Review Article: Lung Cancer



# Challenges of neoadjuvant targeted therapy in early stage non-small cell lung cancer—a narrative review

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**Background and Objective:** There has been little advancement in the management of resectable non-small cell lung cancer (NSCLC) regarding neoadjuvant and adjuvant setting for almost two decades. Five-year survival rates for radically resected early stage NSCLC remain disappointing. The objective of this narrative review is to assess the current aspects and challenges of neoadjuvant targeted therapy in oncogene-driven NSCLC patients.

**Methods:** A search has been performed in PubMed/Medline/Embase and Google for relevant studies, meta-analyses and reviews on neoadjuvant targeted therapy in oncogene-driven NSCLC patients for the period 2010–2022. Following terms were used: oncogene-driven NSCLC/NSCLC, adenocarcinoma, early stage lung cancer, EGFR-mutant NSCLC, ALK rearrangement NSCLC, neoadjuvant molecular/targeted therapy.

**Key Contents and Findings:** A number of neoadjuvant and adjuvant trials with molecular targeted agents, tyrosine kinase inhibitors (TKIs) have been undertaken, several of them showing some clinically meaningful results for EGFR-mutant NSCLC. Few studies have reported on early stage ALK-positive lung cancer patients due to the rarity of this distinct subtype of NSCLC. Challenges of neoadjuvant targeted approach are numerous, however here referred to several important questions based on available data focused on EGFR-mutant NSCLC: treatment efficacy of TKIs, aspects relevant for surgery outcomes, response assessment, the need for comprehensive molecular profiling, prognostic and predictive impact of oncogenic driver alterations in early-stage NSCLC, relationship between tumor mutational burden (TMB) and outcomes to TKI treatment.

**Conclusions:** More studies with much larger patients population and using extensive molecular profiling are needed to assess the determinants of response and resistance in order to develop the optimal neoadjuvant treatment approach for oncogene-driven NSCLC.

**Keywords:** Oncogene-driven non-small cell lung cancer (Oncogene-driven NSCLC); early stage lung cancer; EGFR mutations; ALK rearrangement; neoadjuvant targeted therapy

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## Introduction

Nearly 25% of non-small cell lung cancer (NSCLC) patients have an early stage resectable disease. Increased use of computed tomography (CT) screening has led to detection of more NSCLC patients with early-stage disease who should be treated (1-6).

There has been little advancement in the management of resectable NSCLC regarding neoadjuvant and adjuvant setting for almost two decades. Five-year survival rates for resected early stage NSCLC remain disappointing. They are estimated to be between 41% and 65% (7), ranging from 89% to 71% for stage I, 64% to 55% for stage II, and 37% for stage IIIA (8). The high incidence of recurrence in

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | November 10, 2022 |
| Databases and other sources searched | PubMed/Medline/Embase and Google |
| Search terms used | Oncogene-driven NSCLC/NSCLC, adenocarcinoma, early stage lung cancer, EGFR-mutant NSCLC, ALK rearrangement NSCLC, neoadjuvant molecular/targeted therapy. |
| Timeframe | January 2010 – November 2022 |
| Inclusion criteria | Randomized and retrospective studies, meta-analyses, reviews and case reports; only English language included |
| Selection process | Selection process was carried out by the author |

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

distant sites suggests that systemic therapies are essential to improve cure rates.

New treatment modalities are being studied in the neoadjuvant and adjuvant settings to reduce the risk of systemic relapses and improve outcomes in early-stage NSCLC. Neoadjuvant treatment has the potential to decrease tumor burden and to eliminate subclinical (micro) metastases, at the same time providing valuable information regarding prognosis, tumor response and downstaging. Additional advantage is a comprehensive analysis and evaluation of the diverse biological features of the tumor at resection. The overall survival (OS) as an endpoint for the early-stage trials is very challenging because large randomized clinical studies are needed with long-term follow-up. Significant concern exists that neoadjuvant approach might delay the surgery and increase the risk of disease progression potentially leading to switch from resectable into unresectable tumor (9-12).

Based on data showing significant benefit and better treatment outcomes with a biomarker-driven treatment in advanced stage NSCLC, numerous neoadjuvant and adjuvant studies with molecular targeted agents and immune checkpoint inhibitors, either as monotherapy or combined with chemotherapy have been undertaken, many of them still ongoing. Various challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that are discussed in this review. The focus is mainly on EGFR-mutant NSCLC in the context of neoadjuvant approach, as it has been most studied. This article is written in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-114/rc).

## Methods

A search has been performed between February 5, 2021 and December 14, 2021 in PubMed/Medline/Embase and Google for relevant studies, meta-analyses and reviews on neoadjuvant targeted therapy in oncogene-driven NSCLC for the period 2010–2022, English language only. For this narrative review, an ethics committee approval was not required as it was performed to analyze already published studies, meta-analyses and reviews. Following terms were used: oncogene-driven NSCLC/NSCLC, adenocarcinoma, early stage lung cancer, EGFR-mutant NSCLC, ALK rearrangement NSCLC, neoadjuvant molecular/targeted therapy (*Table 1*). Since this is a narrative review, a certain subjectivity in choice of studies is not excluded.

## Frequency of genomic alterations in early stage non-small cell lung cancer

New molecular, sequencing techniques like NGS (next generation sequencing) have enabled the detection of many genomic alterations with development new targeted therapies (13).

Activating EGFR-mutations are reported in 10–35% of NSCLC cases, almost all adenocarcinoma type, with well-known ethnic differences (8–15% occurring in Caucasians and 30–60% in East Asian populations), prevailing among females, non-smokers and younger population (14-19).

Tumor stage itself appears to impact the EGFR mutation rate as well, although standard biomarker testing in the early stage NSCLC is currently not recommended by guidelines (20). American trial MSK-IMPACT prospectively

analyzed 860 multiple lines treated recurrent/metastatic adenocarcinomas for mutations in >300 cancer-associated genes, and evidenced EGFR-mutations in 27% (21). In The Cancer Genome Atlas (TCGA) cohort of 230 treatment-naive resected adenocarcinomas, 11% were EGFR-mutant tumors (16). The Lungscape ETOP Project (22,23) in a large group of resected stage I–III NSCLC found EGFR mutations in 5.4% (9.7% in adenocarcinomas) (22). In the adjuvant phase III ADAURA, out of 2,447 resected stage IB–IIIA NSCLC, 44% were EGFR mutation positive, with a predominance of Asian *vs.* non-Asian (63% *vs.* 37%) (24,25). A Chinese retrospective study on 790 early-stage resected tumors, found the frequency of EGFR mutations was close to those in the advanced disease (53.6% *vs.* 51.4%) (26). A recent Japanese analysis of 244 resected early stage adenocarcinoma, detected EGFR mutations in 44.6% in the whole cohort, while in 50% of 162 patients having pathological stage I disease (27). In a big South Korean series analysis of 689 stage I–III lung adenocarcinomas displayed EGFR mutations in 438 patients (64%) (28).

As for ALK rearrangements, the Lungscape ETOP Project (22,23) reported them in 6.2% by immunohistochemistry (IHC) and around 2.2% by fluorescence in situ hybridization (FISH) (23). Similar rates were demonstrated in two large Chinese retrospective series of resected stage I–IIIA adenocarcinoma, 4% out of 689 patients (28) and 6.6% out of 1,056 patients (29).

## Selected studies on neoadjuvant targeted therapy

Since most of relapses after surgical resection occur in distant sites, neoadjuvant systemic treatment increases the likelihood of eliminating micrometastases and improving outcomes.

Several randomized controlled trials (RCTs) have clearly evidenced the survival benefit of neoadjuvant chemotherapy, showing the objective response rate (ORR) ranging from 35.4% to 41% (10,11). Meta-analysis of 15 RCTs noted 13% reduction in the death risk in stage IB–IIIA resectable NSCLC patients improving OS from 40% to 45% at 5 years as well (30).

In the last several years, a significant number of neoadjuvant and/or adjuvant studies with molecular targeted agents have been undertaken.

Pivotal prospective trials have proven that first line TKI treatment show better efficacy with the high rate of significant responses and less toxicity than chemotherapy in advanced oncogene-driven NSCLC (15,31-39). These findings support its evaluation in neoadjuvant setting, especially in borderline or potentially resectable tumors or those in which a pneumonectomy would otherwise be indicated. Importantly, this approach enables analysis of tumor specimen before and after targeted treatment and thus additionally provides the opportunity to assess tumor sensitivity, resistance mechanisms to targeted agents and residual tumor burden (40,41). Better insight into the biology of residual disease in oncogene-driven NSCLC might significantly affect the choice of subsequent therapy or combination treatments as well as outcomes.

Moreover, knowing differing characteristics among different TKIs, each generation of targeted therapies needs to be carefully evaluated based on their efficacy, therapy duration and variety of effects on tumor biology characteristics such as intrinsic/acquired resistance mechanisms.

Studies with TKIs in neoadjuvant and adjuvant setting at early stage EGFR-mutant and ALK-rearranged NSCLC, have shown some promising but mixed results.

Findings of ADAURA trial (42) represent the proof of concept that biomarker-driven treatment could be extended from metastatic to the early stage NSCLC and encouraged further investigations in the neoadjuvant setting.

Several clinical trials demonstrated promising efficacy and safety of neoadjuvant TKIs (*Table 2*). EMERGING-CTONG1103 (43) compared efficacy of neoadjuvant (and adjuvant) EGFR-TKI (erlotinib) with platinum-doublet chemotherapy (gemcitabine plus cisplatin). The primary endpoint of overall response rate (ORR) was not met for neoadjuvant erlotinib *vs.* chemotherapy (ORR 54.1% *vs.* 34.3%; P=0.092) in this cohort of 72 patients, and no complete pathological response (pCR) was noted in either arm. Major pathological response (MPR) was evidenced in erlotinib group only (9.7%). Surgery has been performed in 73% of patients in erlotinib group *vs.* 63% of chemotherapy group. Significant benefit in progression-free survival (PFS) over chemotherapy has been shown (21.5 *vs.* 11.4 months; HR 0.39; P=0.001), but not in OS (45.8 *vs.* 39.2 months; HR 0.77; P=0.417).

Three small phase 2 studies with neoadjuvant gefitinib or erlotinib showed ORRs ranging from 42.1% to 61.5% and differing MPR rates from 7.7% to 24.2% (44-46). The CSLC-0702 (44) was the first phase II trial of neoadjuvant EGFR TKI treatment, with 24 stage IIIA (N2) NSCLC patients randomized to receive three cycles of gemcitabine plus carboplatin (EGFR-wild type) or erlotinib (EGFR

**Table 2** Selected studies on neoadjuvant EGFR TKI and ALK TKI therapy

| *Study | Pre-OP Th duration | ORR | Surgery rate | R0 rate | DFS (months) | PFS (months) | OS (months) | Down-staged/ pLN downstaged | MPR (%) | pCR (%) | TRAEs (Gr ≥3) | Post-OP Th |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EGFR TKI therapy | | | | | | | | | | | | |
| Zhong *et al.* 2015 (43): CSLC-0702, Ph II 12 pts, stage IIIA N2 | Erlotinib 6 weeks *vs.* platinum-based 3 cycles | 58.3% *vs.* 25.9% | 100% *vs.* 100% | 50% *vs.* 71% | 8.6 | 6.9 *vs.* 9.0 | 14.5 *vs.* 28.0 | 25% *vs.* 25%/16.7% *vs.* 25.0% | NR | NR | 0 | NR |
| Zhong *et al.* 2019 (44): EMERGING-CTONG 1103 Ph II 72 pts, stage IIIA | Erlotinib 6 weeks *vs.* Cis/Gem 2 cycles | 54.1% *vs.* 34.3% | 83.8% *vs.* 68.6% | 73.0% *vs.* 62.9% | NR | 21.5 *vs.* 11.4, HR 0.39 | 45.8 *vs.* 39.2, HR 0.77, P=0.001 | NR/10.8% *vs.* 2.9% | 9.7% *vs.* 0 | 0 *vs.* 0 | 0 *vs.* 29.4% | Erlotinib 1 year (75.7%) *vs.* Cis/Gem 2 cycles (62.9%) |
| Xiong *et al.* 2019 (45): EASTERN, Ph II 19 pts, stage IIIA | Erlotinib 8 weeks | 42.1% | 73.7% | 68.4% | 10.3 | 11.2 | 51.6 | 21.1%/35.7% | NR | NR | 15.8% | ChemoTh |
| Tan *et al.* 2019 (46): PROGRESS, Ph II 13 pts, stage IA–IIIA | Gefitinib Min 4 weeks (Med 1.4 months) | 61.5% | 100% | 100% | 20.2 | NR | NR | NR/31% | 7.7% | NR | 8% | NR |
| Zhang *et al.* 2021 (47): Ph II 35 pts, stage II–IIIA | Gefitinib 6 weeks | 54.5% | 94.3% | 82.8% | 33.5 | NR | NR | 20.0%/NR | 24.2% | 12.1% | 0 | ChemoTh or RT (all pts) |
| Lyu *et al.* 2021 (48): NEOS Ph II ongoing 38 pts, stage II–IIIB | Osimertinib 6 weeks | 71.1% | 84.2% | 93.8% | – | – | – | 55%/40% | 10.7% | 3.6% | 0 | NR |
| Blakely 2021 (49): Ph II ongoing (NCT03433469) 13 pts, stage IA–IIIA | Osimertinib average of 59 days | 46% | 100% | 100% | – | – | – | 69%/80% | 15% | 0 | NR | NR |
| ALK TKI therapy | | | | | | | | | | | | |
| Zhang *et al.* 2019 (50): 11 pts, stage IIIA N2 | Crizotinib median 30 days | 90.9% | 100% | 91.0% | 10.1[#] | – | – | 90.9%/27.3% | 0 | 18.2% | 9.1% | 90.9% (36.4% crizotinib, 45.5% ChemoTh ± RT, 9.0% RT) |

*, study details: PI, year of publishing or reporting results, study phase, number of pts included in reported results, stage of disease. [#], for 6 patients out of 11 (54.55%) having relapse. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; pts, patients; Ph, phase; OP, operation; Th, therapy; Cis/Gem, cisplatin and gemcitabine; Min, minimum; Med, median; R0, radical resection rate; DFS, disease-free survival; NR, not reported; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; pLN, pathologic lymph nodes; MPR, major pathologic response; pCR, complete pathologic response; TRAEs, treatment related adverse events; Gr, grade; ChemoTh, chemotherapy; RT, radiotherapy; PI, principal investigator.

**Table 3** Ongoing clinical trials investigating neoadjuvant EGFR TKIs

| Study | Phase | Stage | Number of pts planned | Therapy regimen | Primary endpoint |
|---|---|---|---|---|---|
| NeoADAURA (NCT04351555) (51) | III | II–IIIB (N2) | 328 | Osimertinib *vs.* osimertinib + CT *vs.* placebo + CT surgery → investigator choice (osimertinib for 3 years) | MPR |
| ANSWER (NCT04455594) (52) | II | IIIA N2 | 168 | Almonertinib *vs.* erlotinib/CT | ORR |
| NeoIpower (NCT05104788) | II | II–IIIB | 27 | Icotinib + CT for 2 cycles → surgery | MPR |
| NCT04201756 | II | IIIA N2 | 47 | Afatinib 16 weeks → surgery → afatinib for 1 year | ORR |
| NCT03749213 | II | IIIA N2 | 36 | Icotinib for 8 w → surgery → icotinib for 2 years | ORR |

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; pts, patients; CT, chemotherapy; MPR, major pathological response; ORR, objective response rate.

mutated) for 42 days before the surgery. EGFR-mutant NSCLC showed a tendency for an improved RR (58.3% *vs.* 25%), with no significant difference in the PFS and OS between the two arms. A small, single-arm ESTERN trial (45) of neoadjuvant erlotinib for 56 days in 19 patients with stage IIIA N2 EGFR-mutant NSCLC patients, has demonstrated the radical resection rate (RR) of 68.4% (13/19), with an ORR of 42.1%, while median PFS and OS were 11.2 and 51.6 months, respectively. Another small single-arm phase II trial (46) with neoadjuvant gefitinib for 42 days in 35 patients with stage II–IIIA EGFR-mutant NSCLC demonstrated the ORR as primary endpoint of 54.5%, the rate of MPR of 24.2%, the median DFS 33.5 months while median OS not reached.

The PROGRESS trial (47) is an ongoing study evaluating neoadjuvant gefitinib in resectable IA–IIIA EGFR-mutant NSCLC with the primary endpoint to assess EGFR-TKI sensitivity biomarkers in responders *vs.* non-responders and correlation of pathologic responses with serial plasma and tissue sequencing. The ORR in 13 evaluable patients was 62%, all have undergone surgery, and 8% (1/13) had MPR. There was no correlation of residual tumor burden with FDG-uptake or tumor response. RNA sequencing revealed that immune regulatory and inflammatory response genes were upregulated compared to the treatment naive cohort, indicating infiltration of fibroblasts and T cells. This reflected adaptive responses and thus pointed to the consideration of developing relevant combination therapeutic strategies in EGFR-mutant NSCLC (*Table 2*).

Neoadjuvant osimertinib, the third-generation EGFR TKI given for 6 weeks, is shown to be effective and feasible for patients with stage II–IIIB adenocarcinoma with EGFR common mutations, according to interim report of the NEOS Chinese prospective single-arm study (48). In 28 evaluable patients, the primary endpoint, objective RR was 71%—all partial responses, 29% had stable disease with disease control rate (DCR) of 100%. Twenty-two patients (78.6%) were considered for R0 resection and 95% of them underwent R0 resection. The pathological downstaging rate was 55%, with only 1 patient achieving a pCR. Adverse events (AEs) were observed in 93% with no treatment discontinuation. The updated results of the ongoing phase 2 trial (NCT03433469) (49) of neoadjuvant osimertinib show the objective RR 46%, the primary endpoint pCR rate 69%, the MPR rate of 15%, with no serious or grade 3/4 AEs noted. There were neither unexpected delays to surgery, nor tumors turning to unresectable or more surgical complications reported.

Based on the firm evidence of osimertinib efficacy as the adjuvant therapy (41) and the findings of the neoadjuvant phase 2 trial (49), the phase 3 neoADAURA trial (NCT04351555) was started (51), the three-arm trial comparing the use of neoadjuvant osimertinib with or without chemotherapy to chemotherapy alone in patients with resectable, stage II to IIIB EGFR-mutant NSCLC (*Table 3*).

Besides, phase II randomized trial (ANSWER) is evaluating the efficacy of neoadjuvant novel 3$^{rd}$ generation EGFR-TKI Aumolertinib compared with erlotinib or platinum doublet chemotherapy in resectable EGFR-mutant stage IIIA NSCLC, with ORR as the primary endpoint (52) (*Table 3*).

There is growing number of meta-analyses, pooled

 

**Table 4** Ongoing clinical trials investigating neoadjuvant TKIs for ALK rearrangement and other rare mutations

| Study/oncogenic driver mutation | Phase | Stage | Number of pts planned | Therapy regimen | Primary endpoint |
|---|---|---|---|---|---|
| ALNeo (NCT05015010)/ALK rearrangement; Leonetti *et al.* 2021 (56) | II | III | 33 | Alectinib 2 cycles → surgery → alectinib for 2 years | MPR |
| Geometry-N (NCT04926831)/MET; Lee *et al.* 2022 (57) | II | IB–IIIA, N2 and selected IIIB (T3N2 or T4N2) | 38 | Capmatinib → surgery → adjuvant capmatinib | MPR |
| NAUTIKA1 (NCT04302025) ALK/ROS1/BRAF/RET/NTRK (58) | II | II–III | 60 | TKI 2 cycles → surgery → CT + TKI for 2 years (alectinib, entrectinib, pralsetinib, vemurafenib + cobimetinib) | MPR |
| ALINA (NCT03456076)/ALK rearrangement (59) | III | IB (T ≥4 cm) – IIIA | 255 | CT *vs.* alectinib for 2 years | DFS |

TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; pts, patients; CT, chemotherapy; MPR, major pathological response; DFS, disease-free survival.

analysis and retrospective real-world studies as well.

In a large meta-analysis of 9,635 resected NSCLC encompassing 32 studies (53), a significant benefit in disease-free survival (DFS) (HR 0.77; P=0.001) and OS (HR 0.72; P<0.00001) in early-stage EGFR-mutant NSCLC was evidenced. But these findings must be interpreted very carefully not only because of other positive confounding factors, but also given commonly used PCR testing limited to exons 18–21 only in most of the studies. Novel comprehensive molecular tests have significantly contributed increasing knowledge about the complex biology of EGFR-mutant tumors that impact response to EGFR TKIs and natural history of EGFR-mutant tumors.

Five, phase II, prospective, clinical trials comprising 124 patients with resectable or potentially resectable EGFR-mutant NSCLC treated with neoadjuvant erlotinib or gefitinib were included in a pooled analysis showing good surgery results and safety of neoadjuvant EGFR TKI (54). The pooled ORR was 58.5% and the surgical resection and complete resection (R0) rates were 79.9% and 64.3% respectively. In the stage IIIA subgroup (n=68), the pooled ORR, resection rate and R0 rate were 51.4%, 72.9%, and 57.0%, respectively; the downstaging and pCR rates were 14.0% and 0.0%, and the pooled median PFS and OS were 13.2 and 41.9 months, respectively. The most frequent post-surgical complications were lung infection, arrhythmia, and pneumothorax.

Recently published meta-analysis (55) of 3 prospective RCTs, and 2 non-RCTs, all together with large heterogeneity, that included 319 EGFR-mutant stage IIIA NSCLC patients (264 in the subgroup analysis of 3 RCTs), found that neoadjuvant targeted therapy compared with chemotherapy, significantly increased ORR (although it was lower than observed in advanced disease), whereas significantly decreased grade 3/4 AEs, with the surgical rate ~83.8% *vs.* 74.2% respectively. Data for the OS and PFS that were available from four trials only showed no significant difference.

Few studies have reported on early stage ALK-positive lung cancer patients (41,50,56) due to the rarity of this distinct subtype of NSCLC. The first one from 2016 (41) treated patients with early stage NSCLC harboring ALK- or ROS1-fusions or MET ex14 skipping mutations with the ALK/ROS1/MET TKI Crizotinib with the aim to evaluate resected tumor samples for pathologic response to induction therapy, ORR, disease free survival and to identify early mechanisms of resistance to targeted therapy. Another one (50) reported 11 cases of pathologically confirmed N2 ALK-positive NSCLC treated with neoadjuvant crizotinib followed by surgery, 10 of which achieved R0 resection and 2 achieved pCR, but one of them with rapid postoperative relapse (57). The ongoing phase II multicenter ALNEO trial with MPR as the primary endpoint evaluates the efficacy and safety of neoadjuvant alectinib in (potentially) resectable ALK-positive NSCLC (any T stage with N2, T4N0–1) (56) (*Table 4*).

There are several case reports on neoadjuvant crizotinib (60,61), and alectinib (62-65) as well, pointing to neoadjuvant ALK TKI approach as feasible, efficient and well tolerated.

The increasing number of approved targeted therapies—including for KRAS G12C mutations, ROS1, BRAF V600E,

MET exon 14 alterations, HER2 exon 20 insertion, NTRK and RET rearrangements—brings novel opportunities for personalized, oncogene-driven treatment approach in (neo) adjuvant setting (66). Two case reports have been published, one on pCR to neoadjuvant crizotinib in adenocarcinoma with a MET Exon 14 skipping mutation (67), and the other on MPR induced by neoadjuvant BRAF and MEK inhibitors in a patient with stage IIIA lung adenocarcinoma harboring BRAF V600E-mutation (68).

Geometry-N, a phase II trial of neoadjuvant and adjuvant capmatinib in NSCLC with MET exon 14 mutations and/or high MET amplification is ongoing (NCT04926831) (57). Considering those rare mutations, the Lung Cancer Mutation Consortium (LCMC) has initiated the PROMISE umbrella trial in resectable stage I–III NSCLC with matched targeted therapies in neoadjuvant setting (69). Another ongoing trial, NAUTIKA1 evaluates neoadjuvant and adjuvant alectinib, entrectinib, vemurafenib plus cobimetinib, or pralsetinib in patients with resectable stage II–III NSCLC with ALK, ROS1, NTRK, BRAF V600, or RET molecular alterations (NCT04302025) (58,70) (*Table 4*).

## Challenges of neoadjuvant targeted treatment

Challenges of neoadjuvant targeted treatment approach focused on EGFR TKIs, are numerous, however here been referred to several important questions based on available data.

### *Aspects of neoadjuvant TKIs in oncogene-driven early stage lung cancer relevant for surgery outcomes*

The data obtained from the studies on neoadjuvant TKI therapy relate mostly to EGFR TKIs.

From surgical point of view one of the concerns related to neoadjuvant TKI treatment is the TKI toxicity, grade 3 or 4 treatment AEs that might delay surgery.

Neoadjuvant TKI treatment seems to be generally well tolerated, with no new safety concerns noted. Available data have pointed to low rates of grade ≥3 adverse effects, in the range of 0% to 15.8% (43-46,48,54,55). In recently published pooled analysis of 5 prospective clinical trials with small number of patients included, the incidence of grade 3/4 AEs was 5.3% for hepatotoxicity and 14.7% for skin rash, but there was no surgery delay (54).

Delay in surgery and potential transformation into unresectable tumor represent important concerns particularly since the objective RR to EGFR TKIs in clinical studies is lower than evidenced in advanced disease. Additionally, there is also a certain concern about disease flare after EGFR TKI interruption.

Post-operative complications represent another important aspect. The incidence of post-operative complications reported in the EMERGING-CTONG110323 study (43) was similar to neoadjuvant chemotherapy trials (11,71). In another phase II study with neoadjuvant gefitinib in stage II–IIIA NSCLC (46), there was higher incidence of postoperative chylothorax (12.1%) than generally evidenced (1.0%) (71,72). No perioperative mortality was noted in either of these studies.

Although it appears that neoadjuvant EGFR TKIs don't entail more pre-operative complications and more increased surgical risk than neoadjuvant chemotherapy, each generation of targeted agents requires to be thoroughly evaluated for features that might influence preoperative status or surgical risk, in order to make the most adequate selection of patients who will benefit from neoadjuvant approach.

### *Assessment of response to neoadjuvant therapy*

Novel neoadjuvant strategies have denoted some weak points of widely used response parameters, such as the discordance between RECIST response and pathological response, as already mentioned, but at the same time provided expanded possibilities for detection of reliable new biomarkers as well. Incorporating a biomarker testing approach into the routine work-up of early-stage NSCLC is needed, but still there are many challenges such as to establish standardized surrogate endpoints of neoadjuvant treatment. Major pathologic response (MPR) defined as 10% or less residual tumor cells represents a potential surrogate endpoint for OS in NSCLC and a marker for neoadjuvant treatment efficacy (73,74).

Regarding this important issue of assessment of response to neoadjuvant therapy in clinical trials and in everyday practice as well, particularly in the light of novel neoadjuvant/adjuvant approaches, the International Association of Lung Cancer (IASLC) has released the multidisciplinary recommendation for the pathologic assessment of resection specimens, encompassing MPR and pCR (75). They recommend assessment of the percentages of viable tumor, necrosis, and stroma (including inflammation and fibrosis), to be applied for all systemic therapies, given either as monotherapy or in combination.

One of key goals is to enable comparisons of the impact of pathologic responses as potential surrogate endpoints between diverse types of neoadjuvant therapies in clinical studies as well as DFS and OS, but with hope to be implemented as well in routine clinical practice.

Very recently a novel MPR calculator tool (MPRCT) for standardized, comprehensive collection of percentages of viable tumor, necrosis, and stroma in the tumor bed, including tumor width and length in the latter, has been developed (76). It has the potential to validate trials with MPR and pCR as surrogate end points of neoadjuvant therapy efficacy. Data from the ongoing Phase 3 neoadjuvant trials using MPRCT such as IMpower030 are awaited. The MPRCT compared to the IASLC recommendations, might better capture data in areas of tumor heterogeneity and decrease the bias of standard pathology approach selecting viable areas and avoiding necrotic ones, that cause underestimation of pathologic response (76).

There is a need for data on precise histological changes after targeted therapy such as EGFR-TKI, not only to compare with the pre-treatment tumor specimen and assess the level of tumor shrinkage, but, even more importantly to perform in-depth molecular analysis. This analysis is essential for making adequate decision on adjuvant approach. Additionally, it remains to be determined whether histological characteristics of resected specimens differed upon treatment with different EGFR-TKIs.

### *The need for comprehensive molecular profiling in the light of complex mechanisms of intrinsic and acquired resistance to TKIs (EGFR TKIs)*

A very important issue is related to establishment of reliable genomic/epigenetic biomarkers at the time of diagnosis, and consequently the optimal selection of neoadjuvant approach with possibility to predict who would most likely respond to targeted drugs. NSCLC is a highly complex, heterogeneous tumor with co-occurring genomic alterations i.e. with a variety of spatially and temporally different co-mutations. Given this NSCLC complexity, nowadays widely applied molecular profiling at diagnosis such as PCR panels, targeted NGS, FISH, IHC, do not encompass sufficient number of driver genes unlike comprehensive molecular profiling.

Different resistance mechanisms to EGFR TKIs that are responsible for disease progression in advanced NSCLC, have been detected based on analyses of tumor biopsy samples obtained at the time of tumor progression. Around 20–30% of patients with advanced EGFR-mutant NSCLC do not respond at all or show some response to TKIs for a very brief time (<3 months) as the consequence of intrinsic resistance mechanisms which are not yet fully recognized (13,77). Due to clonal tumor heterogeneity of NSCLC, different genetic alterations may exist in clones before treatment initiated, namely *de novo* alterations, that are either cause of intrinsic resistance to EGFR TKIs (78), or may reflect prompt adaptive response by some surviving tumor cells, a phenomenon called "drug tolerance" to the TKI therapy. Those surviving cell subpopulations acquire a dormant or "persister" state of cell-cycle arrest and have the potential for further tumor growth and progression (79).

Comprehensive molecular profiling of tumor biopsy samples at the time of diagnosis has evidenced the co-existence of multiple genetic, epigenetic, and functional mechanisms underlying variety of EGFR-dependent and/or EGFR-independent processes that may cause TKI-resistance (13,16,21,78,80,81). It appears that acquired resistance is the result of combined expansion of certain pre-existing clones and newly developed resistance mechanisms that reflect adaptive tumor response to EGFR TKIs therapy. Some of mechanisms are shared by these two types of resistance, but with clear temporal differences. Thus, since the majority of advanced EGFR-mutant NSCLC do not depend on EGFR only, but also on multiple co-occurring oncogenic events (82), different mechanisms underlying intrinsic and acquired resistance may be identified concomitantly. All this contribute to the complexity of this important aspect for targeted treatment (83). Sensitizing EGFR mutations represent early clonal events in the process of tumor development, while most advanced NSCLCs exhibit heterogeneous regions having late clonal driver aberrations that are in fact TKI-resistance mechanisms, such as mutations in TP53, RB, and genes related to the RAS-RAF-MAPK or PI3K-AKT-PTEN-mTOR pathways, cell cycle regulation, Wnt/β-catenin pathway, DNA damage repair, chromatin remodeling, and histone methylation (82-84). While being treated with the EGFR TKIs, further on during tumor evolution some of those pre-existing clones that most effectively foster tumor progression may be selected to proliferate as the predominant cell subpopulation reflecting prevailing resistance mechanism (13,23,78). Co-occurring TP53 mutation is a highly prevalent mutation and the most frequent co-mutation found in 30% to over 60% of EGFR-mutant tumors. These TP53 alterations reduce

 

responsiveness to EGFR-TKIs and worsen prognosis in EGFR-mutant NSCLC patients (45,84-89).

The fact that diverse and heterogeneous intrinsic TKI-resistance mechanisms may co-exist in the same EGFR TKI-resistant NSCLC, is particularly challenging for treatment in the neoadjuvant setting, but the only way to detect those mechanisms is to endorse comprehensive molecular profiling tests such as NGS in routine clinical practice in early stage disease. In this context, it becomes necessary not only to define EGFR-mutant patients subpopulations who are suitable for neoadjuvant targeted therapy, but also to identify which EGFR TKI to be recommended in an individual case. Comprehensive molecular profiling is of great importance for treatment decision which EGFR TKI to be administered as some of the EGFR-dependent resistance mechanisms cause resistance to EGFR TKIs of all three generations, while others are sensitive to 2- or 3-generation TKIs, whereas on the other hand most of the EGFR-independent resistance mechanisms are common to EGFR TKIs of all three generations.

Selecting the appropriate combination targeted therapy at the diagnosis as well requires the use of extensive molecular profiling. Thus discovered alterations might become additionally actionable targets having then potential to be predictive biomarkers in certain subpopulations of patients (13,17,21,76,80). Consequently, the combination of drugs targeting alterations that are detectable already at the time of diagnosis might have potential to prevent or at least to postpone the predominant proliferation of resistant cancer cells, and thus impact the outcomes in early stage oncogene-driven NSCLC.

Still, there is a risk that certain tumor cell subpopulations harboring other resistance-mechanisms exist while not been discovered (80). Thus, EGFR-mutant NSCLC with its complexity and diversity of baseline co-existing TKI-resistance mechanisms that are not even recognized or/and not targeted, may additionally explain why in a number of studies there has been no evidence of OS benefit or of decreased risk of relapse following neoadjuvant EGFR TKIs treatment.

Moreover, even with extensive molecular profiling tools such as NGS, of most frequently a small tumor biopsy sample at diagnosis, the aspect of tumor heterogeneity is underestimated (82,90,91).

It should be underlined that circulating tumor DNA (ctDNA) that has been analyzed to discover acquired-resistance mechanisms to TKIs (92-95), might have potential as well to detect alterations relevant for selection of optimal treatment approach in early stage disease.

Another very important aspect is that more extensive use of comprehensive molecular profiling in early-stage NSCLC will enable the detection of other, rare oncogene-driven mutations such as ALK, NTRK, RET, BRAF, HER, MET, for which the expanding number of efficient targeted drugs have been developed, but large trials enrolling patients with tumors harbouring any of them are not realistic.

### *Prognostic and predictive impact of EGFR mutations in early-stage EGFR-mutant NSCLC*

Although oncogene addiction is an established predictive factor for TKI response, its prognostic significance in resected oncogene-driven NSCLC has not been elucidated. But, with increasing knowledge about complex mechanisms of intrinsic and acquired resistance, and inevitable shift toward comprehensive genomic profiling in near future, the prognostic role of oncogenic driver alterations in early stage NSCLC and its determinants will be possible to define. EGFR mutations as a prognostic factor in resected NSCLC have been investigated in a number of studies, with conflicting results (28,96-105).

Several retrospective studies pointed to a significant survival benefit in resected EGFR-mutant NSCLC compared with EGFR wild-type (96,101,103,105), unlike some other studies (22,97-100,102,106,107). In a big South Korean series of 438 patients with resected EGFR-mutant stage I–III NSCLC (28), EGFR mutation was independent prognostic factor of the long-term outcomes with a more favorable prognosis in younger patients. The results of two meta-analyses were discordant as well (53,107). A significant benefit in DFS (HR 0.77; P=0.001) and OS (HR 0.72; P<0.00001) in early-stage EGFR-mutant NSCLC was evidenced in a large meta-analysis of 9,635 resected NSCLC patients from 32 studies (53) unlike the other meta-analysis (107).

Regarding this aspect, comprehensive molecular profiling such as NGS may detect co-occurring genomic alterations that might influence prognostic and/or predictive impact of EGFR mutations. The first study to look at the impact of single and multiple cancer-related co-mutations in early stage I–III resected NSCLC using NGS was the study of Jao *et al.* 2018 (85). Somatic mutations were detected in 86% (184 out of 214 patients), single in 47.2% and multiple ≥2, in 38.8% patients. The presence of any known

 

mutation was associated with shorter DFS and an increased risk of disease relapse compared to NSCLC tumors with no mutations. The negative trend was similar for OS but with no significance, which in those with sensitizing EGFR mutations might be explained by the subsequent use of EGFR TKIs upon relapse.

Interestingly, regarding resected stage IA NSCLC patients with no confounding effect of adjuvant therapy, no recurrences were noted during the follow-up period in those with no somatic mutations unlike in patients with NSCLC harbouring mutations (85). This might imply that genomic profiling in this particular subgroup potentially leads to consideration of adjuvant (targeted) therapy in cases of tumors harbouring mutations.

In this study, more than 60% of EGFR positive tumors with co-mutations had TP53 as co-mutation which was associated with worse DFS and worse OS, unlike the LACE-Bio pooled analysis findings (108,109). Negative impact of TP53 co-mutation was confirmed in several studies (44,89,110). A small phase II trial with neoadjuvant erlotinib in EGFR-mutant Stage IIIA N2 NSCLC) found that TP53 co-mutation significantly reduces the efficacy of neoadjuvant EGFR TKIs (89). Absence of TP53 co-mutation, or very low abundance of it was associated with longer PFS, whereas high abundance was associated with short PFS (44). According to updated results from the ongoing phase 2 trial (49) of neoadjuvant osimertinib, a loss-of-function RBM10 mutation was evidenced in tumors lacking pathologic response. This might be explained by the fact that loss-of-function mutation in RBM10 tumor suppressor gene contributes to the pathogenesis of adenocarcinoma, cell proliferation and disease progression (111).

All those results just emphasize the importance of comprehensive genomic profiling in early stage EGFR-mutant NSCLC.

There are some convincing data that the abundance of EGFR mutation is related to the efficacy of targeted treatment that cannot be detected by commonly used PCR test (112,113). In a retrospective real-world study (35) comparing the efficacy and survival outcome of neoadjuvant EGFR TKI *vs.* chemotherapy in patients with stage I–IIIA lung adenocarcinoma, the mechanisms underlying the primary and acquired TKI resistance have been explored by NGS DNA sequencing of both, pre- and post-treatment tumor samples. The prominent finding was the mutant allele frequency (MAF) of EGFR mutation decreasing following targeted therapy except in one case of T790M mutation. It was noted that patients maintaining stable disease exhibited significantly lower EGFR mutation MAF following TKI therapy (P=0.032) which in 3 of them was even undetectable after therapy (35).

In a recent large Chinese study, patients with EGFR and co-occurring other multiple mutations, treated with immunotherapy, had a longer survival time with higher TMB score and distinct immune cell infiltration features compared to patients with EGFR mutation only (114).

### *Prognostic role of EGFR mutations as oncogenic driver alterations of immunotherapy efficacy*

Regarding prognostic impact of EGFR mutations on immunotherapy efficacy, since (neo)adjuvant immunotherapy emerging in early stage setting, it is recognized that EGFR mutations may influence anti-tumor immune responses. The mechanisms underlying poorer response to immunotherapy in EGFR-mutant NSCLC seem to be related to the higher diversity and lower clonality of those tumors (115). Some relatively recent studies have found as well that patients with exon 19 deletion have lower TMB leading to poorer immunotherapy efficacy compared to patients with L858R mutations or wild-type EGFR (116). Recent study on the correlation of the T-cell receptor (TCR) repertoire with EGFR mutations, found that EGFR exon 19 deletion tumors better induce T-cell expansion than EGFR L858R mutant and EGFR rare mutations tumors, thus leading to differing responses to EGFR TKIs as well (115). This was in line with the findings in advanced stage EGFR-mutant NSCLC (98,117,118).

### *Correlation between TMB and outcomes of EGFR TKI treated EGFR-mutant adenocarcinoma*

The issue of TMB affecting the efficacy of EGFR TKI treatment has been explored in recent years (119,120). Higher TMB was demonstrated to be associated with worse DFS (120). The recent study (91) found that TMB is significantly increased post-EGFR TKI based on analysis of paired tumors pre- and post-EGFR-TKI. The initial TMB of those ultimately developing T790M resistance tended to be lower compared to other resistance mechanisms. This points to the distinct biology and course of EGFR-mutant NSCLC related to pre-treatment TMB and

tumor heterogeneity. It has been speculated that mostly the emergence of initially subclonal mutations drive the increase in TMB after 1st/2nd generation EGFR TKI treatment, but unable to increase effective immunogenicity. Further investigation in the 3rd generation EGFR TKI is of interest as well.

Interestingly, recently published study (121) on 198 advanced NSCLC patients explored how TMB affects the efficacy of EGFR TKIs and pemetrexed/platinum. The findings pointed that higher non-synonymous TMB correlates with inferior PFS for 1st generation EGFR TKIs in EGFR-mutant NSCLC and worse response to pemetrexed/platinum in EGFR/ALK wild-type patients. The potential for clinical use of TMB as additional biomarker for neoadjuvant approach in early stage setting needs to be investigated in large clinical studies.

## Conclusions

A number of neoadjuvant and adjuvant trials with molecular targeted agents have been undertaken, several of them showing some clinically meaningful results for patients with EGFR-mutant NSCLC. Various challenges of neoadjuvant targeted therapy in early stage NSCLC are the themes that are discussed in this review. Based on available published data several important issues include treatment efficacy, aspects of neoadjuvant targeted treatment relevant for surgery outcomes, response assessment on resection specimens after neoadjuvant treatment, the need for comprehensive molecular profiling in the light of complex resistance mechanisms, prognostic and predictive impact of oncogenic driver alterations in early-stage NSCLC, relationship between TMB and outcomes.

It should be underscored that conflicting results of studies in last decade interpreted with caution, in particular because of commonly used PCR testing limited to mutations in exons 18–21 only in most of them. Novel comprehensive molecular profiling tools like NGS have significantly changed our increasing knowledge about the biology features of EGFR-mutant tumors and impact of evidenced diverse co-mutations and mechanisms of intrinsic/acquired resistance, not only on response to TKIs, but also on the natural history of EGFR-mutant tumors. More studies with much larger patients population enrolled and with extensive molecular profiling are needed to develop the optimal neoadjuvant treatment approach for oncogene-driven NSCLC.

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