Perioperative treatment strategies in EGFR-mutant early-stage NSCLC

REVIEW ARTICLE

Perioperative Treatment Strategies in *EGFR*-Mutant Early-Stage NSCLC: Current Evidence and Future Challenges

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ABSTRACT

Treatment with 3 years of adjuvant osimertinib is considered a new standard in patients with completely resected stage I to IIIA NSCLC harboring a common sensitizing *EGFR* mutation. This therapeutic approach significantly prolonged the disease-free survival and the overall survival versus placebo and revealed a significant role in preventing the occurrence of brain metastases. However, many unanswered questions remain, including the optimal duration of this therapy, whether all patients benefit from adjuvant osimertinib, and the role of adjuvant chemotherapy in this population. Indeed, there is a renewed interest in neoadjuvant strategies with targeted therapies in resectable NSCLC harboring oncogenic drivers. In light of these considerations, we discuss the past and current treatment options, and the clinical challenges that should be addressed to optimize the treatment outcomes in this patient population.

Keywords: *EGFR*-mutant; Early-stage NSCLC; Adjuvant osimertinib; Minimal residual disease

Introduction

In the past two decades, the field of thoracic oncology has witnessed immense progress, especially for patients with NSCLC. Several breakthroughs have been made in the therapeutic approach of metastatic and early-stage NSCLC, including immune checkpoint blockers (ICBs) and personalized treatment with targeted therapies in oncogene-addicted tumors. These achievements have shifted the treatment paradigm and improved patient outcomes in NSCLC, underscoring the importance of a biomarker-informed approach across all stages of disease.[1–3] In early-stage NSCLC, which represents up to 40% of patients at diagnosis (stage I–IIIA),[4] adjuvant treatment (postoperative approach) with osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI) has been established as the new standard of care (SoC) in patients with completely resected stage IB to IIIA *EGFR*-mutant NSCLC.[5] However, many unanswered questions remain, including the optimal duration of therapy and whether all patients benefit from adjuvant osimertinib. There has also been a renewed interest in neoadjuvant strategies (preoperative), and perioperative

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strategies (neoadjuvant and adjuvant) with EGFR TKI in resectable NSCLC after the success of neoadjuvant and perioperative chemotherapy and ICB combinations, although patients with sensitizing *EGFR*-mutant NSCLC were notably excluded from most of these trials. In light of these considerations, we discuss the past and current treatment options and the clinical challenges that should be addressed to optimize the treatment outcomes in this patient population.

Epidemiology

The prevalence of *EGFR* mutations in NSCLC exhibits substantial variation by ethnicity, ranging from 15% in White populations to more than half in Asian populations.[6] Despite the differences in prevalence, shared characteristics include a lack of association with tobacco exposure and predilection for female patients and adenocarcinomas.[7] As biomarker testing was not routinely performed in early-stage NSCLC until recent years, the stage-specific distribution of *EGFR* mutations is not well characterized. Three large studies from the People's Republic of China and Japan reported similar *EGFR*-mutation frequencies and subtypes between early-stage and advanced-stage,[8–10] whereas a West-European study observed a higher incidence of *EGFR*-mutations (13% versus 9%)—particularly for the *EGFR* L858R subtype (45% versus 15%)—in early-stage compared with late-stage cases.[11] The distribution of *EGFR*-mutation subtypes also exhibits significant variation by ethnicity and different prognostic outcomes, with a higher representation of the *EGFR* L858R subtype among Asian patients.[12] In a retrospective analysis, a more aggressive phenotype and poorer recurrence-free survival (RFS) in univariate and multivariate analysis was reported for tumors with *EGFR* exon 19 deletion (Del19) in comparison to tumors with the *EGFR* L858R subtype.[9] Given the shift toward the use of targeted therapies in early-stage disease, these findings highlight the importance of upfront biomarker testing.

The prognostic value of the *EGFR* mutation in resected NSCLC remains controversial. In the pre-TKI era, no prognostic effect was identified on overall survival (OS) according to the *EGFR*-mutation status.[13,14] Thereafter, *EGFR*-mutated NSCLC consistently revealed improved OS compared with *EGFR*-wildtype NSCLC, likely related to the efficacy of TKIs. In contrast, discordant results have been reported for the association between the presence of an *EGFR* mutation and disease-free survival (DFS) even between systematic reviews and meta-analyses.[15,16] However, more recent data did not reveal differences in DFS according to the *EGFR*-mutation status,[14,17] and have consistently reported no association between the *EGFR*-mutation subtype and DFS.[10,17,18] Furthermore, some studies reported a higher risk of metastatic recurrence associated with *EGFR*-mutant tumors versus wild-type NSCLC,[19] including a higher risk of intracranial progression,[9] whereas other studies suggesting otherwise.[17] Of note, these observations were made in the pre-ADAURA era and it is conceivable that adjuvant osimertinib may affect sites of recurrence.[5]

Evidence for Adjuvant TKI in *EGFR*-mutant NSCLC

The predictive value of *EGFR* mutation and the role of adjuvant EGFR TKIs in this population was initially observed in a cohort of patients with completely resected stages I to III lung adenocarcinoma. In this cohort, adjuvant treatment with first-generation *EGFR* TKI (erlotinib or gefitinib) correlated with a trend toward improvement in DFS compared with patients who did not receive adjuvant TKI, suggesting a role of this strategy for this subset of lung adenocarcinomas.[20,21]

The first phase 3 randomized clinical trials (RCTs), the BR19 study (N = 503) and the RADIANT study (N = 973) evaluating the benefit of adjuvant TKIs in patients with completely resected stage IB to IIIA NSCLC (according to the sixth TNM classification), did not select patients according to the *EGFR*-mutation status (Table 1[22–32]).[22,23] Both trials investigated first-generation TKI treatment (gefitinib and erlotinib, respectively) versus placebo for 2 years, and previous adjuvant chemotherapy (ACT) was allowed in both trials (17% in the BR19 trial and 53% in RADIANT).[22,23] The BR19 trial did not meet the OS and DFS coprimary end points of the study. With only 15 patients with an *EGFR* mutation, gefitinib versus placebo did not result in an improvement in DFS (hazard ratio [HR] = 1.84; 95% confidence interval [CI]: 0.44–7.73, $p = 0.395$) or an OS benefit (HR = 3.16, 95% CI: 0.61–16.45, $p = 0.15$).[22] Similarly, in the overall population, in the RADIANT trial the DFS primary end point was not achieved. Among *EGFR*-mutant NSCLC (n = 161), the median DFS was longer in the erlotinib arm versus placebo (46.4 versus 28.5 mo; HR = 0.61, 95% CI: 0.38–0.98, p = 0.039) but OS was immature and not statistically significant (HR = 1.09, 95% CI: 0.54–2.16).[23]

On the basis of the potential evidence that adjuvant erlotinib may improve the outcome in *EGFR*-selected NSCLC, two other trials explored this strategy in this population (Table 1[22–32]). In the single-arm phase 2 SELECT trial (N = 100), 2 years of adjuvant erlotinib yielded a 2-year and 5-year DFS of 88% and 56%, respectively, with a 5-year OS of 86%,[24] which exceeded the data reported in a large retrospective cohort of patients with resected early-stage *EGFR*-mutant NSCLC who received no adjuvant EGFR TKI.[20] The randomized

Table 1. Phase 2/3 Clinical Trials Evaluating Adjuvant EGFR Tyrosine Kinase Inhibitors in Patients With Completely Resected *EGFR*-Mutant Early-Stage NSCLC

Trial	Country	Stage	N	TKI	DFS (mo) HR (95% CI); *p* Value	OS (mo) HR (95% CI); *p* Value	Crossover, %
BR19[22,a]	North America	IB-IIIA	15	Gefitinib × 2 y vs. Placebo	NR 1.84 (0.44-7.73); 0.395	NR 3.16 (0.61-16.5); 0.15	NtR
RADIANT[23,a]	International	IB-IIIA	161	Erlotinib × 2 y vs. Placebo	46.4 vs. 28.5 0.61 (0.34-0.98); 0.039	NR 1.09 (0.54-2.16)	NtR
SELECT[24]	North America	IA-IIIA	100	Erlotinib × 2 y (Single arm)	NR 5y-DFS: 56% (45%-66%)	NR 5y-OS: 86% (77%-92%)	-
EVAN.[25,26]	People's Republic of China	IIIA	102	Erlotinib × 2y vs. ACT	0.38 (0.20-0.70); 0.001	84.2 vs. 61.1 0.37 (0.19-0.73); 0.003	37
CORIN[27]	People's Republic of China	IB	128	Icotinib × 1 y vs. Placebo	NR 0.23 (0.07-0.81); 0.013	NR $p = 0.098$	83
ADJUVANT/ CTONG1104[28,29]	People's Republic of China	II-IIIA	222	Gefitinib × 2y vs. ACT	30.8 vs. 19.8 0.56 (0.40-0.97); 0.001	75.5 vs. 62.8 0.92 (0.62-1.36); 0.67	52
IMPACT[30]	Japan	II-IIIA	234	Gefitinib × 2 y vs. ACT	35.9 vs. 25.1 0.92 (0.67-1.28); 0.63	NR vs. NR 1.03 (0.65-1.65); 0.89	51
EVIDENCE[31]	People's Republic of China	II-IIIA	322	Icotinib × 2y vs. ACT	47.0 vs. 22.1 0.36 (0.24-0.55); 0.0001	0.91 (0.42-1.94)	NtR
ADAURA[32,b]	International	IB-IIIA	682	Osimertinib × 3 y vs. placebo	Stage II-IIIA: 65.8 vs. 21.8 0.23 (0.18-0.30)	Stage II-IIIA: NR vs. NR 0.49 (0.33-0.73); 0.001 5-y OS: 85% vs. 73%	43

Note: Green boxes reveal significant improvement.
[a]Data in the table for *EGFR*-mutant NSCLC.
[b]Only data based on the primary end point of the trial.
ACT, adjuvant chemotherapy; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NR, not reached; NtR, not reported; OS, overall survival.

phase 2 EVAN trial (N = 102) tested erlotinib versus ACT in resected stage IIIA *EGFR*-mutant NSCLC. Adjuvant erlotinib significantly improved the DFS (HR = 0.38, 95% CI: 0.20–0.70, $p < 0.001$) and the OS (HR = 0.37, 95% CI: 0.19–0.73, $p = 0.003$), with a 5-year OS of 85% and 51.1%, respectively. However, only 37% of patients in the ACT arm received an EGFR TKI at progression.[25,26] Similarly, the randomized phase 2 CORIN study (N = 128) investigated the efficacy of icotinib (first-generation EGFR TKI) for 1 year versus placebo in patients with stage IB NSCLC. ACT was not allowed in this trial. The primary end point of the 3-year DFS was 96% in the icotinib group versus 84.0% in the observation group (HR = 0.23, 95% CI: 0.07–0.81, $p = 0.013$).[27]

Later, three phase 3 RCTs were specifically designed for patients with completely resected *EGFR*-mutant NSCLC investigating adjuvant TKIs for 2 years versus ACT (platinum-vinorelbine) with DFS as the primary end point (Table 1). In the ADJUVANT/CTONG 1104 study (N = 222), DFS was significantly longer in the gefitinib arm compared with ACT (median DFS: 30.8 versus 19.8 mo, respectively, HR = 0.56, 95% CI: 0.40–0.79, $p = 0.001$). However, this DFS advantage did not translate to a significant 5-year DFS (22.6% versus 23.2%, $p = 0.891$) or 5-year OS benefit (53% versus 51%, $p = 0.784$). This is of relevance as in the ACT arm, only 52% of patients who progressed received an EGFR TKI post-progression.[28,29] In the IMPACT study (N = 234), with a crossover rate of 52%, adjuvant gefitinib did not improve the DFS (median DFS: 35.9 versus 25.1 mo; HR = 0.92, 95% CI: 0.67–1.28, $p = 0.63$) nor the OS (5-year OS: 78.0% versus 74.6%; HR = 1.03, 95% CI: 0.65–1.65).[30] Finally, in the EVIDENCE study (N = 322) adjuvant icotinib for 2 years improved the DFS versus ACT (median: 47.9 versus 22.1 mo, HR = 0.36, 95% CI: 0.24–0.55, $p < 0.0001$). The OS data were immature (HR = 0.91, 95% CI: 0.42–1.94).[31]

Overall, adjuvant treatment with first-generation EGFR TKIs improves the DFS, although this benefit seems limited as DFS curves converged after the end of TKI treatment, with no meaningful benefit in OS. This could be explained by the subsequent EGFR TKI treatment postprogression in the ACT arm and suggests that first-generation EGFR TKIs do not change the natural history of the disease. This could be contributed by the lack of central nervous system (CNS) protection, as alluded to by recurrence patterns postadjuvant erlotinib/gefitinib. In the RADIANT trial, among the 66 patients with *EGFR*-mutant tumors who experienced a relapse, a higher rate of brain relapse was reported with erlotinib than with placebo (37% versus 2%).[23] Similarly, in the IMPACT trial brain metastases were more frequently observed in the gefitinib group than in the ACT arm ($p = 0.07$),[30] whereas in the ADJUVANT/CTONG1104 trial, the intracranial recurrence risk was similar in both arms (27% with gefitinib and 24% with ACT, $p = 0.611$).[33] These results suggest that next-generation EGFR TKIs with higher intracranial penetration and activity could overcome this limitation.

On the basis of the improvement in progression-free survival (PFS) and OS with osimertinib versus first-generation EGFR TKIs in advanced-disease stages,[34,35] combined with the better intracranial activity,[36] osimertinib was also assessed in the adjuvant setting.

In the phase 3 ADAURA trial, 682 patients with completely resected *EGFR*-mutant stage IB-IIIA NSCLC (seventh TNM classification) were randomized to receive osimertinib (80 mg once daily) or placebo for 3 years, after optional ACT.[5] The primary end point was DFS in stage II to IIIA, and this was significantly improved with osimertinib versus placebo. After a median follow-up of 44.2 months, the median DFS was 65.8 months versus 21.9 months (HR = 0.23, 95% CI: 0.18–0.30). The median DFS was also improved in the whole population (stage IB–IIIA), with a median DFS of 65.8 months versus 28.1 months (HR = 0.27, 95% CI: 0.21–0.34),[32] without a negative impact on patients' health-related quality of life.[37] The magnitude of the DFS benefit with osimertinib increased with the stage, with an HR of 0.41 (0.23–0.69), HR of 0.34 (0.23–0.52), and HR of 0.20 (0.14–0.29) for stage IB, II, and IIIA, respectively.[32] Similar to previous trials with first-generation EGFR TKI, which does not require baseline brain imaging or positron emission tomography scan,[24–31] in the ADAURA trial patients were under-staged. Half of the patients underwent brain imaging with magnetic resonance imaging, the others with brain computed tomography scan, and no data have been reported about the proportion of patients who underwent a baseline (preoperative) positron emission tomography scan. This potential understaging would confer a marked benefit in DFS with osimertinib over placebo as osimertinib is clearly able to suppress small-volume metastatic disease.[38]

In contrast to previous studies with earlier-generation adjuvant EGFR TKIs, adjuvant osimertinib resulted in both CNS protection and OS improvement. In patients with stage II to IIIA disease, CNS DFS HR was 0.24 (95% CI: 0.14–0.42) with an estimated probability of observing CNS recurrence at 3 years of 2% with osimertinib versus 13% with placebo.[32] Adjuvant osimertinib significantly improved OS versus placebo in patients with stage II to IIIA disease (HR = 0.49, 95% CI: 0.33–0.73, $p = 0.0004$ with a 5-year OS rate of 85% with osimertinib versus 73% with placebo) and in the overall stage IB to IIIA population (HR = 0.49, 95% CI: 0.34–0.70, $p < 0.0001$, with a 5-year OS rate of 88% and 78%, respectively). The benefit in OS was more pronounced with higher disease stages (stage IB, HR = 0.44, 95% CI:

0.17–1.02, stage II, HR = 0.63, 95% CI: 0.34–1.12; and stage IIIA, HR = 0.37, 95% CI: 0.20–0.64). In the trial, the DFS and OS benefit with osimertinib occurred regardless of ACT.[39] The ADAURA trial was unblinded 2 years earlier than expected (April 2020) after a planned review by the independent data monitoring committee, once it revealed superiority and clinically meaningful data in DFS. Therefore, OS data should be interpreted taking into account this consideration. Finally, in the control arm from the ADAURA trial, 85% of patients (174 out of 205 patients who had disease recurrence, excluding deaths) received a first subsequent anticancer treatment. Although osimertinib was approved by health authorities as the first-line treatment approach in the advanced setting in 2018 and ADAURA finished enrollment in February 2019, only 43% of patients in the control arm with progressive disease who received a subsequent treatment, received osimertinib as a subsequent treatment.[39] A higher percentage of crossover could probably have reduced the difference in OS seen between the osimertinib and placebo arms. In the first-line setting in advanced disease, data coming from real-world studies and clinical trials reported that the high crossover rate may explain the comparable OS between upfront osimertinib versus upfront first-generation EGFR TKI.[40,41]

On the basis of the DFS data, osimertinib gained marketing authorization as adjuvant treatment for patients with completely resected stage IB to IIIA NSCLC and common sensitizing *EGFR* mutations (Del 19 or L858R), being the first personalized treatment approved in this setting. Several other ongoing clinical trials are exploring adjuvant EGFR TKI strategy in the same population: NCT02193282 (ALCHEMIST) testing erlotinib; NCT01996098 (ICTAN) testing icotinib; and NCT04853342 (FORWARD), NCT04687241; NCT04762459 (APEX), all three-testing adjuvant treatment with almonertinib. However, some of these drugs and trials are only developed and performed in Asian countries, limiting the access and potential generalizability of these results worldwide. Finally, on the basis of the success of an adjuvant personalized approach in early-stage *EGFR*-mutant NSCLC, several trials explore this approach in other oncogenic-driven NSCLC (such as ALINA [NCT03456076] and ALCHEMIST [NCT02194738] trials in *ALK*-positive NSCLC and LIBRETTO-432 trial [NCT04819100] in *RET*-positive NSCLC).

EGFR-Mutant Early-Stage NSCLC and Adjuvant Treatment: Future Challenges

After the step forward with the ADAURA trial, there are still several challenges to be addressed (Fig. 1), mainly to address the optimal patient selection for adjuvant EGFR TKI.

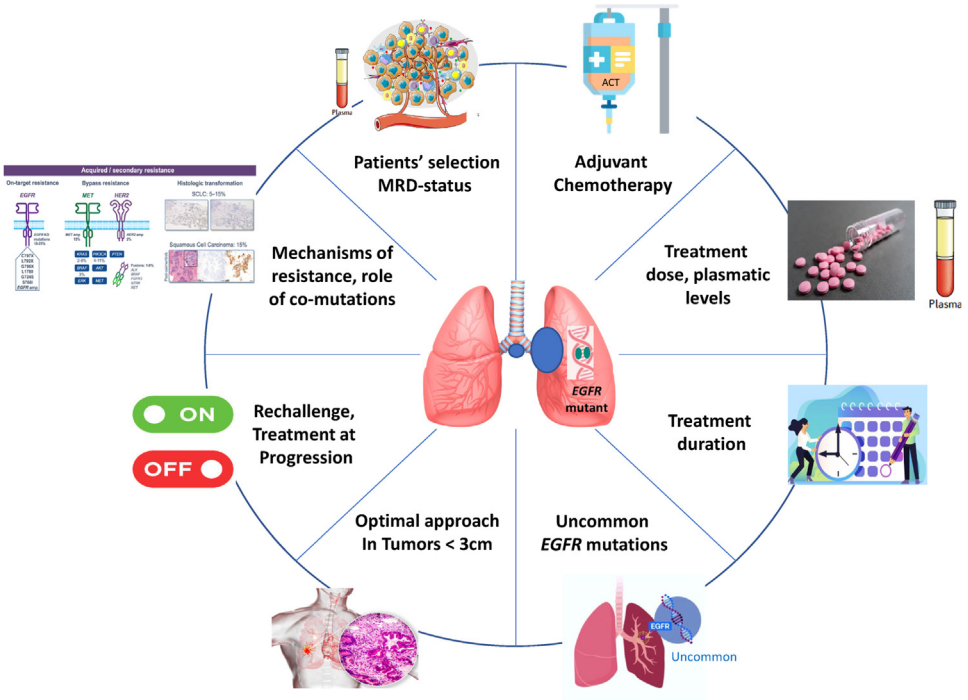

Figure 1. Challenges in early-stage NSCLC harboring *EGFR* mutation. ACT, adjuvant chemotherapy; MRD, minimal residual disease.

Minimal Residual Disease

Individualized risk factors for recurrence in early-stage *EGFR*-mutant NSCLC remain undefined and some patients are cured without adjuvant osimertinib, although the percentage significantly decreases with increasing stage. In a recent retrospective cohort with 729 patients (389 with *EGFR*-mutant stage IA–III NSCLC), the 2-year DFS among patients with resected *EGFR*-positive NSCLC and not treated with adjuvant osimertinib, was 81.0%, 78.4%, 57.1% and 46.4% for stage IA, IB, II, and IIIA, respectively. Overall, in all stages (IB–IIIA) combined, the 5-year DFS was 37.2%,[17] suggesting that more than one-third of these patients may be cured without adjuvant osimertinib. These data support the individualization of adjuvant treatment recommendations to avoid overtreatment of patients, resulting in increased healthcare burden and unnecessary adverse effects.

Among the predictors of relapse, the minimal residual disease (MRD), defined as the detection of circulating tumor DNA (ctDNA) after surgery, has one of the highest correlations with recurrence, and therefore, could potentially identify the patient population who could benefit the most from adjuvant treatment.[42–46] Indeed, the presence of MRD precedes radiographic progression, and even in the first month of the postoperative phase, MRD carried a high negative predictive value for disease recurrence.[45–47]

Given that the detection of MRD can predate the disease recurrence, it has been proposed that future studies incorporate MRD detection in a pragmatic design.[48] A recent prospective cohort including 278 patients with completely resected stage IA to IIII *EGFR*-mutant NSCLC (60% stage IA) explored the longitudinal ctDNA status by digital droplet polymerase chain reaction (ddPCR). Presurgery ctDNA was detected in 67 (24.1%) patients. Among them, 76% (51 of 67) of patients exhibited ctDNA clearance 4 weeks after surgery. A significantly higher 3-year DFS was observed in patients who were ctDNA negative at baseline regardless of the stage or in those who were ctDNA positive and MRD-negative after surgery compared with those who were ctDNA positive at baseline and remained MRD positive after surgery (3-year DFS: 83.3%, 78%, and 50%, respectively, $p = 0.02$). After adjusting for clinicopathologic 63 variables, ctDNA remains an independent risk factor for DFS along with stage ($p < 0.001$).[49] These data suggest that MRD as a prognostic factor that could help to personalize adjuvant treatment. One of the hypothetical treatment algorithms could be the identification of high-risk candidates for disease recurrence postoperatively using staging and MRD data, and administering adjuvant treatment (EGFR TKI) only in this subgroup.[50] Although this strategy looks promising, there are several challenges to be addressed before this approach can be implemented in daily practice, such as the best technology for MRD detection and the sensitivity and specificity of ctDNA in the detection of MRD.[51] In early-stage NSCLC the cutoff limit for MRD to predict recurrence is very low, and not all MRD techniques are sensitive enough. Therefore, the development of robust MRD technologies is vital with the aim of minimizing the false-negative rates in ctDNA MRD assays.[52,53] In a recent cohort of *EGFR*-mutant advanced NSCLC, plasma next-generation sequencing (NGS) trended toward higher sensitivity than ddPCR in detecting *EGFR* at baseline, although both had similar concordance in detecting clearance of *EGFR*.[54] Whether ddPCR should be the optimal technique for MRD in early-stage *EGFR*-mutant NSCLC remains unknown and the use of MRD status in this setting needs to be validated in large and prospective RCT.

Role of Comutations

At present, in clinical guidelines, only *EGFR* testing is mandatory in early-stage NSCLC,[1,55] and this could be done with a single gene test such as PCR, resulting in relatively low costs and a short turn-around time. However, tumors, including early-stage *EGFR*-mutant NSCLC,[56] are heterogenous, and an extensive NGS panel upfront makes more sense aiming to identify comutations associated with decreased EGFR TKI benefit[57,58] and faster resistance evolution.[59] Apart from broader genomic markers, the identification of transcriptomic markers and others may help to stratify *EGFR*-mutant NSCLC in different prognostic subgroups aiming to personalize therapeutic approaches.[60]

In advanced *EGFR*-mutant NSCLC, the co-occurrence of a *TP53*-mutation represents a relevant mechanism of resistance to EGFR TKIs, regardless of their generation[61,62] and *TP53* co-mutant tumors have a higher mutation burden and increased mutagenesis.[59] Similarly, the co-occurrence of *TP53* and *RB1* mutations is associated with an increased risk of SCLC transformation.[63,64] As these comutations correlate with poorer prognosis, there are ongoing clinical trials in the metastatic setting exploring an escalating treatment strategy (adding platinum-based chemotherapy): these are the ACROSS 1 and 2 trial (NCT04500717, evaluating whether the addition of chemotherapy results in a PFS improvement in tumors with a *TP53* comutation), and the NCT03567642 trial, to overcome the risk of histologic transformation in tumors with upfront dual *RB1/TP53* comutation.

Similar to advanced disease, in early-stage *EGFR*-mutant NSCLC, the most frequent comutated gene is

TP53 (reported in up to 70% of cases),[65,66] and is also in this setting associated with a poor prognosis.[66] In another comprehensive genomic analysis in 56 patients with completely resected *EGFR*-mutant stage IB to IIIA NSCLC with matched case-controls, it was reported that the nonterminal respiratory unit (non-TRU) lung adenocarcinoma subtype and the presence of a *TP53* mutation were associated with poor RFS independent of the stage. The median RFS was not reached in the subgroup of tumors with both a TRU subtype and *TP53* wild-type whereas in the higher risk groups (tumors with non-TRU subtype concurrent or not with TP53 mutation) the RFS ranged from 14.2 months to 25.0 months.[65] The prognostic role of these comutations and others should be prospectively validated in future clinical trials to evaluate patients who may benefit from more intensive adjuvant treatment approaches.

Adjuvant Chemotherapy

In the ADAURA trial, 60% of patients received ACT (mostly platinum-combined chemotherapy with vinorelbine and pemetrexed), and this was more frequent in those younger than 70 years and those with stage II or IIIA disease.[5,67] This percentage mirrors data reported in daily practice as the rate of ACT among patients with completely resected early-stage NSCLC ranges between 41% to 57%.[68,69] In the ADAURA trial, both the DFS and OS benefit with osimertinib occurred regardless of ACT use (DFS HR = 0.29, 95% CI: 0.21–0.39; OS HR = 0.49, 95% CI: 0.30–0.79) or not (DFS HR = 0.36, 95% CI: 0.24–0.55; OS HR = 0.47, 95% CI: 0.25–0.83).[32,39] However, ACT was not a stratification factor in the trial, and therefore, these results do not provide solid arguments to omit ACT in this setting. The 5-year OS was higher with ACT versus no-ACT in patients with stage II to IIIA in the osimertinib arm (87% versus 80%) and in the placebo arm (75% versus 66%), suggesting a potential survival benefit with ACT in this population.[39]

Using comutations status to select patients for ACT in the early disease staging seems also logical. In the ADJUVANT/CTONG1104 trial, comprehensive genomic profiling of 171 tumor samples identified five predictive biomarkers for DFS aiming to define a genomic predictive signature (*TP53* exon4/5 mutations, *RB1* alterations, and copy number gains of NKX2-1, CDK4, and MYC). This signature categorizes patients into three subgroups (highly TKI-preferable, TKI-preferable, and chemotherapy-preferable groups). In this exploratory analysis, the *RB1* alterations, present in up to 20% of the tumors, had a positive interaction in favor of ACT as compared with adjuvant TKI (HR = 4.07, 95% CI: 1.56–10.58, $p = 0.004$).[66] However, as data are retrospectively and performed in a small series, these results and their potential implications should be validated in prospective trials. The comutations landscape in ADAURA and its potential impact on the outcome has not been reported to date. As ACT was not a stratification criterion in the ADAURA trial,[32] the only argument for omitting ACT in this population would be a patient unfit for receiving this treatment. Finally, the outcome of ACT in routine clinical practice may be improved by incorporating the right platinum partner with a favorable toxicity profile. In a post hoc exploratory subgroup analysis in patients with nonsquamous early-stage NSCLC harboring *EGFR*-mutations from the phase 3 JIPANG trial, the RFS tended to be better in the group assigned to ACT including vinorelbine instead of pemetrexed although the difference was not statistically significant (HR = 1.38, 95% CI: 0.95–1.99). The toxicity profile clearly favored pemetrexed with 47% of grade 3 to 5 adverse events versus 89% with vinorelbine.[70]

Mechanisms of Resistance

The knowledge of the mechanisms of acquired resistance (AR) on osimertinib allows us to assess potential sequential treatment approaches at progression or to evaluate upfront combination strategies to prevent the development of some of these mechanisms of resistance. In advanced *EGFR*-mutant NSCLC, several mechanisms of AR to osimertinib have been reported,[71] including *MET* amplification in up to 15% of the cases.[72] Although the mechanisms of AR on osimertinib in early-stage NSCLC have not been reported yet, these will probably mirror those described in the metastatic setting. Some trials in the metastatic setting explore combination approaches to prevent the onset of AR mechanisms (e.g., MARIPOSA trial NCT04487080) with the aim to prolong the PFS with the combination versus monotherapy. Whether combination strategies may be a potential treatment approach in the adjuvant setting remains unknown. However, the expected additional benefit compared with EGFR TKI alone must be clearly balanced with the safety profile, quality of life, financial toxicity, and treatment compliance.

Optimal Treatment Duration and Treatment Dose

Cancer cell dormancy is a process whereby cells enter reversible cell cycle arrest, termed quiescence. The quiescence status is essential for cancer cells to acquire additional mutations, to survive in a new environment and initiate metastasis, to become resistant to cancer therapy, and to evade immune destruction. Thus, dormant cancer cells are considered to be responsible for cancer progression.[73,74] In several trials addressing the role of adjuvant EGFR TKI, the Kaplan-Meier curves for DFS began to converge after EGFR TKI

discontinuation,[29] suggesting that adjuvant EGFR TKI can only delay the recurrence of disease but cannot completely destroy the dormant cancer cells, challenging the optimal adjuvant EGFR TKI treatment duration. As an example, in the ADAURA trial, both CNS recurrences and extracranial progression among patients treated with osimertinib occurred after the completion or discontinuation of treatment.[32] These data suggest that brain imaging follow-up by magnetic resonance imaging is strongly recommended after treatment discontinuation and challenges the optimal adjuvant treatment duration in this setting. In other solid tumors, such as gastrointestinal stromal tumors, prolonged adjuvant treatment with imatinib (3 years versus 1 year) correlated with improvement in OS.[75] Conflicting data exist for the duration of adjuvant treatment with EGFR TKIs in early-stage *EGFR*-mutant NSCLC,[29,76] although the recent exploratory phase 2 ICOMPARE trial suggests that 2 years of adjuvant icotinib improve the DFS and OS compared with 1 year.[77] With the aim to enlarge the DFS benefit, the phase 2 TARGET trial (NCT05526755) explores osimertinib for 5 years in patients with completely resected stage II to IIIB *EGFR*-mutant NSCLC. However, in the ADAURA trial, only 66% and 41% of patients completed the 3 years of treatment with osimertinib or placebo, respectively.[32] Therefore, the longer treatment duration must be balanced by treatment compliance, the safety profile,[78] and economic toxicity.

To reduce health care costs and toxicity, alternative osimertinib dosing and therapeutic drug monitoring should also be further explored in the early disease setting. So far, in advanced disease, no clear dose-response relationship for osimertinib has been found in the phase 1 dose-escalation study when assessing doses of 20 mg, 40 mg, 80 mg, 160 mg, and 240 mg once daily.[79] Treatment toxicity, in contrast, increased with doses above 80 mg.[79] Similar evidence was reported in the phase 1 trial with osimertinib.[80]

Currently, all patients are treated with 80 mg daily, while plasma trough levels can vary. However, in real-world series, evaluating patients treated with 80 mg daily, and incorporating plasma trough level assessments of osimertinib, no exposure-efficacy (PFS nor OS) correlation for osimertinib was found and it seems that patients with a plasma trough concentration in steady-state ($C_{min,SS}$) less than 166 μg/liter have a numerically longer median PFS compared with patients with a $C_{min,SS}$ greater than or equal to 166 μg/liter (13.3 versus 9.3 months, respectively, $p = 0.03$).[81] This suggests that patients can potentially be treated with lower doses of osimertinib, with the drawback that data for $C_{min,SS}$ below 100 to 125 ng/mL were limited and no firm conclusions could be drawn regarding this subgroup of patients.[81,82] Furthermore, higher concentrations also do not seem to be beneficial for CNS control, as in the OCEAN study, the brain metastasis-related PFS was not statistically different ($p = 0.357$) between patients with high ($\geq$568 nM) versus low ($<$568 nM [284 ng/mL]) osimertinib blood concentrations.[83] In contrast, with high $C_{min,SS}$ (cutoff determined at 259 ng/mL) toxicity seems to increase.[84] Of note, plasma levels should also be interpreted according to ethnicity, as levels seem to be higher in Asian patients.[81–84]

The lack of an apparent exposure-response relationship for osimertinib in the current dosing scheme is relevant, as one of the most encountered barriers to appropriate treatment in low- and middle-income countries with next-generation TKI is the financial toxicity of these drugs, and lower doses of osimertinib or different treatment schedules may help to reduce treatment inequalities worldwide. Unfortunately, in several countries, the cost of osimertinib is the same regardless of the dose (80 mg or 40 mg); as such, different treatment schedules (e.g., every other day 80 mg) are more appropriate to be tested in early-stage NSCLC when the objective is to reduce the financial toxicity without impacting survival.

Treatment at Progression

After the ADAURA trial, it is important to address whether patients treated with adjuvant EGFR TKI may retain sensitivity to subsequent EGFR TKIs at progression, and achieve a survival benefit with EGFR TKI rechallenge at progression.[85] In the ADJUVANT trial, patients in the gefitinib arm who receive subsequent EGFR TKI at progression (57.2% gefitinib/erlotinib/icotinib; 32.1% osimertinib and 10.7% others) had a longer OS than patients who received other subsequent treatment (not reached versus 35.3 months). Similarly, in the SELECT trial, among the 40 patients who recurred after adjuvant erlotinib completion, 26 (65%) were retreated with erlotinib at progression, with a median duration of treatment of 13.1 months.[24] All these results suggest that adjuvant targeted therapy followed by subsequent targeted therapy on disease progression after completion of adjuvant treatment may provide a longer OS.[29] However, as not all patients benefit from rechallenge EGFR TKI and as patients can also have disease relapse during adjuvant EGFR TKI treatment, repeat biopsy should be performed at progression when feasible to identify potential mechanisms of resistance.

Uncommon EGFR Mutations and Other Groups

EGFR mutations can be classified by the location of the DNA sequence and the structural changes that determine the sensitivity to EGFR TKI. *EGFR* mutations are composed of classical *EGFR* mutations (67.1%) and

atypical *EGFR* mutations (30.8%), which include the exon 20 insertions (9.1%), atypical mutations (12.6%), or a complex mutation including an atypical mutation (9.1%); also, 2.2% had the classical mutation plus the T790M mutation and an atypical mutation. Atypical *EGFR* mutations occurred primarily in exons 18 (23.7%) and 20 (20.9% insertions and 19.2%-point mutations). However, on the basis of the structure-function, four groups of *EGFR* mutations have been reported: classical-like, T790M-like, Exon20 loop insertion, and P-loop C-helix compressing mutations (such as G719X, S768I, L747P/S).[86] These data may explain the different risk ratios and PFS with EGFR TKI, either with osimertinib[87,88] or afatinib,[89] in the whole group of atypical *EGFR*-mutant advanced NSCLC. Recently, the combination of lazertinib and amivantamab has also been tested in patients with atypical *EGFR* mutations NSCLC (exon 20 insertions excluded). The combination yielded a risk ratio of 53%, and the degree of benefit occurred regardless of the atypical *EGFR* mutation subtype. These data might suggest that the addition of amivantamab may overcome the different EGFR TKI sensitivity in this subgroup of tumors. However, this is only hypothesis-generating given the limited sample size.

In early-stage NSCLC, there are no data about atypical *EGFR* mutations, and adjuvant osimertinib is not approved for this subgroup. Whether an adjuvant combination treatment would be more suitable in this setting remains unknown and should further be explored.

As in the ADAURA trial, only patients with tumors the size of at least 4 cm were included and no data are available regarding the very early disease, the ongoing ADAURA2 trial (NCT05120349) explores 3 years of adjuvant osimertinib or placebo in completely resected stage IA2 and IA3 *EGFR*-mutant NSCLC according to the eighth TNM. The primary end point is DFS in high-risk tumors (defined as a tumor with at least one of the following factors: largest diameter of invasive component of primary tumor greater than 2 cm, lymph vascular invasion and/or high-grade tumor: $\geq$20% micropapillary, solid, or complex gland adenocarcinoma). Similarly, as not all patients with early-stage NSCLC are medically operable, a subcohort of the PACIFIC-4 trial (NCT03833154) explores the efficacy of osimertinib for 3 years in terms of PFS in patients with stage I/II *EGFR*-mutant NSCLC after curative stereotactic radiotherapy.

Role of Adjuvant Immunotherapy in Resected *EGFR*-Mutated NSCLC

The role of adjuvant ICB in *EGFR*-mutated NSCLC remains controversial. Whereas in both the IMpower010 and PEARLS/KEYNOTE-091 trials patients with *EGFR* mutation-positive NSCLC were allowed, neither trial was powered to address the benefit of ICB specifically in this population.[90,91] Interestingly, subgroup analysis by programmed death-ligand 1 (PD-L1) status in IMpower010 suggested that patients with PD-L1–positive *EGFR*-mutated NSCLC may derive benefit from adjuvant atezolizumab (HR = 0.57, 95% CI: 0.26–1.24), whereas the DFS benefit of atezolizumab was lost once patients with PD-L1–negative NSCLC were included in the analyses (HR = 0.99, 95% CI: 0.60–1.62).[90] Moreover, in the PEARLS/Keynote-091 trial, a DFS benefit of adjuvant pembrolizumab among the *EGFR*-mutated subgroup was unexpectedly observed, but benefit was not reported according to the PD-L1 status.[91] Whereas it is difficult to draw definitive conclusions from subgroup analyses, especially when biomarker testing was not mandated in both trials, adjuvant ICB as monotherapy is not indicated in *EGFR*-mutant NSCLC regardless of PD-L1 expression.

In *EGFR/ALK*-wildtype metastatic NSCLC, high–PD-L1 expression (PD-L1 $\geq$50%) has predictive value for ICB as monotherapy,[92,93] whereas its predictive value is more controversial in the adjuvant setting.[90,91] For resected *EGFR*-mutated NSCLC, PD-L1 expression has been found to be a poor prognostic biomarker for DFS and OS, probably as tumors with PD-L1 greater than 1% had significantly higher rates of *TP53* mutations (36.1% versus 15.6%, $p = 0.04$), with predominantly missense mutations.[94]

High–PD-L1 expression has also been associated with primary resistance to EGFR TKI in the metastatic setting, including osimertinib.[95,96] However, in a post hoc analysis of the FLAURA trial, clinical benefit with osimertinib was unaffected by the PD-L1 expression status ($<$1% or $\geq$1%), but data in high–PD-L1 expressors have not been reported.[97] To that end, results of the ADAURA trial analyzed by PD-L1 status would be highly relevant to discern therapeutic implications for adjuvant osimertinib.[5] The role of adjuvant ICB could potentially be explored in patients who are predicted to reveal primary TKI resistance, although robust biomarkers to identify these patients upfront are still awaited.[98]

Finally, in stage III NSCLC, a post hoc analysis of the PACIFIC trial (testing durvalumab versus placebo after concurrent chemoradiotherapy) in 35 patients with *EGFR*-mutant stage III NSCLC reported no benefit from durvalumab versus placebo in this population (median DFS: 11.2 versus 10.9 months, HR = 0.91, 95% CI: 0.39–2.13; and median OS: 46.8 versus. 43.0 months respectively, HR = 1.02, 95% CI: 0.39–2.63).[99] Therefore, the role of ICB and the role of MRD in defining the optimal population to receive a consolidation treatment approach remains controversial in this subset of NSCLC. Two ongoing trials explore the consolidation EGFR TKI approach in *EGFR*-mutant stage III NSCLC (NCT03521154, NCT05170204).

Neoadjuvant Strategies in *EGFR*-Mutated NSCLC

After the landmark CheckMate816 study, neoadjuvant nivolumab plus platinum-doublet chemotherapy has been established as the new SoC for resectable EGFR/ALK wild-type NSCLC (tumors ^{3}4 cm or node-positive).[100] More recently, results from the AEGEAN, NEOTORCH (both performed in *EGFR/ALK* wild-type NSCLC) and KEYNOTE 671 trials were reported, similarly exhibiting improved pathologic complete response (pCR) rate and event-free survival in favor of ICB plus platinum-based chemotherapy over placebo plus chemotherapy among resectable NSCLC.[101–103] Of note, in the KEYNOTE 671 trial, molecular testing was not mandated and a limited number or *EGFR* and *ALK*-positive tumors were included. Although pembrolizumab resulted in an event-free survival benefit in this population, subgroup analyses are exploratory and not powered to draw firm conclusions.[103] Whereas many unanswered questions remain, including whether adjuvant ICB should be continued after surgery, another relevant concern is what the optimal treatment should be for patients with resectable oncogene-driven tumors.

Given the high response rates to EGFR TKI observed in the metastatic setting, neoadjuvant TKI strategies have been explored for some time. The only randomized trial performed to date is the phase 2 EMERGING-CTONG 1103 trial enrolling 72 patients and comparing neoadjuvant/adjuvant erlotinib with cisplatin and gemcitabine in patients with stage IIIA to N2 *EGFR*-mutated NSCLC.[104] Although this trial did not meet its primary end point of overall response rate (ORR) (ORR: 54.1% versus 34.3%, $p = 0.092$) and ultimately did not improve OS (median 42.2 mo versus 36.9 mo, HR = 0.83, 95% CI: 0.47–1.47, $p = 0.513$), the PFS was significantly improved in the erlotinib arm (median 21.5 mo versus 11.4 mo, HR = 0.39, 95% CI: 0.23–0.67, $p < 0.001$).[85,104] No pCR were seen and the major pathologic response (MPR) rate was 9.7% in the erlotinib arm.[104] Modest pathologic responses have similarly been encountered in other single-arm neoadjuvant EGFR TKI trials, with MPR rates ranging from 7.7% to 24.2%.[104–107] Most recently, the NEOS trial evaluated the efficacy of 6 weeks of neoadjuvant osimertinib among 40 patients with stage IIA to IIIB (T3–4/N2) *EGFR*-mutated NSCLC. Whereas the primary end point ORR was encouraging at 71.1% with 93.8% microscopically margin-negative (R0) resection rate and an acceptable adverse effect profile, the MPR rate was only 10.7% and pCR 3.6%.[108] However, in another phase 2 trial with 27 patients with *EGFR*-mutant stage IB to IIIA, neoadjuvant osimertinib reported an ORR and MPR of 52% and 15%, respectively, and the median DFS after surgery was 32.4 months. Despite all the patients enrolled having a surgically resectable disease, 11% of patients were converted to definitive chemoradiotherapy.[109] These low pathologic responses could potentially be explained by the mechanism of action of TKI, which applies a selective pressure to control cell proliferation; thus, invariably driving the development of resistant subclones, and therefore, do not achieve sufficient cytotoxicity to eradicate cancer cells in most patients.[110] Furthermore, flare responses resulting in accelerated disease progression have been well described when the EGFR TKI is discontinued in the metastatic setting, which is in line with this.[111] Taken together, these results may suggest that neoadjuvant EGFR TKI monotherapy may not be sufficient to improve cure rates among patients with resectable *EGFR*-mutated NSCLC. In light of these findings, combination strategies are likely to be favored in future trials. Accordingly, in the NeoADAURA trial (NCT04351555) the combination of neoadjuvant osimertinib plus platinum-doublet chemotherapy against osimertinib monotherapy is evaluated, with chemotherapy alone as the control arm.[112] Given the acceptable safety profile and efficacy of EGFR TKI plus pemetrexed-platinum chemotherapy in advanced-stage NSCLC, this combination in the neoadjuvant setting is rational.[113–115] However, combining ICB with EGFR TKI should be cautioned given the risk of interstitial lung disease observed in the metastatic setting, even when a sequential approach is taken.[116,117] Whether other novel therapeutic agents such as antibody-drug conjugates should be evaluated in the early-stage setting will hinge on safety and efficacy signals from late-stage trials, either as a single-agent or in combination with EGFR TKI.[118,119]

End Points in Neoadjuvant Trials for Oncogene-Driven NSCLC

After the experience with neoadjuvant and adjuvant EGFR TKI, other oncogene subtypes are likely to follow suit (Table 2). Notably, pathologic response has been chosen as the primary end point in many perioperative trials, likely owing to the shorter follow-up time needed and increasing acceptance of earlier end points such as DFS in adjuvant trials.[120] However, it is pertinent for clinicians to recognize the limitations of these end points and the impact of a class of therapy. For example, DFS may not be the most appropriate end point in adjuvant EGFR TKI trials given the convergence of DFS curves after TKI is stopped, yet OS is also influenced by the number of patients who receive EGFR TKI on progression in the control arm. Pathologic response to neoadjuvant TKI has also not been validated as a surrogate

Table 2. Ongoing/Upcoming Perioperative Trials in Oncogene-Driven NSCLC

Trial	Phase	Population	Study Arm	Control Arm	Primary End Point	Target Accrual
EGFR						
TKI monotherapy						
[NCT01470716]	2	Resectable stage II-IIIA	Erlotinib presurgery for 8 wk	NA	PFS	26
[NCT03749213]	2	Stage IIIA-N2	Icotinib presurgery for 8 wk, followed by adjuvant icotinib for 2 y	NA	ORR	36
[NCT03349203]	2	Potentially resectable stage IIIB or oligometastatic	Icotinib presurgery for 8 wk, followed by adjuvant icotinib for 2 y	NA	ORR	60
[NCT05469022]	2	Resectable stage I - IVA[a]	Lazertinib presurgery for 9 wk, followed by adjuvant lazertinib for 3 y in stage 2 and above	NA	ORR	40
TKI in combination with chemotherapy						
[NCT05132985]	2	Resectable stage II-IIIB N2	Icotinib + pemetrexed-platinum chemotherapy × 2 cycles presurgery, followed by optional adjuvant chemotherapy × 2 cycles + adjuvant icotinib for 2 y	NA	MPR	45
NEOAFA [NCT04470076]	2	Resectable stage IIA-IIIB	Afatinib + platinum doublet × 3 cycles presurgery, followed by adjuvant afatinib for 2 y	NA	1. MPR 2. ORR	30
NOCE01 [NCT05011487]	2	Resectable stage III-N2	Osimertinib + cisplatin-pemetrexed × 2 cycles presurgery	NA	ypN0	30
FORESEE [NCT05430802]	2	Resectable stage IIIA-IIIB	Furmonertinib + cisplatin-pemetrexed × 3 cycles presurgery	NA	ORR	40
ANSWER [NCT04455594]	2	Stage IIIA-N2	Almonertinib (duration not specified)	Erlotinib + pemetrexed-platinum chemotherapy × 3 cycles presurgery	ORR	168
NeoADAURA [NCT04351555]	3	Resectable stage II-IIIB-N2	A) Osimertinib + platinum doublet × 3 cycles presurgery, followed by optional adjuvant osimertinib for 3 y +/- adjuvant chemotherapy B) Osimertinib alone presurgery for 9 wk, followed by optional adjuvant osimertinib for 3 y +/- adjuvant chemotherapy	Placebo + platinum doublet × 3 cycles presurgery, followed by optional adjuvant osimertinib for 3 y ± adjuvant chemotherapy	MPR	328
ALK						
[NCT05380024]	2	Resectable stage II-IIIB	Ensartinib for 8 wk presurgery	NA	MPR	10
ALNEO [NCT05015010]	2	Potentially resectable stage III	Alectinib for 8 wk presurgery, followed by adjuvant alectinib for 2 y	NA	MPR	33
KRAS G12C						
[NCT05400577]	2	Resectable stage IB-IIIA	Sotorasib for 4 wk presurgery	NA	MPR	25
Neo-Kan [NCT05472623]	2	Resectable stage IB-IIIA	Adagrasib for 6 wk + nivolumab for 3 cycles presurgery, followed by adjuvant chemotherapy	Adagrasib for 6 wk presurgery, followed by adjuvant chemotherapy	pCR	42

(continued)

Table 2. Continued

Trial	Phase	Population	Study Arm	Control Arm	Primary End Point	Target Accrual
[NCT05118854]	2	Resectable stage IIA-IIIB	Sotorasib in combination with cisplatin (or carboplatin) and pemetrexed for 4 cycles	historical control MPR rate for platinum-based chemotherapy alone	MPR	27
Other oncogene drivers						
NAUTIKA1 [NCT04302025]	2	Resectable stage II-III NSCLC with ALK, ROS1, NTRK, BRAF V600 or RET molecular alterations	A) *ALK*: Alectinib for 8 wk presurgery, followed by adjuvant chemotherapy × 4 cycles + 2 y of alectinib B) *ROS1*: Entrectinib for 8 wk presurgery, followed by adjuvant chemotherapy × 4 cycles + 2 y entrectinib C) *NTRK*: Entrectinib for 8 wk presurgery, followed by adjuvant chemotherapy × 4 cycles + 2 y entrectinib D) *BRAF*: Vemurafenib + cobimetinib for 8 wk presurgery, followed by adjuvant chemotherapy × 4 cycles + 2 y vemurafenib + cobimetinib E) RET: Pralsetinib for 8 wk presurgery, followed by adjuvant chemotherapy × 4 cycles + 2 y pralsetinib	NA	MPR	60
Geometry-N [NCT04926831]	2	Stage IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) NSCLC with *MET* Exon 14 skipping mutation or high MET amplification	Neoadjuvant capmatinib for 8 wk presurgery, followed by 3 y of adjuvant capmatinib	NA	MPR	38
LIBRETTO-001 [NCT03157128]	2	Resectable stage IB-IIIA NSCLC with *RET*-fusion (Cohort 7)	Selpercatinib for 8 wk presurgery, followed by adjuvant selpercatinib for 3 y	NA	ORR	875 (entire study)
LIBRETTO-432 [NCT04819100]	3	Stage IB-IIIA NSCLC with *RET*-fusion after surgery or radiotherapy with or without ACT	Selpercatinib for 3 y	Placebo	EFS	170

Note: Trial information obtained from clinicaltrials.gov on May 19, 2023.

[a]EGFR-mutant test performed in bronchoalveolar lavage fluid

ACT, adjuvant chemotherapy; EFS, event-free survival; MPR, major pathologic response; ORR, objective response rate; OS, overall survival; pCR, complete pathologic response; TKI, tyrosine kinase inhibitor; ypN0, complete lymph node clearance.

measure of OS.[121] With these considerations in mind, novel end points such as ctDNA clearance could potentially bridge the gap in traditional end points to further refine risk stratification and personalize adjuvant therapy recommendations.[52,122] Finally, surgical end points, such as 30-day after surgery morbidity and mortality, should be included as the specific outcome in N2 disease.

In conclusion, on the basis of the improved DFS and OS, adjuvant osimertinib has become the new SoC for patients with completely resected stage IB to IIIA NSCLC with an *EGFR* Del 19 or L858R mutation. Future research should focus on identifying patients who either do not need adjuvant osimertinib or need a more intense adjuvant therapy or monitoring. MRD and comutations seem promising prognostic biomarkers to select these patients but should be evaluated in RCT. Finally, the role of neoadjuvant or consolidation EGFR TKI warrants further clinical data. With increasing health care costs, future research should also invest in optimizing treatment and dosing schedules.

CRediT Authorship Contribution Statement

Jordi Remon: Conceptualization, Acquisition and interpretation of data, Validation, Investigation, Writing (original draft, review and editing), Supervision.

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