Editorial Commentary

ADAURA update: only the end of the beginning

Bharathi Muthusamy, Nathan A. Pennell

Department of Hematology and Medical Oncology, Cleveland Clinic-Taussig Cancer Institute, Cleveland, OH, USA

Correspondence to: Bharathi Muthusamy, MD. Department of Hematology and Medical Oncology, Cleveland Clinic-Taussig Cancer Institute, 10201 Carnegie Avenue, Cleveland, OH 44195, USA. Email: muthusb@ccf.org.

Comment on: Herbst RS, Wu YL, John T, *et al.* Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40. Erratum in: J Clin Oncol 2023;41:3877.

Keywords: Non-small cell lung cancer (NSCLC); ADAURA; adjuvant osimertinib

Submitted Apr 06, 2023. Accepted for publication May 17, 2023. Published online May 22, 2023.
doi: 10.21037/tlcr-23-237
View this article at: https://dx.doi.org/10.21037/tlcr-23-237

The treatment of early-stage epidermal growth factor receptor (*EGFR*) mutation-positive (*EGFR*m+) non-small cell lung cancer (NSCLC) finally began to change for the better after the first ADAURA results were published in October 2020. Until then, chemotherapy was the only perioperative, systemic tool available albeit with a meager 5-year overall survival (OS) improvement of 4–5% (1,2). By comparison, the initial results of ADAURA showed that 3 years of adjuvant osimertinib improved 24-month disease-free survival (DFS) by 37% in patients with *EGFR*m+, stage IB–IIIA NSCLC. Moreover, there was an improved 24-month central nervous system (CNS) DFS of 13% compared to placebo (3). A little over a month after ADAURA was presented to the world, adjuvant osimertinib was approved by the Food and Drug Administration and added to National Comprehensive Cancer Network guidelines soon after (4).

One concern about these initial results was that the analysis was premature and done during an unplanned interim analysis at 24 months of follow up. Most patients were still in the midst of their 3 years of treatment at that time, leaving open the possibility that the DFS improvement seen at that time point would disappear after patients stopped osimertinib. However, the final DFS data recently published by Herbst and colleagues confirmed the benefit from adjuvant osimertinib (5). At 48 months and thus at least a year after stopping osimertinib, 73% of patients in the osimertinib arm were disease-free and alive compared to 38% in the placebo arm. Hazard ratios (HRs) for both the intention-to-treat (ITT) (stage II–IIIA) and overall (stage IB–IIIA) populations continued to be low at 0.23 and 0.27 along with a CNS DFS HR of 0.24 in the ITT group (5). Between the persistent and clinically significant DFS improvement in the final analysis, and perhaps more significantly the March 2023 announcement from AstraZeneca that OS was also significantly improved in the tyrosine kinase inhibitor (TKI) arm, osimertinib has solidified its place in the adjuvant space (6). Despite the positive news, however, there are still important questions that still need to be answered.

The first unanswered question is how long should patients be treated with adjuvant osimertinib? Three years was arbitrarily chosen for the ADAURA trial but may not be long enough for certain patients. The DFS curve for the osimertinib arm has a sharper decline after 3 years, most noticeable in the curve for stage IIIA patients in the previous update presented at the European Society of Medical Oncology Congress 2022, suggesting that in some of these patients their disease may have been suppressed by the TKI. The stage IB curve, meanwhile, was relatively stable (7). Also, 15/18 CNS recurrences occurred while off of osimertinib compared to only 3/32 in the placebo group (3). These results could signify that certain subgroups may benefit from a longer duration of adjuvant osimertinib, although who that should be is currently unknown. Presently, the TARGET trial is ongoing to evaluate 5-year of osimertinib for patients with resected stage II–IIIB disease (NCT05526755).

Other important questions include whether TKI treatment is best given before resection, after resection or

both? And how should chemotherapy, with its small but proven OS benefit, be sequenced? The NEOADAURA trial is currently evaluating neoadjuvant osimertinib with or without chemotherapy *vs.* chemotherapy alone for stage II–IIIB (N2) disease (NCT04351555). After resection any adjuvant therapy is left up to investigator choice, which can also include osimertinib (8). It will be interesting to see if the use of adjuvant osimertinib will be balanced between the arms, because if NEOADAURA also has positive results, there may be confusion between using a neoadjuvant and/or adjuvant osimertinib. Ideally, there would be a study directly comparing preoperative *vs.* postoperative treatment, but we might first see a combination of neoadjuvant plus adjuvant *vs.* either neoadjuvant or adjuvant alone.

While we as a field work to answer the above questions, we can confidently say that some manner of perioperative osimertinib will be widely used to prevent recurrence and prolong survival for patients with early-stage *EGFR*m+ NSCLC, exposing many to potential long term side effects. While health-related quality of life does not seem to be drastically affected with adjuvant osimertinib, this does not mean that it is not without negative clinical and financial effects (9,10). While it is critical to continue investigations into perioperative osimertinib combinations and timing, we need to be just as diligent on making osimertinib regimens as patient-specific as possible to reduce the clinical and financial risks to those who may not benefit. For example, a patient with stage IIA disease may not need as long a course of adjuvant treatment as someone with stage IIIA. Ideally, we would have better markers of risk than stage, and this is where research on biomarkers such as using circulating tumor DNA to detect minimal residual disease (MRD), and risk scores similar to Oncotype DX in breast cancer, can help define those who may benefit the most from adjuvant osimertinib and perhaps spare those who don't need it. Some ongoing trials like NEOADAURA are incorporating MRD testing into their exploratory analyses (8). The next step would be to see if such results can be applied clinically for patient selection or treatment de-escalation.

While we wait for more information on the best way to utilize perioperative osimertinib, we at least now know that adjuvant osimertinib improves DFS (and OS of an unknown magnitude) in stage IB–IIIA, *EGFR*m+ NSCLC. And although this is certainly not the end of the question, to paraphrase Winston Churchill, it may be the end of the beginning. We owe it to our patients to continue to be comprehensive in our investigations and continue to find ways to improve survival for early-stage NSCLC while limiting overtreatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-237/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-237/coif). NAP received consulting fees from Merck, Pfizer, Mirati, Eli Lilly, Genentech, Sanofi Genzyme, Novartis, Takeda, Bayer, Summitt Therapeutics, and Anheart for participating in the Advisory Board. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
2. NSCLC Meta-analyses Collaborative Group; Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without

postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
3. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
4. Enttiger D, Wood D, Aisner D, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2. 2023. Available online: https://www.nccn.org/ (Accessed March 16, 2023).
5. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40. Erratum in: J Clin Oncol 2023.
6. Tagrisso demonstrated strong overall survival benefit in the ADAURA Phase III trial for adjuvant treatment of patients with early-stage EGFR-mutated lung cancer. Available online: https://www.astrazeneca.com/media-centre/press-releases/2023/tagrisso-demonstrated-strong-overall-survival-benefit-in-the-adaura-phase-iii-trial.html (Accessed March 20, 2023).
7. Tsuboi M, Wu YL, Grohe C, et al. LBA47 Osimertinib as adjuvant therapy in patients (pts) with resected EGFR-mutated (EGFRm) stage IB-IIIA non-small cell lung cancer (NSCLC): Updated results from ADAURA. Ann Oncol 2022;33:S1413-4.
8. Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. Future Oncol 2021;17:4045-55.
9. Majem M, Goldman JW, John T, et al. Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial. Clin Cancer Res 2022;28:2286-96.
10. Lemmon CA, Zabor EC, Pennell NA. Modeling the Cost-Effectiveness of Adjuvant Osimertinib for Patients with Resected EGFR-mutant Non-Small Cell Lung Cancer. Oncologist 2022;27:407-13.

Cite this article as: Muthusamy B, Pennell NA. ADAURA update: only the end of the beginning. Transl Lung Cancer Res 2023;12(7):1649-1651. doi: 10.21037/tlcr-23-237