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Perioperative Treatment in EGFR-Mutant Early-Stage Non-Small Cell Lung Cancer: Current Evidence and Future Perspectives

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ABSTRACT

Adjuvant osimertinib administered over a 3-year period in patients diagnosed with stage IB–IIIA non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) mutations has not only shown improvement in event-free survival but also demonstrated a prolonged overall survival (OS), leading to its approval as a standard treatment in this context. Meanwhile, no targeted studies have been conducted on the efficacy of adjuvant immune checkpoint inhibitors in these patients. Although studies such as IMPOWER-010 and KEYNOTE-091 have included a small number of patients with positive driver genes, no definitive conclusions regarding the OS benefit have been established. Neoadjuvant targeted therapy is not currently recommended because of insufficient evidence, characterized by a low depth of pathological response and no reported improvement in survival outcomes. The same is true for neoadjuvant immunotherapy in patients with EGFR mutations. Although numerous issues such as refining patient population selection, determining appropriate combination therapy regimens, establishing primary endpoints, assessing the influence of perioperative complications, and accurately evaluating the clinical application of circulating tumor DNA in various scenarios exist, several promising ongoing trials, including ADAURA2 and NEOADURA, are expected to provide valuable insights that will help address these questions. Here, we summarize the available evidence and clinical issues that need to be considered to optimize clinical decision-making for patients with EGFR-mutant NSCLC.

Xiaobei Guo and Xiaoyan Liu contributed equally to this work and shared first authorship.

1 | Introduction

Despite therapeutic advances, lung cancer remains the leading cause of cancer-related deaths worldwide, in which non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases [1, 2]. Notably, 15% patients with NSCLC in the Caucasian populations and more than half in Asia populations harbor epidermal growth factor receptor (EGFR) mutations [3]. As risk factors are identified and early screening awareness improves, the proportion of early-stage lung cancer cases in the population is expected to rise gradually. Radical surgery combined with (neo)adjuvant systemic therapy is the first choice of treatment for patients with resectable stage II-IIIB or stage IB disease. However, 30%–55% patients experience recurrence and have a poor prognosis [4, 5]. Perioperative treatment, including neoadjuvant and adjuvant therapies, can benefit these patients to some extent. Historically, perioperative treatment was primarily limited to chemotherapy (CT). However, the modest improvement rates in overall survival (OS) with either adjuvant or neoadjuvant therapy, at 5.4% and 5% [6, 7], respectively, underscore the urgent need for more effective perioperative strategies. The ADAURA study establishes osimertinib as the standard of care for patients with stage IB–IIIA disease post-surgery. Accumulating evidence supports the efficacy of perioperative immunotherapy. In this review, we examine the historical development of adjuvant targeted therapy, synthesize the most recent evidence regarding the efficacy of various perioperative treatment strategies, and highlight challenges along with potential solutions for personalized perioperative therapy.

2 | Adjuvant Therapy for EGFR-Mutant NSCLC

2.1 | Adjuvant Targeted Therapy

Adjuvant therapy offers several advantages: it mitigates the risk of preoperative complications, eliminates residual cancer cells post-surgery, extends treatment duration, and enhances systemic disease control.

2.2 | History of Adjuvant Therapy With EGFR Tyrosine Kinase Inhibitors

Adjuvant targeted therapy has a long history (Table 1), and its role was first observed in cohort studies [21, 22]. BR19, the first phase III study of adjuvant targeted therapy, in which screening for EGFR mutations (EGFRm) was not mandatory, was designed to evaluate the efficacy and safety of gefitinib-targeted therapy [8]. However, the study was terminated early because of the negative results of SWOG S0023 for gefitinib [23]. RADIANT highlighted EGFRm as an effective, predictive biomarker for adjuvant targeted therapy efficacy [9]. Notably, the SELECT study demonstrated improved 5-year disease-free survival (DFS) and OS rates with erlotinib compared to those in retrospective cohorts of EGFR-mutant patients with stage IA-IIIA disease [10]. Subsequent phase III trials such as CTONG1104, IMPACT, and EVIDENCE showed varied degrees of DFS benefit but no significant OS improvement [11, 13, 16, 24]. EVAN was the first study to report an improvement of the 5-year OS rate, with a result of 84.8% in the erlotinib group versus 51.1% in the CT group (median OS: 84.2 months versus 61.1 months, HR = 0.318, $p = 0.003$). Patients enrolled in the EVAN trial either had stage IIIA NSCLC with an EGFR Exon 19 in-frame deletion (19del) or an exon 21 Leu858RArg point mutation (21L858R) [14, 15].

The focus of adjuvant therapy with first-generation Tyrosine Kinase Inhibitors (TKIs) gradually shifted toward EGFR-mutant patients with a typical treatment duration of 2 years. While DFS improvement was observed, DFS curves crossed post-TKI discontinuation, and OS did not surpass that of CT, except in the EVAN trial. Additionally, the incidence of central metastatic recurrence was higher with targeted adjuvant therapy, indicating inadequate brain protection, similar to findings in advanced disease. Consequently, the ADAURA trial investigated osimertinib, known for its superior central penetration and brain protection in advanced EGFR mutant NSCLC, resulting in significant success.

2.3 | Adjuvant Osimertinib Significantly Improves DFS and OS

Adjuvant osimertinib, administered over a period of 3 years, demonstrated significant efficacy in patients with stage IB–IIIA disease enrolled in the ADAURA trial. Both DFS and OS were notably enhanced across patients with stage II-III disease and the overall study population. The median OS reached 65.8 months (Hazard Ratio (HR) = 0.27, 95% confidence interval (CI): 0.21–0.34), with a remarkable 5-year OS rate of 88% (HR = 0.49) in the overall population. In comparison, the control group exhibited a median OS of 28.1 months and a 5-year OS rate of 78%. The risk of death was reduced by 51% with osimertinib [19].

2.4 | Screening Suitable Targeted Therapy Population

Given the impressive results from the ADAURA trial, the ongoing ADAURA2 trial (NCT05120349) aims to extend adjuvant osimertinib treatment to encompass stages IA2 and IA3. However, the DFS rates of patients with stage IB, II, and III disease in the control group, as reported by the ADAURA trial, after a follow-up of 60 months were 55%, 37%, and 15%, respectively [25], indicating that a considerable portion of patients might not experience disease recurrence without osimertinib. In contrast, the CORIN trial reported a 3-year DFS rate as high as 84% in patients with stage IB disease in the control group [17]. The adoption of a simplistic one-size-fits-all strategy coupled with prolonged treatment regimens may lead to heightened toxicities and economic burdens. Therefore, it is necessary to identify accurate biomarkers to screen suitable patients for adjuvant therapy. Some studies have shown that postoperative circulating tumor DNA (ctDNA) based minimal residual disease (MRD) is an effective biomarker for predicting recurrence, with the ability to anticipate relapse months before imaging changes [26, 27]. For example, LUNGCA-1 reported that ctDNA-based MRD positivity at 3 days and 1 month post-surgery was a strong predictor of disease recurrence in patients with stage I-III NSCLC, with a HR of 8.6 (95% CI: 4.7–15.6, $p < 0.001$) and 14.3 (95% CI: 4.7–15.6, $p < 0.001$), respectively. Meanwhile, among MRD-positive

TABLE 1 | Adjuvant therapy research.

Research name	Phase	Time	Stage	Sample size *N*	Prior adjuvant chemotherapy	Intervention	Treatment duration (years)	Primary endpoints	mDFS (months) / DFS rate HR, *p**	mOS(months)/5-year OS rate HR, *p**	CNS relapse rate/median follow-up (months)
BR19 [8]	III	2002	IB–IIIA	15 EGFRm	Randomized	gefitinib vs. placebo	2	OS	NA HR = 1.84 $p = 0.4$	HR = 3.16 $p = 0.15$	/
RADIANT [9]	III	2006	IB–IIIA (N2)	161 EGFRm	Randomized	erlotinib vs. placebo	2	DFS	46.4 vs. 28.5 HR = 0.61 $p < 0.001$	/	37.1% vs. 1.9%/47
SELECT [10]	II	2008	IA–IIIA	100	According to TNM	erlotinib	2	2-year DFS rate	88%	86%	20%/62.4
ADJUVANT [11, 12] (CTONG1104)	III	2011	II–IIIA (N1/2)	222	None	gefitinib vs. CT	2	DFS	30.8 vs. 19.8 HR = 0.56 $p = 0.001$	75.5 vs. 62.8 HR = 0.92 $p = 0.674$	27.4% vs. 24.1%/36.5
IMPACT [13]	III	2011	II–IIIA	234	None	gefitinib vs. CT	2	DFS	35.9 vs. 25.1 HR = 0.92 $p = 0.63$	78% vs. 74.6% HR = 1.03 $p = 0.89$	30% vs. 18%/70
EVAN [14, 15]	II	2012	IIIA	102	None	erlotinib vs. CT	2	2-year DFS rate	42.4 vs. 21.0 HR = 0.268 $p = 0.0003$	84.2 vs. 61.1 HR = 0.318 $p = 0.003$	/
EVIDENCE [16]	III	2015	II–IIIA	322	None	icotinib vs. CT	2	DFS	47.0 vs. 22.1 HR = 0.36 $p < 0.001$	NR	7% vs. NA/24.9
CORIN [17]	II	2015	IB	128	None	icotinib vs. observation	1	3-year DFS rate	96.1% vs. 84.0% HR = 0.23 $p = 0.013$	NR	0 vs. 9.2%/39.9
ICOMPARE [18]	II	2013	II–IIIA	109	None	icotinib 2 years vs. 1 year	2 vs. 1	DFS	48.9 vs. 32.9 HR = 0.51 $p = 0.029$	88% vs. 72% $p = 0.032$	32% vs. 35%/44.1
ADAURA [19, 20]	III	2015	IB–IIIA	682	Not mandatory	osimertinib vs. placebo	3	DFS	65.8 vs. 28.1 $p < 0.001$	88% vs. 78% HR = 0.49 $p < 0.001$	2% vs. 11%

Abbreviations: CNS, central nervous system; EGFRm, epidermal growth factor receptor mutations; HR, hazard ratio; mDFS, mean disease-free survival; mOS, mean overall survival; NA, not acquired; NR, not reached.

patients, those receiving adjuvant therapy achieved prolonged recurrence-free survival (RFS) (median RFS: 574 days vs. 315 days, $p = 0.008$) compared to those without [28]. Moreover, Zhang et al. [29] reported that among 261 post-surgery patients with stage I-III NSCLC, the negative predictive value of longitudinal monitoring MRD for DFS was as high as 96.8%. In the prospective DYNAMIC (Australian New Zealand Clinical Trials Registry number, ACTRN12615000381583.) study, stage II colon cancer patients made informed decisions regarding adjuvant chemotherapy based on postoperative ctDNA results. Notably, the ctDNA-guided group achieved a comparable 2-year DFS rate (93.5% vs. 92.4%) to the pathologically classified risk group, while significantly reducing the proportion of patients receiving adjuvant chemotherapy (15% vs. 28%). This provides compelling new evidence for guiding adjuvant therapy decisions in this patient population [30].

Given the high sensitivity and specificity of ctDNA, Cohen SA et al. recommended that ctDNA testing be performed at 2 weeks post-surgery and that standard adjuvant therapy be administered based on the results [31]. However, several obstacles exist in guiding clinical practice with ctDNA-based MRD detection in early-stage NSCLC. Clonal hematopoiesis of indeterminate potential (CHIP) is defined by the presence of age-dependent acquired mutations in hematopoietic progenitor cells and has been reported to occur in up to 30% of individuals between 60 and 70 years of age [32]. Thus, CHIP may lead to false-positive plasma genotyping, compromising ctDNA reliability. The development of highly sensitive assays for ctDNA testing in early-stage NSCLC, along with the establishment of standardized techniques and optimal time points for plasma collection, remains crucial [33].

2.5 | Combined Treatment Strategy of Adjuvant Targeted Therapy

For many years, adjuvant CT has served as the standard treatment strategy for postoperative patients, offering some improvement in OS. However, in the context of the ADAURA trial, adjuvant CT was not obligatory. Interestingly, the 5-year OS rates with osimertinib in both the CT group and CT-naive groups were comparable, at 87% and 88%, respectively [19]. However, considering that combined CT was performed in 76% patients with stage II-IIIA NSCLC and only in 26% patients with stage IB NSCLC, the role of adjuvant CT should not be ignored, even in patients planning to undergo targeted adjuvant therapy [34].

2.6 | Duration of Adjuvant Targeted Therapy

Several studies have highlighted the importance of the duration of adjuvant targeted therapy, as evidenced by the crossover of DFS curves post-TKI discontinuation, suggesting TKIs may inhibit recurrence but not eliminate tumor cells entirely. The ICOMPARE trial compared the 2-year and 1-year results of adjuvant icotinib in patients with stage II-IIIA lung adenocarcinomas. Although the DFS of N0 and N1 stage disease did not benefit from extended treatment, the DFS and 5-year OS rates across the whole population were 48.9 months versus 32.9 months (HR = 0.51, $p = 0.029$) and 88% versus 72% ($p = 0.032$), respectively, with 2-year therapy compared to those with 1-year therapy, indicating potential OS benefits with prolonged adjuvant icotinib treatment [18]. The ADAURA trial extended adjuvant therapy duration to 3 years and notably achieved benefits in both DFS and OS. However, whether this was attributable to the efficacy of the third-generation TKI or simply the extension of treatment duration remains uncertain. Future insights from the TARGET (NCT05526755) trial, a phase II prospective study aiming to extend adjuvant osimertinib treatment to 5 years in patients with stage II-IIIb NSCLC, holds promise in providing valuable insights into the optimal duration of adjuvant therapy. Notably, the ADAURA study observed that 34% patients in the osimertinib group did not complete the treatment as planned, underscoring the importance of considering, adverse effects, economic burden, and clinical benefits when determining treatment duration.

Owing to its low toxicity and high efficacy, osimertinib has been approved as a standard adjuvant treatment for stage IB–IIIA EGFRm NSCLC in many countries and regions. Nevertheless, unanswered questions persist, necessitating further data collection and analysis in the future.

2.7 | Adjuvant Immunotherapy

Immune checkpoint inhibitors (ICIs) are used as perioperative treatment. However, owing to the poor performance of ICIs in patients with advanced NSCLC with EGFR-mutation, there have been no specific clinical trials of ICIs targeting patients with EGFRm mutations in the adjuvant setting.

The Impower-010 trial was the first phase III study to demonstrate the survival benefits of adjuvant ICI therapy. Despite all patients having received chemotherapy prior to adjuvant immunotherapy, atezolizumab did not show significant improvement in DFS compared to best supportive care (BSC) in completely resected stages II-IIIA disease. In the EGFRm subgroup (sample size = 109), the DFS was 24.1 months with atezolizumab compared to 24.0 months with BSC (HR 0.99, 95% CI: 0.6–1.62). Among the subset of patients with programmed cell death-ligand 1 (PD-L1) ≥ 1% ($n = 43$), DFS was 29.7 months with atezolizumab versus 16.6 months with BSC (HR = 0.57, 95% CI: 0.26–1.24). Similarly, in the stage II-IIIA population with EGFRm, no statistically significant differences were observed in OS, regardless of the PD-L1 level [35, 36].

In contrast, in the KEYNOTE-091 trial, which included 73 patients with EGFRm, 14% patients did not receive CT, and the HR of DFS in the EGFRm group was 0.44 (95% CI: 0.23–0.84), lower than that in the non-mutation group (HR = 0.78, 95% CI: 0.59–1.05) [37]. However, OS data from KEYNOTE-091 are still pending.

The Impower-010 subgroup analysis did not reveal any DFS or OS benefits in stage II-III patients with EGFRm. In contrast, in KEYNOTE-091, a DFS benefit was noted in the intention-to-treat population with EGFRm. However, owing to the limited number of cases and different PD-L1 testing methods, these results should be interpreted with caution. Currently, there is no consensus on the role of immunotherapy in this setting and it is

uncertain whether PD-1 is superior to PD-L1. Similarly, the predictive value of PD-L1 in response to immunotherapy remains controversial.

3 | Neoadjuvant Therapy

Neoadjuvant therapy offers several advantages, including better tolerability, compliance with adjuvant therapy, tumor downgrading or staging, creation of surgical opportunities, reduction in surgical resection area, improvement in R0 resection rate, early control of micrometastases, and evaluation of drug efficacy to guide adjuvant therapy. The Checkmate-816 study has provided evidence supporting neoadjuvant therapy for early-stage lung cancer without driver gene mutations. However, there is currently no standard mode of neoadjuvant therapy for early-stage EGFR-mutated NSCLC, and research on targeted therapy in this context is rapidly evolving.

3.1 | Neoadjuvant Targeted Therapy

Many studies have investigated the efficacy of EGFR-TKIs in the field of neoadjuvant therapy. NCT00188617, the first study involving neoadjuvant targeted therapy, showed that 43% patients with stage I NSCLC treated with gefitinib exhibited tumor shrinkage, which was correlated with EGFRm [38]. Zhang et al. reported that the objective response rate (ORR) and major pathological response (MPR) were 54.5% and 24.2%, respectively, with neoadjuvant therapy with gefitinib for 6 weeks in resectable, EGFRm patients with stage II-IIIA NSCLC. The median DFS was 33.5 months, with patients achieving MPR exhibiting longer DFS ($p = 0.019$) [39]. The phase 2 clinical trials CSLC 0702 and ESTERN evaluated neoadjuvant erlotinib In EGFRm patients with stage IIIA (N2) NSCLC. The treatment duration was 6 weeks and 8 weeks, the ORRs were 58.3% and 42.1%, and the R0 resection rates were 50% and 68.4%, respectively [40–43]. However, because of small sample sizes and single-arm designs, these studies had limited statistical power. In contrast, the randomized controlled trial (RCT), CTONG1103, compared erlotinib versus CT as neoadjuvant therapy, reporting an MPR of 9.7% in the erlotinib group and 0% in the control group. Although erlotinib showed a statistical progression-free survival (PFS) benefit, no OS benefit was observed [41, 43].

Studies such as ASCENT and TEAM-LungMate004 evaluated the efficacy of neoadjuvant afatinib therapy in patients with stage IIIA-IIIB and IIIA-IIIC NSCLC, respectively. In the ASCENT study, patients subsequently received neoadjuvant chemoradiotherapy and underwent surgery. The ORRs were 58% and 70.2%, MPR were 70% and 9.1%, PFS/event-free survival (EFS) were 34.6 months and not reached (NR), and OS was 69.1 months and NR, respectively [44, 45].

By April 2021, 13 patients were enrolled in the NCT03433469 trial, implementing 4–8 weeks of neoadjuvant osimertinib treatment in patients with stage I-IIIA NSCLC. Results indicated an MPR rate of 15%, no pathological complete response (pCR), an ORR of 46%, and an 80% lymph node downstaging rate, with no delayed surgeries reported [46]. NEOS, a multicenter, single-arm study, boasted the largest sample size in neoadjuvant osimertinib therapy. Forty patients with stage IIA-IIIB received neoadjuvant osimertinib for 6 weeks, demonstrating an ORR of 71.1%, a 93.8% R0 resection rate, a 10.7% MPR rate, and a 3.6% pCR rate [47]. Detailed information is listed in Table 2.

To date, data on neoadjuvant targeted therapy have only been obtained from phase 2 studies with small cohorts. Osimertinib appeared to exhibit superior ORR and R0 rates compared to first- and second-generation TKIs, while MPR and pCR showed little improvements. The DFS and OS data demonstrate considerable heterogeneity across various studies (Table 2), which may be attributed to the varying disease stages of the study populations, the relatively limited sample sizes and insufficient follow-up time. Moreover, most neoadjuvant therapy studies are single-arm trials, thereby limiting both direct and indirect comparisons. CTONG1103, the only RCT in this field, reported no benefit in OS with erlotinib compared to that with CT. The low pCR and MPR rates might be attributed to the mechanisms of EGFR-TKIs, which inhibit but do not kill tumor cells. Moreover, given the findings from the ADAURA trial, indicating benefits from 3 years of adjuvant osimertinib therapy, the duration of neoadjuvant targeted therapy may be insufficient. Given the lack of robust evidence in neoadjuvant settings, targeted therapy is not currently recommended and warrants further investigation with larger cohorts and longer follow-up periods. The ongoing NEOADAURA international multicenter phase III study, incorporating three arms, including neoadjuvant osimertinib monotherapy, osimertinib plus CT, and neoadjuvant CT, in patients with stage II-IIIB EGFRm NSCLC, may shed light on this matter. The primary endpoint of NEOADAURA is MPR, with secondary endpoints, including EFS, pCR, DFS, OS, baseline ctDNA levels, and other indicators, providing potential evidence for future recommendations [51].

3.2 | Neoadjuvant Immunotherapy

CheckMate-816 was the first phase III trial to confirm the promising efficacy and safety of neoadjuvant immunotherapy [52]. Since then, many studies had adopted the strategy of perioperative whole-course immunotherapy, in which patients with EGFRm were often excluded or EGFRm testing was not mandatory.

KEYNOTE-671 was the first and only phase III RCT of perioperative immunotherapy with positive endpoints of EFS and OS [53]. In this trial, 33 patients with stage II-IIIB (N2) NSCLC identified with EGFRm were enrolled. While the EFS of this subgroup was improved, there was no significant improvement in OS (HR = 0.24, 95% CI 0.03–2.03) [54]. The AEGEAN study, initially ongoing when osimertinib was approved as the standard adjuvant treatment for EGFR-positive IB–IIIA NSCLC in 2020, subsequently revised its protocol and ceased recruitment of such patients. Ultimately, 51 patients with EGFR mutations were enrolled. The EFS of perioperative durvalumab or placebo combined with neoadjuvant platinum-based CT in EGFR-positive stage IIA-IIB NSCLC was 30.8 months and 19.6 months, respectively (HR = 0.86, 95% CI 0.35–2.19), with a pCR rate of 3.8% vs. 0%, showing no statistically significant difference [55]. Forty-four patients were enrolled in the phase 2 platform NEOSTAR trial which evaluated neoadjuvant CT plus

TABLE 2 | Neoadjuvant targeted therapy studies.

Study name	Phase	Stage	Sample Size *N*	Interventions	Treatment cycles (d)	Primary endpoints	ORR (%) *p**	R0 resection rate (%)	MPR/ pCR (%)	EFS/ DFS/PFS (month)	OS (month)/ OS rate
NCT00188617 [38]	II	I	36	gefitinib	28	ORR	11	/	/	/	/
LOGIK0902 [48]	II	III non-resectable	20	gefitinib	56	2-year OS rate	85	75	/	/	2-year OS: rate 90%
NCT01833572 [39]	II	II-IIIA	35	gefitinib	42	ORR	54.5	/	24.2/12.1	DFS 33.5	NR
CSLC0702 [40]	II	IIIA	EGFRm 12	erlotinib	42	ORR	58.3	50	/	PFS 6.9	14.5
CTONG-1103 [41]	II	IIIA	72	erlotinib vs. CT	42	ORR	54.1 vs. 34.3 $p=0.09$	73	9.7/0	PFS 21.5 vs. 11.4	42.2 vs. 36.9
ESTERN [42]	II	IIIA	19	erlotinib	56	R0 resectionrate	42.1	68.4	/	DFS 10.3 PFS 11.2	51.6
ASCENT [49]	II	IIIA	19	afatinib	60	ORR	69	/	70/NA	PFS 34.6	69.1 2-year OS rate 88%
TEAM-LungMate004 [44]	II	IIIA–IIIC	47	afatinib	56–112	ORR	70.2	87.9	9.1/3	NR	NR
NCT02824952 [50]	II	III Inoperable	21	osimertinib	84	ORR	95.2	/	/	NR	NR
NEOS [47]	II	IIA–IIIB	40	osimertinib	42	ORR	71.1	93.8	10.7/3.6	/	/

Abbreviations: DFS, disease-free survival; EFS, event-free survival; epidermal growth factor receptor mutations; MPR, major pathological response; NA, not acquired; NR, not reached; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival.

nivolumab (Nivo) with or without ipilimumab (Ipi) in operable NSCLC. There were five patients in the Nivo+CT group and six in the Nivo+Ipi + CT group. The MPR rates were 32.1% and 50%, respectively. In patients without known EGFR/ALK mutations, the MPR rates were 41.2% (7/17) and 62.5% (10/16), respectively. No difference was observed in the median residual tumor size between patients with EGFR mutations and those with wild-type EGFR mutations [56].

A multicenter retrospective study reported that, in 40 stage II-IVa patients with positive driver gene mutations (of which 19 patients had EGFR mutations), the PR, MPR, and pCR rates were 62.5%, 37.5%, and 12.5%, respectively, with neoadjuvant immunotherapy. Meanwhile, MPR was not related to PD-L1 expression, and the DFS of patients with EGFRm was 28.5 months [57]. Indirect comparison with the CTONG1103 trial showed that the ORR, MPR, and pCR of neoadjuvant immunotherapy combined with CT were significantly higher than those of targeted therapy or CT alone in resectable EGFRm NSCLC. This was the first multicenter cohort study to preliminarily demonstrate the potential clinical feasibility of neoadjuvant immunotherapy plus CT for resectable NSCLC with driver gene mutations, especially EGFRm NSCLC.

Neoadjuvant immunotherapy has achieved a deeper pathological response in studies involving negative driver genes. A phase 2, open-label, single-center, Simon two-stage design study, NEOTIDE (CTONG2104), evaluated neoadjuvant sintilizumab plus leucovar and carboplatin in patients with stage IIB-IIIB EGFRm NSCLC. The reported disease control rate (DCR) and MPR rates were 100% and 44%, respectively. Notably, four patients (22%) were close to pCR, with an acceptable safety profile [58].

EGFR mutations are the most common driver gene mutations in patients with NSCLC. While significant progress has been made in adjuvant therapy, achieving a good pathological response to neoadjuvant therapy remains difficult. Moreover, although studies on advanced lung cancer have shown that immunotherapy has poor efficacy in patients with EGFRm mutations, neoadjuvant immunotherapy appears to elicit deeper pathological responses. Nonetheless, further evidence regarding the correlation between MPR and survival benefits is essential for informing clinical practice and treatment decisions in the future.

3.3 | Challenges of Neoadjuvant Therapy

Neoadjuvant targeted therapy can shrink tumors, reduce lymph node staging, increase surgical opportunities, and improve surgical resection rates. However, the existence of numerous unresolved inquiries persists (Figure 1).

3.3.1 | Potential Population for Neoadjuvant Therapy

The target population for targeted therapy has gradually expanded from patients with stage III to stage II NSCLC and even to patients with stage I NSCLC. However, preoperative genetic testing for patients with stage I disease is not routine in clinical practice, and obtaining genetic test results requires sufficient samples and is time-consuming. Challenges, such as primary resistance to TKI, perioperative adverse reactions, and delayed radical surgery, persist even in the presence of sensitive mutations. For instance, in the NCT03433469 trial, which planned to enroll patients with stage I disease, 13 patients were enrolled with no delayed surgery reported. Furthermore, the ORR and R0 resection rates of the 14 patients with stage II NSCLC enrolled in the NEOS study were higher than those achieved with first- and second-generation TKIs. However, survival data were not obtained, and further evidence is required.

3.3.2 | Treatment Options and Potential Biomarkers

The primary objective of neoadjuvant therapy is to enhance therapeutic efficacy. Targeted therapy and immunotherapy possess distinct merits and demerits.

Neoadjuvant targeted therapy is rapidly evolving, with numerous clinical trials underway. Given its favorable tolerance and the characteristic of inhibiting tumor growth without completely eradicating tumors, some studies have opted for a combination with CT. Besides, the ASCENT trial achieved a MPR of 70% in patients receiving afatinib and neoadjuvant chemoradiotherapy. Hence, the incorporation of these strategies may potentially enhance the efficacy of target therapy alone, thereby contributing to an improved MPR rate. Further studies with larger data are warranted.

Theoretically, immunotherapy combined with CT exerts complementary effects. CT aids in enhancing the immune response by eliminating tumor cells, augmenting their immunogenicity to some extent, inhibiting negative immune signals produced by tumors, and modifying the immune microenvironment of tumors and surrounding tissues. Neoadjuvant immunotherapy, with its potential to activate a broader array of T cells due to increased tumor neoantigens and enhanced antigen presentation, holds promise for better clinical efficacy [59]. Therefore, in theory, neoadjuvant immunotherapy may be applicable to all early-stage lung cancers. Although existing evidence suggests that patients receiving neoadjuvant immunotherapy with or without CT exhibit a higher MPR, the IA2 results of KEYNOTE-671 reported that the OS of the subgroup with EGFRm did not benefit from perioperative immunotherapy compared to that from CT alone. However, owing to the limited sample size, definitive conclusions cannot be drawn, and further exploration is warranted.

Data from the NEOTIDE trial provide additional insights into neoadjuvant immunotherapy in EGFRm NSCLC. However, further follow-up data are required to evaluate application prospects. In the phase 2 platform of the NEOSTAR study, Nivo+Ipi combined with CT appeared promising in enhancing MPR compared to Nivo plus CT alone. However, inconsistent results were observed in patients with EGFRm, leaving the optimal choice between targeted therapy and immunotherapy for neoadjuvant treatment in patients with EGFRm still uncertain.

Exposing the patients who are more likely going to respond and benefit from immunotherapy would seem to us even more important in the neoadjuvant setting. As is known to us, the level of PD-L1 expression exhibited a strong correlation with

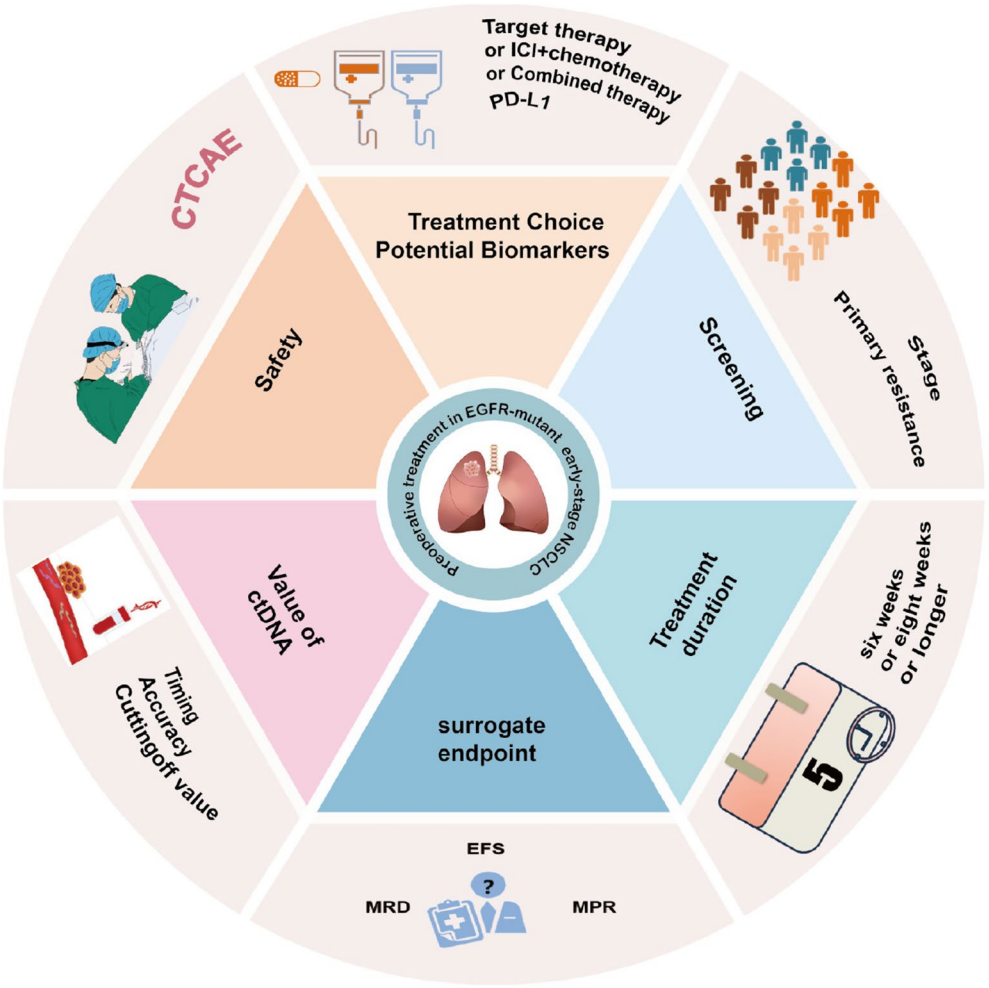

FIGURE 1 | Title: Issues needed to be considered in the clinical practice of preoperative management with NSCLC. CTCAE, Common Terminology Criteria for Adverse Events; ct-DNA, circulating tumor DNA; EFS, event-free survival; ICI: Immune checkpoint inhibitors; MPR, major pathological response; MRD, minimal residual disease; PD-L1: Programmed cell death-ligand 1.

the efficacy in advanced NSCLC lacking driver mutations. Likewise, the relative benefit in the pembrolizumab group increased with increasing PD-L1 expression in KEYNOTE-671(HR for disease progression, recurrence, or death of 0.42 for PD-L1 tumor proportion score (TPS) of ≥ 50%, 0.51 for a PD-L1 1%–49%, and 0.77 for a PD-L1 < 1%) and PD-L1 expression was associated with improved radiological and pathologic outcomes in NEOSTAR [53, 60]. However, no significant difference in MPR of immunotherapy between PD-L1 negative and positive patients in the LCMC3 trial, nor in the NADIM or Checkmate 816 trials [52, 61, 62]. Given that the majority of these studies were conducted in patients lacking sensitive driver genes and had a limited number of EGFRm patients, further evidence is required to establish a correlation between PD-L1 expression level and the efficacy of neoadjuvant immunotherapy in this particular context.

3.3.3 | Duration of Treatment

Generally, a therapeutic regimen of neoadjuvant therapy last for 6–8 weeks or 2–4 cycles, during which a dynamic evaluation of tumor changes is needed. The neoSCORE trial (NCT04459611) was the first randomized trial to assess the efficacy and safety of different cycles of immuno-chemotherapy for resectable NSCLC in the neoadjuvant setting and turned out that three cycles of sintilimab with platinum-based chemotherapy in resectable IB-IIIA NSCLC patients present a 14.5% increase in MPR rate in comparison to two cycles [63]. Notably, squamous NSCLC achieved more favorable pathological remissions and driver mutation NGS testing showed a high mutation rate in non-squamous NSCLC, which might be a possible explanation for the low MPR rate in non-squamous subtype. Thus, two cycles of immuno-chemotherapy might not be enougy. While, the NCT02716038 trial, which designed a neoadjuvant atezolizumab and chemotherapy for 4 cycles at most, showed that 17% patients proceeded to surgery early because of treatment-related toxic effects [64]. Consequently, the optimal duration in this setting has not been established and consideration should be given for enhancing both therapeutic efficacy and minimizing adverse reactions.

3.3.4 | Primary Endpoint

A series of clinical endpoints such as ORR, MPR, pCR, DFS, event-free survival (EFS), PFS, and OS can be used to evaluate the effect of neoadjuvant therapy, with OS being the gold standard.

However, achieving OS data may require a lengthy follow-up period post-enrollment. For example, the ANITA study took 12 years from enrollment to the publication of the OS data [65]. Stable and powerful surrogate markers are crucial to accelerate the development and approval of new therapies. Trials, including ADAURA, EVAN, ICOMPARE, as well as other adjuvant therapy studies, have shown that DFS is associated with OS, and osimertinib has been approved because it significantly improves DFS. However, the DFS benefit did not translate to OS in both the CTON1104 and IMPACT studies, suggesting that DFS is not always associated with OS. EFS serves as an acceptable endpoint in neoadjuvant therapy and is recommended by the FDA for expedited approval because of its reliance on smaller sample sizes [66]. However, it may be influenced by non-tumor-related deaths and subsequent adjuvant therapy. The degree of pathological response is increasingly used as a surrogate or secondary endpoint for neoadjuvant therapy. The low incidence of pCR, regardless of immunotherapy, targeted therapy, or CT, limits its use as a primary endpoint. In contrast, MPR has a high incidence rate, making it a feasible alternative endpoint than pCR. NEOADAURA, Neolpower, and NEOAFA represent neoadjuvant targeted studies that used MPR as the primary endpoint. In the Checkmate-816 trial, an exploratory analysis suggested that patients who achieved pCR appeared to exhibit longer EFS [52]. In contrast, KEYNOTE-671 showed that improved EFS with pembrolizumab was independent of either MPR or pCR [53]. The variability in MPR assessment caused by subjective factors and lack of standardized interpretation standards underscores the need for more robust evidence to assess its impact on survival outcomes.

Ohara et al. analyzed the correlation between RFS and preoperative ctDNA in 20 patients with stage IIA-IIIA NSCLC, with negative results [27]. However, NADIM reported a clear correlation between low ctDNA levels at baseline and negative ctDNA after neoadjuvant therapy with improved PFS and OS in stage IIIA NSCLC [61]. In the Checkmate-816 trial, patients with ctDNA clearance after neoadjuvant therapy were associated with potentially longer EFS (Immunotherapy group, HR = 0.60; 95% CI: 0.20–1.82; CT group, HR = 0.63; 95% CI, 0.20–2.01) and higher pCR rates [52]. The application of preoperative ctDNA-based MRD for predicting long-term survival remains controversial. Meanwhile, the same questions of ctDNA discussed in the adjuvant setting including accuracy of assay, standardized techniques and optimal time points for plasma collection also exist.

3.3.5 | Sequential Therapy

Osimertinib remains the recommended adjuvant therapy regimen for patients with resected stage IB–IIIA EGFRm NSCLC. Despite this, neoadjuvant therapy was not included in the ADAURA study. Current investigations into perioperative treatment involve both neoadjuvant and adjuvant therapies, with studies aiming to determine if this approach surpasses the outcomes seen in ADAURA. Additionally, the necessity of adjuvant therapy following neoadjuvant treatment is under exploration. The APPROACH trial (NCT04841811) is the first ongoing phase III study (group B) evaluating the use of almonertinib as adjuvant therapy based on ctDNA-based MRD status post-surgery, shedding light on the role of ctDNA in guiding treatment decisions and predicting prognosis.

Combining osimertinib with durvalumab or pembrolizumab, while showing promise in advanced NSCLC, poses a heightened risk of adverse events [67, 68]. Therefore, investigating perioperative treatment regimens involving neoadjuvant immunotherapy followed by adjuvant targeted therapy warrants careful consideration.

However, data on neoadjuvant immunotherapy followed by adjuvant immunotherapy in this population is limited. Therefore, it is necessary to screen for populations that might benefit from immunotherapy. Generally, the duration of adjuvant immunotherapy last for 12–13 cycles or 1 year, whereas NADIM II is shortened to 6 months. However, the optimal treatment duration remains uncertain, necessitating a careful balance between clinical benefits, adverse reactions, and economic burden. Moreover, ctDNA clearance may serve as a bridge between traditional endpoints and risk stratification, enabling the formulation of individualized treatment strategies.

4 | Safety

Target therapy is generally deemed safe. In the ADAURA study, 20% of patients experienced grade 3 or higher adverse events (AEs), with no fatal adverse reactions reported [20]. In the IMPOWER010 trial, 11% of patients experienced grade 3–4 immune-related adverse events, and there were 4 cases of grade 5 adverse events (AEs) [35]. In the KEYNOTE-091 study, 34% of patients experienced grade 3 or higher AEs, and 4 patients experienced grade 5 AEs [37]. Overall, adjuvant targeted therapy appears to exhibit a more favorable safety profile. However, potential delays, increased difficulties, increased risk of surgical complications, and postoperative complications in the neoadjuvante setting should be thoroughly evaluated. The CTONG1103 study reported that postoperative complications in the erlotinib group were comparable to those in the control group and were mostly mild [43]. Similarly, no unexpected perioperative AEs were reported in various single-arm trials of neoadjuvant therapy involving three generations of TKIs [39, 44, 47].

The AEGEAN trial reported that neoadjuvant durvalumab plus CT or CT alone did not prolong the time to surgery, with similar surgical approaches observed. Surgery-related AEs were 40.2% and 39.2%, and surgical complications were 59.1% and 60.1%, respectively, most of which were graded as 1–2 according to the Clavien–Dindo classification. These results suggest that neoadjuvant durvalumab therapy did not exacerbate surgical risks [69]. Similarly, findings from the Checkmate-816 trial indicated no significant delays in surgery, maintaining an overall acceptable safety profile. Surgery-related complications were reported at rates of 41.6% and 46.7% in the CT plus nivolumab (Nivo) group and CT alone group, respectively. Grade 3–4 surgery-related AEs were recorded at 11.4% and 14.8% in the respective groups [53]. While in the Keynote-671 study, grade 3–5 treatment-related adverse events occurred in 45% of the participants and treatment-related AEs led to death in four (1%) in the pembrolizumab group. Although these safety data for perioperative immunotherapy were not specific to patients with EGFR

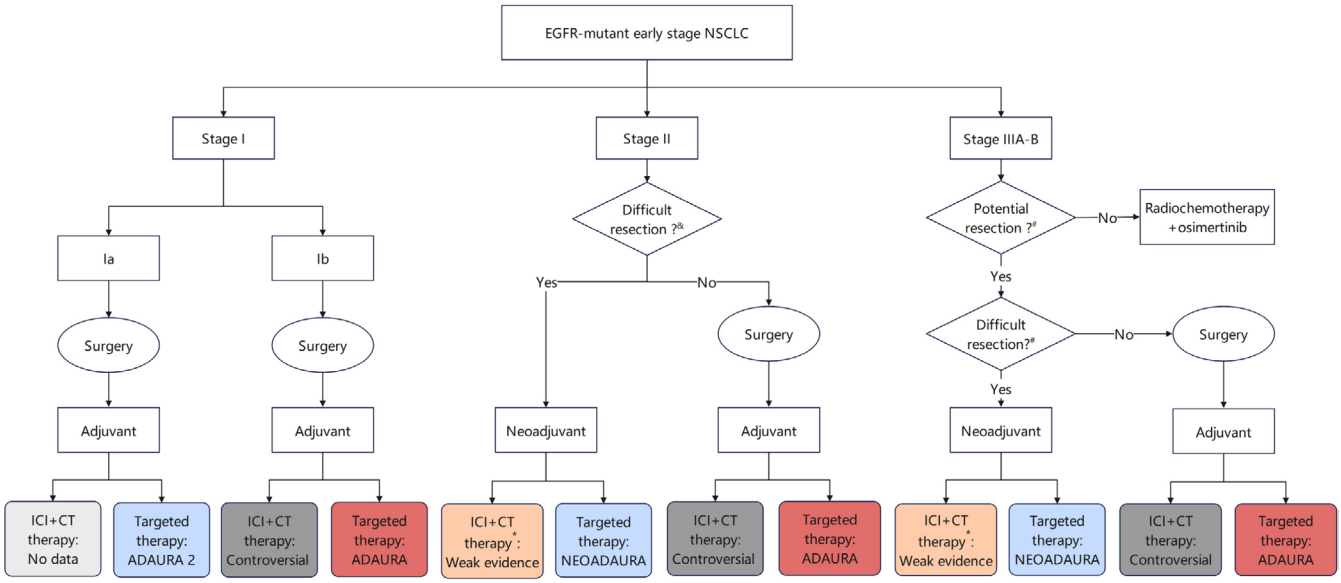

FIGURE 2 | The flowchart of the decision-making process for perioperative treatment in EGFR-mutant NSCLC. * The decision-making process must also address the potential impact of treatment-related AEs on subsequent surgical outcomes. &This step necessitates an assessment of surgical feasibility conducted by an experienced thoracic surgeon. #Multidisciplinary team discussion recommended. CT: Chemotherapy; ICI: Immune checkpoint inhibitors.

mutations, the incidence of grade 5 AEs was higher compared to targeted therapy, warranting caution during treatment.

5 | Summary of the Current Evidence for the Decision-Making Process for Perioperative Treatment in EGFR-Mutant NSCLC

Perioperative treatment decision-making for early-stage NSCLC with EGFR mutations presents significant challenges. We have synthesized the existing evidence and presented it in a flowchart (Figure 2). For patients with stage IB-IIIA disease, postoperative adjuvant therapy with osimertinib is supported by robust high-level evidence. However, data on both neoadjuvant and adjuvant therapy combining CT and immunotherapy remain either limited or inconsistent. In particular, when considering neoadjuvant CT combined with immunotherapy, the decision-making process must also address the potential impact of treatment-related AEs on subsequent surgical outcomes. In summary, further targeted studies are necessary.

6 | Perspective

Perioperative treatment is no longer limited to CT in patients without driver gene mutations. However, considerable challenges persist, especially in patients with EGFRm. NEOADAURA, a trial investigating neoadjuvant targeted therapy followed by surgery and comprehensive care, is currently ongoing. While there are limited data available from KEYNOTE-671, the observed negative OS outcomes underscore the uncertainty surrounding the optimal treatment strategy in these patients. Moreover, various factors such as co-mutations, rare mutations, pathological transformations, primary or secondary resistance to EGFR-TKIs, and the overall efficacy of ICIs in the perioperative period remain ambiguous.

Given the low MPR rate achieved in neoadjuvant targeted therapy, attention should be directed toward investigating TKIs combined with CT or radiotherapy, antivascular therapy, combined immunotherapy, and the development of novel drugs. Antibody-drug conjugates (ADCs) exert a precise and potent antitumor effect by coupling with ICI, TKI, or CT drugs through targeted antibodies. The HERTHENA-Lung01 study revealed the impressive efficacy of patritumab deruxtecan (HER3-DXd), with a DCR of 73.8% and an OS of 11.9 months in patients with EGFRm and baseline brain metastases showing resistance to TKI and CT [70]. The NCT04152499 study promising outcomes with SKB264, showing an ORR of 60%, a DCR of 100%, and a median PFS of 11.1 months in EGFRm patients with locally advanced or metastatic NSCLC treated with TKIs [71]. The potential application of ADC drugs in the advanced setting may reshape the landscape of perioperative NSCLC treatment in the future.

7 | Summary

Perioperative therapy for EGFRm NSCLC is rapidly developing. Osimertinib is the standard treatment for patients with stage IB–IIIA NSCLC with resected disease, and ongoing research is investigating neoadjuvant targeted therapy. While perioperative immunotherapy appears to offer a deeper pathological response, available research data are limited, and evidence remains insufficient. We conducted an exhaustive review and critical analysis of the available evidence to provide robust support for clinicians in selecting appropriate perioperative treatments for NSCLC patients with EGFRm and underscored the pressing necessity to refine patient selection criteria to prevent both over- and undertreatment, identify reliable biomarkers for regimen selection, determine optimal treatment durations, establish appropriate research endpoints. The ctDNA holds significant potential as a biomarker, and future research should prioritize in-depth exploration of its value in guiding prognosis and informing clinical

decision-making. Addressing these aspects comprehensively would maximize improvements in patient survival while minimizing adverse reactions.

Author Contributions

Xiaobei Guo: data curation, writing – original draft preparation. **Xiaoyan Liu:** data curation, writing – review and editing. **Chao Guo:** data curation. **Qian Miao:** data curation. **Xinghua Cheng:** data curation. **Xuan Hong:** data curation. **Hongru Li:** data curation. **Xiaoming Qiu:** data curation. **Yi Xiang:** data curation. **Di Zheng:** data curation. **Jian Zhou:** data curation. **Liyan Jiang:** data curation. **Yan Xu:** conceptualization, writing – review and editing. **Mengzhao Wang:** writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study's findings are available on request from the corresponding author.

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