Neoadjuvant osimertinib: a promising therapeutic option for locally advanced EGFR-mutant lung adenocarcinoma

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We are delighted for the opportunity to comment on the article "Osimertinib as neoadjuvant therapy in patients with EGFR-mutant resectable stage II-IIIB lung adenocarcinoma (NEOS): A multicenter, single-arm, open-label phase 2b trial" written by Lv *et al.* (1). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been widely used as first-line treatment for advanced EGFR-mutant non-small cell lung cancer (NSCLC) (2). However, limited evidence suggests that neoadjuvant EGFR-TKIs can lead to significant tumor responses and survival benefits. The summary of the study design and primary results of prospective trials for neoadjuvant EGFR-TKIs are listed in *Table 1* (1,3-9). These trials have demonstrated the safety, feasibility, and significant radiological or pathological response of neoadjuvant EGFR-TKIs for resectable locally advanced EGFR-mutant NSCLC. However, the survival benefit compared with neoadjuvant chemotherapy has not been proven at least for the moment. Recently, osimertinib, a third-generation EGFR-TKI, has become the preferred first-line agent for advanced EGFR-mutant NSCLC and has gained a vital role in the adjuvant treatment of resected EGFR-mutant NSCLC. In the FLAURA study, a double-blind phase 3 trial to compare osimertinib with standard EGFR-TKIs in patients with EGFR-mutant advanced NSCLC, osimertinib showed significant improvement in the median progression-free survival (PFS) when compared with standard EGFR-TKIs (10). The ADAURA study, a double-blind phase 3 trial that assessed the efficacy and safety of adjuvant osimertinib for patients with resected EGFR-mutant NSCLC, showed that the osimertinib group had significantly longer disease-free survival than the placebo group (11). Additionally, the ADAURA trial finally demonstrated a significant overall survival (OS) benefit of adjuvant osimertinib (12). Considering the results of the FLAURA study (10) and the ADAURA study (11), the efficacy of neoadjuvant osimertinib appears promising. However, there only have been limited case reports and case series (13,14). Therefore, the authors conducted a prospective trial to evaluate the efficacy and safety of neoadjuvant osimertinib. To our knowledge, this is the first published report of a prospective trial, and we would like to express our sincere admiration for the great achievement of the authors.

The authors conducted a prospective study to explore the efficacy and safety of neoadjuvant osimertinib followed by surgery in patients with stage IIA–IIIB (T3–4 N2) lung adenocarcinoma with EGFR mutations in exons 19 and/or 21. The patients received osimertinib 80 mg/day for 6 weeks

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Table 1 Summary of prospective trials for neoadjuvant EGFR-TKIs

Authors	Study name	Published year	Treatment	Sample size, n	Stage	Staging system	Primary endpoint	ORR	MPR	RRR	Mediastinal LN biopsy
Aredo *et al.* (3)	N/A	Presented in ASCO 2023	Osimertinib	27	I–IIIA	7th	MPR	51.9% (14/27)	14.8% (4/27)	N/D	N/R
Zhong *et al.* (4)	EMERGING-CTONG 1103	2019	Erlotinib	37	IIIA (N2)	7th	ORR	54.1% (20/37)	9.7% (3/31)	73.0% (27/37)	N/R
Xiong *et al.* (5)	EASTERN	2020	Erlotinib	19	IIIA (N2)	7th	RRR	42.1% (8/19)	N/A	68.4% (13/19)	Required
Zhang *et al.* (6)	ECTOP-1001	2021	Gefitinib	35	II–IIIA	7th	ORR	54.5% (18/33)	24.2% (8/33)	82.9% (29/35)	N/D
Bian *et al.* (7)	TEAM-LungMate 004	2023	Afatinib	47	IIIA–C	8th	ORR	70.2% (33/47)	9.1% (3/33)	87.9% (29/33)	N/R
Tsuboi *et al.* (8)	NeoADAURA	Ongoing	Osimertinib	Recruiting	II–IIIB (N2)	8th	MPR	N/A	N/A	N/A	N/D
Piper-Vallillo *et al.* (9)	ASCENT	Early closure	Afatinib with CRT	19	IIIA–B	7th	ORR	57.9% (11/19)	70.0% (7/10)	N/D	N/D
Lv *et al.* (1)	NEOS	2023	Osimertinib	40	IIA–IIIB (T3-4, N2)	8th	ORR	71.1% (27/38)	10.7% (3/28)	93.8% (30/32)	N/R

EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; ORR, objective response rate; MPR, major pathological response; N/D, not described; N/R, not required; RRR, radical resection rate; N/A, not applicable; LN, lymph node; CRT, chemoradiation therapy.

and then underwent surgical resection. The primary endpoint was the objective response rate (ORR), defined as the proportion of patients with a complete or partial response (PR), evaluated by radiological findings based on response evaluation criteria in solid tumors (RECIST) version 1.1. According to RECIST ver1.1, a radiological PR was defined as a minimum of a 30% reduction in the sum of diameters of target lesions compared to the baseline (15). Forty patients were enrolled, of which 32 underwent surgery. The ORR was 71.1%, and 7.5% of the patients had treatment-related adverse events of grade 3, demonstrating the promising efficacy and good safety of neoadjuvant osimertinib for patients with locally advanced EGFR-mutant NSCLC. The sample size in the present article was comparable to or larger than that in previous reports on neoadjuvant EGFR-TKIs. For neoadjuvant osimertinib, this study was the largest conducted thus far. Although a favorable trend was observed in the ORR and radical resection rate, the major pathological response (MPR), which was defined as the proportion of viable cancer cells ≤10% in the resected primary tumor, remains comparable. No previous trial has demonstrated superiority in OS compared with neoadjuvant chemotherapy. For example, the EMERGING-CTONG 1103 study, which assessed the efficacy of neoadjuvant erlotinib compared with standard chemotherapy, showed a significant improvement in PFS; however, no significant difference in OS was found (4). In the present study, survival outcomes were not achieved. Therefore, we look forward to further investigations by the authors, including the assessment of the association between OS and the ORR.

There may be room for discussing the surrogate marker suitable for OS in a trial of neoadjuvant EGFR-TKIs for locally advanced NSCLC. When considering downstaging or lymph nodal downstaging rates, the lack of preoperative information about the pathological diagnosis of the lymph node status could lead to the overestimation or underestimation of the clinical stage. Whether the ORR or MPR is a more appropriate primary endpoint for clinical trials concerning neoadjuvant treatment has long been debated. Several trials, including the EMERGING-CTONG 1103, set the primary endpoint as the ORR (4), whereas in the neoADAURA trial, a large prospective phase 3 study of neoadjuvant osimertinib for patients with stage II–IIIB EGFR-mutant NSCLC, the primary endpoint was the MPR (8). Compared with the NEOS study, a phase 2 trial conducted by Zhang *et al.*, which assessed neoadjuvant gefitinib for stage II–IIIA EGFR-mutant NSCLC, revealed a

higher MPR rate (24.2%) despite a lower ORR (54.5%) (1,6).

Although the ORR is largely objective and shows relatively little variation because of its consistency in radiological evaluation, its validity as the primary endpoint in the neoadjuvant setting warrants closer scrutiny. Indeed, a robust association between the ORR and PFS has been observed in patients with advanced NSCLC receiving targeted and standard therapies (16). This suggests that the ORR is a pivotal endpoint in predicting long-term outcomes, particularly in single-arm phase 2 trials. In the FLAURA phase 3 trial, which assessed the efficacy and safety of osimertinib in patients with EGFR-mutant advanced NSCLC, the ORRs were comparable at 80% for osimertinib and 76% for standard EGFR-TKIs (10). By contrast, the ORR of the present study stood at 71.1%. The ORR after neoadjuvant 1st- or 2nd-generation EGFR-TKI therapy has been reported to range from 42.1% to 70.1% (4-7). Additionally, Hu *et al.* conducted a case series study of neoadjuvant osimertinib for stage IB–IIIB NSCLC with an ORR of 69.2% (14). Collectively, although the ORR in the neoadjuvant EGFR-TKI settings appears commendable, it is not particularly remarkable when accounting for the differences in the treatment durations for advanced versus surgically resectable diseases. Furthermore, the correlation between the ORR and survival outcomes such as OS and recurrence-free survival remains arguably inconclusive, even for advanced EGFR-mutant NSCLC.

Accumulating evidence suggests that the MPR is a better surrogate marker for OS in patients with NSCLC treated with neoadjuvant chemotherapy. Chen *et al.* reviewed articles on neoadjuvant therapy in lung cancer (17). Previous studies have demonstrated the inconsistent trend in the MPR and ORR and the high discordance rate between histopathological and radiographic responses. Moreover, William *et al.* reported that histopathologic response was a statistically stronger predictor of OS than radiographic response in 160 patients with NSCLC who received neoadjuvant chemotherapy and underwent surgery (18). Based on these findings, the authors concluded that the MPR may be a more effective surrogate marker for OS than the ORR in patients receiving neoadjuvant therapy (17). However, the authors of the present study contend that the MPR in the study may be underestimated (1). They argue that a 6-week neoadjuvant osimertinib therapy might be insufficient and suggest that the appropriate MPR cutoff value could vary depending on the histologic type. Liu *et al.* demonstrated that the optimal cutoff values of the MPR for lung adenocarcinoma and squamous cell carcinoma were 58% and 12%, respectively (19). Qu *et al.* also suggested that the cut off value of the MPR for lung adenocarcinoma and squamous cell carcinoma should be 65% and 10%, respectively (20). Additionally, the accuracy of the MPR may differ based on the expertise of individual pathologists. Considering that resistance to EGFR-TKIs is nearly inevitable, the MPR might not be the most reliable surrogate marker of OS, particularly in the majority of EGFR-mutant NSCLCs, compared with patients receiving neoadjuvant chemo-immunotherapies. Qu *et al.* also suggested that an optimal MPR cutoff value might be different among agents used in the neoadjuvant therapies (20). However, given that the eligibility criteria, such as the disease stage or inclusion of locally advanced cases, can vary depending on the type of clinical trials, the MPR can still offer an efficient and consistent means for evaluating drugs, even in the context of neoadjuvant targeted therapy.

Currently, it is challenging to conclusively determine whether radiological or pathological response rates have a more significant impact on survival outcomes after neoadjuvant TKIs followed by surgery. The present study demonstrated a high ORR of 71% and a disease control rate of 100%, which align with the results of the FLAURA study (10). Notably, we observed a MPR of 10.7% and a pathological complete response (pCR) of 3.6%. These radiological and pathological findings are promising compared to those from the CTONG1103 study (4) that assessed the benefit of neoadjuvant erlotinib. In that context, neoadjuvant osimertinib appears more promising.

Additionally, Ohtaki *et al.* found that radiological responses were significantly associated with better outcomes in salvage surgery after EGFR-TKI treatments, indicating favorable survival outcomes in patients with a PR according to RECIST criteria (21). Similarly, Fujita *et al.* reported a patient who achieved a pCR and experienced improved disease-free survival after osimertinib therapy followed by salvage surgery, suggesting a good prognosis (22). For further insights, the ongoing neoADAURA study (8), a randomized phase 3 trial that considers the MPR as a primary endpoint, is expected to provide more definitive evidence on the prognostic significance of neoadjuvant osimertinib, potentially contributing to a deeper understanding of this complex issue.

In conclusion, neoadjuvant osimertinib therapy appears to be a promising option for resectable stage II–IIIA EGFR-mutant NSCLC, with satisfactory efficacy and safety profile. However, previous studies have not demonstrated the long-term survival benefit of neoadjuvant EGFR-TKIs

(3-7,9). We anticipate that updated analyses of the current study and other phase 3 trials will unveil the impact of neoadjuvant osimertinib on survival outcomes, as well as the correlation of the ORR and MPR with definitive outcomes. This will enhance the impact and forward-thinking nature of our commentary.

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