Highlights in Lung Cancer

Commentary by Edward S. Kim, MD

Adjuvant Osimertinib Improves Overall Survival in *EGFR*-Mutated Lung Cancer

The use of osimertinib (Tagrisso, AstraZeneca) after surgery improves overall survival (OS) in patients with early-stage, *EGFR*-mutated non–small cell lung cancer (NSCLC), according to the most recent results of the ADAURA trial. ADAURA is the first phase 3 trial to show improved OS with an epidermal growth factor receptor (EGFR)-targeting agent following surgery for NSCLC.

For the study, Dr Roy S. Herbst and colleagues enrolled 682 patients who had undergone a complete resection of stage IB to IIIA, *EGFR*-mutated NSCLC. After stratification by stage (IB vs II vs IIIA), type of *EGFR* mutation (exon 19 deletion vs L858R), and race (Asian vs non-Asian), patients were randomly assigned in a 1:1 ratio to receive osimertinib at 80 mg once daily or a placebo once daily for up to 3 years. The primary endpoint was disease-free survival (DFS) by investigator assessment.

In the updated primary DFS analysis published online in the *Journal of Clinical Oncology* on January 31, 2023, the median DFS was 65.8 months with osimertinib vs 28.1 months with placebo, for a hazard ratio (HR) of 0.27 (95% CI, 0.21-0.34). The same analysis also showed a reduction in brain metastases with osimertinib vs placebo, with an HR of 0.24 (95% CI, 0.14-0.42) for median central nervous system DFS. Osimertinib had a tolerable safety profile, with grade 3 or higher adverse events (AEs) occurring in 23% of patients in the osimertinib group vs 14% in the placebo group, and no fatal AEs in either group.

The current analysis showed that osimertinib vs placebo improved OS in the overall group (HR, 0.49; 95.03% CI, 0.34-0.70; *P*<.0001) and in the stage II to IIIA group (HR, 0.49, 95.03% CI, 0.33-0.73; *P*=.0004). The 5-year OS rate was also higher for osimertinib vs placebo in the overall group than in the placebo group, at 88% vs 78%, respectively, and in the stage II to IIIA group, at 85% vs 73%, respectively. The OS benefit with osimertinib vs placebo occurred across subgroups, including by disease stage and regardless of prior adjuvant chemotherapy use.

Dr Herbst concluded that the results of this study "reinforce adjuvant osimertinib as standard of care for patients with resected *EGFR*-mutated stage IB to IIIA NSCLC." Follow-up is ongoing.

Herbst RS, Tsuboi M, John T, et al. Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC) [ASCO abstract LBA3]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: The ADAURA study is truly a game changer. The improvement in OS that was reported at this year's meeting clearly demonstrates the promise of osimertinib that was initially seen several years ago when we first saw data on the improvement in DFS. We have always dreamed of approaching patients with early-stage lung cancer similarly to the way we approach patients with breast cancer, with the ability to provide biomarker-based treatment. Thanks to the results of this study, we can feel confident in doing so.

Perioperative Pembrolizumab Improves Survival in Resected NSCLC

The addition of neoadjuvant and adjuvant pembrolizumab (Keytruda, Merck) to standard treatment improves event-free survival (EFS) in patients with resected NSCLC, according to the results of the phase 3 KEYNOTE-671 trial. Many patients experience recurrence when pembrolizumab is used either before or after surgery.

The study, which was presented by Dr Heather A. Wakelee, enrolled 797 patients with resectable stage II to IIIB NSCLC who had not received prior therapy and were able to undergo surgery. All patients received neoadjuvant chemotherapy with cisplatin plus either gemcitabine or pemetrexed for 4 cycles, followed by surgery. In addition, patients were randomly assigned in a 1:1 ratio to receive neoadjuvant pembrolizumab (200 mg every 3 weeks for 4 cycles) and adjuvant pembrolizumab (200 mg every 3 weeks for an additional 13 cycles), or neoadjuvant and adjuvant placebo. The primary endpoints were investigator-assessed EFS and OS.

After a median follow-up of 25.2 months, the median EFS rate was not reached in the pembrolizumab group vs 17.0 months in the placebo group, for an HR of 0.58 (95% CI, 0.46-0.72; *P*<.001). The estimated 24-month EFS rate was 62.4% vs 40.6%, respectively, and perioperative pembrolizumab benefited EFS across all subgroups analyzed. The response rates were significantly higher with pembrolizumab than with placebo, at 30.2% vs 11.0% for major pathologic response and 18.1% vs 4.0% for pathologic complete response. The OS rate in the pembrolizumab group did not reach statistical significance at this

first interim analysis. No new safety signals were noted.

Dr Wakelee concluded that the results of this study "support the use of perioperative pembrolizumab as a promising new treatment option for patients with resectable stage II to IIIB NSCLC." She emphasized the need for more widespread adoption of lung cancer screening to detect more cases of NSCLC at an early stage.

Wakelee HA, Liberman M, Kato T, et al. KEYNOTE-671: randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early stage NSCLC [ASCO abstract LBA100]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The KEYNOTE-671 study further demonstrates the importance of immunotherapy treatment in NSCLC, adding to the data on the efficacy of immunotherapy in the neoadjuvant or perioperative setting. We are observing a clear benefit with the use of chemotherapy and immunotherapy—in this case, pembrolizumab—in patients we are treating with curative intent. We tried for decades to demonstrate a role for neoadjuvant or perioperative therapy, and now we have seen that immunotherapy is an important part of this treatment regimen.

Pembrolizumab Does Not Improve Survival in Pretreated, *EGFR*-Mutated, Metastatic Nonsquamous NSCLC

The addition of pembrolizumab to chemotherapy does not improve progression-free survival (PFS) or OS in patients with *EGFR*-mutated, metastatic nonsquamous NSCLC that is resistant to tyrosine kinase inhibitors (TKIs), according to the results from the phase 3 KEYNOTE-789 study. EGFR TKIs are the standard first-line treatment for patients with metastatic NSCLC who have sensitizing *EGFR* mutations, but most patients eventually develop resistance.

The study, presented by Dr James Chih-Hsin Yang, enrolled patients with stage IV nonsquamous NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, an exon 19 deletion or L858R *EGFR* mutation, and progression after EGFR TKI treatment. A total of 492 patients were randomly assigned in a 1:1 ratio to treatment with either pembrolizumab at 200 mg or placebo every 3 weeks for 35 cycles; all patients received pemetrexed or a platinum agent every 3 weeks for the first 4 cycles. Patients in the placebo group had the option of crossing over to the pembrolizumab group. The primary endpoints were PFS, as determined by blinded independent central review, and OS.

At the final analysis, which took place after a median follow-up of 42 months, 50 patients had crossed from the placebo group to the pembrolizumab group, and an additional 38 patients from the placebo group had received a subsequent programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor, for an effective crossover rate of 35.6%. At the second interim analysis, with a median follow-up of 29 months, the median PFS was 5.6 months in the pembrolizumab group and 5.5 months in the placebo group, which was not a statistically significant difference (HR, 0.80; 95% CI, 0.65-0.97; *P*=.0122). Median OS at the final analysis also was not statistically significantly different between the pembrolizumab group and the placebo group, at 15.9 vs 14.7 months, respectively (HR, 0.84; 95% CI, 0.69-1.02; *P*=.036). PD-L1 expression did not statistically significantly affect OS. Grade 3 or higher treatment-related AEs occurred in 43.7% of patients in the pembrolizumab arm and 38.6% of those in the placebo arm, with AEs being manageable in both patient groups.

Dr Yang said that the results were "consistent with prior findings that TKI-resistant, *EGFR*-mutant metastatic NSCLC derives less benefit from anti–PD-1/PD-L1 treatment than *EGFR* wild-type metastatic NSCLC." The results were simultaneously published in the *New England Journal of Medicine* with Tsuboi as the first author.

Yang JC-H, Lee DH, Lee J-S, et al. Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, EGFR-mutant, metastatic nonsquamous NSCLC: phase 3 KEYNOTE-789 study [ASCO abstract LBA9000]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The KEYNOTE-789 study looked at the potential role of pembrolizumab in patients with *EGFR*-mutated NSCLC. This study looked at patients with TKI-resistant disease and showed there was no benefit with the addition of pembrolizumab in this population. Thanks to the results of this trial, we can clearly state that immunotherapy should be avoided in patients with *EGFR* mutations.

Tumor Treating Field Therapy Improves OS in Platinum-Resistant, Metastatic NSCLC

Tumor-treating field therapy, known as TTFields (Optune Lua, Novocure), improves OS in patients with platinum-resistant, metastatic NSCLC, according to results of the phase 3 LUNAR trial.

"TTFields therapy should be considered part of standard of care [SOC] for metastatic NSCLC following progression after platinum-based chemotherapy," said Dr Ticiana Leal, who presented the results of the study.

LUNAR enrolled 276 adults with metastatic NSCLC that was progressing despite current or prior platinum therapy and an ECOG performance status of 0 to 2. Previous use of checkpoint inhibition was permitted. Patients

were randomly assigned in a 1:1 ratio to receive TTFields (delivered until progression or intolerable toxicity) plus SOC or SOC alone. SOC consisted of the physician's choice of either a checkpoint inhibitor or docetaxel. The primary endpoint was OS.

After a median follow-up of 10 months, median OS was significantly higher in the TTFields group than in the control group, at 13.2 vs 9.9 months, respectively (HR, 0.74; 95% CI, 0.56-0.98; *P*=.035). There was also a trend toward improved 1-year OS in the TTFields group vs the control group, at 53% vs 42%, respectively, and improved median PFS, at 4.8 vs 4.1 months, respectively (HR, 0.87; 95% CI, 0.67-1.14). The difference in median OS between the TTFields group and the control group was especially pronounced among the 134 patients who were receiving a checkpoint inhibitor, at 18.5 vs 10.8 months, respectively (HR, 0.63; 95% CI, 0.41-0.96; *P*=.032), a difference of approximately 8 months. The difference in median OS between the TTFields group and the control group was not statistically significant among the 142 patients in the docetaxel subgroup, at 11.1 vs 8.7 months, respectively (HR, 0.81; 95% CI, 0.55-1.19; *P*=.28). The AE rate was similar between the TTFields group and the SOC group, at 97% vs 91%. No grade 4 toxicities and no deaths were attributed to TTFields.

TTFields is a type of electromagnetic field therapy that uses low-intensity, intermediate frequency electrical fields to treat patients with cancer. Preclinical models have shown that it amplifies the effects of checkpoint inhibitors and taxanes. TTFields received US Food and Drug Administration approval in 2011 for glioblastoma and in 2019 for mesothelioma.

Leal T, Kotecha R, Ramlau R, et al. Tumor Treating Field (TTFields) therapy with standard of care (SOC) in metastatic non-small cell lung cancer (mNSCLC) following platinum failure: randomized, phase 3 LUNAR study [ASCO abstract LBA9005]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: The LUNAR study continues to show encouraging results with the use of tumor-treating field therapy across different tumor types. This study enrolled 276 patients with metastatic NSCLC and demonstrated an improvement in OS with the addition of tumor treatment fields to standard treatment with chemotherapy or checkpoint inhibition. Based on these results, this approach should be further investigated.

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