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Neoadjuvant Targeted Therapy in Resectable NSCLC: Current and Future Perspectives

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Abstract

The standard of care (SoC) for medically operable patients with early-stage (stages I–IIIB) NSCLC is surgery combined with (neo)adjuvant systemic therapy for patients with stages II to IIIB disease and some stage IB or, rarely, chemoradiation (stage III disease with mediastinal lymph node metastases). Despite these treatments, metastatic recurrence is common and associated with poor survival, highlighting the need for systemic therapies that are more effective than the current SoC. After the success of targeted therapy (TT) in patients with advanced NSCLC harboring oncogenic drivers, these agents are being investigated for the perioperative (neoadjuvant and adjuvant) treatment of patients with early-stage NSCLC. Adjuvant osimertinib is the only TT approved for use in the early-stage setting, and there are no approved neoadjuvant TTs. We discuss the importance of comprehensive biomarker testing at diagnosis to identify individuals who may benefit from neoadjuvant targeted treatments and review emerging data from neoadjuvant TT

trials. We also address the potential challenges for establishing neoadjuvant TTs as SoC in the early-stage setting, including the identification and validation of early response markers to guide care and accelerate drug development, and discuss safety considerations in the perioperative setting. Initial data indicate that neoadjuvant TTs are effective and well tolerated in patients with *EGFR*- or *ALK*-positive early-stage NSCLC. Data from ongoing trials will determine whether neoadjuvant targeted agents will become a new SoC for individuals with oncogene-addicted resectable NSCLC.

Keywords

Early-stage NSCLC; Neoadjuvant treatment; Targeted therapy; Resectable NSCLC; NGS testing

Introduction

Approximately half of all patients with NSCLC present with early-stage disease,[1] and this figure will increase with the expansion of screening programs for high-risk populations. Surgery is the primary curative-intent treatment option for patients with resectable NSCLC (stages I–IIIB) and is recommended with neoadjuvant or adjuvant systemic therapy for stages II to IIIB disease and selected stage IB cases or, rarely, chemoradiation for stage III disease with mediastinal lymph node metastases.[2,3] Despite available treatments, disease recurrence is common in patients who have undergone resection and is associated with poor survival and socioeconomic burden.[4-7] A pooled analysis of five adjuvant chemotherapy trials in patients with resected NSCLC demonstrated a modest 5.4% improvement in overall survival (OS) at 5 years compared with surgery alone.[8] Similarly, in a meta-analysis of patients with resectable NSCLC, neoadjuvant chemotherapy improved 5-year OS by 5% compared with surgery alone.[9] Thus, there is a need for additional treatments that reduce disease recurrence, prolong survival, and increase cure rates in patients with early-stage NSCLC (eNSCLC). Recent advances in the eNSCLC setting include the approval of multiple adjuvant treatment options including the following: osimertinib for patients with resected NSCLC (stages IB–III) whose tumors harbor classic *EGFR* mutations[10]; atezolizumab after platinum-based chemotherapy for patients with resected NSCLC (stages II–III) whose tumors have programmed death ligand-1 (PD-L1) expression according to country-specific thresholds[11,12]; and pembrolizumab after optional platinum-based chemotherapy for patients with resected NSCLC (stage IB [T2a ≥ 4 cm], II, or IIIA; seventh edition of the TNM cancer staging system).[13] Ongoing studies may lead to the approval of additional adjuvant targeted therapies (TTs), including the ALINA trial investigating adjuvant alectinib for patients with resected *ALK*-positive NSCLC.[14] The neoadjuvant field is also rapidly evolving with the recent approval of neoadjuvant nivolumab in combination with platinum-doublet chemotherapy for the treatment of patients with resectable NSCLC.[15] Currently, there are no approved neoadjuvant TTs for resectable NSCLC.

For patients with advanced NSCLC (aNSCLC), it is standard of care (SoC) to perform comprehensive biomarker testing to assess PD-L1 status and identify the presence of oncogenic driver mutations (including various *EGFR* mutations, *ALK, RET, NTRK, ROS1, KRAS* G12C, *BRAF* V600E, *MET*ex14 skipping, *ERBB2*).[3] The recommended first-line

treatment for patients with oncogene-addicted aNSCLC is TT, except for patients with *KRAS* G12C mutation, *ERBB2* mutation, or *EGFR* exon 20 insertion mutation where TT is recommended as a second-line treatment.[3] Clinical evidence has shown that patients with advanced, *EGFR*-mutant, or *ALK*-positive NSCLC derive little or no benefit from cancer immunotherapy (CIT),[16-20] and there is no additional benefit from combining CIT with TT.[21] Importantly, both TT in combination with CIT,[21-25] and sequential treatment approaches are associated with increased toxicity in patients with advanced disease.[26,27] In the early-stage setting, it is unknown whether the efficacy of CIT is also reduced in patients with *EGFR* or *ALK* alterations; various ongoing perioperative trials have different criteria regarding whether patients with known *EGFR* or *ALK* alterations are permitted and whether genetic testing is required before enrollment.[28-32] Preliminary subgroup analyses from adjuvant CIT trials have demonstrated efficacy in a small group of patients with activating *EGFR* mutation[31,32]; however, these results should be interpreted with caution and considered in relation to the impressive OS benefits demonstrated with adjuvant osimertinib.[33]

In light of these efficacy and safety considerations and recent approvals in the early-stage setting that exclude tumors with *EGFR* and *ALK* mutations, it is important to test patients for oncogenic drivers and guide perioperative treatment decisions. We discuss the importance of biomarker testing to identify patients who may benefit from neoadjuvant targeted treatments and address the potential challenges for establishing perioperative TT as standard of care. The objective of this review is to provide a comprehensive summary from the existing literature and ongoing clinical trials to assess the feasibility, efficacy, and safety of neoadjuvant TT for patients with eNSCLC.

Materials and Methods

Table 1[34-45] was compiled based on known neoadjuvant clinical trials that have published results. Associated abstracts and journal articles were reviewed independently by the authors and the results of these studies were summarized narratively. Given the limited number of neoadjuvant targeted trials from which results have already been published, a systematic search was not appropriate. To identify all ongoing clinical trials of neoadjuvant TT in patients with eNSCLC, we performed a systematic search of clinicaltrials.gov using the search terms “neoadjuvant” AND “lung cancer.” Trials with terminated and completed statuses were excluded. Studies were then categorized by study treatment; clinical trials investigating only CIT and only chemotherapy or radiotherapy or other treatments were excluded. Resulting trials were further categorized by monotherapy (Table 2[46-48]) and TT plus chemotherapy (Table 3[49]). Studies were screened a final time for eligibility, and studies deemed unsuitable were excluded; full details on systematic search and excluded studies are described in Figure 1. The systematic search was first completed on June 14, 2022, and was conducted by two independent reviewers. An additional search was conducted on October 19, 2022, to identify any additional studies that had been registered since the first search.

Rationale for Neoadjuvant Therapy in eNSCLC

Neoadjuvant treatment of resectable NSCLC has multiple potential benefits, including the following: neoadjuvant therapy is better tolerated than adjuvant therapy[50]; earlier systemic therapy may control micrometastatic disease; and patients may require less extensive surgical resection (lung-sparing surgery) and have improved complete (R0) resection rates.[30] Neoadjuvant treatment allows for surrogate end point evaluation of survival estimates (OS, disease-free survival [DFS]) such as clinical, pathologic, or correlative biomarker assessment of treatment response. A preoperative treatment approach also facilitates evaluation of in vivo treatment efficacy and may guide adjuvant treatment. Another anticipated benefit is improved compliance of neoadjuvant versus adjuvant therapy.[51] One common argument against neoadjuvant treatment is that despite a short duration of treatment (three to four cycles), it may prolong the time from diagnosis to curative-intent surgery, during which period patients may experience disease progression. However, evidence from neoadjuvant CIT trials provides confidence that this does not impact patient outcomes.[30]

Rationale for Biomarker Testing at Time of Diagnosis and Necessity to Collect Sufficient Biopsy Sample at Time of Diagnosis

As the utility of TTs is explored in eNSCLC, biomarker testing has become critical to guide treatment selection and optimize clinical outcomes. After recent approvals of perioperative systemic therapies for patients with eNSCLC, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend to test patients with stages IB to IIIA and stage IIIB (T3,N2) NSCLC for *EGFR* mutations, *ALK* rearrangements, and PD-L1 status with U.S. Food and Drug Administration–approved tests to inform (neo)adjuvant treatment decisions.[3] In metastatic NSCLC, the NCCN Guidelines recommend molecular testing before initiation of first-line treatment if clinically feasible.[3] Despite this, a real-world analysis reported that only 46% of patients with metastatic NSCLC were assessed for the five biomarkers that are recommended for testing.[52] This highlights that the barriers to molecular testing in the advanced disease setting may also limit testing in the early-stage setting, as the treatment landscape is expected to evolve and require testing beyond *EGFR* mutations, *ALK* rearrangements, and PD-L1 status.

Several considerations exist regarding the integration of preoperative biomarker testing at diagnosis as part of routine clinical practice and as a guide to neoadjuvant treatment decisions. Minimizing turnaround times for obtaining test results is important to ensure that the correct systemic treatment is initiated as soon as possible. Collection of an adequate biopsy sample is imperative for biomarker testing (PD-L1 expression and oncogenic driver mutations) and low yields can make testing unfeasible.[53] In the neoadjuvant setting, treatment may result in pathologic complete response (pCR) and biomarker testing using resected tissue specimens may not be feasible, emphasizing the importance of collecting sufficient biopsy tissue at the time of diagnosis.

Comprehensive genomic profiling using next-generation sequencing (NGS) is increasingly accessible and widely used on tissue and plasma samples to inform treatment decisions for aNSCLC. However, the routine adoption of NGS in eNSCLC will be dependent on the

availability of approved TTs in this setting, the need to exclude patients with oncogenic drivers before treatment with CIT, and the availability of clinical studies investigating TTs in early-stage disease.[10-12,15] Blood-based biomarker testing for oncogenic drivers in the preoperative setting has the potential to overcome the inherent limitations of tissue sampling: it is convenient and minimally invasive, with faster turnaround times.[54] Indeed, the BFAST study (NCT03178552) reported clinical benefit for patients with aNSCLC who received TTs based solely on the results of blood-based NGS.[55,56] Nevertheless, as disease burden is lower in eNSCLC versus aNSCLC, plasma samples may not contain sufficient circulating tumor DNA (ctDNA) for analysis. The detection of genetic alterations in blood samples from patients with eNSCLC is highly dependent on the assay used, and more sensitive technologies are required to avoid false-negative results. Furthermore, blood-based NGS for eNSCLC is not routinely conducted outside of clinical trials at specialized cancer centers.[57,58] Finally, a limitation of approaches using liquid biopsy only, without tissue analysis, is the inability to assess PD-L1 expression.

The LEADER trial (NCT04712877) is a diagnostic study with the primary objective of determining the proportion of patients with early-stage (IA2–III) NSCLC whose tumors harbor oncogenic drivers (Fig. 2).[59] The screening approach taken in this trial will be considered feasible if oncogenic drivers are identified in more than 35% of enrolled patients. Assessment of tumor mutational burden is a secondary end point. Approximately 1000 patients will be recruited to undergo NGS (FoundationOne) using tissue and plasma samples. Results will be shared with treating physicians to guide therapy or permit referral to neoadjuvant clinical trials and could be an ideal framework for assessing actionable biomarkers in the neoadjuvant setting. Plasma samples will be collected pre- and post-neoadjuvant treatment and post-surgery to enable correlative research. Evidence from CIT trials, CheckMate 816 and IMpower010, demonstrates that not all patients respond to neoadjuvant or adjuvant CIT and there is a need to test patients for PD-L1 expression and oncogenic driver mutations, and additional prognostic factors such as co-mutations, to identify those most likely to benefit from CIT or TT.[30,32,60] This emphasizes the need for comprehensive molecular testing with NGS to guide treatment options in the resectable NSCLC setting.

Data From Clinical Trials Investigating Neoadjuvant TT

Given the success of TTs in the advanced disease setting and impressive survival benefits found with adjuvant osimertinib,[33] neoadjuvant TTs are being increasingly investigated for treatment of oncogene-addicted resectable lung cancer. Most neoadjuvant TT trials focus on EGFR and ALK tyrosine kinase inhibitors (TKIs) as these are the most established TTs in this landscape (Table 1). It is important to note that patients with *EGFR*-mutant and *ALK*-rearranged NSCLC have inherent differences in tumor biology and the respective TKIs, of which there are multiple generations, are associated with distinct mechanisms of resistance.[61] As such, EGFR and ALK TKIs and their associated targets are uniquely distinguished.

To date, the EGFR TKIs gefitinib, erlotinib, and osimertinib have been explored in the neoadjuvant setting (Table 1). An open-label, single-arm phase 2 study (NCT00188617)

reported that gefitinib was a generally safe and feasible regimen in unselected patients with stage I NSCLC, with an objective response rate (ORR) of 11%; the strongest predictor of response was the presence of an *EGFR* mutation.[34] Another single-arm phase 2 study (NCT01833572) demonstrated that neoadjuvant gefitinib was a viable treatment option for patients with *EGFR*-mutant, stages II to IIIA NSCLC; ORR was 54.5%, major pathologic response (MPR) was 24.2%, and median DFS was 33.5 months.[36] In a retrospective study of 10 patients who underwent salvage surgery for borderline resectable NSCLC after neoadjuvant gefitinib, median progression-free survival (PFS) was 14 months and OS was more than or equal to 36 months.[35] Erlotinib was also reported to be an effective neoadjuvant therapy in a study of Chinese patients with stage IIIA NSCLC (NCT01217619): erlotinib resulted in a higher ORR (67% versus 19%), pathologic response rate (67% versus 38%), and OS (51.0 versus 20.9 mo) than cisplatin-based doublet chemotherapy.[37] The EMERGING-CTONG 1103 study was a randomized phase 2 trial comparing neoadjuvant chemotherapy with erlotinib in patients with stages IIIA to N2 *EGFR*-mutant NSCLC. The primary end point of ORR was not met (54.1% erlotinib versus 34.3% chemotherapy), but an improvement in median PFS was observed (21.5 versus 11.4 mo, respectively),[39] though this did not translate into an OS benefit.[40] Preliminary results from ongoing clinical trials of osimertinib suggest that this third-generation EGFR TKI is a generally safe and may be an effective neoadjuvant treatment. In a small phase 2 study of 27 patients with stages I to IIIA *EGFR*-mutant NSCLC (NCT03433469), neoadjuvant osimertinib-induced pathologic responses (MPR: 15%) and downstaging of disease before surgery; however, the study did not meet its primary end point.[41] Final results from the NEOS study in 38 patients with resectable stages II to IIIB *EGFR*-mutant NSCLC revealed an ORR of 71.1%, R0 surgical resection rate of 93.8%, and MPR rate of 10.7%.[43]

In patients with resectable, locally advanced, *ALK*-positive NSCLC, Zhang et al.[44] reported that neoadjuvant crizotinib was feasible and well tolerated (Table 1). Overall, 10 of 11 patients had a partial response and one had stable disease. Ten of the patients received an R0 resection and two achieved a pCR. In a retrospective study of patients with stage III *ALK*-positive NSCLC who received surgery after induction therapy of alectinib (n = 16) or crizotinib (n = 13), alectinib was found to have superior efficacy compared with crizotinib (pCR: 37.5% versus 15.4%).[45] Multiple ongoing clinical trials are investigating the efficacy and safety of newer-generation ALK inhibitors in the neoadjuvant setting (Table 2).

The investigation of neoadjuvant TTs is still early, and the optimal duration of treatment is not yet known. In the ADAURA study, at time of relapse after adjuvant osimertinib for at least 3 years, 41% of patients were treated with osimertinib; suggesting that some patients may need more than 3 years of adjuvant osimertinib.[33] Treatment duration in the neoadjuvant setting is constrained by the need to undergo resection limiting the number of TT cycles and challenges associated with assessing efficacy. Additional data from ongoing clinical trials will be essential for determining the optimal duration of neoadjuvant TT.

Compared with neoadjuvant CIT trials,[30,62-66] preliminary data indicate that MPR or pCR rates may be lower in neoadjuvant TT trials, whereas other efficacy end points (R0 resection rate, downstaging, event-free survival [EFS], DFS, PFS) are comparable (Table 1). This may be due to inherent differences in mechanism of action; the antitumor effects of

chemotherapy are driven by cytotoxic effects and CIT by enhanced immunosurveillance, whereas TTs are cytostatic which may impact the necessary duration of TT in the perioperative setting. Until there is better understanding of pathologic response after neoadjuvant TT, surgical resection should still be conducted in the early-stage setting and survival assessment remains an essential end point.

Ongoing Trials of Neoadjuvant TT

Most ongoing neoadjuvant (or perioperative) trials are investigating TT for *EGFR*-mutant NSCLC, although trials exploring targeted agents against other oncogenic drivers are also recruiting patients (Table 2). Clinical trial design of the non-*EGFR* trials is similar between these studies, with neoadjuvant treatment time proposed to be two cycles (6–8 wk); most trials also include adjuvant therapy (1–3 y). These trials have a variety of primary end points, including pathologic response (MPR, complete response), ORR, DFS, EFS, and PFS. NAUTIKA1 is an ongoing, phase 2 umbrella trial investigating the efficacy and safety of multiple therapies as (neo)adjuvant treatments in patients with resectable NSCLC with specific biomarkers (Fig. 3[67]).[48] This clinical trial depicts a potential future management paradigm for directing patients with tumors that harbor oncogenic drivers to perioperative TT, or patients without to CIT.

Given that TTs are generally well tolerated, multiple ongoing neoadjuvant trials are assessing the combination of TT with chemotherapy (Table 3). Most are investigating EGFR inhibitors, but one phase 2 study (NCT05118854) is examining the efficacy of neoadjuvant sotorasib, a KRAS G12C inhibitor, in combination with chemotherapy for patients with resectable (stages IIA–IIIB) *KRAS* G12C-mutant NSCLC. Results from these trials are highly anticipated and will provide further information on whether neoadjuvant TTs (alone or in combination with chemotherapy) are feasible and effective treatment strategies for patients with NSCLC. In future perioperative TT trials, it will be interesting to explore the interactions of *KRAS* G12C with co-mutations and to investigate the efficacy and safety of combinations of TTs in this setting.

End Points Used in Neoadjuvant TT Trials

A range of clinical end points can be used to assess the efficacy of neoadjuvant treatments for patients with eNSCLC. OS is the principal end point in oncology clinical trials, but time from enrollment to publication of OS data from neoadjuvant trials takes 10 to 13 years, suggesting the need for robust surrogate markers to accelerate development and approval of new therapies in the early-stage setting.[68,69] Surrogate markers of drug response are commonly used in other areas of oncology and have been demonstrated to correlate with OS. A meta-analysis of neoadjuvant therapy for early-stage breast cancer showed a strong association with pCR and long-term survival (EFS and OS).[70] Similarly, in the hallmark neoadjuvant chemotherapy trials for resectable lung cancer, a robust correlation between DFS and OS was reported.[68] In the CheckMate 816 trial of neoadjuvant nivolumab plus chemotherapy for patients with resectable NSCLC, EFS seemed to be longer in patients who achieved a pCR compared with those who did not (median EFS: not reached versus 26.6 mo).[30] Additionally, a recent review assessing response evaluations in neoadjuvant

NSCLC trials identified MPR as a better predictor of long-term OS compared with ORR.[71] Interestingly, digital assessment of pathologic response has demonstrated utility in ongoing neoadjuvant CIT trials and may also be useful for assessment of similar endpoints in TT trials.[72]

Available results from trials of adjuvant TT for resectable NSCLC suggest that surrogate markers (pCR, MPR, EFS, and DFS) may correlate with survival; however, these studies are not designed to assess OS and more data are required to determine a clear association. The single-arm phase 2 SELECT trial investigating adjuvant erlotinib in patients with *EGFR*-mutant eNSCLC demonstrated high DFS and OS rates: 2-year and 5-year DFS, 88% and 56%, respectively; 5-year OS, 86%.[73] The phase 2 EVAN trial assessed adjuvant erlotinib compared with chemotherapy in patients with *EGFR*-mutant stage III NSCLC and found that erlotinib improved survival outcomes compared with chemotherapy, and DFS correlated with OS: 5-year DFS and OS rates with erlotinib were 48.2% and 84.8%, respectively.[74] Results from the randomized, phase 3 IMPACT study revealed an improved 2-year DFS rate with adjuvant gefitinib compared with chemotherapy, but this advantage was lost at 5 years and did not translate into OS benefit.[75] Similarly, a significant improvement in DFS did not translate into OS benefit in the final analysis of the phase 3 ADJUVANT-CTONG1104 trial of gefitinib versus chemotherapy for patients with resected stages I to IIIA *EGFR*-mutant NSCLC.[76] The phase 3 ADAURA study demonstrated significant improvements in DFS with adjuvant osimertinib compared with placebo in patients with stages II to IIIA NSCLC: 3-year DFS rate was 84% versus 34%, respectively.[77] Osimertinib also showed an improvement in DFS in the overall population (stages IB–IIIA), alongside decreased locoregional recurrence, distant recurrence, and central nervous system (CNS) recurrence.[77,78] Despite immature OS at time of approval, the U.S. Food and Drug Administration approved adjuvant osimertinib for patients with resected NSCLC on the basis of DFS data from this study.[10] Updated data from this trial showed that osimertinib demonstrated a statistically significant and clinically meaningful improvement in OS.[33] This depicts the first TT to show translation of a DFS benefit into improved OS in this setting and validating DFS as a surrogate marker for OS.

In the neoadjuvant setting, it is not yet clear whether surrogate markers will correlate with survival in trials of TT for resectable NSCLC. A phase 2 study of neoadjuvant gefitinib demonstrated that MPR correlated with DFS but not OS.[36] A small study of erlotinib compared with chemotherapy showed marginal improvements in ORR and MPR; these did not correlate with an improvement in DFS or PFS, but there was a trend towards improved OS with erlotinib.[37] Results from the EMERGING-CTONG 1103 study of erlotinib versus chemotherapy demonstrated that ORR correlated with PFS, but there was no relationship between pathologic response and PFS, and the PFS advantage did not translate into an OS benefit.[39,40] However, it is important to note that these studies were not powered for OS analysis.

Preliminary findings from neoadjuvant CIT trials have suggested the value of ctDNA assessment as an early surrogate marker for response and survival, however, more data are needed. The LCMC3 study showed that ctDNA reductions following neoadjuvant treatment with atezolizumab correlated with pathologic response and reduced radiographic

tumor size.[79] An exploratory analysis of the phase 2 NADIM study revealed that pre-treatment ctDNA levels were associated with long-term survival more accurately than radiologic assessments in patients with resectable stage IIIA NSCLC who received neoadjuvant nivolumab and chemotherapy.[80] In the CheckMate 816 study, EFS was longer in patients with ctDNA clearance compared with those without in both the nivolumab plus chemotherapy and chemotherapy alone groups.[30] However, there are currently no data demonstrating the utility of ctDNA as a surrogate marker for response or survival to neoadjuvant TTs. ctDNA could also be a useful tool to help guide the duration and de-escalation of (neo)adjuvant therapy. The evidence supporting the feasibility of this approach is limited and dependent on assay sensitivity, for which technology is rapidly evolving. One ongoing study investigating this is the APPROACH study (NCT04841811), which will assess the effectiveness and safety of using ctDNA to guide the duration of (neo) adjuvant almonertinib, an EGFR TKI, in patients with unresectable stage III NSCLC (Table 2).

Safety Considerations of Neoadjuvant TTs

TTs have unique safety profiles, and it is important to consider whether any toxicities may occur during neoadjuvant treatment which may delay or prevent curative-intent surgery. For example, the RET inhibitors pralsetinib and selpercatinib are associated with impaired wound healing, which could impact surgical recovery.[81,82] Rare cases of severe respiratory adverse events (AEs) (including pneumonitis and interstitial lung disease) have been reported with some ALK, EGFR, and MET inhibitors, which could limit the use of these therapies before surgical resection.[83,84] Other reported rare toxicities that may impact surgery include the following: cardiotoxicity (osimertinib),[85,86] bradycardia (alectinib and crizotinib),[87,88] thrombocytopenia (osimertinib),[89] fever (dabrafenib plus trametinib),[90] hepatotoxicity (sotorasib),[91] and CNS toxicity (lorlatinib).[92] Preliminary results from the *ALK*-positive cohort of the NAUTIKA1 study demonstrated that neoadjuvant alectinib was well tolerated in patients with resectable NSCLC, and to date, all patients have undergone surgery without delays or major complications.[67] In addition to surgery, the safety of TTs in relation to radiotherapy must also be considered. The BRIGHTSTAR study showed that local consolidative therapy (surgery or radiation or a combination of both) administered after treatment with brigatinib was feasible and safe in patients with *ALK*-rearranged, aNSCLC; however, additional data in the early-stage setting are required.[93]

When selecting treatments in the curative setting, it is important to consider the sequence in which treatments may be given, as the sequential administration of CIT followed by TT in the advanced disease setting has been associated with increased toxicity.[16,26,27] An increased risk of hepatotoxicity has been identified in patients treated with CIT (pembrolizumab, nivolumab, or atezolizumab) followed by crizotinib.[26] CIT (nivolumab, pembrolizumab, or ipilimumab + nivolumab) followed by osimertinib has also been associated with severe immune-related AEs[29]; in a phase 2 clinical trial of pembrolizumab followed by osimertinib, a treatment-related death occurred that was attributed to pneumonitis.[16] These data reveal the importance of testing for oncogenic drivers in eNSCLC to ensure that patients receive appropriate first-line neoadjuvant treatments and avoid toxicity with subsequent therapies.

Overall, neoadjuvant targeted treatments are expected to be well tolerated and compatible with curative-intent surgery. The safety and tolerability profile of osimertinib is consistent in the advanced and early-stage (adjuvant) setting, providing confidence that new safety concerns related to neoadjuvant osimertinib treatment are unlikely.[78,94,95] Furthermore, preliminary data from the NAUTIKA1 study indicated no new safety concerns for neoadjuvant treatment with alectinib.[67] Ongoing clinical trials will provide further information on the safety and tolerability of a broader range of TTs for the neoadjuvant treatment of eNSCLC.

Conclusions

Surgery plus (neo)adjuvant chemotherapy or rarely neoadjuvant chemoradiation for patients with early-stage, resectable NSCLC is associated with unacceptable rates of recurrence and poor survival. Given the survival benefits of TT in the advanced disease setting, these agents are now being investigated in patients with eNSCLC. Results from ongoing clinical trials indicate that neoadjuvant TTs are likely to be effective and improve outcomes in patients with *EGFR*- and *ALK*-positive eNSCLC. Additional data from ongoing trials are highly anticipated and will indicate whether neoadjuvant targeted treatments are feasible for patients with eNSCLC with different oncogenic driver mutations.

As the field moves towards using TTs for eNSCLC, it is essential that molecular testing and biomarker screening at diagnosis are integrated into clinical practice to optimize treatment options and clinical outcomes. The need for unified and robust surrogate markers that may expedite the approval of TTs remains a challenge. Building on the demonstrated efficacy of TTs in the aNSCLC setting and promising preliminary clinical trial results, neoadjuvant TT is expected to improve outcomes of patients with eNSCLC with oncogenic drivers and transform the early-stage treatment landscape.

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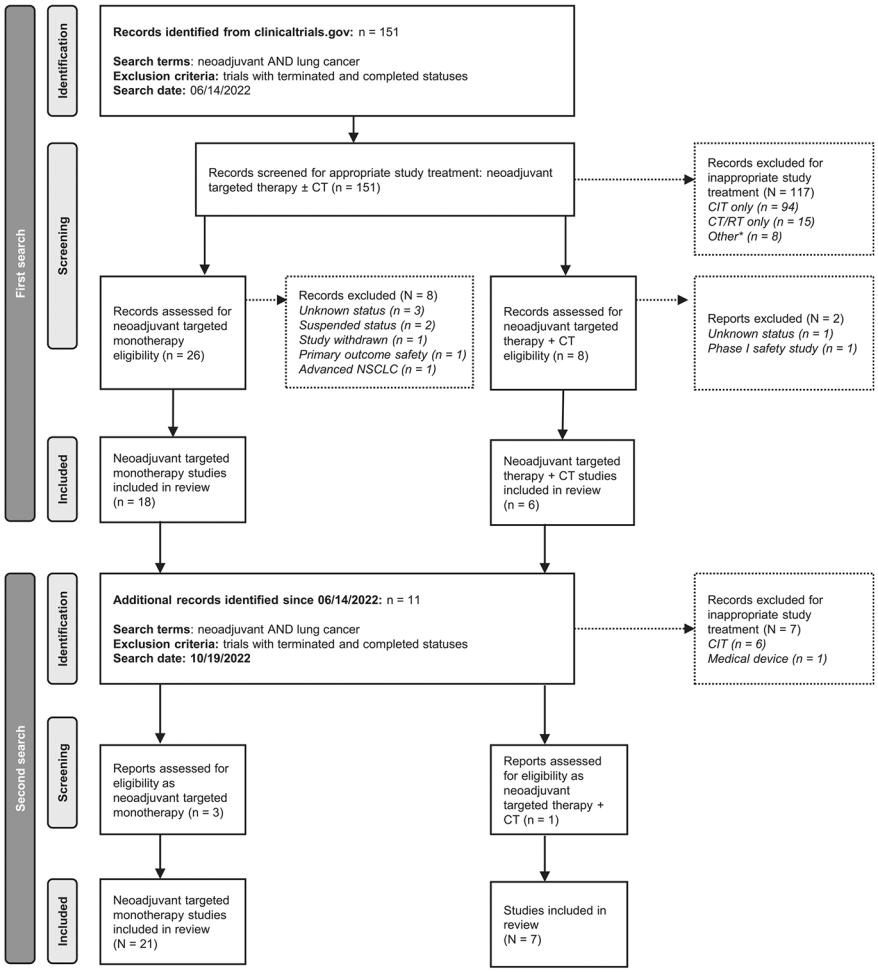

Figure 1.

PRISMA flow diagram for systematic search of ClinicalTrials.gov. Other reasons for exclusion include diagnostic clinical trial (n = 3), alternative treatments (vitamin A and leucoselect phytosome, n = 1 each), bifunctional fusion protein (bintrafusp alfa, n = 1), proteasome inhibitor (bortezomib, n = 1), unknown drug (n = 1). CIT, cancer immunotherapy; CT, chemotherapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RT, radiotherapy.

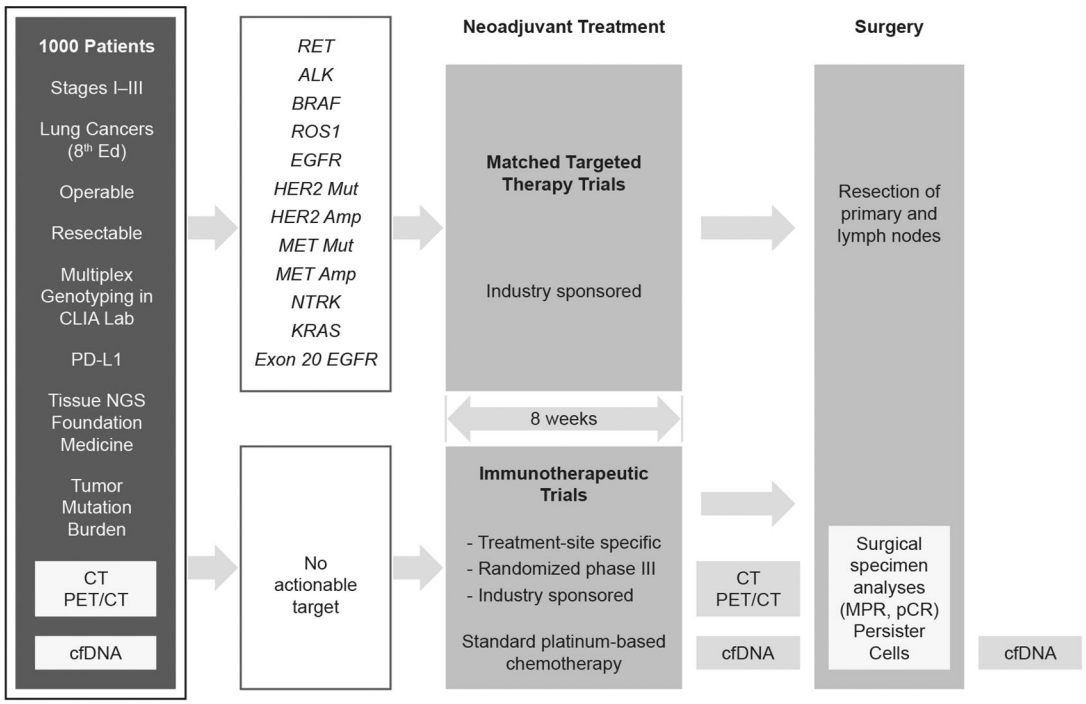

Figure 2.

LCMC leader study schema. Figure from: Sepesi et al.[59] [presented at ASCO 2022]. amp, amplification; cfDNA, cell-free DNA; CLIA, Clinical Laboratory Improvement Amendments; CT, computed tomography; LCMC, Lung Cancer Mutation Consortium; *MET*, c-MET; MPR, major pathologic response; mut, mutation; NGS, next-generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; PET, positron emission tomography.

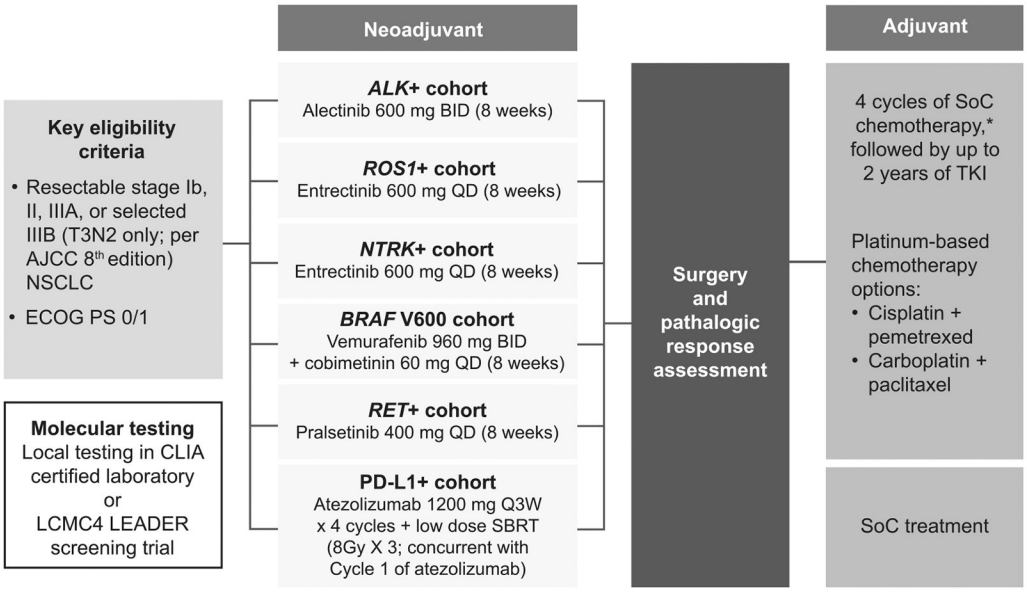

Figure 3.

NAUTIKA1 study schema. Figure adapted from: Lee et al.[67] [data presented at WCLC 2022]. *Unless contraindicated or patient refusal. AJCC, American Joint Committee on Cancer; BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; ECOG PS, Eastern Cooperative Oncology Group performance status; LCMC, Lung Cancer Mutation Consortium; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; QD, once daily; SBRT, stereotactic body radiotherapy; SoC, standard of care; TKI, tyrosine kinase inhibitor.

Table 1.

Key Efficacy and Safety Results From Neoadjuvant TT Trials in Patients With Resectable NSCLC

									Key Efficacy Results						
Ref	**Drug**	**Target**	**Neoadjuvant Therapy**	**Ph**	**Total Patients**	**TKI Group**	**Adjuvant Therapy**	**Stage**	**ORR, %**	**PFS/EFS/DFS, mo**	**OS, mo**	**Downstaging**	**Pathologic Response, %**	**R0 rxn Rate, %**	**Key Safety Results**
[34]	Gefitinib	*EGFR*	28 (range: 27-30 d)	II	36	36	SoC	I[a]	11.0	-	-	TNM: 43.0%	-	-	8.3% (n = 3) ≥Grade 3 toxicities during therapy 11.1% (n = 4) ≥Grade 3 postoperative toxicities
[35]	Gefitinib	*EGFR*	3-5 mo	-	10	10	Gefitinib (6 mo)	IIIA[b]	-	PFS: 14.0	36.0	TNM: 100.0% Nodal: 70.0%	-	-	One patient died 7 d postoperatively due to respiratory failure
[36]	Gefitinib	*EGFR*	42 d	II	35	33	SoC	II-IIIA[b]	54.5	DFS: 33.5	-	-	MPR: 24.2 pCR: 12.1	87.9	No patients reported ≥Grade 3 AEs
[37,38]	Erlotinib vs. CT	*EGFR*	4-7 wk	II	31	15	SoC	IIIA[b]	67.0 vs. 19.0	PFS: 12.1 vs. 11.0 DFS: 10.2 vs. 8.0	51.0 vs. 20.9	-	MPR: 67.0 vs. 38.0 pCR: 0.0 vs. 12.5	-	5.3% (n = 1) ≥Grade 3 AEs 10.5% (n = 2) ≥Grade 3 TRAEs 10.5% (n = 2) SAEs
[39,40]	Erlotinib vs. CT	*EGFR*	42 d	II	72	37	Erlotinib until PD or toxicity	IIIA-N2[a]	-	PFS: 21.5 vs. 11.4 (HR 0.39; $p < 0.001$)	42.2 vs. 36.9 (HR 0.83; $p = 0.5$)	-	MPR: 9.7 vs. 0 pCR: 0.0 vs. 0	-	0% vs. 29.4% (n = 10) ≥Grade 3 preoperative TRAEs
[41]	Osimertinib	*EGFR*	1-2 cycles (28-56 d)	II	27	27	-	I-IIIA[b]	48.0	DFS: 32	-	Nodal: 44%	MPR: 15.0 pCR: 0	-	Significant AEs occurred in 3 patients Perioperative complications occurred in 38% (9/24) of patients
[42,43]	Osimertinib	*EGFR*	6 wk	II	40	38	SoC	IIA-IIIBN2[c]	71.0	-	-	TNM: 53.3% Nodal: 42.9%	MPR: 10.7 pCR: 3.6	93.8	7.5% (n = 3) ≥Grade 3 TRAEs
[44]	Crizotinib	*ALK*	28-120 (median: 30 d)	-	11	11	SoC	IIIA-N2[a]	90.9	-	-	-	pCR: 18.2	91.0	9.1% (n = 1) ≥Grade 3 TRAE

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									Key Efficacy Results						
Ref	**Drug**	**Target**	**Neoadjuvant Therapy**	**Ph**	**Total Patients**	**TKI Group**	**Adjuvant Therapy**	**Stage**	**ORR, %**	**PFS/EFS/DFS, mo**	**OS, mo**	**Downstaging**	**Pathologic Response, %**	**R0 rxn Rate, %**	**Key Safety Results**
[45]	Crizotinib vs. alectinib	*ALK*	Median: 95 d	-	29	13 vs. 16	Crizotinib or alectinib	IIIA-IIIB[a]	-	PFS: 17.9 vs. NR (p = 0.002)	62.6 vs. NR (p = 0.226)	-	MPR: 30.8 vs. 56.3 pCR: 15.4 vs. 37.5	100.0	-

[a] Version of the cancer staging system not specified.

[b] According to the seventh edition of the AJCC cancer staging system.

[c] According to the eighth edition of the AJCC cancer staging system.

AE, adverse event; AJCC, American Joint Committee on Cancer; CT, chemotherapy; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; MPR, major pathologic response; NR, not reached; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD, progressive disease; PFS, progression-free survival; Ph, phase; rxn, resection; R0, no residual tumor after resection; SAE, serious adverse event; SoC, standard of care; TKI, tyrosine kinase inhibitor; TT, targeted therapy; TRAE, treatment-related adverse event.

Table 2.

Summary of Ongoing Neoadjuvant TT Trials in Patients With Resectable NSCLC

NCT Number	Study Title	Status	Location	First Posted	Target Enrollment	Driver Mutation	Targeted Agent	Neoadjuvant Therapy	Adjuvant Therapy	Phase	Stage	Primary End Point
NCT01470716	Neoadjuvant erlotinib for operable stage II or IIIA NSCLC with *EGFR* mutations	Active, not recruiting	South Korea	2011	26	*EGFR*	Erlotinib	8 wk	None	II	II-IIIA[a]	PFS
NCT04201756	Neoadjuvant afatinib therapy for potentially resectable stage III *EGFR* mutation-positive lung adenocarcinoma	Recruiting	People's Republic of China	2019	47	*EGFR*	Afatinib	8-16 wk	1 y	II	III[b]	ORR
NCT02824952	Neoadjuvant trial with AZD9291 in *EGFR-mutant*-positive stage IIIA/B NSCLC	Recruiting	Israel	2016	40	*EGFR*	Osimertinib	6 or 12 wk	None	II	IIIA/B[a]	ORR
NCT03433469	Osimertinib in treating participants with stages I-IIIA *EGFR*-mutant NSCLC before surgery	Active, not recruiting	USA	2018	27	*EGFR*	Osimertinib	1-2 cycles (28-56 d)	None	II	I-IIIA[a]	MPR
NCT04816838	A window of opportunity study for investigating DTP to neoadjuvant osimertinib in resectable NSCLC harboring *EGFR* mutations	Recruiting	South Korea	2021	25	*EGFR*	Osimertinib	8 wk	3 y	-	I-IIIA[a]	ORR
NCT02820116	The role of icotinib in the perioperative treatment of patients with IIIA-IIIB NSCLC with *EGFR* mutation	Recruiting	People's Republic of China	2016	67	*EGFR*	Icotinib	8 wk	None	II	IIIA-IIIB[a]	R0 rxn
NCT03349203	Icotinib as neoadjuvant and adjuvant therapy in *EGFR*-mutant stage IIIB or oligometastatic NSCLC	Recruiting	People's Republic of China	2017	60	*EGFR*	Icotinib	8 wk	2 y	II	IIIB[a]	ORR
NCT03749213	Icotinib as neoadjuvant therapy in *EGFR*-mutant stages IIIA-N2 NSCLC	Recruiting	People's Republic of China	2018	36	*EGFR*	Icotinib	8 wk	2 y	II	IIIA-N2[a]	ORR
NCT04685070	Neoadjuvant almonertinib therapy for resectable stage III *EGFR* mutation-positive lung adenocarcinoma	Recruiting	People's Republic of China	2020	56	*EGFR*	Almonertinib	8-16 wk (4 wk per cycle; 2-4 cycles)	1 y (48 wk)	II	III[b]	ORR

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NCT Number	Study Title	Status	Location	First Posted	Target Enrollment	Driver Mutation	Targeted Agent	Neoadjuvant Therapy	Adjuvant Therapy	Phase	Stage	Primary End Point
NCT04455594	ANSWER: Almonertinib vs. erlotinib or chemotherapy for neoadjuvant treatment of stages IIIA-N2 *EGFR*-mutated NSCLC	Not yet recruiting	People's Republic of China	2020	168	*EGFR*	Almonertinib vs. erlotinib	3 cycles	None	II	IIIA-N2[b]	ORR
NCT04841811	APPROACH: ctDNA guiding treatment after almonertinib induction therapy for *EGFR*-mutant NSCLC in the MDT diagnostic model	Not yet recruiting	People's Republic of China	2021	156	*EGFR*	Almonertinib	8 wk	ctDNA guided, max: 2 y[c]	II	III[b]	ORR EFS
NCT05469022	Neoadjuvant lazertinib therapy in *EGFR* mutation-positive lung adenocarcinoma detected by BALF liquid biopsy	Recruiting	South Korea	2022	40	*EGFR*	Lazertinib	9 wk	3 y	II	I-IIIB[a]	ORR
NCT05503667	Neoadjuvant furmonertinib + bevacizumab or furmonertinib monotherapy for resectable and potentially resectable stages III-IVA *EGFR* mutation-positive lung adenocarcinoma	Recruiting	People's Republic of China	2022	96	*EGFR*	Furmonertinib	16 wk	None	II	III-IVA[b]	ORR
NCT05015010	ALNEO: Alectinib in neoadjuvant treatment of stage III NSCLC	Recruiting	Italy	2021	33	*ALK*	Alectinib	8 wk	96 wk	II	III[b]	MPR
NCT05380024	A study of ensartinib as neoadjuvant therapy for patients with *ALK*-positive resectable NSCLC	Recruiting	People's Republic of China	2022	10	*ALK*	Ensartinib	8 wk	None	II	IIA-IIIB[a]	MPR
NCT05361564	A window of opportunity study for investigating DTP to preoperative brigatinib in resectable NSCLC harboring *ALK* fusions	Not yet recruiting	South Korea	2022	12	*ALK*	Brigatinib	4-10 wk	None	II	I-IIIA[b]	To identify molecular mechanism of DTP
NCT04926831	GEOMETRY-N: Phase II study of neoadjuvant and adjuvant capmatinib in NSCLC[46]	Recruiting	USA	2021	38	*MET*[d]	Capmatinib	8 wk	3 y	II	IB-IIIA and selected IIIB[a]	MPR

NCT Number	Study Title	Status	Location	First Posted	Target Enrollment	Driver Mutation	Targeted Agent	Neoadjuvant Therapy	Adjuvant Therapy	Phase	Stage	Primary End Point
NCT03157128	LIBRETTO-001: A study of selpercatinib (LOXO-292) in participants with advanced solid tumors, *RET* fusion-positive solid tumors, and medullary thyroid cancer[47]	Recruiting	International	2017	19	*RET*	Selpercatinib	2 cycles	3 y	I/II	IB-IIIA[b]	MPR
NCT05400577	Sotorasib in *KRAS*G12C-mutated, resectable, stage IB-IIIA NSCLC	Recruiting	USA	2022	25	*KRAS* G12C	Sotorasib	4 wk	None	II	IB-IIIA[b]	MPR
NCT05472623	Neo-Kan: Neoadjuvant *KRAS* G12C directed therapy with adagrasib with or without nivolumab	Not yet recruiting	USA	2022	42	*KRAS* G12C	Adagrasib	6 wk	None	II	IB-IIIA[a]	pCR
NCT04302025	NAUTIKA1: A study of alectinib, entrectinib, vemurafenib plus cobimetinib, or pralsetinib in patients with resectable stages II-III NSCLC with *ALK, ROS1, NTRK, BRAF* V600, or *RET* molecular alterations[48]	Recruiting	USA	2020	80	*ALK* *ROS1* *NTRK* *BRAF* V600 *RET* *KRAS* G12C	Alectinib, entrectinib, vemurafenib, cobimetinib, pralsetinib, divarasib	8 wk	2 y	II	IB-III[b]	MPR

Note: Search was performed on ClinicalTrials.gov on October 19, 2022, with the following search terms: “neoadjuvant” AND “lung cancer.” Trials with the status completed or terminated were excluded.

[a]Version of the cancer staging system not specified.

[b]According to the eighth edition of the AJCC cancer staging system.

[c]Length of time patients receive adjuvant almonertinib is guided by ctDNA dynamic monitoring: ctDNA is tested every 3 months, and if positive, patients continue to receive almonertinib; if negative, patients stop almonertinib until ctDNA positivity returns and almonertinib treatment is initiated again.

[d]*MET* exon 14 skipping mutation or high *MET* amplification.

AJCC, American Joint Committee on Cancer; BALF, bronchoalveolar lavage fluid; ctDNA, circulating tumor DNA; DTP, drug tolerant persister; EFS, event-free survival; MDT, multidisciplinary team; MPR, major pathologic response; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival; rxn, resection; R0, no residual tumor after resection; TT, targeted therapy; USA, United States of America.

Table 3.

Summary of Ongoing Neoadjuvant TT Plus Chemotherapy Trials in Patients With Resectable NSCLC

NCT Number	Study Title	Status	Location	First Posted	Target Enrollment	Driver Mutation	Targeted Agent	Neoadjuvant Therapy	Adjuvant Therapy	Phase	Stage	Primary End Point
NCT04470076	NEOAFA: Neoadjuvant afatinib combination with chemotherapy for stages IIA-IIIB NSCLC with *EGFR*-activating mutation	Not yet recruiting	People's Republic of China	2020	30	*EGFR*	Afatinib + CT	3 cycles	Afatinib for ≥2 y	II	IIA-IIB[a]	MPR, ORR
NCT04351555	NeoADAURA: A study of osimertinib with or without chemotherapy vs. chemotherapy alone as neoadjuvant therapy for patients with *EGFR-mutant*-positive resectable NSCLC[49]	Recruiting	International	2020	328	*EGFR*	Osimertinib vs. osimertinib + CT	3 cycles	-	III	II-IIIB[a]	MPR
NCT05011487	NOCE01: Neoadjuvant osimertinib + chemotherapy for *EGFR*-mutant stage III NSCLC	Recruiting	People's Republic of China	2021	30	*EGFR*	Osimertinib + CT	Osimertinib for 60 d + CT for 2 cycles	-	II	III[a]	Complete lymph node clearance rate
NCT05104788	NeoIpower: A study of icotinib with chemotherapy as neoadjuvant therapy for patients with *EGFR* mutant-positive resectable NSCLC	Recruiting	People's Republic of China	2021	27	*EGFR*	Icotinib + CT	2 cycles	-	II	II-IIIB[b]	MPR
NCT05132985	Neoadjuvant icotinib with chemotherapy for *EGFR*-mutated resectable lung adenocarcinoma	Not yet recruiting	People's Republic of China	2021	45	*EGFR*	Icotinib + CT	3-wk cycles until stable disease or partial response	2 cycles of icotinib + chemotherapy and continued icotinib for ≥2 y	II	II-IIIB[a]	MPR
NCT05430802	FORESEE: Neoadjuvant furmonertinib and cisplatin/pemetrexed in *EGFR*-mutated stages IIIA-IIIB resectable NSCLC	Recruiting	People's Republic of China	2022	40	*EGFR*	Furmonertinib + CT	Furmonertinib for 9 wk + CT for 3 cycles	-	II	IIIA-IIIB[b]	ORR

NCT Number	Study Title	Status	Location	First Posted	Target Enrollment	Driver Mutation	Targeted Agent	Neoadjuvant Therapy	Adjuvant Therapy	Phase	Stage	Primary End Point
NCT05118854	A phase 2 study of neoadjuvant sotorasib in combination with cisplatin or carboplatin and pemetrexed for surgically resectable stages IIA-IIIB nonsquamous NSCLC with a *KRAS p.G12C* mutation	Recruiting	USA	2021	27	*KRAS*	Sotorasib + CT	4 cycles	-	II	IIA-IIIB[a]	MPR

Note: Search was performed on ClinicalTrials.gov on October 19, 2022, with the following search terms: “neoadjuvant” AND “lung cancer.” Trials with the status completed or terminated were excluded.

[a]According to the eighth edition of the AJCC cancer staging system.

[b]Version of the cancer staging system not specified.

AJCC, American Joint Committee on Cancer; CT, chemotherapy, MPR, major pathologic response; ORR, objective response rate; TT, targeted therapy; USA, United States of America.

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