Lung Cancer: Targets and Therapy

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COMMENTARY

LAURA Completes the Osimertinib Treatment Jigsaw Puzzle of *EGFR*+ NSCLC from Stage IB to IV: Adjuvant Osimertinib Significantly Improves PFS and CNS Progression in Unresectable Stage III *EGFR*-Mutated NSCLC Compared to Placebo (LAURA, NCT03521154)

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Abstract: The current standard of care for unresectable stage III non-small cell lung cancer (NSCLC) involves a concurrent platinum-based doublet chemotherapy and chest radiotherapy, followed by consolidative therapy with durvalumab, an anti-programmed death ligand 1 (PD-L1) antibody, based on the PACIFIC trial (NCT02125461). However, the utility of durvalumab in *EGFR*-mutated lung cancer patients is questionable based on post-hoc analysis and multi-institutional retrospective analysis. Osimertinib is a third-generation *EGFR*-tyrosine kinase inhibitor (TKI) with proven clinical efficacy in NSCLC. Given that durvalumab showed no benefit in unresectable Stage III *EGFR*-mutated NSCLC, it is exciting that most recently, the LAURA trial has demonstrated promising outcomes with adjuvant osimertinib in unresectable, stage III *EGFR*-mutated NSCLC after definitive chemoradiotherapy with significant improvement in PFS compared to placebo. Furthermore, the LAURA trial demonstrates that osimertinib has a protective effect against distant metastases and CNS progression in this patient population. Here, we explore the results of the LAURA trial and how it transforms the standard-of-care treatment for patients with unresectable, stage III *EGFR*-mutated NSCLC moving forward.

Keywords: stage III, chemoradiation, consolidation therapy, epidermal growth factor receptor, tyrosine kinase inhibitor

Introduction

Among patients with non-small cell lung carcinoma (NSCLC), about one-third present with unresectable, locally advanced Stage III disease.[1] Of these patients with unresectable stage III NSCLC, up to one-third of patients have epidermal growth factor receptor (*EGFR*) mutations.[2–4] The current standard of care for unresectable stage III NSCLC involves a concurrent platinum-based doublet chemotherapy and chest radiotherapy, followed by consolidative therapy with durvalumab, an anti-programmed death ligand 1 (PD-L1) antibody, based on the PACIFIC trial (NCT02125461).[5,6] The PACIFIC trial was a randomized, phase III study comparing durvalumab as a consolidation therapy (n=473) to placebo (n=236). Durvalumab or placebo was administered every 2 weeks for up to 12 months to patients with locally advanced, unresectable stage III NSCLC and without disease progression after chemoradiotherapy. PFS was found to be significantly longer with durvalumab than with placebo, with median PFS being 16.8 months (95% confidence interval [CI]: 13–18.1) with durvalumab compared to 5.6 months (95% CI: 4.6–7.8) with placebo.[5] Additionally, overall survival

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was significantly improved with durvalumab (66.3% at 24 months [95% CI: 61.7–70.4]) compared to placebo (55.6% [95% CI: 48.9–61.8]), with stratified hazard ratio (HR) for death 0.68; 99.73% CI: 0.47–0.997; P=0.0025.[6]

However, the utility of durvalumab in *EGFR*-mutated lung cancer patients is questionable. In 2021, a post-hoc analysis and a multi-institutional retrospective analysis demonstrated no OS or PFS benefit with consolidation durvalumab in patients with *EGFR*-mutated NSCLC.[7] Though the mechanism of suboptimal outcomes with immunotherapy in *EGFR*-mutated NSCLC remains unknown, studies have suggested that low rates of PD-L1 expression and CD8+ tumor-infiltrating lymphocytes are contributory, causing impaired response to PD-1 blockade, leading to poor immune system recognition of the tumor and reduced anti-tumor activity.[8,9] Moreover, a subgroup analysis of the PACIFIC trial revealed more frequent occurrences of all-grade pneumonitis in *EGFR*-positive patients treated with durvalumab compared to *EGFR*-negative patients (59% vs 36%, respectively).[10] Furthermore, there are concerns of increased susceptibility to immune-related adverse events (irAEs) when initiating *EGFR* TKIs after immunotherapy such as durvalumab.[11] Given the growing concerns of lack of benefit and evidence of harm of durvalumab in *EGFR*-mutated NSCLC, the search for alternative therapies in such patients continued.

Osimertinib is a third-generation *EGFR*-tyrosine kinase inhibitor (TKI) with proven clinical efficacy in NSCLC. Osimertinib has been approved as a first-line treatment for locally advanced and metastatic *EGFR*-mutated NSCLC,[12] as well as *EGFR* T790M mutation-positive NSCLC.[13,14] It is also approved as targeted adjuvant therapy in post-surgical resection, early-stage (IB-IIIA) *EGFR*-mutated NSCLC.[15] Figure 1 demonstrates the development timelines of osimertinib. Given that durvalumab showed no benefit in unresectable Stage III *EGFR*-mutated NSCLC, it is exciting that most recently, the LAURA trial has demonstrated promising outcomes with adjuvant osimertinib in unresectable, stage III *EGFR*-mutated NSCLC post chemoradiation.

Design of LAURA

The LAURA study is a randomized phase III study conducted internationally (including sites in the US, South America, Asia, and Europe) that compared osimertinib versus placebo in adults aged 18 or older with stage III unresectable, predominantly non-squamous NSCLC harboring one of the two common *EGFR* mutations (Ex19del, L858R). Patients must have undergone chemoradiation therapy (CRT), conducted either concurrently or sequentially, and without disease progression. There were three stratification factors: concurrent versus sequential CRT, stage IIIA versus IIIB/IIIC, and Chinese patients enrolled in China versus non-Chinese patients or patients enrolled outside of China.

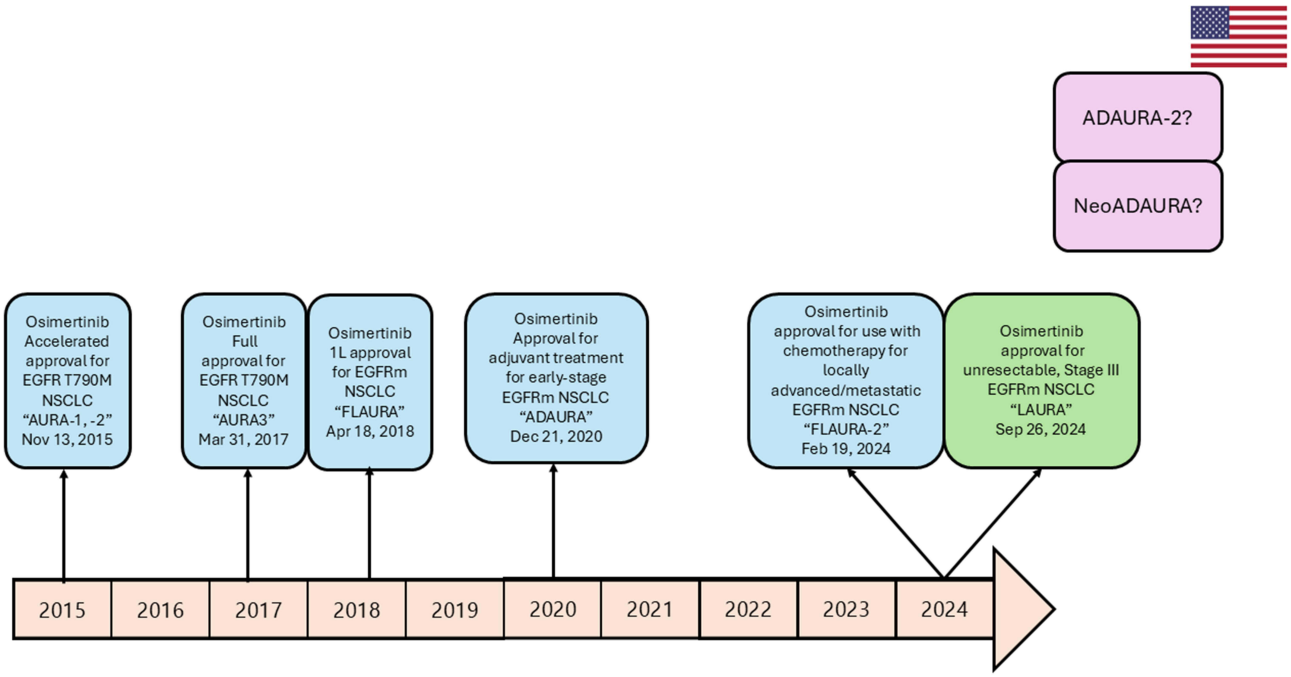

Figure 1 Timeline of the development and approval of osimertinib in different settings.

Patients within 6 weeks of completion of chemoradiation were randomized in a 2:1 ratio to receive osimertinib 80 mg once daily or placebo until blinded independent central review (BICR)-confirmed disease progression per RECIST v1.1, unacceptable toxicity or other discontinuation criteria were met. The sample size of 120 events was based on 90% power to detect a hazard ratio of 0.53 in disease progression or death with $\alpha = 0.05$.[16]

Conduct of LAURA

Two hundred and sixteen patients were enrolled over six years from August 2018 to July 2022 across 145 centers in more than 15 countries. One hundred and forty-three were assigned to received osimertinib and 73 to receive placebo. Patient characteristics were generally well balanced between the two groups though of note, the osimertinib group had a higher percentage of patients with better World Health Organization (WHO) performance-status (PS 0 was 56% for osimertinib group vs 52% in placebo group).[16]

The median PFS with osimertinib was 39.1 months (95% CI: 31.5 to not calculable) and 5.6 months (95% CI: 3.7–7.4) with placebo (HR = 0.16; 95% CI: 0.10–0.24; P<0.001). Subgroup analysis revealed PFS benefit favoring osimertinib over placebo across all subgroups with hazard ratios ranging from 0.16 to 0.48. This included patients of all WHO performance-status scores.

The incidence of local progression and distant metastases were lower in the osimertinib group (21% and 16%, respectively) compared to the placebo group (48% and 37%, respectively). Importantly, the osimertinib group had lower incidence of new lesions (22%) than placebo group (68%), including new brain lesions (8% vs 29%, respectively). In the secondary analysis of CNS PFS by neuroradiologist BICR, median CNS PFS was not reached with osimertinib compared to 14.9 months (95% CI: 7.4-NC) with placebo. With osimertinib, there was an 83% reduction in the risk of CNS progression or death compared to placebo [HR 0.17 (95% CI: 0.09–0.32), P<0.001]. In the secondary analysis of time to death or distant metastases (TTDM) by BICR, median TTDM for osimertinib was also not reached (95% CI: 39.3-NC) compared to 13 months (95% CI: 9-NC) with placebo. There was a 79% reduction in the risk of distant metastases or death with osimertinib versus placebo [HR 0.21 (95% CI: 0.11–0.38), P<0.001].[17]

At 36 months, the overall survival for the osimertinib group was 84% (95% CI: 75–89) compared to 74% (95% CI: 57–85) for the placebo group (HZ = 0.81; 95% CI: 0.42–1.56; P=0.53). This was not significant at this interim analysis, although it is important to note the objective response rate (ORR) was higher in the osimertinib group than in the placebo group (57% [95% CI: 49–66] versus 33% [95% CI: 22–45]; odds ratio (OR) = 2.77 [95% CI: 1.54–5.08]).[16]

In terms of safety, 140 patients (98%) receiving osimertinib and 64 patients (88%) receiving placebo reported adverse events. The most common adverse events, regardless of cause, were radiation pneumonitis (48% with osimertinib vs 38% with placebo), diarrhea (36% vs 14%) and rash (24% vs 14%). Grade 3 or higher adverse events were reported in 50 patients (35%) in the osimertinib group and 9 patients (12%) in placebo group.[16]

Discussion

The LAURA study demonstrated a significant benefit to PFS with osimertinib treatment (median PFS [mPFS] 39.1 months) after definitive CRT compared to placebo (mPFS 5.6 months) with HR for disease progression or death of 0.16 (95% CI: 0.10–0.24; P<0.001), equivalent to an 84% reduction in the risk of disease progression or death with osimertinib compared with placebo.

Currently, the standard of treatment for unresectable stage III NSCLC is CRT followed by consolidation therapy with immune checkpoint inhibitor durvalumab.[5,6] Prior to the LAURA trial, durvalumab was the only adjuvant maintenance therapy that was approved as consolidation therapy in unresectable stage III NSCLC through the PACIFIC trial. However, durvalumab did not result in PFS or OS improvement in *EGFR*-mutated or *ALK*-rearranged NSCLC.[18] In fact, the mPFS with durvalumab was similar to that with placebo (11.2 months [95% CI: 7.3–20.7] vs 10.9 months [95% CI: 1.9-not evaluable], respectively) in a post hoc subgroup analysis of patients with *EGFR*-mutated NSCLC.[19] The LAURA trial helps fill this gap in treatment for unresectable stage III, *EGFR*-mutated NSCLC after CRT given the efficacy of osimertinib in significantly improving PFS, with mPFS being 33.6 months longer compared to placebo.

Additionally, LAURA has demonstrated efficacy in lowering incidence of distant metastases, including in the CNS. The osimertinib group had lower incidence of new lesions (22%) than placebo group (68%), including new brain lesions (8% vs 29%,

respectively). This is significant as the presence of distant metastases in the CNS is a poor prognostic factor that negatively impacts quality of life, Moreover, studies have shown that patients with unresectable stage III, *EGFR*-mutated NSCLC after definite CRT have a higher tendency to develop distant metastases, including in the CNS, compared to patients without *EGFR* mutations.[18,20,21] Formal statistical testing has yet to be completed for CNS PFS pending whether OS data reach statistical significance (planned at 60% maturity); however, the magnitude of CNS PFS and TTDM improvements are considered clinically meaningful. The efficacy of osimertinib in significantly reducing the risk of distant metastases and CNS progression compared to placebo in patients with unresectable stage III *EGFR*-mutated NSCLC after CRT further solidifies its efficacy in such patients, helping address an unmet need against CNS progression and distant metastases in this patient population.

Importantly, the safety and tolerability of osimertinib remained consistent with its established profile. The majority of reported adverse effects were mild to moderate in terms of severity (grade 1–3) and did not lead to discontinuation. The most frequently reported grade 3 or higher adverse events in both treatment groups was pneumonia (3% with osimertinib, 4% with placebo). Other grade 3 or higher adverse events reported included radiation pneumonitis and diarrhea though both were previously known and expected adverse events either with osimertinib or CRT. Previous reports highlighted possible association of increased risk of radiation pneumonitis with the use of *EGFR*-TKIs together with CRT or radiotherapy.[7,10] In the LAURA trial, the most frequently reported adverse event in both osimertinib and placebo arms was radiation pneumonitis with no significant difference (48% vs 38%, respectively). The overall incidence of grade 3 pneumonitis was low at 2%, and there were no grade 4 or 5 pneumonitis reported.[16] Radiation pneumonitis of any grade was reported in 48% of patients receiving osimertinib after CRT, which is equivocal or decreased compared to the incidence of radiation pneumonitis with the use of durvalumab (59%) in *EGFR*-mutated NSCLC after CRT as seen in the PACIFIC trial, though this cross-trial comparison should be interpreted with caution.[7,16] To note, CRT is a risk factor for the development of pneumonitis and is likely a contributor to the increased incidence seen in both arms and both trials.[22] To summarize, the incidence of radiation pneumonitis as an adverse event was similar between both osimertinib and placebo arms. Additionally, osimertinib may lead to a reduced or at least equivocal incidence of radiation pneumonitis compared to durvalumab.

In addition to following up on the final OS, CNS PFS, safety analysis of the LAURA trial, future research evaluating the efficacy and safety of *EGFR*-TKIs as either induction treatment before CRT or concomitantly with CRT in *EGFR*-mutated unresectable stage III NSCLC would be of interest.

The promising results of statistically and clinically improved PFS with osimertinib compared to placebo, as well as its substantial reduction in distant metastases including in the CNS, support the use of osimertinib as a new standard of care for *EGFR*-mutated unresectable stage III NSCLC after CRT. Additionally, these results demonstrate the significant benefit of using appropriate targeted therapy as adjuvant treatment after definitive treatment in locally advanced unresectable, *EGFR*-mutated NSCLC, and potentially in patients with NSCLC harboring other driver alterations such as *ALK*, *ROS1*, and *RET* mutations, advocating for the need for such studies.

Conclusion

The LAURA trial has demonstrated promising efficacy of osimertinib as an adjuvant consolidation therapy in unresectable stage III *EGFR*-mutated NSCLC after definitive chemoradiotherapy given the statistically and clinically significant improvement in PFS compared to placebo. Furthermore, osimertinib provides a protective effect against distant metastases and CNS progression in patients with unresectable stage III *EGFR*-mutated NSCLC following CRT. Together with the primary PFS benefit, reduced risk of CNS progression and prolongation of TTDM, the LAURA study supports the use of osimertinib as the new standard of care in patients with unresectable stage III *EGFR*-mutated NSCLC following CRT. This exciting finding also advocates for the importance of evaluating the appropriate targeted therapy as adjuvant treatment in unresectable NSCLC with other driver alterations such as *ALK*, *ROS1*, and *RET* mutations through future clinical trials.

Disclosure

Dr. Sai-Hong Ou reports stock ownership of Nuvalent, MBrace Therapeutics, and BlossomHill Therapeutics; stock options of Nuvation Bio, outside the submitted work. Dr. Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Pfizer, Lilly, Genentech, Regeneron, Boehringer Ingelheim, Caris Life Sciences, Takeda, Johnson and Johnson/Janssen, Mirati/

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