Editorial Commentary

Consolidation osimertinib for unresectable stage III epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer: redefining standard care

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Chemoradiotherapy (CRT) followed by consolidation durvalumab is the current standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) (1). However, for tumors with epidermal growth factor receptor (*EGFR*) mutation, this may not be an ideal option. In the post-hoc analysis of the EGFR-mutated subgroup from PACIFIC trial, involving a limited number of 35 patients, progression-free survival (PFS) and overall survival (OS) were not improved when receiving durvalumab after CRT compared with placebo group (2). Osimertinib is recommended as first-line treatment for advanced NSCLC and as adjuvant therapy for resected NSCLC with EGFR mutation (3,4). There are limited data regarding the consolidation of EGFR tyrosine kinases inhibitors (TKIs) for unresectable stage III EGFR-mutated NSCLC.

The LAURA trial is a phase 3, double-blind, placebo-controlled trial, to assess the efficacy and safety of osimertinib following chemoradiation in patients with stage III unresectable EGFR-mutated NSCLC (exon 19 deletion or exon 21 L858R point mutation, alone or with other EGFR mutations). Patients were randomized to receive either osimertinib or placebo group after completing CRT. The primary endpoint was PFS as assessed by blinded independent central review. Recently, Lu *et al.* reported the interim analysis of LAURA trial. In patients with unresectable stage III EGFR-mutated NSCLC, consolidation osimertinib after CRT led to impressively prolonged PFS, marking a paradigm shift in the treatment of locally advanced EGFR-mutant NSCLC (5). What insights can the LAURA trial offer clinicians?

Was placebo an appropriate control? Durvalumab is approved in the same patient population regardless of EGFR mutation status. However, it is not an acceptable standard of care—as demonstrated by the lack of effect of immunotherapy in metastatic EGFR-mutated NSCLC, a retrospective study suggests favorable results with osimertinib (6), and high rates of synergistic toxicity when osimertinib is given to patients with disease recurrence within 6 months of the last dose of durvalumab (7). Therefore, osimertinib is the only appropriate consolidation therapy that should be considered for EGFR mutant NSCLC and placebo control was appropriate for this study.

Is changing practice based on PFS appropriate? Yes—the improvement in PFS was dramatic, with a hazard ratio of 0.16, mirroring that was seen in ADAURA trial for surgically resected stage II (0.17) and IIIa (0.12) and much better than durvalumab in PACIFIC trial (0.52) (1,4).

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But should we wait for OS data? OS was not significantly improved at this interim analysis, but at progression on placebo, 81% of patients received osimertinib. This population should not be compared to FLAURA directly, because frequent mandated surveillance scans—including magnetic resonance imaging (MRI) scan (MRI's)—would have detected low disease burdens of metastatic recurrence, which we expect to be sensitive to osimertinib for a longer duration than the 18.9 months median PFS (3). Therefore, we would not expect OS to be positive based on this study design, and would not wait for further data for using this therapy in practice tomorrow.

Is appropriate to use indefinite osimertinib treatment following CRT? Perhaps surprisingly, it appears that only a minority of patients in LAURA—probably fewer than 10%—have long term disease-free survival without osimertinib. Indefinite treatment may also offer advantages in protecting against intracranial metastases, a common site of recurrence in the control arm which did undergo routine surveillance brain MRI's. However, it also raises concerns such as potential side effect and increased cost burden. While some patients will discontinue due to side effects or personal preference, we hope that eventually ultrasensitive methods of residual tumor detection, likely either circulating tumor DNA molecular residual disease testing, or more sensitive imaging, could identify those in whom it is safe to discontinue and proceed with observation alone, because they may actually be cured, or alternatively, identify early signs of progression to restart therapy in those who have chosen to discontinue. The biomarker-guided adaptive therapy warrants further exploration due to its potential to enable patients to benefit from "drug holidays".

Are there risks to this therapy? Beyond expected toxicities from osimertinib, which has a generally well tolerated safety profile, exacerbation of radiation pneumonitis is of particular concern, as drug pneumonitis was observed in 5% of patients on osimertinib alone (3). Radiation pneumonitis occurred in 48% of patients in the osimertinib group compared to 38% in the placebo group. While it is difficult to discern the contribution of radiation versus osimertinib, the rates of pneumonitis were only 10% higher with osimertinib, and the majority were grade 1 and 2. Therefore, no strong safety concern is apparent at this time. Additionally, in the osimertinib group, 87% of patients who underwent radiation therapy were able to restart osimertinib therapy under management of toxic side effects and did not develop further radiation pneumonia. From a safety perspective, osimertinib consolidation following CRT remains safe and manageable.

How might improve on this new standard of care? In the LAURA trial, 70% of patients enrolled before concurrent CRT were not eligible and missed the opportunities for consolidation treatment. These patients were quickly transited to palliative care for advanced state. We are curious about the future role of neoadjuvant EGFR TKIs therapy, which is being tested in the Neo-ADAURA study, and raises the possibility of induction or concurrent EGFR-TKI in the setting of CRT (8,9). The ASCENT trial demonstrated a promising major pathological response rate and PFS with induction afatinib combined with neoadjuvant CRT in stage III EGFR-mutated NSCLC (9). Additionally, preliminary data suggest that induction EGFR TKIs may reduce the size of radiation fields (10). A new "sandwich" treatment model of induction therapy + surgery/radical CRT + maintenance therapy is highly anticipated and of great interest. Other investigations into induction or neoadjuvant therapy include the NEOLA trial 2 months of induction osimertinib followed by the "LAURA" approach—combined with CRT plus maintenance osimertinib (NCT06194448), neoadjuvant immunotherapy (11), and neoadjuvant EGFR TKIs combined with immunotherapy (NCT06300424) in stage III EGFR-mutated NSCLC.

There are also unresolved issues that need further discussion, such as whether consolidation targeted therapy is also suitable for other tumors with driver gene mutations, including non-classical EGFR mutations, anaplastic lymphoma kinase fusions, and ROS1 proto-oncogene receptor tyrosine kinase fusions, among others. As each target can lead to different clinical behavior and each paired therapy has different risk profiles, we would not generally advocate for using approved metastatic therapies indiscriminately in the locally advanced setting, but some may be considered on an individual basis. The LAURA study led to Food and Drug Administration (FDA) approval of consolidation osimertinib in September of 2024, and sets the direction for future studies to evaluate risk and efficacy across all of these targets in NSCLC.

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Footnote

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