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Review

The Role of Osimertinib in Stage I–II Non-Small-Cell Lung Cancer with Activating EGFR Mutation

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Abstract: Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide with only approximately 30% of new diagnoses manifesting with localized stages IA–IIA. Osimertinib is a third-generation inhibitor of the epidermal growth factor receptor (EGFR), which is used for treating metastatic, locally advanced, and early-stage NSCLC expressing common EGFR mutations. Two phase III clinical trials supported yresectable locally advanced disease, consisting of the ADAURA and LAURA studies, respectively. On the other hand, conflicting data on neoadjuvant efficacy led to the design of the ongoing Neo-ADAURA trial. In this review, we describe the pivotal trials that led to the approval of osimertinib use as an adjuvant treatment in radically resected NSCLC patients and as maintenance therapy after chemoradiotherapy. We also summarize the principal ongoing clinical trials in the neoadjuvant and adjuvant settings. Finally, we analyze several issues about the use of osimertinib in those different early settings while also depicting future perspectives and the potential evolution of treatment strategies.

Keywords: adjuvant; early-stage lung cancer; neoadjuvant; perioperative; osimertinib; resistance

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1. Introduction

Despite recent therapeutic advances, non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide with only approximately 30% of new diagnoses manifesting with localized stages IA–IIIA [1,2]. For the past two decades, radical surgery combined with (neo)adjuvant cisplatin-based chemotherapy has been the standard of care for "all-comers" patients with resectable stage II–III NCLSC and high-risk stage IB, but more than half of these patients inevitably experience disease recurrence within five years [3]. Recently, the advent of immunotherapies and targeted drugs in both the adjuvant and neoadjuvant settings has radically changed the paradigm of treatment for early-stage NSCLC, highlighting molecular tumor profiling as already imperative at initial diagnosis.

About 10–20% of Caucasian and 50% of Asian NSCLC patients harbor epidermal growth factor receptor (EGFR)-activating mutations [4]. The emergence of EGFR-TKIs at the beginning of the 21st century constituted a paradigm shift in the management of EGFR mutation-positive NSCLC, heralding an era of precision medicine. However, acquired resistance to first-generation (e.g., erlotinib or gefitinib) and second-generation (e.g., afatinib or dacomitinib) EGFR-TKIs typically develops after a median of 9-15 months with the EGFR T790M gatekeeper mutation appearing to mediate the development of resistance in about 50–60% of patients. Third-generation EGFR-TKIs have been designed to selectively inhibit the sensitizing and T790M mutant forms of EGFR tyrosine kinase whilst largely sparing wild-type EGFR activity and thus reducing off-target toxicity relative to earlier-generation

EGFR-TKIs. Osimertinib is an orally administered, third-generation EGFR-TKI that binds irreversibly to clinically relevant mutant EGFR kinase forms (e.g., L858R, ex19del, and T790M) to selectively inhibit mutant EGFR kinase activity as well as potently inhibits EGFR phosphorylation in EGFR-TKI-sensitizing mutant and T790M mutant NSCLC cell lines, exhibiting less activity against wild-type cell lines [5].

The advent of EGFR–tyrosine kinase inhibitors (TKIs) in metastatic and unresectable settings prompted clinical trials in the adjuvant setting. In 2020, the remarkable outcomes of the ADAURA trial led to approval by the Food and Drug Administration (FDA) of the adjuvant osimertinib for up to three years in stage IB/IIIA resected NSCLC with EGFR common activating mutations (exon 19 deletion or exon 21 p. L858R point mutation) after optional adjuvant chemotherapy [6]. A few years later, in 2024, positive data from the LAURA trial led osimertinib to receive another FDA indication for use among patients with unresectable stage III EGFR-mutated NSCLC that had not progressed during or after concurrent or sequential platinum-based chemoradiation [7]. In the neoadjuvant setting, data are still conflicting, and thus the use of osimertinib in routine clinical practice is not recommended. Started in 2021, the NeoADAURA trial is the first phase III multicenter clinical trial that evaluates the efficacy and safety of neoadjuvant osimertinib alone or in combination with chemotherapy in stage II–III NSCLC with common EGFR mutations [8].

2. Materials and Methods

The aim of this review is to summarize up-to-date clinical studies in early-stage EGFR-mutated SCLC and to analyze their clinical therapeutic implications in the adjuvant and locally advanced settings. We also summarize the principal ongoing clinical trials on osimertinib with the aim of addressing several issues raised by the use of osimertinib in locally advanced and early-stage patients. Finally, we depict future perspectives and the potential evolution of treatment strategies, focusing on potential biomarkers with the aim of selecting the best patient who will benefit the most from osimertinib.

3. Adjuvant Osimertinib in Resected Stage IB–IIIA

Before the ADAURA trial, worldwide guidelines recommended platinum-based chemotherapy as an adjuvant treatment for all patients with stage IIB–III but only select patients with stage IIA, according to the TNM 8th edition stage [9]. However, rates in terms of overall survival (OS) and disease-free survival (p) were only marginally improved by 5%, and more than half of the patients experiencing recurrence and a negative impact on prognosis [10].

The treatment benefit of EGFR-TKIs in advanced settings has resulted in the study of their role in the early stages [11–16]. Several trials investigated adjuvant treatment with first- and second-generation inhibitors, with disappointing results that did not translate into an OS benefit, which was probably due to higher rates of EGFR-TKI use at relapse (55–83%). The only positive EVAN trial observed an OS improvement in the resected stage IIIA Chinese population treated with erlotinib for 2 years. However, the choice of a placebo as the control arm, the inclusion of higher-risk patients, and the low rate of patients treated with an EGFR-TKI at disease recurrence (about 30%) raised some doubts about the data [16]. Last but not least, central nervous system (CNS) recurrences were confirmed to be higher after adjuvant targeted therapy, highlighting the inability of the brain to protect the body, according to studies reported for the advanced stage.

Based on these data, the ADAURA trial started to investigate the role of osimertinib as an adjuvant tool. This drug is a third-generation EGFR-TKI demonstrating superior cerebral protection and good tolerability in the pivotal FLAURA trial [17]. The phase III ADAURA trial enrolled 682 patients after the complete resection of stage IB–IIIA (classi-

fied according 7th TNM edition) with a common EGFR mutation plus optional adjuvant chemotherapy [18]. These patients were randomized to receive either 3 years of osimertinib at 80 mg or placebo, orally once daily, and were stratified according to race (Asian or not), type of EGFR mutation (EX19del/L858R) and disease stage (IB, II, III). Baseline characteristics were balanced between two arms; in the osimertinib group, the majority of the population was Asiatic (64%), female and never smoker (68%) with adenocarcinoma as the predominant histology (96%), according to clinical features of EGFR molecular alteration. The adjuvant platinum-based chemotherapy was administered in more than half of patients before trial arms (60%). At primary analysis occurring after median follow-up of 22 months, the primary endpoint was met, improving significantly DFS among patients with stage II–IIIA with an 83% reduction in the risk of recurrence of death (hazard ratio [HR], DFS 0.17, median DFS: not reached vs. 19.6 months in osimertinib and placebo arms, respectively) as well as OS (secondary endpoint). A similar rate of DFS benefit was reported in the overall stage IB–IIIA population (secondary endpoint; HR DFS: 0.20). Osimertinib notably enhanced results in all the pre-specified subgroups, including different disease stages and regardless of previous adjuvant chemotherapy administration. The favorable benefit of osimertinib was confirmed at 4 years with a persistent reduction in risk of recurrence or death more than 70% (HR DSF: 0.27 and 0.23 for overall and stages II–III population, respectively) [19]. Focusing on pattern of relapse, osimertinib more than halved both loco-regional and distant recurrence rates, and notably, these patients had a 70% chance of being CNS relapse-free at 4 years (CNS DFS HR: 0.24) [19]. In the final OS analysis published in 2023, osimertinib robustly reduced risk of death of 51% in both the stage II–IIIA population and IB–IIIA population (HR OS: 0.49), and the probability of being alive at 5 years was 85% and 88%, respectively [6]. Similar to DFS data, the survival improvement was consistent across all pre-specified groups, including chemotherapy use and stage. Interestingly, almost all of the placebo population received an EGFR-TKI at relapse (88%, consisting of osimertinib at 43% of choice), excluding the hypothesis of a survival gain due to the lack of an active subsequent treatment. If the toxicity profile was similar to that seen in advanced disease, with diarrhea (46%), paronychia (25%), dry skin (23%), and pruritus (23%) as the most common adverse events (AEs), higher dose reduction and interruption rates emerged in adjuvant compared with advanced disease, which was probably due to there being a different toxicity perception in a different setting. These results led to the worldwide approval of osimertinib as the standard of care for patients with IB–IIIA EGFR mutated NCSLC post-surgery with or without adjuvant chemotherapy. The first approval of a targeted therapy in the early stage highlights the key role of a molecular profile test also in this setting not only to guide the best adjuvant choice but also to avoid immunotherapy in the presence of an EGFR mutation.

Undoubtedly, the ADAURA trial changed worldwide guidelines, but unanswered questions persist. Firstly, the role of adjuvant chemotherapy—not obligatory in the context of the ADAURA trial—is debated. Notably, combined chemotherapy was performed mainly in younger patients ($\leq$70 years old), and in 76% patients with stage II–IIIA, while it is performed only in 26% of patients with stage IB NSCLC [20]. Despite no stratification according to previous chemotherapy use being planned, the trial suggested the benefit of osimertinib regardless of previous adjuvant chemotherapy with no additional benefit from chemotherapy use. However, it does not mean that chemotherapy can be safely omitted. So, the role of previous chemotherapy should not be ignored and should be proposed to "fit" patients at high risk of relapse for tumor stage.

The optimal duration of adjuvant targeted therapy is another unclear issue. On the hand, one third of patients did not complete the planned three years of osimertinib treatment, highlighting the importance of several factors when determining duration such

as clinical benefit, adverse events and, not least, economic burden. On the other hand, Kaplan–Meier DFS curves appeared to show an increase in relapse after just 3 years of osimertinib, suggesting that a longer duration of adjuvant treatment might further improve efficacy outcomes. The ongoing phase II TARGET trial was designed to address the 5-year duration of adjuvant osimertinib treatment in stage II–IIIB NSCLC, enrolling patients with common and—for the first time uncommon—EGFR mutations. These prospective data could suggest the potential efficacy of adjuvant osimertinib in those patients excluded from the ADAURA trial for whom current use is not recommended. Results are expected in 2029 with 5-year DFS in the cohort with common mutations as the primary endpoint [21].

Thirdly, prognostic and predictive biomarkers are needed even in the selection of patients planning to undergo adjuvant osimertinib. Notably, 38% of the placebo group were alive without recurrence at 2 years, highlighting that some patients have already been cured with surgery alone. So, accurate biomarkers to screen suitable patients for adjuvant therapy are necessary. The detection of circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) after surgery is the most promising biomarker for predicting relapse, and data on ctDNA from the ADAURA were recently presented. Of 682 patients randomized, only 32% (220 patients) had samples evaluable for MRD. At baseline, 5 and 13 patients were MRD-positive in the osimertinib and placebo arms, respectively. MRD-negativity occurred in four of five patients in the osimertinib arm (80%) but none of the 13 receiving placebo. At 3 years, 86% of patients treated with osimertinib vs. 36% of those with placebo were MRD-negative and without disease (HR: 0.23). Notably, this biomarker seems to have the ability to anticipate relapse more than 4 months before imaging changes, supporting its potential use identifying those patients suitable for longer adjuvant therapy [22]. The CTONG2201 is an ongoing prospective trial aimed to evaluate an adjuvant therapy-free strategy for stage IB–IIIA NSCLC patients with longitudinal undetectable MRD after radical resection [23]. The phase III ECTOP-1022 trial will evaluate the use of adjuvant osimertinib vs. observation in ctDNA-positive EGFR-mutated patients after the radical surgery of II–IIIA (N1-N2) NSCLC (NCT06323148).

Tumors smaller than 4 cm are another setting not assessed in the ADAURA trial. The ongoing ADAURA2 phase III trial aims to extend adjuvant osimertinib therapy (at 80 mg daily for a maximum of 3 years) to encompass stage IA2 and IA3 (according to the 8th edition TNM staging system) EGFR-mutant NSCLC after radical surgery, stratifying for race, EGFR mutation type and pathological risk of disease recurrence. The primary endpoint in a high-risk group is DFS [24].

Finally, a further topic is how to treat patients who progressed during or after adjuvant osimertinib, as there are limited data from randomized clinical trials. Notably, the current knowledge of several resistance mechanisms to EGFR-TKIs derived mainly from studies enrolling metastatic patients. Recently, two case reports described complete response to osimertinib rechallenge after relapse from previous adjuvant osimertinib use and a serial molecular panel exhibiting a lack of acquired resistance mechanisms [25]. Clearly, the osimertinib (plus or minus chemotherapy) rechallenge should be considered in those patients relapsed after the completion of adjuvant time, according to an adequate time interval. On the other hand, patients who progressed during adjuvant time could be candidates for chemotherapy (plus or minus the anti-EGFR/MET monoclonal antibody amivantamab) or, when possible, should be re-biopsied to identify specific resistance alterations. Several trials are ongoing with the aim to clarify the efficacy of osimertinib rechallenge (NCT065307169) and to evaluate resistance mechanisms or recurrence gene profiles of adjuvant osimertinib (ROSIE and RAISE trial, respectively, NCT06053099, NCT06477055).

4. Osimertinib in Unresectable Stage IIII NSCLC

Approximately 25–30% of patients are diagnosed at stage III, which is characterized by significant heterogeneity. Patients with stage IIIC and the majority of those with stage IIIB are classified as unresectable, and durvalumab as consolidation immunotherapy for one year following concurrent chemoradiotherapy (CRT) has become the standard of treatment for those patients expressing programmed death-ligand 1 (PD-L1), resulting in a 5-year survival rate of 42.9% [26]. However, about 5% of the PACIFIC population (35 of 713 randomized patients) harbored EGFR mutations and failed to achieve significant survival benefits with durvalumab maintenance compared to placebo; thus, the preferential treatment for this proportion of patients remains controversial [27]. Data should be interpreted with caution, owing to small patient numbers and, notably, the predominance of smoker male patients. On the other hand, the benefit of immunotherapy agents, specifically among patients with EGFR mutations, is still uncertain and not so encouraging, and there are no approved targeted agents specifically in this stage III setting. Over the last few years, the exploration of an EGFR-TKI as maintenance in unresectable stage III NSCLC has started, but until LAURA, prospective, randomized data were lacking. Beginning in 2018, the randomized placebo-controlled phase III LAURA trial was the first to assess the efficacy and safety of osimertinib consolidation after CRT for unresectable EGFR-mutant NSCLC [7]. The 216 patients who had not progressed after two or more cycles of either concomitant or sequential platinum-based CRT were randomly assigned 2:1 to receive osimertinib or placebo (143 and 73 patients in each arm, respectively). The duration of treatment was not predefined, prolonging administration until disease progression or unacceptable toxicities. Female, never smoker and Asiatic represented the majority of patients enrolled in the study, consisting of 63%, 71% and 81% in the osimertinib group, respectively. The EGFR exon 19 deletions were detected in slightly more than half of each cohort (52% and 59% in the osimertinib and placebo arms, respectively) with L858R mutations detected in the remainder. The radiotherapy was predominantly concomitant to chemo (92% and 85%, respectively) with lower sequential strategy choice (8% and 15%, respectively). According to the 8th TNM edition, about half of each group had stage IIIB disease (47% and 52%, respectively), which was followed by stage IIIA (36% and 33%, respectively) and IIIC (17% and 15%, respectively). The primary endpoint was progression-free survival (PFS) by blinded independent central review. At primary analysis occurring after median follow-up of 22 months, osimertinib demonstrated a statistically significant and highly clinically meaningful improvement in PFS over placebo (median PFS 39.1 vs. 5.6 months, respectively), with a hazard ratio for disease progression or death of 0.16, and showing superiority in all predefined subgroups. At 12 and 24 months, 74% and 65% of patients of the osimertinib arm were alive and progression free in contrast to 22% and 13% of the placebo arm, respectively. Higher and durable responses were reported in the experimental arm with an objective response rate (ORR) of 57% and median duration of response (DOR) of 36.9 months compared to 33% and 6.5 months of placebo, respectively. Safety was as expected and manageable consistently with established profiles of osimertinib in previous randomized clinical trials. The most common AEs in both arms were radiation pneumonitis, mainly low grade and manageable (48% with osimertinib vs. 38% with placebo), followed by diarrhea and rash.

As well established in previous clinical settings, osimertinib confirmed its robust CNS efficacy with a protective effect against CNS progression accounting for new brain lesions in only 8% compared with 29% of the placebo arm. Analyses of CNS efficacy and distant progression from the LAURA trial were recently published [7]. Compared with placebo, osimertinib was associated with an 83% reduction in the risk of CNS progression or death (HR for CNS PFS 0.17, median CNS PSF not reached vs. 14.9 months, respectively). With

similar benefit, osimertinib reduced by 79% the risk of distant metastases or death, (HR 0.21). The protective CNS effect and the delay of distant metastases, together with the primary PFS benefit, supported the approval of osimertinib as the new standard of care for unresectable stage III EGFR mutant NSCLC following CRT.

Also, the LAURA data raised some questions to answer. Differing from other studies conducted in stage III, the LAURA design lacked a defined duration, prolonging therapy indefinitely until disease progression or unacceptable toxicities. A continuous treatment might be analyzed focusing on different aspects from economic burden to the toxicities profile and overtreatment of patients and inevitably resistance development. An OS interim analysis (data mature of 20%) favored osimertinib as well but without a significant difference. Awaiting maturity of the OS data, the long-term efficacy of an "indefinite" osimertinib is still unclear.

As ADAURA, patients with uncommon EGFR mutations are excluded from the LAURA trial, lacking prospective data to support use in these subgroups. Also, the best treatment to offer at progression is an open debate. In the trial, 81% of patients in the placebo group crossed to open-label osimertinib at progression, while about 30% of patients who experienced progression during osimertinib went beyond. If maintaining TKI, adding chemotherapy or switching to chemotherapy plus or minus anti-EGFR/MET monoclonal antibody amivantamab is necessary to clarify and to explore.

5. Osimertinib as Neoadjuvant Treatment of Stage I–IIIA

Patients with NSCLC with stage IIIA and a proportion of stage IIIB are classified as resectable or potentially resectable and may benefit from surgery. Neoadjuvant platinum-based chemotherapy alone can improve the 5-year OS by approximately only 5% in patients with stage IIIA [28].

Encouraging data from three pivotal phase III clinical trials, including CheckMate816 and KEYNOTE-671, have witnessed a profound transformation in the paradigm of neoadjuvant/perioperative treatment for early-stage NSCLC [29,30]. In these trials, the addition of immune checkpoint inhibitors (ICIs) to neoadjuvant chemotherapy improved pathological complete response (pCR), major pathological response (MPR) rates and event-free survival (EFS) compared to chemotherapy alone. However, the unsatisfied results of ICIs in EGFR mutated advanced NSCLC lead to excluding those patients from enrolling in mainly perioperative immunotherapy trials except for KEYNOTE-671.

The field of neoadjuvant EGFR-mutant targeted therapy is currently in the beginning stage and holds great promise. In the literature, data on neoadjuvant targeted therapy have only been obtained from phase II 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 improvement. Two single-arm phase II clinical trials have been reported with neoadjuvant osimertinib. Boasting the largest sample size in a neoadjuvant osimertinib setting, the NEOS trial evaluated 6 weeks of osimertinib before surgery in 40 Chinese patients affected by stage IIA–IIIB NSCLC (according to 8th TNM edition) with common EGFR mutations [31]. The primary endpoint of ORR was 71%, with an encouraging R0 resection in 93.8% of patients, but with only 15% of pathological responses (10.7% major and 3.6% complete responses). Another multicenter phase II—the UCSF trial—enrolled a smaller cohort of 27 patients with stage I–IIIA EGFR-mutant NSCLC, evaluating neoadjuvant osimertinib for 4–8 weeks [32]. The MPR rate was only 14.8%, failing to reach its primary endpoint (50% MPR).

The ongoing NEOADAURA international multicenter phase III study is evaluating the safety and efficacy of neoadjuvant osimertinib alone or in combination with chemotherapy versus chemotherapy alone in patients with stage II–IIIB NSCLC (based on 8th TNM

edition) and expressing common EGFR mutations [8]. After neoadjuvant experimental arms, all patients performed surgery and adjuvant treatment. The primary endpoint is MPR at resection, with secondary endpoints, including EFS, pCR, DSF, OS, baseline circulating tumor DNA (ctDNA) levels, and other indicators, providing potential evidence for future recommendations.

6. Discussion and Future Directions

The recent approval of osimertinib as a 3-year adjuvant for resected stage II–IIIA and as consolidation therapy for stage III unresectable NSCLC EGFR mutant patients highlighted the mandatory knowledge of EGFR mutational status in all settings. Several trials on osimertinib in (neo)adjuvant, locally advanced, and early-stage settings are ongoing, as shown in Tables 1 and 2, and a summary of key published trials is available in Table 3.

Table 1. Ongoing randomized phase II–III clinical trials on adjuvant osimertinib in NSCLC.

Trial	Phase	N. Pts	Pathological Stage	Treatment	Primary Endpoint	Status	Study Completion Estimated
ECTOP-1022 (NCT06323148)	III	226	II–IIIA (N1-N2)	Osimertinib 80 mg vs. placebo for 3 years in pts with ctDNA positivity	3-year DFS	Active, not recruiting	2029
TARGET (NCT05526755)	II	180	II–IIIB	Osimertinib 80 mg for 5 years in both common and uncommon EGFRm pts	5-year DFS in common mutation cohort	Active, not recruiting	2029
ADAURA2 (NCT05120349)	III	380	IA2-IA3	Osimertinib 80 mg vs. placebo for 3 years	DFS in high risk group	Active, not recruiting	2032
OSTAR (NCT05686434)	II	65	I with high-risk factors	Osimertinib 80 mg for 3 years	3-year DFS	Active, recruiting	2029
NCT05536505	II	180	IB–IIIB (MRD positive)	Icotinib or osimertinib (if T790M positive) until MRD negative	DFS, 3-year DFS rate	Active, recruiting	2030
NCT05546866	II		IB–IIIB EGFR uncommon mutations	Osimertinib for 3 years	3-year DFS rate	Active, not recruiting	2029

Abbreviations: ctDNA: circulating tumor DNA, DFS: disease-free survival, EGFR: epidermal growth factor receptor, MRD: minimal residual disease.

Moreover, various factors remain ambiguous, such as the prognostic role of co-mutations p53, the benefit of osimertinib in uncommon EGFR mutant patients, and how to overcome primary and secondary resistance mechanisms occurred in earlier settings.

Regarding adjuvant therapy, one potential approach to identify patients at higher risk for recurrence is the detection of minimal residual disease. Several studies in patients with early-stage NSCLC who have undergone curative treatment support the use of tumor-informed MRD assays to predict radiographic clinical recurrence by a median of 3 and 7 months [8,33]. Despite limited studies, these data suggested the potential utility of tumor-informed MRD assays to monitor MRD in early-stage NSCLC, identifying patients who may benefit from longer adjuvant osimertinib. A recently published exploratory analysis

investigated whether plasma-based, tumor-informed MRD analysis could predict disease recurrence during and after adjuvant treatment in a patient cohort of 220 from an ADAURA trial [34]. As expected, the frequency of MRD detection at randomization was greater among subgroups with more advanced disease, ranging from 0% in stage IB and 39% in stage II, to the highest, 61%, in stage III. Molecular recurrence based on detected MRD events preceded clinical recurrence or death with a median lead time of 4.7 months, using both plasma ctDNA-based or tumor-informed MRD panels. The DFS and MRD event-free status was maintained for most patients during adjuvant treatment (75%) and 2 years after the completion or discontinuation of osimertinib treatment (66%), suggesting the potential eradication of the micrometastatic component of the disease in some patients, leading to the long-term benefit that persists after the completion of adjuvant therapy. In contrast, MRD monitoring may provide a powerful tool to personalize the use of post-adjuvant treatment, targeting the subset of patients at higher risk of recurrence at the end of preplanned therapy, prolonging beyond 36 months or intensifying with combination strategies; in addition, the continued undetected MRD status may represent a population for whom disease has been eradicated and no further treatment is necessary. These interesting suggestions requires prospective studies to fully elucidate the risk/benefit of such an approach. To note, the sample availability and limited sensitivity (65%) of tissue-informed MRS panels are key limitations of the MRD analysis. Prospective studies to understand the optimal frequency of MRD monitoring following adjuvant treatment completion, the potential use during the adjuvant treatment to determine the optimal duration, and the appropriate clinical interventions following MRD detection—such as restarting adjuvant treatment or intensifying treatment via combination strategies for patients at high risk of recurrence—are warranted before this can be applied routinely to the real-world clinical setting.

Table 2. Ongoing phase II–III clinical trials on osimertinib in locally advanced, neoadjuvant, and early-stage NSCLC.

Trial	Phase	N. Pts	Clinical Stage	Treatment	Primary Endpoint	Status	Study Completion Estimated
NEOLA (NCT06194448)	II	70	III, unresectable	Osimertinib for 8 weeks → CRT con for 6 weeks → osimertinib maintenance until PD	PFS	Recruiting	2028
PACIFIC4 (NCT03833154)	III	60	I–II	SBRT → osimertinib for 3 years	4-year PFS	Active, recruiting	2028
GALAXY02 (NCT06383728)	II	51	II–IIIB squamous	Osimertinib ≥ 9 weeks	ORR, safety	Active, recruiting	2030
NCT06018688	II	44	IIA–IIIA	Osimertinib + aspirin for 2 months	MPR	Active, not yet recruiting	2026
NOCE01 (NCT05011487)	II	30	IIIA–B (N2)	Osimertinib for 60 days + chemo cis + pem for 2 cycles	Complete lymph clearance rate (ypN0)	Active, recruiting	2028

Abbreviations: MPR: major pathologic response, ORR: overall response rate, PFS: progression-free survival.

Another unsolved question is about the prognostic and predictive value of EGFR/TP53 co-mutations, lacking data in patients with resected EGFR mutated NSCLC, and with unclear clinical impact in the advanced stage [35]. In this analysis published by Herbst et al.,

adjuvant osimertinib provided clear benefit irrespective of co-occurring TP53 alterations, suggesting baseline TP53 mutations as having a prognostic role in the resected EGFR mutant NSCLC setting [34]. Further analyses enrolling larger cohorts of early-stage patients are warranted to better understand the correlation between TP53 mutations, adjuvant chemotherapy and the disease stage.

Table 3. Summary of key published phase II–III trials on osimertinib in stage I–III.

Trial	Phase	Stage	N. Pts	Treatment Arms	Primary Endpoint	Outcomes (Months)
ADAURA	III	IB–IIIA	682	Osimertinib vs. placebo	DFS in stage II–IIIA	mDFS in stage II–IIIA: NR vs. 19.6
LAURA	III	III	143	Osimertinib vs. placebo	PFS	mPFS: 39.1 vs. 5.6
NEOS	II	II–IIIB	40	Osimertinib for 6 weeks followed by surgery	ORR	71.1%
NORA	II	IA–IIIA	25	Osimertinib for 2 cycles of 28-day each, followed by surgery and adj osimertinib for 3 years +/− adj chemo	Expected ORR 65%	ORR 44% (negative trial)

Abbreviations: adj: adjuvant, NR: not reached.

As neoadjuvant treatment, osimertinib is still be considered experimental with controversial data from the literature to date. Monitoring ctDNA represents the most promising biomarker to follow in time responses to osimertinib as maintenance or in neoadjuvant settings and to define residual disease after resection, suggesting a de-escalation approach to adjuvant targeted therapy. Considering that there is an overlap of neoadjuvant (NEOADAURA) and adjuvant (ADAURA) settings in resectable tumors ab initio, it could be crucial to understand the patient's selection criteria in clinical practice for each strategy.

Further studies need to define the potential clinical use of ctDNA, both in tissue and blood, identifying patients with a higher risk of recurrence and helping to define the duration or discontinuation of treatment. Translational research is currently active in the identification of molecular mechanisms of resistance whose use may guide clinicians for the best treatment to choose when progression occurred.

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