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RESEARCH HIGHLIGHT

Exciting progress in targeted therapy innovation for unresectable stage III *EGFR*-mutated NSCLC: the phase III LAURA study

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Based on the PACIFIC trial (NCT02125461), the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC) is chemoradiotherapy (CRT) followed by durvalumab consolidation [1]. However, a subsequent post-hoc analysis revealed no advantage of durvalumab in terms of progression-free survival (PFS) for patients with epidermal growth factor receptor (*EGFR*) mutations (hazard ratio [HR] = 0.91) [2]. This indicates that "PACIFIC" treatment does not meet the clinical needs of unresectable stage III *EGFR*-mutated NSCLC patients, who have short PFS and are prone to new metastases.

The results of the LAURA study (NCT03521154) were recently published in *The New England Journal of Medicine* [3]. This was a double-blind, randomized, placebo-controlled phase III study that enrolled 216 patients from 145 centers who were diagnosed with unresectable stage III *EGFR*-mutated NSCLC without disease progression after CRT. They were randomized in a 2:1 ratio to consolidation therapy with osimertinib or placebo until disease progression or death. The primary endpoint was PFS, whereas the secondary endpoints included overall survival (OS), central nervous system PFS, objective response rate (ORR), and safety.

The LAURA study revealed that osimertinib significantly prolonged the median PFS compared with placebo (39.1 months vs. 5.6 months, HR = 0.16, $P < 0.001$), with substantial PFS benefits across all subgroups. Moreover, the osimertinib group demonstrated remarkable reductions in new metastases compared to placebo, particularly in the brain (8% vs. 29%) and lung (6% vs. 29%).

The safety of osimertinib has been closely scrutinized by clinicians and patients. Although there was a higher rate of adverse events (AEs) over grade 3 in the osimertinib group (35% vs. 12%), these events were largely predictable, and there were no new safety concerns. Furthermore, the rate

List of Abbreviations: NSCLC, non-small cell lung cancer; CRT, chemoradiotherapy; PFS, progression-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; ORR, objective response rate; AEs, adverse events; EGFR-TKI, EGFR-tyrosine kinase inhibitor; NR, not reached; MRD, minimal residual disease; TRT, thoracic radiotherapy.

Ziyan Tong and Ning Zhu contributed equally to this study.

of radiation pneumonitis, which is often the most concerning AE, did not differ significantly between the osimertinib and placebo groups (48% vs. 38%). Overall, the safety was within the expected manageable range.

For *EGFR*-mutated NSCLC, previous studies have demonstrated the favorable efficacy of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) (Table 1) [4–7]. Osimertinib has been approved as a first-line treatment for stage IV NSCLC and an adjuvant treatment for resectable stage I-III NSCLC. However, for unresectable stage III NSCLC, it remains an unmet clinical need. Recently, an international multicenter real-world study involved 136 patients with unresectable stage III *EGFR*-mutated NSCLC who received CRT followed by treatment with osimertinib, durvalumab, or observation [8]. Results revealed that osimertinib outperformed durvalumab and observation in real-world median PFS (not reached [NR] vs. 12.7 months vs. 9.7 months), supporting the successful launch of the LAURA study.

However, practical concerns remain for the future.

First, the LAURA study underscored the need for gene tests in early- to mid-stage NSCLC patients to enable timely targeted therapy. The type and abundance of *EGFR* mutations often impact the effectiveness of EGFR-TKI targeted therapies. Thus, advancements in precise quantitative assays are crucial to guide accurate clinical targeted therapies.

Second, despite the mention of AEs in the LAURA study, osimertinib demonstrated better safety than durvalumab (rate of pneumonitis, 15% vs. 25%), and improved PFS benefits (NR vs. 12.7 months, HR = 0.20, $P < 0.001$) [8]. However, close monitoring for potential AEs is still necessary. Healthcare professionals should be well-prepared to address possible drug-related pulmonary toxicity events.

Notably, the OS curves of both treatment arms are highly crossed over. The interim OS data did not suggest a favorable trend for osimertinib over placebo (36-month OS rate, 84% vs. 74%, HR = 0.81, $P = 0.53$), indicating that the long-term efficacy of LAURA treatment remains unclear. However, osimertinib has demonstrated excellent PFS and significantly reduced metastasis in existing results. These findings indicated that osimertinib could prolong the duration of disease progression and decrease the tumor burden, improving patients' quality of life. Further clinical trials are needed to identify the suitable patient population for LAURA treatment, possibly younger individuals who can tolerate AEs with prolonged PFS expectations.

Furthermore, the clinical application requires comprehensive consideration of multiple factors, including cost, efficacy, AEs, and patient's quality of life. Determining the optimal duration of long-term osimertinib administration is essential to ensure efficacy. Active exploration of potential biomarkers, such as minimal residual disease (MRD), should be pursued to guide step-down treatment decisions. In patients with resectable *EGFR*-mutated NSCLC, MRD^+ status could precede disease-free survival events by a median lead time of 4.7 months. Further analysis also suggested that MRD could identify patients who may benefit from prolonged osimertinib therapy, guiding decisions on treatment duration and dosage [9]. Therefore, for patients with unresectable stage III NSCLC, exploring MRD monitoring is also instructive and warrants further MRD-related clinical trials, to improve patients' quality of life and alleviate the burden of treatment.

Additionally, osimertinib achieved an ORR of up to 80% in advanced *EGFR*-mutated NSCLC [4]. Therefore, for unresectable stage III NSCLC patients, who were excluded from the LAURA study and unresponsive to CRT, early intervention with osimertinib may improve their survival outcomes. Further large-scale clinical trials are warranted to comprehensively investigate the efficacy and safety of pre-CRT induction therapy, whether with targeted therapies such as osimertinib or other forms of immunotherapy.

More importantly, the optimal treatment modality for patients with stage III *EGFR*-mutated NSCLC still requires further precise differentiation, which should consider factors such as age, tumor burden, and biomarkers. Combining CRT with EGFR-TKIs might not be the best treatment. Compared with previous studies [7, 8, 10], CRT appeared to result in a median PFS of approximately 10.0 months or less, indicating its unsatisfactory efficacy. Especially for individuals with poor underlying conditions who cannot tolerate chemotherapy, radiotherapy combined with EGFR-TKIs may be more effective. The WJOG6911L phase II trial (UMIN000008366) revealed that gefitinib with thoracic radiotherapy (TRT) was not inferior to gefitinib with CRT in efficacy (24-month PFS, 33.3% vs. 37%) [6]. Furthermore, TRT significantly reduced local recurrence to 7.4% [6], achieving results that are challenging with conventional CRT. While the LAURA trial has provided promising results, more phase III clinical trials are needed to ascertain the optimal treatment modality by comparing the efficacy of osimertinib as monotherapy, in combination with TRT, or alongside CRT.

Overall, the LAURA study could inspire medical practitioners to further explore mutations in other genes such as *ALK*, *KRAS*, and *HER2*, serving as a valuable reference. Considering the remarkable PFS benefit in the LAURA study, osimertinib is anticipated to revolutionize clinical practice for unresectable stage III *EGFR*-mutated NSCLC. However, further disclosure of OS data is necessary to fully demonstrate the efficacy of osimertinib and improve the long-term prognosis of patients.

TABLE 1 Clinical trials of EGFR-TKI (especially osimertinib) targeted therapy in *EGFR*-mutated NSCLC.

Disease stage	Study name	Phase	Treatment	Median PFS/DFS (months)		ORR (%)
IIIB/IV	FLAURA [4]	III	Osimertinib	18.9 (95% CI, 15.2-21.4)	HR = 0.46 (95% CI, 0.37-0.57, $P < 0.001$)	80 (95% CI, 75-85)
			Gefitinib	10.2 (95% CI, 9.6-11.1)		76 (95% CI, 70-81)
IB-IIIA	ADAURA [5]	III	Osimertinib	65.8 (95% CI, 61.7-NR)	HR = 0.27 (95% CI, 0.21-0.34, $P < 0.001$)	NA
			Placebo	28.1 (95% CI, 22.1-35.0)		
III	WJOG6911L [6]	II	Gefitinib with TRT	18.6 (95% CI, 12.0-24.5)	NA	81.5 (95% CI, 63.3-91.3)
	RECEL [7]	II	Grlotinib with TRT	24.5 (95% CI, 13.7-29.4)	HR = 0.104 (95% CI, 0.028-0.389, $P < 0.001$)	70.0 (95% CI, 45.7-88.1)
			Etoposide/cisplatin with TRT	9.0 (95% CI, 5.8-15.4)		61.9 (95% CI, 38.4-81.9)
	Nassar et al. [8] (A Real-world Multicenter Retrospective Study)	NA	Osimertinib after CRT	NR	$HR_{\text{Osimertinib vs. Durvalumab}} = 0.20$ (95% CI, 0.09-0.49, $P < 0.001$)	NA
			Durvalumab after CRT	12.7 (95% CI, 10.5-15.5)	$HR_{\text{Osimertinib vs. Observation}} = 0.14$ (95% CI, 0.06-0.33, $P < 0.001$)	
			Observation after CRT	9.7 (95% CI, 6.1-12.0)	$HR_{\text{Durvalumab vs. Observation}} = 0.67$ (95% CI, 0.42-1.05, $P = 0.083$)	
	Bi et al. [10] (A Real-world Multicenter Retrospective Study)	NA	CRT + Gefitinib/Erlotinib/Icotinib	26.2 (95% CI, 19.8-36.4)	$HR_{\text{EGFR-TKI + CRT vs. CRT}} = 0.40$ (95% CI, 0.29-0.54, $P < 0.001$)	NA
			CRT	12.4 (95% CI, 11.4-15.5)	$HR_{\text{EGFR-TKI + CRT vs. EGFR-TKI}} = 0.60$ (95% CI, 0.46-0.79, $P < 0.001$)	
			Gefitinib/Erlotinib/Icotinib	16.2 (95% CI, 14.1-19.5)	$HR_{\text{EGFR-TKI vs. CRT}} = 0.66$ (95% CI, 0.50-0.87, $P = 0.003$)	
	LAURA [3]	III	Osimertinib after CRT	39.1 (95% CI, 31.5-NR)	HR = 0.16 (95% CI, 0.10-0.24, $P < 0.001$)	57 (95% CI, 49-66)
			Placebo after CRT	5.6 (95% CI, 3.7-7.4)		33 (95% CI, 22-45)

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; DFS, disease free survival; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; NA: not available; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TRT, thoracic radiotherapy.

AUTHOR CONTRIBUTIONS

Ziyan Tong and Ning Zhu conceived and drafted the manuscript. Hong Shen and Ying Yuan provided corrective comments and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors disclose no conflicts.

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DATA AVAILABILITY STATEMENT

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Not applicable.

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REFERENCES

1. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022;40(12):1301–1311.
2. Naidoo J, Antonia S, Wu YL, Cho BC, Thiyagarajah P, Mann H, et al. Brief Report: Durvalumab After Chemoradiotherapy in Unresectable Stage III EGFR-Mutant NSCLC: A Post Hoc Subgroup Analysis From PACIFIC. J Thorac Oncol. 2023;18(5):657–663.
3. Lu S, Kato T, Dong X, Ahn MJ, Quang LV, Soparattanapaisarn N, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. N Engl J Med. 2024;391(7):585–597.
4. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113–125.
5. Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, 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(10):1830–1840.
6. Akamatsu H, Murakami H, Harada H, Shimizu J, Hayashi H, Daga H, et al. Gefitinib With Concurrent Thoracic Radiotherapy in Unresectable Locally Advanced NSCLC With EGFR Mutation; West Japan Oncology Group 6911L. J Thorac Oncol. 2021;16(10):1745–1752.
7. Xing L, Wu G, Wang L, Li J, Wang J, Yuan Z, et al. Erlotinib Versus Etoposide/Cisplatin With Radiation Therapy in Unresectable Stage III Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer: A Multicenter, Randomized, Open-Label, Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2021;109(5):1349–1358.
8. Nassar AH, Kim SY, Aredo JV, Feng J, Shepherd F, Xu C, et al. Consolidation Osimertinib Versus Durvalumab Versus Observation After Concurrent Chemoradiation in Unresectable EGFR-Mutant NSCLC: A Multicenter Retrospective Cohort Study. J Thorac Oncol. 2024;19(6):928–940.
9. John T, Grohe C, Goldman JW, Kato T, Laktionov KK, Bonanno L, et al. Molecular residual disease (MRD) analysis from the ADAURA trial of adjuvant (adj) osimertinib in patients (pts) with resected EGFR-mutated (EGFRm) stage IB-IIIA non-small cell lung cancer (NSCLC). J Clin Oncol. 2024;42(16_suppl):8005–8005.
10. Bi N, Xu K, Ge H, Chen M, E M, Zhang L, et al. Real-world treatment patterns and clinical outcomes in EGFR-mutant locally advanced lung adenocarcinoma: A multi-center cohort study. J Natl Cancer Cent. 2023;3(1):65–71.

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