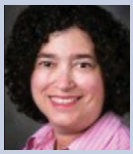
Thoracic Cancer: 2022 ASCO Annual Meeting Highlights for the Advanced Practitioner



Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC, of MD Anderson Cancer Center, reviews research in thoracic cancers presented at the 2022 ASCO Annual Meeting, including neoadjuvant immunotherapy for resectable stage IIIA non–small cell lung cancer, a new drug inhibiting *KRAS* G12C, and options after disease progression on immune checkpoint inhibitor treatment or targeted treatment.

Abstract 8501

Neoadjuvant Nivolumab and Chemotherapy: A New Standard for Resectable Stage IIIA NSCLC?

By JADPRO Staff

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.8501 to read the full abstract and view author disclosures.

At the annual American Society of Clinical Oncology (ASCO) meeting, more data was presented demonstrating that neoadjuvant chemoimmunotherapy is superior to chemotherapy in patients with resectable stage IIIA non-small cell lung cancer (NSCLC).

J Adv Pract Oncol 2022;13(6):579-585
https://doi.org/10.6004/jadpro.2022.13.6.3 • © 2022 Harborside™

Mariano Provencio-Pulla MD, PhD, lead author of the study, reported the results from the phase II NADIM clinical trial comparing neoadjuvant immunotherapy plus chemotherapy vs. chemotherapy for patients with resectable stage IIIA NSCLC. The results confirmed the superiority of combination neoadjuvant immunotherapy plus chemotherapy over chemotherapy in patients with resectable stage IIIA lung cancer.

Study Details

NADIM II is an open-label, randomized, phase II, multicenter clinical trial. Patients with resectable clinical stage IIIA NSCLC, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 to 1, and no known *EGFR*/ALK alterations were randomized to receive nivolumab 360 mg + paclitaxel 200 mg/m^2 + carboplatin area under the curve (AUC) 5 for 3 cycles every 21 days as neoadjuvant treatment followed by surgery, or paclitaxel + carboplatin at the same doses and schedule as the experimental arm followed by surgery. Patients with R0 resection confirmed by pathological evaluation started adjuvant administration of nivolumab within the third to eighth week (+7 days) from surgery and for 6 months.

The primary endpoint was pathological complete response (pCR) in the intent-to-treat population (ITT). pCR was defined as 0% viable tumor cells in resected lung and lymph nodes; patients who did not undergo surgery were classified as non-responders. Major pathological response (MPR; ≤ 10% viable tumor), overall response rate

(ORR), toxicity profile, and potential predictive biomarkers were secondary endpoints.

Study Findings

Between February 8, 2019, and November 11, 2021, 90 patients were enrolled, of whom 87 patients were evaluable. The combination of nivolumab + chemotherapy as neoadjuvant treatment significantly increased the pCR rate compared with chemotherapy (36.2% vs. 6.8%). There were also improved MPR rates (52% vs. 14%) and ORR (74% vs. 48%) in the ITT compared with the chemotherapy arm.

Almost all patients (91%) treated in the combination nivolumab + chemotherapy arm had surgical resection of their lung tumors, whereas 69% of patients treated with chemotherapy had surgery. Rarely was surgery canceled due to adverse events (1 patient in the combination arm) or due to disease progression (1 patient in the combination arm and 4 patients in the chemotherapy arm, respectively).

Patients in the combination arm had a higher incidence of grade 3 to 4–related adverse events compared with the chemotherapy arm (24% vs. 10%, respectively). In the combination arm, patients with higher pCR had higher PD-L1 tumor proportion score (median 70%) compared with non-responders (median 0%).

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

Immunotherapy has changed the treatment paradigm for patients in various stages of non–small cell lung cancer (NSCLC). It is US Food and Drug Administration (FDA)-approved in the adjuvant setting after surgical resection (atezolizumab; Tecentriq) or after concurrent chemotherapy and radiation therapy (durvalumab; Imfinzi). It has been approved in the metastatic setting either as a single agent or in combination with chemotherapy. Researchers are currently focusing on immunotherapy in the neoadjuvant setting.

Results of the NADIM II clinical trial were presented at this year's ASCO meeting. This was a small (90 patients enrolled, 87 treated) randomized clinical trial with chemotherapy (carboplatin and paclitaxel) plus immunotherapy (nivolumab; Opdivo) as the experimental arm compared with chemotherapy in the control arm. Patients with confirmed R0 resection received adjuvant nivolumab.

The results of the NADIM II study demonstrated the benefit of adding immunotherapy (nivolumab) to chemotherapy. The patients in the experimental arm had higher pathologic complete response rates, and nearly all the patients (91%) in the experimental arm had surgical resection. A lower percentage of patients (69%) in the control arm had surgery. Toxicities of grades 3 to 4 were higher, with 24% in the immunotherapy plus chemotherapy arm compared with 10% in the chemotherapy arm.

The phase II NADIM clinical trial and CheckMate 816 clinical trials demonstrate the benefit of adding immunotherapy to chemotherapy as neoadjuvant treatment. The combination of immunotherapy plus chemotherapy should be, if it is not already, the standard of care for patients with resectable lung cancer.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

Abstract 9002

Adagrasib Improves Outcomes in *KRAS*-Mutated NSCLC, Phase II Study Shows

By The ASCO Post Staff

Visit https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.9002 to read the full abstract and view author disclosures.

Nearly 43% of patients with non–small cell lung cancer (NSCLC) whose lung cancers harbored a specific *KRAS* mutation responded to the experimental drug adagrasib, and the targeted agent also showed activity against lesions in the brain that metastasized from the lung tumors, according to results of the KRYSTAL-1 trial presented at the 2022 ASCO Annual Meeting.

Mutations in *KRAS*, a potent oncogene, occur in about one in four patients with NSCLC, and approximately 13% of NSCLC patients' tumors are driven by a specific *KRAS* mutation called G12C. *KRAS* mutations have long been considered nearly impossible to attack with targeted drugs after many years of research attempts. However, in 2021 a targeted drug, sotorasib, became the first drug approved by the US Food and Drug Administration (FDA) for patients with NSCLC whose tumors harbored the G12C mutation, based on a clinical trial showing a 36% response rate in those patients after having initially received treatment with chemotherapy and a PD-1 immune checkpoint inhibitor.

KRYSTAL-1

Reporting the results of a new phase II trial, investigators led by Pasi Jänne, MD, PhD, Director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute, showed that treatment with a different *KRAS* G12C inhibitor, adagrasib, yielded a 42.9% objective response rate and a median overall survival rate of 12.6 months in a cohort of 112 patients who had previously received both chemotherapy and immunotherapy with a PD-1 immune checkpoint blocker. Notably, adagrasib treatment also achieved a 33.3% response rate in 33 patients who had stable metastatic lesions in the brain and central nervous system that had spread from the lung tumors.

"These data highlight that inhibiting *KRAS* G12C can lead to clinically meaningful benefits to NSCLC patients with this form of lung cancer," said Dr. Jänne. "Brain metastases are challenging to treat, and having a pharmacologic agent that shows activity in this setting is an advancement and movement in the right direction."

Patients with *KRAS* G12C mutations have had few options after initial chemotherapy and immunotherapy stopped working. In the new clinical trial of adagrasib, median progression-free survival was 6.5 months and the median response duration was 8.5 months. The oral drug was taken twice a day.

Because the *KRAS* G12C–mutated tumor cells typically continue to proliferate, researchers believe sustained inhibition with drugs may be necessary. Consequently, adagrasib was optimized for favorable properties including a long half-life (23 hours) and ability to penetrate the central nervous system. Clinical activity with adagrasib has been shown in patients with other *KRAS* G12C–mutated tumors, including colorectal, pancreatic, biliary tract, and other cancers.

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

KRAS is the most common driver mutation in non–small cell lung cancer (NSCLC). It is present in 25% of nonsquamous (adenocarcinoma) lung cancers. *KRAS* G12C is the most common of the *KRAS* mutations, comprising 40% to 50% of the *KRAS* mutations. The incidence of *KRAS* G12C is 13% in adencocarinoma (Liu et al., 2020; Skoulidis et al., 2021; Kempf et al., 2016). *KRAS* mutations are associated with poorer outcomes in NSCLC and are generally less sensitive/responsive to chemotherapy.

There is now an FDA-approved treatment for patients with *KRAS* G12C mutations, sotorasib (Lumakras). Adagrasib (MRTX849) is another treatment being studied in clinical trials for patients with *KRAS* G12C mutations. The results of cohort A in the phase II KRYSTAL-1 clinical trial were presented at this year's ASCO meeting.

In KRYSTAL-1 cohort A, 116 patients were enrolled and treated with adagrasib 600 mg bid orally. The majority of patients (112 patients, 98.3%) had previous treatment with immunotherapy and chemotherapy.

The overall response rate (ORR) was 42.9% (48/112 patients) for patients who had prior chemotherapy plus immunotherapy, and the disease control rate was 79.5% (89/112 patients). Many patients had stable disease on adagrasib after previous triplet therapy. The duration of response (DOR) was just under 9 months, progression-free survival (PFS) was 6.5 months, and the median overall survival (OS) was 12.6 months. Additionally, there are findings that adagrasib has activity in treating brain metastases.

The most common treatment-related adverse events (TRAEs) were gastrointestinal, including diarrhea, nausea, vomiting, and fatigue. Elevated liver enzymes, increased alanine aminotransferase/aspartate aminotransferase (ALT/AST), elevated creatinine, increased lipase, and anemia were also reported.

The findings from this study show the efficacy of adagrasib for patients with NSCLC and *KRAS* G12C mutation. A phase III clinical trial is ongoing. What was once a difficult mutation to treat may soon have two oral therapeutic options.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

References

Liu, S. V., Vanderwalde, A. M., Mamdani, H., Raez, L. E., Baca, Y., Xiu, J.,...Borghaei, H. (2020). Characterization of KRAS mutations (mt) in non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology, 38*(15_suppl), 9544. https://doi.org/10.1200/JCO.2020.38.15_suppl.9544

Skoulidis, F., Li, B. T., Dy, G. K., Price, T. J., Falchook, G. S., Wolf, J.,...Tran, Q. (2021). Sotorasib for lung cancers with KRAS p.G12C mutation. *New England Journal of Medicine, 384*(25), 2371–2381. https://doi.org/10.1056/nejmoa2103695

Kempf, E., Rousseau, B., Besse, B., & Paz-Ares, L. (2016). *KRAS* oncogene in lung cancer: Focus on molecularly driven clinical trials. *European Respiratory Review, 25*(139), 71–76. https://doi.org/10.1183/16000617.0071-2015

Abstract 9004

Ramucirumab/Pembrolizumab vs Standard of Care in Patients With Advanced NSCLC Previously Treated With Immune Checkpoint Inhibitors

By Matthew Stenger

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.9004 to read the full abstract and view author disclosures.

In the phase II Lung-MAP substudy S1800A presented at the 2022 ASCO Annual Meeting, the combination of ramucirumab and pembrolizumab improved overall survival vs investigator's choice of standard-of-care treatment in patients with advanced non–small cell lung cancer (NSCLC) who experienced disease progression on prior immune checkpoint inhibitor therapy.

As stated by the investigators, "Resistance to immune checkpoint inhibition in advanced NSCLC represents a major unmet need. Combining immune checkpoint inhibition with vascular endothelial growth factor (VEGF)/VEGF receptor inhibition has yielded promising results in multiple tumor types."

Study Details

The US multicenter open-label trial included 136 eligible patients with stage IV or recurrent disease previously treated with an immune checkpoint inhibitor and platinum-based chemotherapy who had progressive disease at least 84 days after initiation of immune checkpoint inhibitor treatment. They were randomly assigned between May 2019 and November 2020 to receive ramucirumab plus pembrolizumab (n = 69) or investigator's choice of standard-of-care treatment (n = 67). Patients had to be ineligible for a biomarker-matched substudy within the Lung-MAP trial. Treatment consisted of ramucirumab at 10 mg/kg plus pembrolizumab at 200 mg once every 21 days, with standard-of-care choices including docetaxel/ramucirumab (n = 45), docetaxel

(n = 3), gemcitabine (n =12), or pemetrexed (n = 1); six patients in the standard-of-care group received no treatment. The primary objective was to compare overall survival using a one-sided 10% level using a standard log-rank (SLR) and weighted log-rank (WLR) test; if either *P* value was < .0972, the study was considered to have rejected the null hypothesis.

Overall Survival

Median follow-up among surviving patients was 17.9 months (range = 1–30 months). Median overall survival was 14.5 months (80% confidence interval [CI] = 13.9–16.1 months) in the ramucirumab/pembrolizumab group vs 11.6 months (80% CI = 9.9–13.0 months) in the standard-of-care group (hazard ratio [HR] = 0.69, 80% CI = 0.51–0.92, SLR *P* = .05, WLR *P* = .15).

Investigator-assessed median progression-free survival was 4.5 months (80% CI = 4.2–6.1 months) vs 5.2 months (80% CI = 4.2–5.7 months; HR = 0.86, 80% CI = 0.66–1.14, SLR P = .25, WLR *P* = .14). Objective response rates were 22% vs 28% (*P* = .19).

Adverse Events

Grade ≥ 3 treatment-related adverse events occurred in 42% of patients in the ramucirumab/pembrolizumab group and 60% of the standard-of-care group. Treatment-related grade 4 events occurred in 4 vs 15 patients. Treatment-related death occurred in three patients in the ramucirumab/pembrolizumab group, due to cardiac arrest, respiratory failure, and unknown cause, respectively. Treatment-related death occurred in four patients in the standard-of-care group: due to sepsis in one patient and respiratory failure in two patients receiving docetaxel/ramucirumab, and sepsis in one patient on single-agent chemotherapy.

The investigators concluded, "This randomized phase II trial demonstrated significantly improved overall survival with ramucirumab/pembrolizumab compared with standard of care in patients with advanced NSCLC previously treated with immune checkpoint inhibitors and chemotherapy. The safety was consistent with known toxicities of both drugs. These data warrant further evaluation."

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

Lung cancer treatments, including immune checkpoint inhibitors (ICI), may develop resistance and lose their efficacy. Chemotherapy or a clinical trial may be considered for second-line treatment. This phase II randomized trial evaluated a non-chemotherapy–containing arm compared with standard of care (SOC) treatment. The results from the phase II randomized study of ramucirumab (Cyramza) plus pembrolizumab (Keytruda) vs. standard of care for advanced non–small cell lung cancer (NSCLC) previously treated with immunotherapy—Lung-MAP substudy S1800A—were presented at this year's ASCO meeting.

S1800A is a randomized clinical trial for patients who are not eligible for a biomarker-matched substudy and whose lung cancer developed resistance to ICI. Patients were stratified by PD-L1 expression, histology, and intent to receive ramucirumab in the SOC arm. Patients were randomized to the experimental arm (ramucirumab plus pembrolizumab) or the SOC arm. Treatments on the SOC arm were investigator's choice, including docetaxel + ramucirumab, docetaxel, pemetrexed, and gemcitabine.

The primary objective of the study was comparison of overall survival (OS) between the two arms; secondary endpoints were response, duration of response (DOR), progression-free survival (PFS) and safety. Out of 166 patients enrolled, 137 patients were eligible to participate in the clinical trial; 69 patients received ramucirumab + pembrolizumab; 68 patients received SOC treatment.

Results of the study demonstrated improved OS with the ramucirumab + pembrolizumab arm; the median is 15 months vs. 11.6 months for SOC. PFS was similar between the two arms, with median PFS 4.5 months for the experimental arm and 5.2 months for SOC. ORR was also similar between the two arms.

This study has shown that patients previously treated with an ICI may still benefit from the combination of ramucirumab plus ICI (pembrolizumab). Again, immunotherapy is changing the treatment for patients with lung cancer.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

Abstract 9006

Amivantamab and Lazertinib Combination Shows Promise for *EGFR*-Mutated Osimertinib-Resistant NSCLC

By JADPRO Staff

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.9006 to read the full abstract and view author disclosures.

Updated results from the CHRYSALIS-2 study reveal that amivantamab (a bispecific antibody targeting EGFR and MET receptors) and lazertinib (a third-generation EGFR tyrosine kinase inhibitor) demonstrate durable efficacy in patients whose disease progressed after standard-of-care osimertinib and platinum-based chemotherapy. For patients who have exhausted options, including heavily pretreated patients, the combination holds promise.

Study Details

Cohort A evaluated amivantamab and lazertinib in patients with *EGFR* exon 19 deletion or exon 21 *L858R* NSCLC whose disease progressed on first- or second-line osimertinib followed by chemotherapy as last line of therapy (target population, n = 106) and among a more heavily-pretreated population (n = 56) whose disease progressed after osimertinib and chemotherapy along with other therapies without regard to number and sequence of these therapies. Patients received 1,050 mg IV amivantamab (1,400 mg, ≥ 80 kg) + 240 mg oral lazertinib.

Study Results

162 patients were enrolled in Cohort A. The median time between last osimertinib treatment to first dose of amivantamab + lazertinib was 6.3 months and 2.0 months for the target and heavily-pretreated populations, respectively. Of 50 efficacy-evaluable patients in the target population, the overall response rate (ORR) by blinded independent central review (BICR) was 36%, with 1 complete response (CR) and 17 partial responses (PRs), and the clinical benefit rate (CBR) was 58%.

Median duration of response (mDOR) was not reached based on BICR. At a median follow-up of 8.3 months, 39% (7 responders) achieved a DOR lasting ≥ 6 months by BICR. Investigator-assessed responses were consistent with BICR. Of 56 efficacy-evaluable patients in the heavily-pretreated population (8.7-mo median follow-up), ORR was 29%, with 1 CR and 15 PRs. CBR was 55% and mDOR was 8.6 mo. BICR results are pending.

Adverse Events

Preliminary evidence of central nervous system antitumor activity was reported among 8 patients with baseline brain lesions (7 non-target, 1 target) who had not received radiation within 1 year prior to study enrollment. The most frequent adverse events (AE) were infusion-related reaction (65%), paronychia (49%), rash (41%), and stomatitis (39%). Most common grade ≥ 3 treatment-related AEs (TRAEs) were infusion-related reactions (7%), acneiform dermatitis (5%), and hypoalbuminemia (4%). TRAEs leading to discontinuation of either or both amivantamab and lazertinib occurred in 12% and 7%, respectively.

Conclusions

Among an unselected population that has exhausted SOC osimertinib and chemotherapy, amivantamab and lazertinib demonstrate encouraging antitumor activity with a manageable safety profile. The phase III MARIPOSA and MARIPOSA-2 trials are now investigating amivantamab plus lazertinib as a first-line regimen and in combination with carboplatin plus pemetrexed after osimertinib, respectively.

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

Osimertinib (Tagrisso) is the first-line treatment for patients with *EGFR* exon 19 deletion or exon 21 *L858R* mutations. When resistance to osimertinib occurs, second-line treatment has been platinum-based chemotherapy. The phase I CHRYSALIS trial evaluated the combination of amivantamab (Rybrevant) plus lazertinib (Leclaza) for patients who had disease progression after treatment with osimertinib and subsequent doublet chemotherapy.

The combination of amivantamab and lazertinib showed efficacy in the phase I CHRYSALIS clinical trial. Those results were presented at the 2021 ASCO Annual Meeting. At this year's ASCO Annual Meeting, results from the larger phase II clinical trial were presented.

Results again demonstrated the combination of amivantamab plus lazertinib has activity in patients previously treated with osimertinib and chemotherapy. The median follow-up for 50 efficacy-evaluable patients was 8.3 months; median duration of response was not reached. Seven responders (39%) achieved a duration of response of > 6 months. One patient had a complete response, and 17 patients had partial responses. There are preliminary data that the combination has an effect on central nervous system disease.

The results of the phase II CHRYSALIS-2 clinical trial confirmed the findings from the phase I CHRYSALIS trial. The combination of amivantamab and lazertinib has activity in patients previously treated with osimertinib and chemotherapy.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.