From ADAURA to LAURA: The Evolving Role of EGFR-Targeted Therapy in NSCLC

Kelsey Pan, MD, MPH[a]; and Suresh S. Ramalingam, MD[a]

[a]Department of Hematology and Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, Georgia

Corresponding author:
Suresh Ramalingam, MD
Department of Hematology and Medical Oncology
Winship Cancer Institute of Emory University
1365 Clifton Road NE
Atlanta, GA 30322
Email: ssramal@emory.edu

Abstract: Epidermal growth factor receptor gene (*EGFR*) mutations, most commonly involving exon 19 deletion or leucine-858-to-arginine substitution (L858R), define a biologically distinct subset of non–small cell lung cancers (NSCLCs). Third-generation EGFR tyrosine kinase inhibitors have transformed outcomes in metastatic disease, and this benefit has since been extended into localized and locally advanced NSCLC through 3 landmark randomized trials: ADAURA, which established adjuvant osimertinib as standard of care after the resection of stage IB-IIIA disease; NeoADAURA, which demonstrated improved pathologic responses with neoadjuvant osimertinib in resectable stage II-IIIB disease; and LAURA, which established osimertinib consolidation after chemoradiation in unresectable stage III disease. Together, these trials mark a shift away from the mutation-agnostic treatment paradigms that previously guided the treatment of earlier stages of NSCLC toward targeted therapy across curative-intent settings. This review summarizes the evidence supporting perioperative and consolidation EGFR tyrosine kinase inhibitor therapy in resectable and unresectable locally advanced *EGFR*-mutant NSCLC, and it addresses practical considerations including treatment sequencing, the management of radiation-related toxicity, and central nervous system surveillance. It also examines unresolved questions, including the optimal duration of adjuvant and consolidation therapy, the role of circulating tumor DNA in guiding treatment decisions, and the management of atypical *EGFR* mutations, which remain outside the evidence base guiding current guidelines. As precision oncology extends further into curative-intent settings, molecular selection is becoming central to treatment planning in locally advanced NSCLC.

Keywords
Adjuvant therapy, consolidation therapy, EGFR, locally advanced disease, NSCLC, osimertinib

Introduction

Epidermal growth factor receptor gene (*EGFR*) mutations, most commonly in exon 19 or exon 21, occur in up to 15% of cases of non–small cell lung cancer (NSCLC) in Western populations and in 40% to 50% of cases of lung adenocarcinoma in East Asian populations.[1] These mutations disproportionately arise in never-smokers and women, and the associated tumors are biologically distinct, with

a lower tumor mutation burden, a less-inflamed tumor microenvironment, and a predilection for central nervous system (CNS) metastases.[2,3] Third-generation EGFR tyrosine kinase inhibitors (TKIs), such as osimertinib (Tagrisso, AstraZeneca), have transformed the treatment paradigm and clinical outcomes in metastatic *EGFR*-mutant NSCLC, with a median overall survival (OS) now exceeding 3 years when they are given as monotherapy.[4,5] That success has resulted in the integration of osimertinib into the treatment of earlier-stage disease, as established by dedicated randomized clinical trials in resectable and unresectable locally advanced disease.[6,7] Adjuvant osimertinib is now the standard-of-care therapy after the complete resection of stage IB to IIIA disease, and neoadjuvant osimertinib has recently been shown to improve pathologic response in resectable disease.[6,8] The phase 3 LAURA study has extended the use of osimertinib to the setting of unresectable stage III disease.[7,9]

Localized NSCLC encompasses resectable stage II and IIIA disease, treated with curative-intent surgery, as well as unresectable stage III disease, treated with definitive chemoradiation. In both circumstances, a high incidence of local and systemic recurrence is observed following definitive therapy, resulting in 5-year OS rates of only 40% to 50% among patients who have stage II to IIIA disease with lymph node metastasis.[10] Although both resectable and unresectable cases have historically been treated with mechanism-agnostic approaches, the integration of adjuvant osimertinib following surgery and chemoradiation has substantially improved long-term outcomes. This review summarizes the evidence for managing locally advanced *EGFR*-mutant NSCLC across both the resectable and unresectable settings. It also addresses practical considerations regarding treatment sequencing, toxicity management, and CNS surveillance.

Determining Staging and Resectability

Stage III NSCLC comprises a heterogeneous group of conditions based on tumor location, extent of invasion, and nodal status. It is important to distinguish stage III tumors that are amenable to upfront resection from those that are unresectable owing to bulky, multistation mediastinal nodal involvement or the invasion of central structures by the primary tumor. A multidisciplinary discussion among molecular pathology, pulmonology, thoracic surgery, radiation oncology, and medical oncology teams is necessary for patients with stage III disease. Imaging with positron emission tomography/computed tomography (PET/CT) is helpful for initial clinical staging and for identifying the lesions most amenable to biopsy; although it is highly sensitive in detecting distant metastatic disease, false negatives and positives can occur in detecting nodal involvement.[11,12] For this reason, mediastinal nodes that are positive on PET should be sampled to confirm nodal metastasis. The American Joint Committee on Cancer staging system was recently updated to its ninth edition, which further subdivides node staging (into N2a if a single ipsilateral mediastinal or subcarinal node is positive and N2b if >2 ipsilateral stations are positive) and guides the classification of borderline resectable cases.[13]

Brain magnetic resonance imaging is also an essential part of initial staging for all patients with locally advanced disease, especially given the CNS tropism observed in *EGFR*-mutant lung cancer. Unresectable locally advanced disease with *EGFR* mutations has historically demonstrated intracranial recurrence rates of up to 38% after treatment with chemoradiation[14]; therefore, CNS imaging as part of initial staging is crucial for this patient population.

Resectable Locally Advanced Disease

Adjuvant Therapy

The phase 3 ADAURA trial established a treatment paradigm for resected stage II-IIIA NSCLC harboring classic *EGFR* mutations. In this study, which randomized patients to osimertinib (n=339) or placebo (n=343) following surgical resection and adjuvant chemotherapy, treatment with 3 years of adjuvant osimertinib improved disease-free survival (DFS), with a hazard ratio (HR) of 0.23 (Table). The OS rate was also improved, with an HR of 0.49 (5-year survival rate of 88% with osimertinib and 78% with placebo). In addition, osimertinib therapy was associated with an 82% reduction in the risk of CNS recurrence or death.[6,15] Given the magnitude of these effects, osimertinib was rapidly incorporated into the adjuvant therapy setting, and this trial became a model for evaluating adjuvant targeted therapy in other genomically defined subsets of NSCLC. The trial also underscored the importance of molecular testing in early-stage NSCLC, a practice that historically had been reserved for the advanced or metastatic setting.

The role of adjuvant chemotherapy before osimertinib remains debated. Although ADAURA was not designed to answer this question directly, its subgroup data showed similar DFS and OS benefit from osimertinib whether the patients received adjuvant chemotherapy or not. Given the lack of direct evidence assessing the additive benefit of chemotherapy, adjuvant chemotherapy in eligible patients, followed by osimertinib, remains the preferred sequence. Furthermore, despite the DFS benefit seen with the 3-year course of osimertinib treatment, many patients are vulnerable to disease relapse after treatment is completed. The TARGET trial is now investigating whether continuing adjuvant osimertinib for 5 years offers survival benefits in comparison with 3 or 4 years of therapy.[16]

Table. Clinical Trials in Locally Advanced E*GFR*-Mutated NSCLC

Trial	Design/Population	Regimen	Key Results
ADAURA[6,15]	Phase 3; resected, E*GFR* ex19del/ L858R, stage IB-IIIA (n=682)	Adjuvant osimertinib vs placebo × 3 y	Stage II-IIIA DFS HR 0.23; stage II-IIIA 5-y OS 85% vs 73% (HR 0.49)
TARGET[16]	Phase 3; resected, *EGFR*-mutated, prior adjuvant osimertinib (ongoing)	Osimertinib × 5 y vs 3-4 y	Ongoing; testing whether extended adjuvant duration improves outcomes
NeoADAURA[8]	Phase 3; resectable, *EGFR*-mutated, stage II-IIIB (n=358)	Neoadjuvant osimertinib ± chemo vs chemo alone, then adjuvant osimertinib	MPR 26% (osi + chemo) and 25% (osi mono) vs 2% (chemo alone); EFS data immature
RECEL[33]	Phase 2; unresectable stage III, *EGFR*-mutated (n=20)	Erlotinib + concurrent RT, then consolidation erlotinib vs CRT alone	Median PFS 24.9 vs 6.4 mo (HR 0.05, *P*<.001)
LOGIK0902/ OLCSG0905[35]	Phase 2; unresectable stage III, *EGFR*-mutated	Induction gefitinib, then CRT	5-y OS 70%, median OS 5.5 y
Gefitinib + concurrent RT study[36]	Phase 2; unresectable stage III, *EGFR*-mutated (n=27)	Concurrent gefitinib + RT, then gefitinib	Primary endpoint not met; 2-y PFS 30%
ASCENT[34]	Phase 2; unresectable stage III, *EGFR*-mutated (n=19)	Neoadjuvant afatinib, then CRT ± surgery, optional afatinib × 2 y	Median PFS 2.6 y; median OS 5.8 y
Ph2 study of neoadjuvant osimertinib followed by radiation/ surgery[32]	Phase 2; unresectable stage III, *EGFR*-mutated (n=31)	Induction osimertinib × 12 weeks, then RT and/or surgery	ORR 94%
NEOLA[31]	Phase 2; unresectable stage III, *EGFR* ex19del/L858R (ongoing)	Induction osimertinib × 8 wk, then CRT, then continued osimertinib	Ongoing; testing induction-before-CRT sequencing
PACIFIC *EGFR*-mutant subgroup[26]	Post hoc subgroup (n=35) of phase 3 PACIFIC	Consolidation durvalumab vs placebo after CRT	No clear PFS/OS benefit in *EGFR*-mutated subgroup
LAURA[7,28]	Phase 3; unresectable stage III, *EGFR* ex19del/L858R, no progression after CRT (n=216)	Osimertinib vs placebo after definitive CRT	PFS 39.1 vs 5.6 mo (HR 0.16); CNS PFS HR 0.17; OS trend HR 0.67
POLESTAR[30]	Phase 3; unresectable stage III, *EGFR*-mutated	Aumolertinib vs placebo after definitive CRT	PFS 30.4 vs 3.8 mo (HR 0.20); OS immature

CNS, central nervous system; CRT, chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; HR, hazard ratio; L858R, leucine-858-to-arginine substitution; mo, month(s); MPR, major pathologic response; n, number; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; osi, osimertinib; PFS, progression-free survival; RT, radiation therapy; wk, week(s); y, year(s).

The integration of circulating tumor DNA (ctDNA) to assess measurable residual disease (MRD) and potentially guide the duration of adjuvant therapy is an area of ongoing investigation. A post hoc analysis of ADAURA that used MRD assays in 220 patients (n=112 osimertinib, n=108 placebo) detected molecular relapse a median of 4.7 months before radiographic progression of disease.[17] Among the 112 patients on osimertinib, MRD events occurred in 28 patients. With most molecular relapses (19 of 28) occurring after the 3-year duration of osimertinib therapy, the use of serial ctDNA status to guide adjuvant therapy is currently being studied.[18,19]

Neoadjuvant/Perioperative Therapy

For resectable stage II-IIIA NSCLC without driver oncogene mutations, perioperative chemoimmunotherapy is now the standard of care, on the basis of evidence of improvements in the pathologic complete response rate, event-free survival (EFS), and OS in comparison with chemotherapy alone, as demonstrated by several randomized trials.[20-23] Although some patients with *EGFR* mutations were included in the KEYNOTE-671 study evaluating perioperative pembrolizumab (Keytruda, Merck), immunotherapy monotherapy has demonstrated very limited efficacy (with a response rate of ~12%) in the

setting of *EGFR*-mutant advanced/metastatic disease.[24] Therefore, perioperative chemoimmunotherapy is not preferred for classic *EGFR*-mutant disease when more efficacious targeted therapies are available.

Until recently, no randomized data were available supporting the use of neoadjuvant targeted therapy in *EGFR*-mutant disease. As a result, the recommended treatment has been upfront surgery followed by adjuvant therapy. The phase 3 NeoADAURA trial randomized 358 patients with resectable stage II-IIIB *EGFR*-mutant NSCLC to receive neoadjuvant osimertinib plus platinum-based chemotherapy, osimertinib monotherapy, or chemotherapy alone for 9 weeks before surgery, followed by adjuvant osimertinib in all arms. Major pathologic response was significantly improved in both the neoadjuvant osimertinib-plus-chemotherapy (26%) and the osimertinib monotherapy (25%) groups in comparison with the chemotherapy-only group (2%; *P*<.001). EFS rates at 12 months were 93% with neoadjuvant osimertinib plus chemotherapy, 95% with osimertinib, and 83% with chemotherapy alone (see Table).[8] However, the complete pathologic response rate was less than 10% in all 3 groups, which raises the question of whether TKI therapy can improve cure rates in this patient population. Subgroups, such as those with more advanced nodal disease involvement, that preferentially benefit from a neoadjuvant approach remain to be identified. Until the data mature further, adjuvant osimertinib after surgical resection remains the approach with the most robust survival evidence. However, patients with resectable N2 disease may be offered chemotherapy plus osimertinib as neoadjuvant therapy.

An MRD analysis of the ADAURA cohort further characterized the usefulness of ctDNA-based MRD testing during adjuvant osimertinib treatment. When a tumor-informed assay was used, MRD detection had a clinical sensitivity of 65% and specificity of 95% for identifying disease recurrence. At 36 months, the combined DFS and MRD EFS rate was 86% with osimertinib and 36% with placebo (HR, 0.23; 95% CI, 0.15-0.36), a difference of magnitude comparable with that of the trial's DFS endpoint.[25] These findings support the feasibility of incorporating longitudinal ctDNA monitoring into routine follow-up for patients with resected *EGFR*-mutant NSCLC and reinforce ongoing efforts to use MRD status to individualize the duration of adjuvant therapy.

Unresectable Stage III Disease

For several years, the standard of care for unresectable stage III NSCLC was concurrent platinum-based chemoradiation followed by 1 year of consolidation durvalumab (Imfinzi, AstraZeneca), regardless of mutation status, on the basis of the phase 3 PACIFIC trial.[9] Although this trial demonstrated a significant improvement in both progression-free survival (PFS) and OS in a comparison of durvalumab with placebo, it did not stratify patients by *EGFR* mutation status. In the study, only 35 of 713 randomized patients had *EGFR*-mutated tumors; a post hoc subgroup analysis of this patient subset demonstrated no difference in PFS between those who received durvalumab and those who received placebo (11.2 vs 10.9 months; see Table).[26] Although the trial was not powered specifically to detect a statistically significant survival difference, the absence of benefit among the *EGFR*-mutant cohort was consistent with the broader literature suggesting limited immunotherapy efficacy in that subpopulation. The subsequent PACIFIC-5 trial amended its protocol to exclude patients with *EGFR* or anaplastic lymphoma kinase (*ALK*) gene alterations from its efficacy analyses, owing to the emergence of targeted therapy options and uncertain benefit with durvalumab in patients with these 2 oncogene drivers.[27] In clinical practice, many clinicians had already begun withholding consolidation durvalumab in the setting of certain oncogene drivers like *EGFR* mutations, which set the stage for the LAURA trial.

A double-blind, international phase 3 trial (LAURA) enrolled patients with unresectable stage III NSCLC harboring a classic *EGFR* mutation whose disease had not progressed after definitive platinum-based chemoradiation. Patients were randomized in a 2:1 manner to receive osimertinib at 80 mg daily (n=143) or placebo (n=73) until disease progression. The primary endpoint of PFS was superior with osimertinib in comparison with placebo (39.1 vs 5.6 months; HR, 0.16). In addition, a prolongation of time to death or distant metastasis was observed with osimertinib (HR, 0.21; *P*<.001). Importantly, an improved CNS PFS (HR, 0.17; *P*<.001) was achieved in the treatment arm, translating into an 83% reduction in the risk of CNS progression or death relative to placebo. New brain lesions developed in 8% of patients on osimertinib and in 29% on placebo, and osimertinib also reduced local (21% vs 48%) and overall distant metastasis (16% vs 37%).[7] Despite crossover allowing the placebo group to receive a third-generation EGFR TKI, a trend toward improved OS was observed in the osimertinib group at an interim analysis (HR, 0.67; 95% CI, 0.40-1.14; see Table).[28] Thus, osimertinib now carries a category 1 National Comprehensive Cancer Network recommendation for consolidation therapy for stage III *EGFR*-mutant NSCLC.

With osimertinib being continued indefinitely until disease progression in LAURA, ctDNA-based risk stratification has become a key area of investigation. ctDNA positivity after chemoradiation has consistently been correlated with higher recurrence risk and worse outcomes, raising the

possibility that it could guide treatment de-escalation and optimize duration of therapy. A recent exploratory analysis of the LAURA cohort found that 57% of the 52 patients with evaluable MRD data were ctDNA-positive after chemoradiation. Among these MRD-positive patients, osimertinib led to ctDNA clearance in 84% (16 of 19), in comparison with 0% (0 of 10) of the placebo patients. MRD detection yielded a clinical sensitivity of 63% and a specificity of 86% for predicting progression events, and MRD positivity preceded radiographic progression by 5.1 months (95% CI, 3.8-8.5). Osimertinib improved outcomes in both MRD-positive and MRD-negative subgroups at baseline, suggesting its benefit regardless of detectable MRD at the start of consolidation therapy.[29]

In effect, the PACIFIC subgroup data and the LAURA studies separate consolidation strategy for unresectable stage III disease by molecular status, with durvalumab recommended for *EGFR*/*ALK*-negative disease and osimertinib for classic *EGFR* mutations. The POLESTAR study evaluated aumolertinib, another third-generation EGFR TKI, in locally advanced NSCLC. This study reported efficacy comparable with that in LAURA, reinforcing the benefit of EGFR inhibition in this setting (Table).[30] In practice, expediting comprehensive next-generation sequencing testing before or during chemoradiation is essential to guide selection of the proper consolidation therapy. As the field moves toward increased precision across every disease stage, this represents a clear example within thoracic oncology of a mutation-agnostic approach being replaced by targeted treatment in a curative-intent setting.

Clinical Considerations in Sequencing and Toxicity Management

Therapeutic Sequencing

In LAURA, consolidation osimertinib was started within 6 weeks after the completion of chemoradiation to allow the patient to recover from acute toxicities and to allow imaging to assess response. Given the high efficacy of targeted therapy for *EGFR*-mutant disease and the hypothesized benefit from earlier exposure, the administration of osimertinib before chemoradiation, rather than solely as consolidation therapy, is under active investigation in the phase 2 NEOLA trial. In this study, patients undergo treatment with 8 weeks of induction osimertinib, followed by 6 weeks of platinum-based chemoradiation (sequential or concurrent), followed by continued osimertinib.[31] Several small phase 2 studies of induction EGFR TKIs (gefitinib, afatinib [Gilotrif, Boehringer Ingelheim], and osimertinib) before chemoradiation and/or surgery in stage III *EGFR*-mutant NSCLC have reported encouraging survival outcomes, with 5-year OS rates up to 70% and objective response rates as high as 94% with induction osimertinib.[32-36] However, these studies are small and heterogeneous in design, and the optimal sequencing of induction EGFR TKI with chemoradiation remains undefined. Currently, outside a clinical trial, sequential treatment with osimertinib after the completion of concurrent chemoradiation per the LAURA trial remains the evidence-based approach.

The order of the immune checkpoint inhibitor (ICI) and the EGFR TKI carries important safety and efficacy implications. In a retrospective cohort of 41 patients treated with sequential programmed death 1/(PD-1) or programmed death ligand 1 (PD-L1) blockade followed by osimertinib, severe immune-related adverse events developed in 15%. The risk was highest among those who began osimertinib within 3 months of the last ICI dose (24%), and no severe events occurred when osimertinib predated ICI treatment.[37] This is particularly relevant in stage III disease, in which ICI exposure may precede the identification of an *EGFR* mutation. In a multicenter retrospective study of 136 patients with unresectable stage III *EGFR*-mutant NSCLC, consolidation durvalumab was not associated with improved real-world PFS over observation (24-month rate, 30% vs 27%), and pneumonitis or diarrhea occurred in 36% of the patients who started an EGFR TKI within 90 days of the last durvalumab dose.[38] In the metastatic setting, adding pembrolizumab or nivolumab (Opdivo, Bristol Myers Squibb) to platinum/pemetrexed after EGFR TKI failure did not improve survival in the phase 3 KEYNOTE-789 trial or the CheckMate 722 trial.[39,40] Hence, consolidation durvalumab and perioperative chemoimmunotherapy should not be started before *EGFR* status is known.

Sequencing decisions also arise when disease progresses to stage IV from an earlier stage after curative-intent osimertinib. Because pivotal frontline trials in the metastatic setting, including FLAURA, FLAURA2, and MARIPOSA, enrolled treatment-naive patients with advanced-stage disease, management at recurrence is extrapolated. Repeat tissue or plasma next-generation sequencing is recommended to identify resistance mechanisms on progression, especially if progression occurs during adjuvant or consolidation osimertinib. In the absence of a targetable alteration, amivantamab (Rybrevant, Janssen) plus platinum/pemetrexed was associated with improved PFS in comparison with chemotherapy alone after progression on osimertinib in the phase 3 MARIPOSA-2 trial (n=657; HR, 0.48).[41] The COMPEL trial (n=98) also supports the continuation of osimertinib with chemotherapy, which has demonstrated improved PFS (HR, 0.43) in comparison with chemotherapy alone in patients who have extracranial progression on frontline osimertinib monotherapy.[42] In contrast, recurrence after

the completion of 3 years of adjuvant osimertinib likely reflects osimertinib-sensitive disease, and rechallenge with osimertinib and local consolidative therapy for oligometastatic recurrence in this setting could be considered. Intensified frontline regimens for advanced/metastatic disease, such as osimertinib plus chemotherapy as in FLAURA2 (n=557; OS HR, 0.77) or amivantamab plus lazertinib (Lazcluze, Janssen) as in MARIPOSA (n=1074; OS HR, 0.75), are also reasonable, although their benefit after prior osimertinib was not evaluated in the original trials.[43,44]

Management of Toxicities

In LAURA, radiation pneumonitis was the most common adverse event (48% with osimertinib vs 38% with placebo); it was predominantly grade 1 to 2, with nearly all cases occurring within the first 18 weeks of treatment and no grade 4 or 5 events in either arm. Of the patients in whom pneumonitis developed and who had to have osimertinib withheld, 87% were able to resume treatment without recurrence of pneumonitis. Interstitial lung disease (ILD) occurred in 8% of the osimertinib arm vs 1% of the placebo arm; although mostly low-grade in nature, one grade 5 event was reported in the osimertinib group. Overall, grade 3 adverse events occurred more frequently with osimertinib than with placebo (35% vs 12%), and approximately half of the osimertinib group required at least one treatment interruption due to an adverse event.[7] The following toxicity management guidelines were used for the LAURA study and are thus appropriate for routine clinical practice: continue without modification for asymptomatic grade 1 events, interrupt therapy for symptomatic grade 2 events until resolution to no more than grade 1 before rechallenge, and discontinue permanently for symptomatic grade 3 or higher pneumonitis or ILD. Known side effects of diarrhea, paronychia, stomatitis, cytopenia, and rash occurred more frequently with osimertinib than with placebo, but they were mostly low-grade and manageable with supportive care or brief interruption. It is important to counsel patients about the risk of radiation pneumonitis and ILD before they start treatment, including their expected timing of onset within the first few months of treatment.

Future Directions and Conclusion

The management of locally advanced *EGFR*-mutant NSCLC has been transformed by the ADAURA, NeoADAURA, and LAURA trials, which collectively replaced a mutation-agnostic treatment framework with molecularly selected targeted therapy across both resectable and unresectable locally advanced disease settings. Several active areas of investigation aim to optimize these treatment indications and extend their benefit. Treatment duration remains unresolved in both settings, with ongoing trials (including TARGET) seeking to evaluate extending adjuvant osimertinib beyond the standard 3-year course for resected stage II-IIIA disease. On the basis of what is known, it is likely that a prolonged duration of treatment or continuous treatment may be required to maintain disease control for early-stage *EGFR*-mutant NSCLC. ctDNA-based monitoring is emerging as a tool to individualize this decision, with its ability to detect molecular relapse several months before radiographic progression, and it represents a promising avenue for identifying patients who need extended or intensified adjuvant therapy and, conversely, those who might safely de-escalate consolidation therapy following chemoradiation. The prospective validation of ctDNA-guided treatment algorithms, including exploratory analyses from ADAURA and LAURA, remains a priority.

Alternative sequencing strategies are also being explored in both the resectable and unresectable settings. Whether neoadjuvant osimertinib, with or without chemotherapy, offers a survival advantage over the standard adjuvant-only approach is still undetermined, as is whether sequencing osimertinib before chemoradiation improves outcomes in comparison with the sequential consolidation approach established by LAURA. Until these trials mature, adjuvant osimertinib after resection and consolidation osimertinib after chemoradiation remain the most evidence-based approaches.

Atypical *EGFR* mutations represent one of the most significant evidence gaps in this space. No prospective data exist for adjuvant, neoadjuvant, or consolidation targeted therapy in this population, and clinicians must extrapolate from metastatic data and limited real-world cohorts showing attenuated immunotherapy benefit in oncogene-driven disease. Structured real-world comparative studies—or ideally, dedicated prospective trials—comparing the outcomes of targeted therapy and durvalumab for this subgroup are needed to guide clinical management.

As biomarker-directed targeted therapy becomes standard across earlier stages of NSCLC, timely and comprehensive molecular testing is now a prerequisite for optimal treatment selection. Expediting next-generation sequencing during the initial diagnostic and staging workup, rather than after treatment has begun, is essential to selecting the optimal consolidation or perioperative strategy for those with locally advanced disease. As further studies evaluating alternative approaches mature, the treatment of locally advanced *EGFR*-mutant NSCLC is likely to continue evolving toward a more individualized model of curative-intent care.

References

1. Melosky B, Kambartel K, Häntschel M, et al. Worldwide prevalence of epidermal growth factor receptor mutations in non-small cell lung cancer: a meta-analysis. *Mol Diagn Ther*. 2022;26(1):7-18.
2. Chen P-M, Huang Y-H, Li C-Y. Lung cancer in never-smokers: risk factors, driver mutations, and therapeutic advances. *Diagnostics (Basel)*. 2026;16(2):245.
3. Ju J-S, Huang AC-C, Tung P-H, et al. Brain metastasis, EGFR mutation subtype and generation of EGFR-TKI jointly influence the treatment outcome of patient with EGFR-mutant NSCLC. *Sci Rep*. 2023;13(1):20323.
4. Soria J-C, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125.
5. Ramalingam SS, Vansteenkiste J, Planchard D, et al; FLAURA Investigators. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
6. Tsuboi M, Herbst RS, John T, et al; ADAURA Investigators. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med*. 2023;389(2):137-147.
7. Ramalingam SS, Kato T, Dong X, et al. Osimertinib (osi) after definitive chemoradiotherapy (CRT) in patients (pts) with unresectable stage (stg) III epidermal growth factor receptor-mutated (EGFRm) NSCLC: primary results of the phase 3 LAURA study [ASCO abstract LBA4]. *J Clin Oncol*. 2024;42(17)(suppl).
8. He J, Tsuboi M, Weder W, et al; NeoADAURA Investigators. Neoadjuvant osimertinib for resectable EGFR-mutated non-small cell lung cancer. *J Clin Oncol*. 2025;43(26):2875-2887.
9. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *J Clin Oncol*. 2022;40(12):1301-1311.
10. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.
11. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009;361(1):32-39.
12. Bradley C, Novoa N, Riva L, et al. Mediastinal staging of nonsmall cell lung cancer: what's new? *Breathe (Sheff)*. 2025;21(3):230191.
13. Kahya Y, Marım F, Ömeroğlu Şimşek G, et al. Breaking: the new 9th version TNM classification for lung cancer is now in use. *Thorac Res Pract*. 2026;27(1):47-56.
14. Kim H, Park S, Jung HA, et al. EGFR mutation-positive unresectable stage III non-squamous lung cancer is associated with a high incidence of brain metastasis. *Cancer Res Treat*. 2023;55(2):498-505.
15. Herbst RS, Wu Y-L, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non–small-cell lung cancer: updated results from the phase III randomized ADAURA trial. *J Clin Oncol*. 2023;41(10):1830-1840.
16. Soo RA, de Marinis F, Han J-Y, et al. TARGET: a phase II, open-label, single-arm study of 5-year adjuvant osimertinib in completely resected EGFR-mutated stage II to IIIB NSCLC post complete surgical resection. *Clin Lung Cancer*. 2024;25(1):80-84.
17. Herbst RS, John T, Grohé C, et al. Molecular residual disease analysis of adjuvant osimertinib in resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer. *Nat Med*. 2025;31(6):1958-1968.
18. Wang K, Ma J, Luo W, et al. Adjuvant osimertinib therapy guided by ctDNA-assessed MRD in resected EGFR-mutated stage IA-IIA non-small-cell lung cancer: a randomized clinical trial study protocol. *Am J Cancer Res*. 2024;14(11):5427-5433.
19. Dong S, Yan B, Liu S-Y, et al. Monitoring of circulating tumor DNA and indication of de-escalation adjuvant targeted therapy for EGFR-mutated NSCLC after complete resection. *JTO Clin Res Rep*. 2024;6(1):100758.
20. Wakelee H, Liberman M, Kato T, et al; KEYNOTE-671 Investigators. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. *N Engl J Med*. 2023;389(6):491-503.
21. Heymach JV, Harpole D, Mitsudomi T, et al; AEGEAN Investigators. Perioperative durvalumab for resectable non–small-cell lung cancer. *N Engl J Med*. 2023;389(18):1672-1684.
22. Cascone T, Awad MM, Spicer J, et al. Perioperative nivolumab (NIVO) vs placebo (PBO) in patients (pts) with resectable NSCLC: updated survival and biomarker analyses from CheckMate 77T [ASCO abstract LBA8010]. *J Clin Oncol*. 2025;43(17)(suppl).
23. Forde PM, Spicer J, Lu S, et al; CheckMate 816 Investigators. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973-1985.
24. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30(8):1321-1328.
25. John T, Grohe C, Goldman JW, et al. Molecular residual disease (MRD) analysis from the ADAURA trial of adjuvant (adj) osimertinib in patients (pts) with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC) [ASCO abstract 8005]. *J Clin Oncol*. 2024;42(17)(suppl).
26. Naidoo J, Antonia S, Wu Y-L, et al. Brief report: durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutant NSCLC: a post hoc subgroup analysis from PACIFIC. *J Thorac Oncol*. 2023;18(5):657-663.
27. Wu Y-L, Wu L, Bi N, et al. PACIFIC-5: a phase III clinical trial of consolidation durvalumab in patients with unresectable stage III NSCLC and no progression after concurrent or sequential chemoradiotherapy. *J Hematol Oncol*. 2025;18(1):111.
28. Ramalingam S, Ozguroglu M, Ahn M, et al. LBA4: Osimertinib (osi) after definitive chemoradiotherapy (CRT) in patients (pts) with unresectable (UR) stage III EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC): updated overall survival (OS) analysis from the LAURA study. *J Thorac Oncol*. 2025;20(3):S123-S124.
29. Aperribay EA, Robichaux J, Le V, et al. 1817MO Molecular residual disease (MRD) analysis from the LAURA study of osimertinib (osi) in unresectable (UR) stage III EGFR-mutated (EGFRm) NSCLC. *Ann Oncol*. 2025;36:S1052.
30. Yu J, Meng X, Ge H, et al. PL04.13 Aumolertinib maintenance after chemoradiotherapy in stage III non-small-cell lung cancer: interim results of the phase III study (POLESTAR). *J Thorac Oncol*. 2024;19(10):S6-S7.
31. Aredo JV, Peled N, Arriola E, et al. Osimertinib before and after chemoradiotherapy for unresectable stage III EGFR-mutated NSCLC: NEOLA trial protocol. *Future Oncol*. 2025;21(29):3731-3737.
32. Peled N, Roisman LC, Levison E, et al. Neoadjuvant osimertinib followed by sequential definitive radiation therapy and/or surgery in stage III epidermal growth factor receptor–mutant non-small cell lung cancer: an open-label, single-arm, phase 2 study. *Int J Radiat Oncol Biol Phys*. 2023;117(1):105-114.
33. Xing L, Wu G, Wang L, et al. Erlotinib versus etoposide/cisplatin with radiation therapy in unresectable stage III epidermal growth factor receptor mutation-positive non-small cell lung cancer: a multicenter, randomized, open-label, phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2021;109(5):1349-1358.
34. Chang AEB, Piper-Vallillo AJ, Mak RH, et al. The ASCENT trial: a phase 2 study of induction and consolidation afatinib and chemoradiation with or without surgery in stage III EGFR-mutant NSCLC. *Oncologist*. 2024;29(7):609-618.
35. Hotta K, Saeki S, Yamaguchi M, et al. Gefitinib induction followed by chemoradiotherapy in EGFR-mutant, locally advanced non-small-cell lung cancer: LOGIK0902/OLCSG0905 phase II study. *ESMO Open*. 2021;6(4):100191.
36. Akamatsu H, Murakami H, Harada H, et al. Gefitinib with concurrent thoracic radiotherapy in unresectable locally advanced NSCLC with EGFR mutation; West Japan Oncology Group 6911L. *J Thorac Oncol*. 2021;16(10):1745-1752.
37. Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol*. 2019;30(5):839-844.
38. Nassar AH, Kim SY, Aredo JV, et al. Consolidation osimertinib versus durvalumab versus observation after concurrent chemoradiation in unresectable EGFR-mutant NSCLC: a multicenter retrospective cohort study. *J Thorac Oncol*. 2024;19(6):928-940.
39. Yang JC-H, Lee DH, Lee J-S, et al. Phase III KEYNOTE-789 study of pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor–resistant, EGFR-mutant, metastatic nonsquamous non-small cell lung cancer. *J Clin Oncol*. 2024;42(34):4029-4039.
40. Mok T, Nakagawa K, Park K, et al. Nivolumab plus chemotherapy in epidermal growth factor receptor-mutated metastatic non-small-cell lung cancer after disease progression on epidermal growth factor receptor tyrosine kinase inhibitors: final results of CheckMate 722. *J Clin Oncol*. 2024;42(11):1252-1264.
41. Passaro A, Wang J, Wang Y, et al; MARIPOSA-2 Investigators. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol*. 2024;35(1):77-90.
42. Pasello G. COMPEL: osimertinib + platinum based chemotherapy in patients with EGFRm advanced NSCLC and progression on 1L osimertinib. *J Thorac Oncol*. 2025.
43. Felip E, Cho BC, Gutiérrez V, et al. Amivantamab plus lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. *Ann Oncol*. 2024;35(9):805-816.
44. Planchard D, Jänne PA, Kobayashi K, et al. First-line osimertinib + chemotherapy versus osimertinib monotherapy in EGFRm advanced NSCLC: FLAURA2 final overall survival [World Conference on Lung Cancer abstract PL02.06]. *J Thorac Oncol*. 2025;20:10(suppl 1).