly featuring hypertension and thrombosis.

"The RAMES Study demonstrates that ramucirumab plus gemcitabine can be considered a new option for the second-line treatment in patients with MPM," concluded Dr. Pagano.

Pagano M, et al. ASCO 2020 virtual meeting, abstract 9004

Capmatinib In Patients With High-Level MET-Amplified Lung Cancer

■ MET-amplified advanced non–small cell lung cancer (NSCLC) responds well to MET-inhibitor capmatinib

MET-mutations and MET-amplifications are reported in 1-6% of patients with NSCLC. In the ongoing, multicohort phase 2 GEOMETRY trial, patients with stage III/IV NSCLC and high-level MET-amplification (gene copy number >10) respond well to capmatinib, a highly potent and selective inhibitor of the MET receptor tyrosine kinase, researchers reported at the virtual meeting of the American Society of Clinical Oncology.

In the GEOMETRY trial, 84 patients with high-level MET-amplification (ALK and EGFR wild-type, stage IIIB/IV) received capmatinib 400 mg twice daily (n=15 were treatment-naïve, n=69 were second or third-line). The primary endpoint of the trial was the objective response rate (ORR), while secondary endpoints were duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

"The ORR in the treatment-naïve patients was 40%, and 29% in the pre-treated patients," reported Jürgen Wolf, MD, PhD, Medical Director, University Hospital Cologne in Germany. "In the majority of patients these were partial responses." In addition, 40.6% of the pre-treated patients and 26.7% of the treatment-naïve patients showed stable disease, which results in a disease control rate of 71% and 66.7%, respectively. "The response rates observed in patients with high-level MET-amplification are more moderate compared with MET exon14 skipping mutation cohorts," said Dr. Wolf.

Median DOR was 8.31 months and 7.54 months and median PFS was 4.07 and 4.17 months in pre-treated and treatment-naïve patients, respectively. Median OS was 10.61 and 9.56 months in pre-treated and treatment-naïve patients, respectively. Capmatinib was well tolerated with a favorable safety profile, consistent with previous reports. "The most frequently observed toxicity was peripheral edema, nausea, vomiting, decreased appetite, and diarrhea," reported Dr. Wolf.

"In conclusion, these results show that capmatinib demonstrates clinical activity in patients with high-level MET-amplification NSCLC. As is the case in patients with MET exon 14-skipping mutation NSCLC, response rates seems somewhat higher in treatment-naïve patients compared with pre-treated patients."

Wolf J, et al. ASCO 2020 virtual meeting, abstract 9509

MET Antibody Mixture Sym015 is Safe and Efficacious in Patients with NSCLC

■ MET-mutations and MET-amplifications are reported in 1-6% of patients with NSCLC.

In a phase 2 basket trial Sym015, a mixture of antibodies targeting MET, was well tolerated and demonstrated clinical activity in 20 patients with MET-exon14 skipping deletion or MET-amplification non-small cell lung cancer (NSCLC), researchers reported at the virtual meeting of the American Society of Clinical Oncology.

"The two monoclonal antibodies of Sym015 bind to non-overlapping epitopes on MET," explained Ross Camidge, MD, PhD, Professor of Medicine and Medical Oncology at Colorado University. "The particular importance of this approach is that it's an additional way of downregulating MET signaling separate from that of tyrosine kinase inhibitors and may well work when kinase inhibitors fail because of kinase domain mutations."

In this phase 2 basket trial, 45 patients were treated with Sym015, including 20 NSCLC patients. Ten NSCLC patients were MET TKI-naïve, and 10 had been previously treated with a MET-directed therapy. Both groups had a mixture of tumors with MET-amplifications and with deletions resulting in MET-exon 14 skipping.

"Sym015 was well tolerated. There were relatively few dose reductions and in de NSCLC population peripheral edema, some fatigue, some mild gastrointestinal were the most common side effects," reported Dr. Camidge. "Six out of 45 patients experienced grade 3 adverse events, but no patients had to discontinue the treatment because of adverse events." Many the NSCLC patients were able to stay on the treatment for quite a long period of time. The average was 4.6 months, 5.2 months in those who were MET TKI-naïve, and 3.5 in those who were MET TKI pre-treated.

In MET TKI-naïve NSCLC patients, Sym015 was an active agent (50% overall response rate, 100% disease control rate) whereas in NSCLC patients who had previously had treatment with a MET TKI, only minor responses were observed. The trial also showed that circulating tumor DNA (ctDNA) was highly concordant for MET-exon 14 skipping deletions, but was not robust in detecting MET-amplification.

Camidge R, et al. ASCO 2020 virtual meeting, abstract 9510.

Adding Pembrolizumab to Concurrent Neoadjuvant Chemoradiation Feasible for Locally Advanced NSCLC

■ Long-term outcomes are still poor for patients with locally advanced NSCLC with about 60% of the stage IIIA patients recurring in 3 years, despite chemoradiation with or without surgery. Immune checkpoint inhibitor consolidation has improved outcomes in unresectable stage III patients. Therefore, the addition of concurrent neoadjuvant pembrolizumab to chemoradiation is an attractive target of investigation.

In a poster presentation at ASCO this year, researches from the Cleveland Clinic Foundation and the Perlmutter Cancer Center rereported the results of a phase 1 trial exploring the feasibility and safety of neoadjuvant chemoradiation plus pembrolizumab followed by consolidation pembrolizumab. A total of 9 patients with stage IIIA, resectable NSCLC were enrolled. They received neoadjuvant chemoradiation consisting of cisplatin, etoposide, and concurrent pembrolizumab (200 mg every 3 weeks x 3) with 45 Gy in 25 fractions. Patients without progression underwent resection followed by 6 months of consolidation pembrolizumab.

Six patients underwent complete resection with a pathologic complete response rate (pCR) of 67% (4/6). Consolidation pembrolizumab was started on 4 patients, with 3 completing treatment and 1 declined further treatment after 3 cycles.

Median follow-up was 19.6 months and median progression-free survival (PFS) had not yet been reached at data cut-off (6 month PFS 55.6%). None of the patients who underwent resection have recurred. Serious adverse events were reported in all 9 patients with most significant being 2 grade 5 events: 1 due to pneumocystis pneumonia after resection but prior to consolidation, and 1 due to cardiac arrest during the neoadjuvant phase. Grade 3 events included 1 episode each of pneumonitis, bronchopleural fistula, acute kidney injury, colon perforation, and febrile neutropenia.

The addition of pembrolizumab to neoadjuvant chemoradiation in resectable stage IIIA NSCLC patients resulted in a high pCR rate at resection, warranting further study, the researchers conclude. Larger studies are underway.

Lemmon C, et al. ASCO 2020 virtual meeting, abstract 9009.