Review Article

What do we know about the role of neoadjuvant targeted therapy in early-stage *EGFR*-mutant and *ALK*-fused non-small cell lung cancer?—a narrative review of the current literature

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Background and Objective: The standard first-line treatment for patients with advanced non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) fusions is targeted therapy using tyrosine kinase inhibitors (TKIs). However, data are still lacking on the use of TKIs as a neoadjuvant or induction approach. Therefore, this narrative review aims to summarize the current knowledge on resectable *EGFR*-mutant and *ALK*-fused NSCLC regarding available perioperative treatment regimens and off-label neoadjuvant use of targeted therapy.

Methods: The relevant literature was identified by using PubMed and ClinicalTrials.gov (last search phase June 2024) and was restricted to English language. Peer-reviewed manuscripts but also conference abstracts that did not undergo peer-review were included.

Key Content and Findings: Patients with *EGFR*-mutations and *ALK*-fusions have typically been excluded from available phase III perioperative immunotherapy trials due to lower efficacy and higher toxicity of immunotherapy in those patients. In the adjuvant setting, recent evidence from the phase III ALINA and ADAURA trials demonstrated efficacy and safety of targeted therapy in resected *ALK*-fused and *EGFR*-mutant NSCLC. However, to date there is no approval for the use of TKIs as neoadjuvant or induction therapy in those patients. We have therefore identified a number of case series and phase II trials using targeted therapy in resectable *EGFR*-mutant and *ALK*-fused NSCLC.

Conclusions: Current evidence suggests that targeted therapies might be effective in patients with resectable *EGFR*-mutant and *ALK*-positive NSCLC, but ongoing trials will need to provide further evidence on the safety and efficacy of perioperative TKI therapy.

Keywords: Non-small cell lung cancer (NSCLC); resectable; anaplastic lymphoma kinase (*ALK*); epidermal growth factor receptor (*EGFR*); targeted therapy

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Introduction

Rationale and background

Non-small cell lung cancer (NSCLC) is a tumour that often recurs, even after complete resection and either neoadjuvant or adjuvant chemotherapy. As a result, it remains the leading cause of cancer-related mortality worldwide (1). To reduce the risk of recurrence and to improve long-term survival in early-stage NSCLC, many studies have investigated neoadjuvant, adjuvant and perioperative approaches including chemotherapy, immunotherapy and targeted therapies.

For years, adjuvant or neoadjuvant platinum-based chemotherapy was the only approved treatment option for resectable NSCLC (2). In the immune-checkpoint-inhibitor (ICI) era, phase III trials such as IMpower010 and KEYNOTE-091 demonstrated a survival benefit of adding adjuvant immunotherapy after platinum-based chemotherapy in early-stage disease (3,4). More recently, phase III trials such as CheckMate816 (5), KEYNOTE-671 (6), CheckMate77T (7) and AEGEAN (8) also demonstrated the efficacy and survival benefit of neoadjuvant and/or perioperative chemoimmunotherapy regimens in resectable NSCLC. Thus, the therapeutic landscape for early-stage resectable NSCLC has become much more diverse.

However, there is a paucity of such data for early-stage tumours harbouring actionable genetic alterations (AGAs) in the genes for epidermal growth factor receptor (*EGFR*), v-Raf murine sarcoma viral oncogene homolog B (*BRAF*), anaplastic lymphoma kinase (*ALK*), tyrosine protein kinase ROS proto-oncogene (*ROS*) or RET proto-oncogene (*RET*). In advanced tumours harbouring driver mutations, first-line targeted therapy is the current standard of care and is superior to standard chemotherapy in terms of survival and quality of life (9). Among these driver mutations, *EGFR*-mutations are the most common in NSCLC and are found in approximately 16% of lung adenocarcinomas (9). Second most common alterations (approximately 4%) are fusions of the *ALK* gene with other genomic partners, such as the echinoderm microtubule-associated protein-like 4 (*EML4*) gene, resulting in the *EML4-ALK* oncogene and subsequent aberrant ALK kinase activity (9). *EGFR*-mutant and *ALK*-fused tumours can be specifically inhibited with tyrosine kinase inhibitors (TKIs) such as third-generation EGFR TKI osimertinib, second-generation ALK TKIs alectinib and brigatinib or the third-generation ALK TKI lorlatinib, respectively (10-13). Efficacy data for alectinib with a 5-year overall survival (OS) of 62.5% in advanced-stage NSCLC is promising even regarding the application of TKI in earlier tumour stages (14). Apart from adjuvant treatment with EGFR TKI osimertinib, which is approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for adjuvant therapy after resection in *EGFR*-mutated NSCLC based on the results of the ADAURA trial (15), recently published data from the phase III ALINA trial (16) led to the approval of alectinib as adjuvant treatment after tumour resection in *ALK*-fused NSCLC by both the FDA and the EMA. However, so far there is only little evidence for a neoadjuvant or perioperative treatment approach in *EGFR*-mutated and *ALK*-fused NSCLC. Although there are a few case reports and ongoing trials, there is still a lack of sufficient and reliable data. Moreover, it remains unclear whether (neo-) adjuvant TKI therapy alone is sufficient to eliminate residual tumour cells, or whether additional chemotherapy is required.

Objectives

In this narrative review, we aim to summarize the landscape of perioperative treatment regimens and their relevance for resectable NSCLC harbouring *EGFR*-mutations and *ALK*-fusions. We will continue to review the current evidence for neoadjuvant targeted therapy, focusing on pathological treatment effects, survival outcomes and safety data. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-359/rc).

Methods

The authors conducted an electronic literature search to identify the relevant literature that was published in PubMed and ClinicalTrials.gov (last search phase June 2024) (*Table 1*). The search was restricted to English language. Apart from peer-reviewed manuscripts, also conference

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Table 1 Search strategy summary

Items	Specification
Date of search	June 2024
Databases and other sources searched	PubMed, ClinicalTrials.gov
Search terms used	((NSCLC) OR (lung cancer)) AND ((perioperative) OR (adjuvant) OR (neoadjuvant)) AND ((ALK) OR (EGFR))
Timeframe	2008 to 2024
Inclusion criteria	All study types written in English. We included peer-reviewed manuscripts but also conference abstracts that have not yet been published following peer review
Selection process	Study selection was conducted by M.K. and G.E.

NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

abstracts have been included in this review, even though they have not yet been published following peer review. The titles and abstracts of the search results were screened and irrelevant publications were excluded by authors' choice. Only the relevant manuscripts were further examined for their full text to extract the relevant information. However, as this is meant to be a narrative review, we did not perform a systematic literature search and the included literature is based on authors' choice. The literature selected for this manuscript covers a period from 2008 to 2024.

Case report

In 09/2021, a 70-year-old female non-smoker presented at the University Hospital Muenster (Germany) with a lung lesion in the right upper lobe that was incidentally detected on an external cardiac magnetic resonance imaging (MRI) scan. The MRI was performed to evaluate for progression of underlying coronary artery disease after percutaneous coronary intervention in 07/2016. At the time of presentation, the patient was in good physical condition [Eastern Cooperative Oncology Group (ECOG) 1] and did not suffer from relevant symptoms. She had worked as an occupational health physician in a hospital until 2017. Her medical history included coronary artery disease, pulmonary tuberculosis in 1975 (treated), cerebral ischaemia and a history of hepatitis B. Her cardiovascular risk was increased by elevation of lipoprotein (a), dyslipoproteinemia, arterial hypertension and obesity (body mass index 29.6 kg/m^2).

Imaging by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET), computed tomography (CT) and MRI of the brain revealed a pulmonary tumour in the right upper lobe (*Figure 1*) with suspected infiltration of the visceral pleura and ipsilateral lymphogenic metastases (right hilum, mediastinal level 4R, infracarinal level 7), but no evidence of contralateral or distant organ/brain metastases.

A biopsy was then taken using endobronchial ultrasound, transbronchial needle aspiration and cryobiopsy. Pathological examination of the tissue revealed a thyroid transcription factor 1 (TTF1)-positive lung adenocarcinoma (*Figure 2A*,*2B*) with intermediate programmed cell death ligand 1 (PD-L1) expression (tumour proportion score 30%, combined positivity score 40%) as determined by immunohistochemistry. Fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) by RNA sequencing revealed an *EML4-ALK* fusion variant 1 (exon 13/exon 20) (*Figure 2C*). Neither FISH analysis, nor NGS revealed other genetic alterations (including *ROS*, *RET*, *MET*, *EGFR*, *BRAF* and *KRAS* genes).

In summary, we diagnosed an advanced staged *ALK*-fused NSCLC [Union for International Cancer Control (UICC) 8th edition stage IIIA; cT1b cN2 cM0]. The tumour was initially regarded as resectable via lobectomy and radical lymphadenectomy. Due to the multi-level lymphonodular advanced tumour stage we decided to perform neoadjuvant treatment with ALK inhibition prior to surgery, similar to current neoadjuvant trials in resectable NSCLC. ALK inhibition was initiated with the second-generation TKI brigatinib (180 mg/day). This approach was in accordance with current EMA approval of brigatinib as first-line treatment in advanced *ALK*-fused NSCLC. Treatment was well-tolerated by the patient without evidence of side effects. Response was assessed by PET/CT after 2 months showing a radiologic stable disease but metabolic partial remission of the primary tumour (*Figure 2*). After 2 more months of ALK inhibition, a further PET/CT showed

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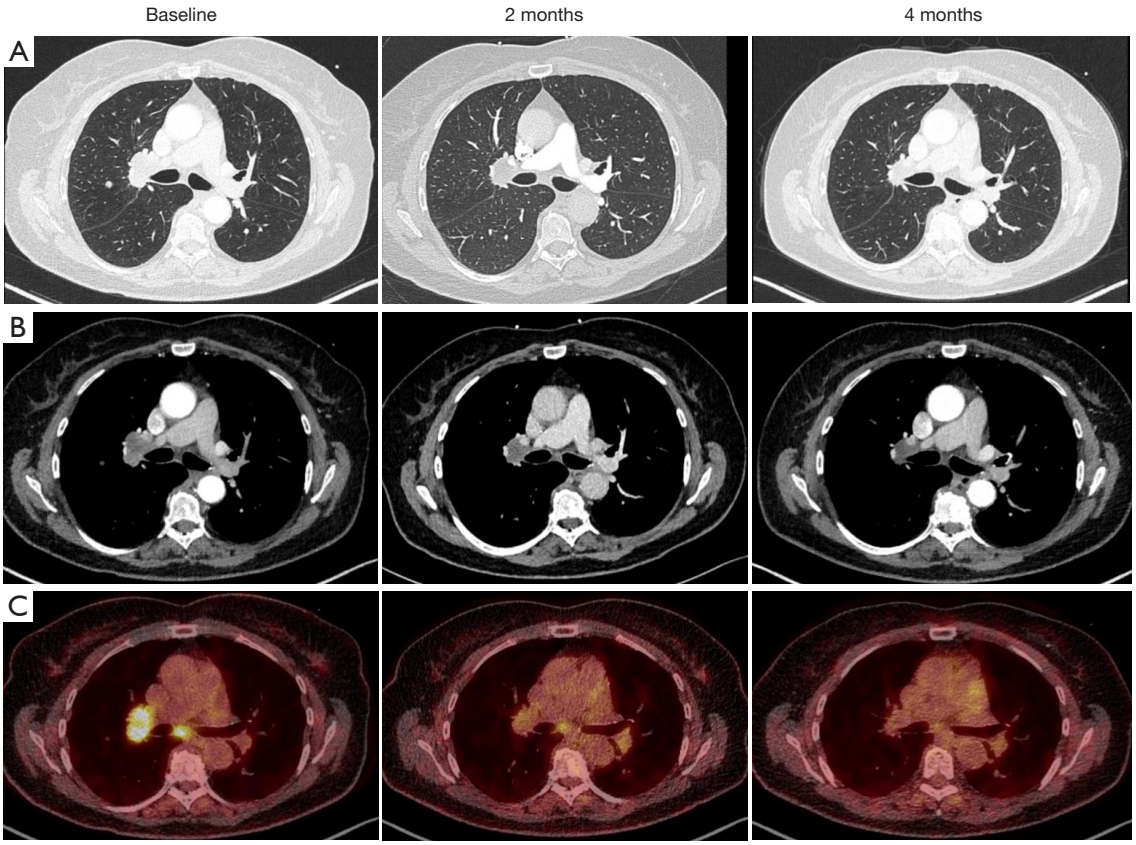

Figure 1 CT and PET/CT scan at baseline and after 2 and 4 months of neoadjuvant brigatinib. (A) Axial CT images, lung window. (B) Axial CT images, chest window. (C) Axial fused PET/CT images. CT, computed tomography; PET, positron emission tomography.

a complete metabolic response of the morphologically identical tumour mass (*Figure 1*; ycT1b ycN2 ycM0). The patient was therefore assessed for subsequent tumour resection in our thoracic surgery department. In 02/2022, a right upper lobe lobectomy combined with a radical lymphadenectomy was performed. TKI therapy was stopped perioperatively to limit side effects on surgical morbidity.

Post-treatment pathological examination confirmed a pathological complete response (pCR) of the primary tumour to neoadjuvant brigatinib (*Figure 1D*). Immunohistochemical staining revealed a highly regressive adenocarcinoma in one hilar lymph node without evidence of vital tumour cells. After neoadjuvant treatment and histopathological examination, the tumour was downstaged to IIA (UICC 8th edition). Following the discussion in our molecular tumour board, adjuvant platinum-based chemotherapy was recommended, followed by continuation of brigatinib due to a high risk of relapse. However, the patient refused chemotherapy and only started adjuvant brigatinib. Based on the patient's decision brigatinib was stopped in 12/2022. To date (03/2024), remission monitoring has shown durable complete remission of the tumour (*Figure 3*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

To reduce the risk of disease recurrence in early-stage NSCLC several different perioperative treatment strategies have recently been investigated. Here we will discuss the

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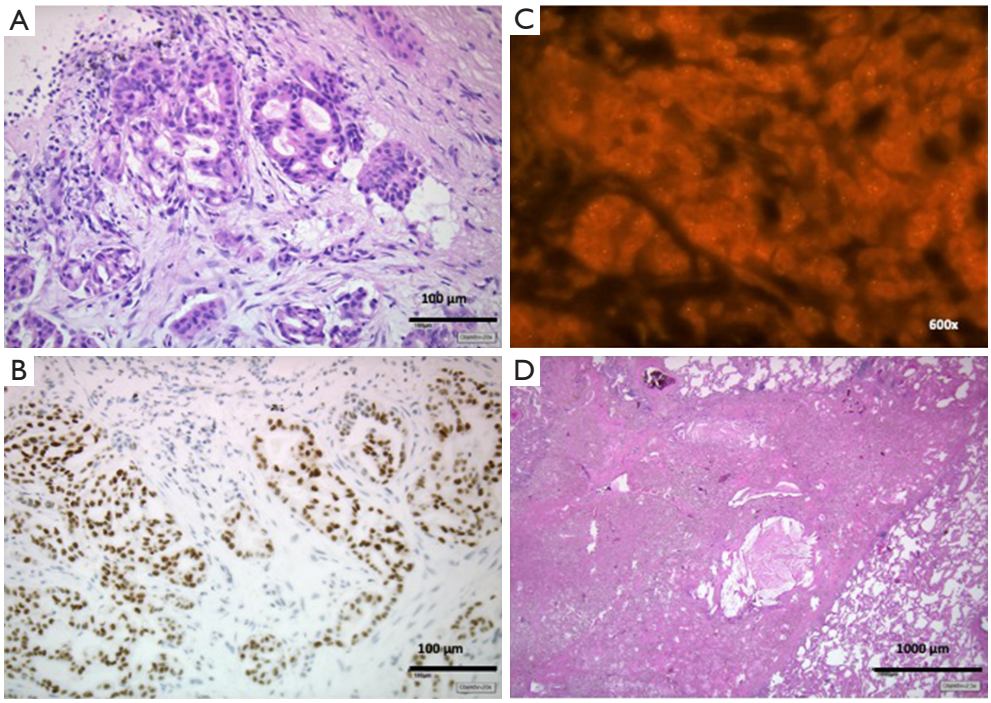

Figure 2 Histopathological tissue analysis from endobronchial cryobiopsy. Histopathological analysis of the primary tumour in the right upper lobe from endobronchial cryobiopsy showing a lung adenocarcinoma (A, hematoxylin and eosin staining) which was found positive for TTF1 (B, TTF1 staining). FISH analysis detected an *ALK*-fusion (C, ZytoLight® SPEC ALK/EML4 TriCheckTM Probe, 600× magnification), which was later confirmed via RNA-sequencing. After 4 months of neoadjuvant ALK inhibition the patient subsequently received R0 tumour resection via lobectomy and post-treatment pathological analysis documented a complete pathological tumour regression (D, hematoxylin and eosin staining). TTF1, thyroid transcription factor 1; FISH, fluorescence in situ hybridization; ALK, anaplastic lymphoma kinase.

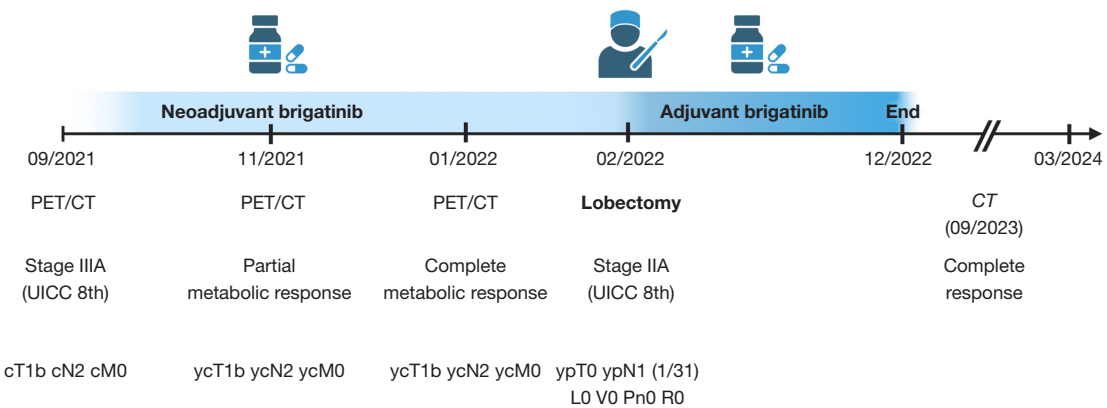

Figure 3 Treatment timeline of the patient in this case report receiving perioperative ALK inhibition. Remission status was evaluated via PET/CT after 2 and 4 months. Adjuvant brigatinib was stopped in 12/2022 based on the patient's decision (image created in BioRender. Kemper M, 2024. BioRender.com/l12h184). CT, computed tomography; PET, positron emission tomography; ALK, anaplastic lymphoma kinase; UICC, Union for International Cancer Control.

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most recent and current evidence.

Adjuvant and perioperative immunotherapy in non-oncogenic NSCLC

In patients with stage II–III NSCLC, adjuvant and neoadjuvant platinum-based chemotherapy after R0 tumour resection has been shown to improve OS by approximately 5% (2,17,18). Although this benefit is small, it has long been the only approved additional treatment option in this patient population. In 2021 and 2023, additional data from the IMpower010 trial demonstrated a significant benefit in disease-free survival (DFS) and OS for atezolizumab compared to best supportive care after adjuvant chemotherapy in resected stage II–IIIA NSCLC (3,19); this regimen is currently approved by the EMA for patients at high risk of relapse whose tumours are *EGFR/ALK* wild-type and have a PD-L1 expression (tumour cells score) ≥50% and by the FDA for tumours that have a PD-L1 expression (tumour cells score) ≥1%, respectively. Similarly, the interim analysis of the phase III KEYNOTE-091 trial in 2022 showed improved DFS for pembrolizumab after adjuvant chemotherapy in resected stage IB–IIIA NSCLC regardless of PD-L1 status (4). Thus, pembrolizumab is approved by FDA and EMA for the adjuvant treatment of NSCLC patients who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Similar to adjuvant strategies, neoadjuvant chemotherapy can improve survival and reduce the risk of disease recurrence in early-stage NSCLC (18). Neoadjuvant and/or perioperative regimens may also be the best choice for stage IIIA–N2 NSCLC in terms of OS (20). As these regimens aim to reduce primary tumour volume, this has the potential not only to reduce the invasiveness of tumour resection, but also to control the response to neoadjuvant chemo-immunotherapy according to pathological remission status. In the phase III CheckMate816 trial, three cycles of nivolumab in combination with platinum-based chemotherapy resulted in a significantly longer median event-free survival (EFS) [31.6 versus 20.8 months; hazard ratio (HR) =0.63, 97.38% confidence interval (CI): 0.43–0.91] and achieved higher pCR rates (24.0% versus 2.2%) compared to chemotherapy alone in stage IB–IIIA resectable NSCLC (5). As a result, the CheckMate816 protocol was the first neoadjuvant immunotherapy regimen approved by the EMA for patients with resectable NSCLC and PD-L1 expression ≥1%. KEYNOTE-671 was another phase III study that evaluated four cycles of perioperative pembrolizumab versus placebo plus cisplatin-based chemotherapy followed by surgery and adjuvant pembrolizumab for up to 13 cycles versus placebo in patients with stage II–IIIB (N2) resectable NSCLC. The addition of perioperative pembrolizumab significantly improved EFS, major pathological response (MPR) and pCR (6), leading to approval by both the FDA and EMA. Other recently published phase III trials further support the efficacy of perioperative nivolumab [CheckMate77T (7)] or durvalumab [AEGEAN (8)] regarding pathological outcome (pCR and MPR rates) and EFS in early-stage resectable NSCLC. The ongoing NeoCOAST trial (NCT03794544) is evaluating the potential of neoadjuvant durvalumab alone or in combination with novel agents in resectable NSCLC (21). In summary, these studies confirm the efficacy and safety of neoadjuvant/perioperative chemo-immunotherapy in early-stage NSCLC.

Adjuvant therapy in EGFR-mutant and ALK-fused NSCLC

In contrast to these promising data on (neo-)adjuvant and perioperative chemo-immunotherapy in non-oncogenic NSCLC, there are few such data in early-stage oncogenic NSCLC, as immunotherapy is known to be less effective and associated with a higher risk of toxicities in *EGFR*-mutant or *ALK*-fused NSCLC (22-27). Both the IMpower010 and the KEYNOTE-091 trials included patients with known *EGFR*-mutations and *ALK*-fusions, but neither trial required initial testing, so the exact number of patients in these subgroups is unknown. On the one hand, for the small number of patients with known *EGFR*-mutation or *ALK*-fusion in Impower010, there was no survival benefit for adjuvant atezolizumab (3,19). On the other hand, in the KEYNOTE-091 trial there was a significant benefit for adjuvant pembrolizumab in patients harbouring an *EGFR*-mutation (HR =0.44; 95% CI: 0.23–0.84) (4). These conflicting data reflect the so far unknown relevance of adjuvant immunotherapy in oncogenic NSCLC and must be interpreted with caution due to small patient numbers.

Regarding the use of adjuvant targeted therapy, results from early phase II studies suggested beneficial effects of adjuvant EGFR inhibition in resected *EGFR*-mutant NSCLC. In the SELECT trial, 100 patients with resected stage IA to IIIA *EGFR*-mutant NSCLC and 2 years of adjuvant erlotinib (after adjuvant chemotherapy with or without radiotherapy) had an improved 2-year DFS

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compared to historic genotype-matched controls (88% versus 76%), while no changes in OS were observed (28). In a Chinese trial, 2 years of adjuvant erlotinib as compared to four cycles of chemotherapy prolonged 2-year DFS (81.4% versus 44.6%) in patients with stage IIIA *EGFR*-positive NSCLC, but mature OS data is still missing (29). Data from the phase III CTONG1104 trial further supported the evidence for adjuvant targeted therapy in *EGFR*-mutant NSCLC. Here, adjuvant gefitinib for 24 months resulted in a significantly longer median DFS compared to four cycles of adjuvant chemotherapy (28.7 versus 18 months; HR =0.60; 95% CI: 0.42–0.87), but with no difference in OS (30,31). In contrast, data from the Japanese phase III IMPACT trial could not confirm this beneficial effect of adjuvant gefitinib on DFS (32). Although these trials demonstrate the efficacy of first-generation EGFR TKIs as adjuvant treatment in *EGFR*-positive NSCLC, their application is limited due to development of resistance mutations, that might explain the missing translation to OS benefits in these trials. Therefore, the development of osimertinib, a third-generation EGFR TKI that covers a wide range of resistance mutations, has shed new light on the role of adjuvant targeted therapy in resected *EGFR*-mutant NSCLC. Subsequently, the randomized controlled phase III ADAURA trial demonstrated the efficacy and safety of 3 years of adjuvant osimertinib in resected stage IB–IIIA NSCLC harbouring common *EGFR* mutations (15). The updated 2023 data showed a significant OS benefit for adjuvant osimertinib versus placebo (88% versus 78%; HR =0.49; 95.03% CI: 0.34–0.70) (33). Therefore, adjuvant osimertinib is the current standard of care (34) for resected early-stage *EGFR*-mutant NSCLC. Of note, 60% of patients in both the osimertinib and in the placebo arms received adjuvant platinum-based chemotherapy prior to initiation of adjuvant osimertinib or placebo. Therefore, this study cannot answer the question of whether adjuvant TKI treatment is sufficient to eliminate residual tumour cells or whether synergistic effects resulting from the addition of chemotherapy may also be relevant. More recently, data from the phase III LAURA trial demonstrated efficacy of adjuvant osimertinib in unresectable *EGFR*-mutated stage III NSCLC after chemoradiotherapy resulting in a significantly longer median PFS compared to placebo (39.1 versus 5.6 months; HR =0.16, 95% CI: 0.10–0.24) (35).

Based on the results from the phase III ALINA trial (NCT03456076), alectinib has recently been approved both by FDA and EMA as adjuvant treatment after tumour resection in *ALK*-fused NSCLC. Alectinib was shown to be the first ALK inhibitor to significantly improve DFS compared to standard chemotherapy after a median follow-up of 27.8 months (88.7% versus 54%; HR =0.24; 95% CI: 0.13–0.43) in patients with resected *ALK*-positive NSCLC (16). Although this trial has defined a new standard of care, it remains unclear whether adjuvant alectinib is sufficient to eliminate residual tumour cells as patients were not allowed to receive prior adjuvant platinum-based chemotherapy. With this in mind, OS data are still immature and missing from the ALINA trial. The randomized controlled phase III ALCHEMIST trial (NCT02194738) is another study investigating the role of adjuvant targeted therapy. Completely resected stage IB–IIIA NSCLC patients with *EGFR* mutations will be randomized to either adjuvant erlotinib or observation, while those with *ALK*-fusions will be randomized to adjuvant crizotinib or observation. The trial will hopefully provide further evidence to support the role of adjuvant targeted therapy. Finally, the second-generation ALK TKI ensartinib is currently being tested in a single-arm phase II trial (NCT05241028) as adjuvant therapy for 3 years in stage IB–IIIA *ALK*-fused NSCLC.

Perioperative immunotherapy in EGFR-mutated and ALK-fused NSCLC

As mentioned above, neoadjuvant and/or perioperative regimens have the potential to monitor pathological response and reduce tumour burden prior to resection. Here, immunotherapy can induce pCR rates between 17.2% to 25.3% and MPR rates between 30.2 to 36.9%, respectively (5-8). However, patients with oncogenic drivers have typically been excluded from immunotherapy trials such as CheckMate816, AEGEAN and CheckMate77T (5,7,8). Only the KEYNOTE-671 trial included patients with *EGFR*- or *ALK*-alterations as molecular testing was not mandatory. Subgroup analysis found evidence of a survival benefit for perioperative pembrolizumab in patients with *EGFR*-mutations (6). However, as the subgroup numbers are very small, the current evidence is insufficient to clarify the role of perioperative immunotherapy in patients with *EGFR*-mutations and *ALK*-fusions.

Neoadjuvant EGFR inhibition

Previously, neoadjuvant erlotinib and gefitinib, both first-generation EGFR TKIs, have shown activity in stage II–IIIA *EGFR*-mutant NSCLC (36-38). The randomized phase II EMERGING-CTONG 1103 trial randomly assigned 72 patients with stage IIIA (N2) NSCLC harbouring *EGFR*

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exon 19 or 21 mutations, to receive erlotinib 150 mg daily (neoadjuvant for 42 days, adjuvant for up to 12 months) or gemcitabine and cisplatin (neoadjuvant for two cycles, adjuvant for up to two cycles). Although the objective response rate (ORR) was better for erlotinib versus chemotherapy (54.1% versus 34.3%), this difference was not significant. Regarding the pathological outcome after surgery, no pCR was detected in either arm and the MPR rate in the erlotinib arm was only 9.7% (3/31) compared to 0% (0/23) in the chemotherapy arm. Nevertheless, perioperative erlotinib resulted in an improved progression-free survival (PFS) compared to chemotherapy in stage IIIA (N2) *EGFR*-mutant NSCLC (21.5 versus 11.4 months; HR =0.39; 95% CI: 0.23–0.67), but with no difference in OS (36,39). In a phase II study from China, 19 patients with stage IIIA (N2) *EGFR*-positive NSCLC received erlotinib 150 mg daily for 56 days as neoadjuvant therapy prior to surgery and primary endpoint was the radical resection rate. Here, the radical resection rate was 68.4% (13/19) and pathological downstaging was achieved in 21.1% (4/19) of the patients (38). The authors conclude that neoadjuvant erlotinib might improve the radical resection rate, however, this message is limited as only 14/19 patients underwent surgery. Similar to erlotinib, preoperative gefitinib 250 mg was administered for 42 days to 33 patients with stage II–IIIA NSCLC with common *EGFR* exon 19 and 21 mutations prior to surgical tumour resection in a phase II trial from Shanghai. Here, the MPR rate was 24.2% and was associated with improved survival (37). The safety and efficacy of afatinib (40 mg daily), a second-generation EGFR TKI, for 2 months in combination with concurrent chemoradiotherapy (cCRT) with or without surgery in stage III *EGFR*-mutated NSCLC was evaluated in the phase II ASCENT trial. Recently published data showed an ORR of 63% (12/19) to induction afatinib. Twenty-two percent (2/9) of previously unresectable patients became resectable after afatinib induction. Sixty percent (6/10) of the patients that underwent surgery had a major or complete pathological response. With a median follow-up of 5 years, median PFS and OS were 2.6 and 5.8 months, respectively (40). However, the relevance of these studies remains questionable as first- and second-generation EGFR TKIs have been replaced by the third-generation EGFR TKI osimertinib in the treatment of newly diagnosed *EGFR*-mutant NSCLC patients according to the results of the FLAURA trial (33). For osimertinib, the single-arm phase IIb NEOS trial showed an ORR of 71.1% (27/38) after 6 weeks of neoadjuvant EGFR inhibition with osimertinib 80 mg daily in patients with stage IIA–IIIB (T3–4, N2) lung adenocarcinoma harbouring *EGFR* exon 19 and/or 21 mutations, followed by surgical resection. Although osimertinib appeared to be safe in this trial (7.5% treatment-related grade 3 adverse events) and 93.8% of patients underwent a successful R0 resection, only 10.7% achieved a MPR (41). Similar data was generated in a multi-institutional phase II trial (NCT03433469), in which a total of 27 patients with resectable stage I–IIIA *EGFR*-mutated (L858R or exon 19 deletion) NSCLC received osimertinib 80 mg daily for a median of 56 days prior to surgical resection. Eighty-nine percent (24/27) of the patients subsequently underwent surgery, whereas 11% (3/27) converted to definitive chemoradiotherapy. The MPR rate was only 15% and no pCR was observed, thus the primary endpoint was not met in this study (42) (conference abstract, not peer-reviewed yet). Compared to the impressive pathological response rates after neoadjuvant immunotherapy in non-oncogenic NSCLC, these data demonstrate the limited efficacy of neoadjuvant EGFR inhibition to induce pathological response. Retrospective real-word data (43-45) further support these findings and suggest that neoadjuvant EGFR inhibition might not be sufficient to induce a relevant pathological tumour regression (46). Recent data from the FLAURA2 trial in patients with advanced *EGFR*-mutant NSCLC provide evidence for the efficacy of a combination of a TKI and chemotherapy (47), which can be further supported by recent findings from the LAURA trial (35). A similar strategy is currently being investigated in the PACE-LUNG trial, in which a biomarker-driven strategy using circulating tumour DNA (ctDNA) is being used to decide whether to escalate treatment by adding chemotherapy to osimertinib in advanced *EGFR*-mutant NSCLC (48). However, these studies lack data on pathological outcome, as they are performed in advanced unresectable NSCLC. Therefore, in patients with resectable stage II–IIIB N2 *EGFR*-mutated NSCLC, the ongoing phase III NeoADAURA trial (NCT04351555) is evaluating the role of neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone before surgery (49). As it remains unknown, whether TKIs have the potential to eliminate tumour cells rather than just inhibiting their proliferation, this and other ongoing trials (50) will hopefully provide further information on this unanswered question (*Table 2*).

Neoadjuvant ALK inhibition

In addition to targeting *EGFR*-mutations in early-stage NSCLC with EGFR TKIs, the question arises as to

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Table 2 Overview of neoadjuvant EGFR inhibition trials [adopted from Grant et al.'s work (50)]

Trial	Phase	Number of patients	Stage	Treatment	Primary endpoint
NCT01470716	II	26	II–IIIA	Neoadjuvant erlotinib for 6 weeks	PFS
NCT04816838	II	25	I–IIIA	Neoadjuvant osimertinib for 8 weeks and adjuvant osimertinib for 3 years	ORR
LungMate-004 (NCT04201756)	II	47	III	Neoadjuvant afatinib for 8-16 weeks and adjuvant afatinib for 1 year	ORR
Neoafa (NCT04470076)	II	30	IIA–IIIB	3× cycles of neoadjuvant platin/pemetrexed with concurrent afatinib and adjuvant afatinib for 2 years	MPR, ORR
NOCE01 (NCT05011487)	II	30	III	2× cycles of neoadjuvant cisplatin/pemetrexed with concurrent osimertinib for 60 days	Complete lymph node clearance
NeoADAURA (NCT04351555)	III	328	II–IIIB (N2)	Neoadjuvant chemo + placebo versus chemo + osimertinib versus osimertinib 9 weeks followed by surgery and adjuvant osimertinib for 3 years +/– chemotherapy	MPR

EGFR, epidermal growth factor receptor; PFS, progression-free survival; ORR, objective response rate; MPR, major pathological response.

whether ALK inhibition may also be a therapeutic option in resectable NSCLC, as *ALK*-fusions are the second most common driver mutations in NSCLC. However, there is a lack of evidence on the use of ALK TKIs as neoadjuvant treatment in resectable early-stage *ALK*-positive NSCLC. To date, there are only a few case reports with small patient numbers using predominantly neoadjuvant alectinib (51,52), but also crizotinib (53) or ceritinib (conference abstract, not yet fully published) (54). These reports may show that neoadjuvant ALK inhibition appears to be reasonable in early-stage NSCLC (55). For example, a case series of 9 patients found high rates of MPR (33.3%) and pCR (44.4%) after neoadjuvant ALK inhibition (52). In line with these findings, the above-mentioned patient received the second-generation ALK TKI brigatinib for approximately 4 months prior to surgery, resulting in a pCR, which is consistent with previous reports for neoadjuvant alectinib and demonstrates its efficacy as an alternative neoadjuvant treatment strategy. A recently published real-world head-to-head comparison of first-line alectinib and brigatinib showed similar clinical benefits as well as similar rates of adverse events (56). In addition, the ALTA-3 trial found that brigatinib was not superior to alectinib for PFS in crizotinib-pretreated advanced *ALK*-fused NSCLC (57), providing further evidence that the two drugs can be used similarly. However, phase II and III trials are still required to confirm the safety and efficacy of neoadjuvant ALK inhibition in early-stage NSCLC (*Table 3*). A number of phase II trials such as RTOG 1306 (NCT01822496), SAKULA (UMIN00017906) and ARM (NCT03088930) had to be stopped due to recruitment problems as *ALK*-fusions are very rare and not (yet) routinely tested in early-stage NSCLC (34,55,58). The ongoing ALNEO trial (NCT05015010) is currently evaluating the safety and efficacy of neoadjuvant alectinib for 8 weeks followed by surgery and adjuvant alectinib for up to 96 weeks (34). The NAUTIKA1 trial (NCT04302025) is another phase II trial investigating the role of perioperative targeted therapy in biomarker-selected stage IB–III NSCLC patients (58). In line with the results of the recently presented ALINA trial, it seems conceivable that neoadjuvant ALK inhibition has the potential to downstage tumours and induce pathological remission in early-stage *ALK*-driven NSCLC prior to tumour resection. There is also similar evidence for locally advanced tumours (59). However, it remains unclear which patients are best suited for these approaches and for how long they should be treated with ALK TKIs prior to surgery, as there is also a risk of tumour progression with ALK inhibition, which in turn reduces the likelihood of complete tumour resection. Furthermore, the value of additional adjuvant TKI therapy and the value of perioperative chemotherapy in this setting is not known.

Surgical outcomes after neoadjuvant treatment

Neoadjuvant immunotherapy regimens have been shown to achieve high MPR and pCR rates with a positive impact on surgical outcome and survival (60,61). For example, the

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Table 3 Overview of neoadjuvant ALK inhibition trials [adopted from Chen *et al*. and de Scordilli *et al*. (55,58)]

Trial	Timeframe	Phase	Number of patients	Stage	Treatment	Primary endpoint
ALNEO (NCT05015010)	Start: 8/2021 Completion: 05/2026	II (recruiting)	33	III (resectable)	Neoadjuvant alectinib for 8 weeks followed by adjuvant alectinib for 96 weeks (single arm)	MPR
NAUTIKA-1 (NCT04302025)	Start: 3/2020 Completion: 02/2029	II (recruiting)	80	IB–III (resectable)	Neoadjuvant alectinib for 8 weeks followed by adjuvant alectinib for 104 weeks	MPR
ALCHEMIST (NCT02201992)	Start: 8/2014 Completion: 2036	III (recruiting)	168	IB–IIIA (resected)	Adjuvant crizotinib for 2 years versus placebo	OS
NCT05241028	Start: 5/2022 Completion: 2/2029	II (recruiting)	80	IB–IIIA (resected)	Adjuvant ensartinib for 3 years	DFS
RTOG 1306 (NCT01822496)	Start: 11/2013 Closed: 06/2018	II (closed)	16/59	III (unresectable)	Neoadjuvant crizotinib for 12 weeks	PFS
SAKULA (UMIN00017906)	Start: 03/2015 Closed: 10/2019	II (closed)	7/19	II–III (resectable)	Neoadjuvant ceritinib for 12 weeks	MPR
ARM (NCT03088930)	Start: 03/2017 Closed: 02/2022	II (closed)	3/26	IA–IIIA (resectable)	Neoadjuvant crizotinib for 6 weeks	ORR

EGFR, epidermal growth factor receptor; MPR, major pathological response; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; ORR, objective response rate.

CheckMate816 trial found a shorter median duration of surgery (185.0 versus 213.5 min), less pneumonectomies (16.8% versus 25.2%) and more minimally invasive approaches (29.5% versus 21.5%) for neoadjuvant addition of nivolumab compared to chemotherapy alone. R0 resection rates were also higher for the nivolumab combination (83.2% versus 77.8%). These findings were particularly true for patients with stage IIIA NSCLC (5). However, it needs to be shown whether this correlation between MPR/pCR rates and surgical and survival outcomes can also be assumed after neoadjuvant targeted therapy (46,62). In a case series of five patients with stage IIA to IIIA NSCLC from McGill University Health Centre (Canada), two *ALK*-positive patients were treated with alectinib 1–2 months prior to surgery, and three *EGFR*-mutated (exon 19) patients were treated with gefitinib or osimertinib 1–2 months prior to surgery. Two of these patients achieved a MPR, but none achieved a pCR. The initially assessed surgical approach before neoadjuvant TKI therapy would have been a thoracotomy-guided lobectomy in four patients and a video-assisted thoracoscopic surgery (VATS)-guided bilobectomy in the other patient. After neoadjuvant TKI therapy, all five patients underwent VATS-guided (bi-)lobectomy. The authors conclude that despite the unconvincing rates of MPR and pCR after neoadjuvant ALK/EGFR inhibition, this approach has simplified the surgical procedure for these patients (63). Whether this "simplification" of the surgical procedure translates into a long-term survival benefit remains unproven. Therefore, standardized surgical endpoints should be included in future neoadjuvant trials for resectable NSCLC (64).

Safety data on perioperative targeted therapy

Despite the promising effects of perioperative targeted therapy on tumour shrinkage and survival, potential safety issues and toxicities should be carefully considered. Adverse side effects of targeted therapies may delay the timing of surgery (62) and increase the perioperative risk (65). Severe toxicities associated with osimertinib include cardiomyopathy and heart failure (66,67) as well as QT interval prolongation, neutropenia and thrombocytopenia (68,69). With alectinib, bradycardia is a common side effect but reversible by dose reduction or discontinuation (70,71). In addition, the

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choice of neoadjuvant therapy may affect the side effects of subsequent lines of treatment, as sequential immunotherapy and targeted therapy are known to be associated with a significantly increased risk of severe immune-related adverse events, such as hepatotoxicity (22,72,73).

Summary

Taken together, current data underline the need for molecular testing for driver mutations even in early-stage NSCLC in order to carefully select the right treatment regimen for these patients (62). In addition to *EGFR*- and *ALK*-alterations, neoadjuvant strategies are also being tested for other AGAs. For example, the LEADER trial (NCT04712877) is evaluating the feasibility of using comprehensive genomic profiling (CGP) to detect AGAs to guide neoadjuvant therapy selection (74) (conference abstract, not yet fully published). In summary, despite conflicting results, neoadjuvant targeted therapy has the potential to reduce tumour burden through tumour shrinkage and pathological response. To this end, neoadjuvant treatment seems to be safe and may improve surgical procedures and thus morbidity and mortality. It also aims to reduce the risk of disease recurrence in patients with resectable NSCLC. Early molecular testing should be included in current guidelines and novel biomarkers, such as ctDNA, may help to distinguish responders from non-responders to neoadjuvant treatment. Most importantly, in the era of perioperative strategies, a multidisciplinary approach among involved specialists is needed. There is a high unmet need to further investigate the role of neoadjuvant and/or perioperative targeted therapy in early-stage NSCLC.

Conclusions

Results from ongoing clinical trials suggest that neoadjuvant targeted therapies might be effective and improve outcomes in patients with *EGFR*-mutant and *ALK*-positive resectable NSCLC. Ongoing trials will provide further evidence on the safety and efficacy of the perioperative use of TKIs in patients with resectable NSCLC. To date, it remains unclear, which treatment regimen (adjuvant, neoadjuvant and/or perioperative) is the best to reduce the risk of tumour recurrence. To improve treatment strategies, patient survival and outcomes, molecular testing should be routinely incorporated in non-metastatic NSCLC.

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