REVIEW

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# Tyrosine kinase inhibitors as induction therapy in nonsmall-cell lung cancer

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**Purpose of review**
TKI therapy has shown excellent efficacy and favorable tolerability in patients with mutation-positive nonsmall cell lung cancer. However, there is no clear consensus on the role of TKI as induction therapy. In this article, we reviewed recently published studies to analyze the benefits of tyrosine kinase inhibitors, in particular, EGFR TKIs and ALK TKIs, as inducible treatments for NSCLC.

**Recent findings**
Several clinical trials have recently presented their latest data, giving analysis of patient's survival benefits and adverse events. Initial results have demonstrated promising efficacy and safety data. Some clinical case reports and retrospective analysis demonstrated that EGFR/ALK TKIs can significantly improve PFS and the rate of radical surgery. However, there was no statistically significant difference in overall survival time of almost all clinical trials.

**Summary**
TKIs are increasingly accepted by clinicians as induction therapy in NSCLC. Many studies have demonstrated that neoadjuvant therapy increases the likelihood of surgery and is associated with good resection rates, as evidenced by high prospective downstaging rates in patients with locally advanced NSCLC. However, the risk of recurrence remains high with no evidence of overall survival benefits being reported. Now that more clinical trials are being conducted and more data will be available for analysis, a clearer and more comprehensive view of what role TKIs play in induction therapy will emerge.

**Keywords**
induction therapy, nonsmall-cell lung cancer, survival benefit, tyrosine kinase inhibitor

## INTRODUCTION

Nonsmall-cell lung cancer (NSCLC) is the most common type of lung cancer and is traditionally managed with operation, radiotherapy, chemotherapy and target therapy. Five-year overall survival (OS) rate after stage II–IIIA lung cancer resection is estimated to be between 41 and 65% [1]. The development of targeted therapy has enhanced lung cancer treatments. Epidermal growth factor receptor (EGFR) mutations, such as 19 deletions and L858R mutations are frequently found in patients of East Asia. Rearrangement of the anaplastic lymphoma kinase (*ALK*) gene is a distinct subtype of lung cancer. Tyrosine kinase inhibitors (TKIs) of EGFR and ALK have shown excellent efficacy in advanced EGFR-mutation positive and ALK-rearranged NSCLC.

Tyrosine kinase inhibitors as induction therapy includes preoperative and preconcurrent chemoradiotherapy. TKI therapy and preoperative treatment with EGFR-TKI are of concern to many oncologists. What are the goals of neoadjuvant therapy? First, survival benefits are expected. Second, improving the surgical resection rate and reducing the postoperative recurrence rate are also important. We summarize for these two aspects.

## THE SURVIVAL BENEFIT OF INDUCTION THERAPY BEFORE SURGERY/ CONCURRENT CHEMORADIOTHERAPY

Induction therapy has the potential to shrink tumor mass, improve complete resection rate and reduce the risk of recurrence. On the other hand, neoadjuvant therapy might delay the surgery and possess

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## KEY POINTS

- The ORR and safety of EGFR TKIs as induction therapy of stage II–IIIA NSCLC have been confirmed.
- Compared with chemotherapy, use of EGFR TKIs as induction therapy can improve the rate of radical surgery and PFS for locally advanced EGFRm/ALK-rearranged NSCLC patients.
- Some studies with small samples show good radiological and metabolic response may be achieved for salvage surgery after ALK TKI treatment.
- There has not been evidence of overall survival benefits and reducing the risk of recurrence for EGFR/ALK TKIs as induction treatment.

risk of disease progression. Recent clinical trial data explored the feasibility of EGFR-TKI neoadjuvant therapy. The primary endpoint of most clinical trials conducted on EGFR-TKI neoadjuvant therapy was objective response rate (ORR), which is defined as the proportion of patients achieving complete response (CR) or partial response (PR) according to RECIST version 1.1 [2]. Secondary endpoints were disease-free survival (DFS), OS, the rate of major pathologic response (MPR), and adverse events.

## EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

EMERGING-CTONG 1103 was a randomized phase II study, which was performed to assess the benefits of EGFR-TKI as neoadjuvant/adjuvant therapies in locally advanced EGFR mutation-positive NSCLC. This was a multicenter (17 centers in China), open-label, randomized controlled trial of erlotinib versus gemcitabine with cisplatin (GC chemotherapy) as neoadjuvant/adjuvant therapy in patients with stage IIIA-N2 nonsmall-cell lung cancer with EGFR mutations in exon 19 or 21 (EMERGING). The ORR for neoadjuvant erlotinib versus GC chemotherapy was 54.1 versus 34.3%, and there was no significant difference. No pathologic complete response was identified in either arm. 9.7% and zero, respectively, in the erlotinib and GC chemotherapy arms had a major pathologic response. Median progression-free survi was significantly longer with erlotinib than GC chemotherapy (21.5 versus 11.4 months $P < 0.001$) [3▪▪].

Three single-arm prospective phase II studies used different treatment regimens to determine the efficacy and safety of EGFR-TKI neoadjuvant therapy. In 2019, a phase II study showed that neoadjuvant erlotinib was well tolerated and might improve the radical resection rate in patients with stage IIIA-N2 EGFR mutation-positive NSCLC. The ORR was 42.1%; 89.5% (17/19) of patients achieved disease control, with a 10.3-month median DFS among patients who underwent surgery. Among all 19 patients who received neoadjuvant therapy, media PFS and OS were 11.2 and 51.6 months, respectively. Adverse events occurred in 36.8% (7/19) of patients, and 15.8% experienced grade 3/4 adverse events [4]. *TP53* gene mutation (7/8) in addition to an EGFR mutation was particularly interesting. Having no TP53 mutation, or very low abundance, was associated with longer PFS (36 and 38 months, respectively), whereas high abundance was associated with short PFS (8 months). Therefore, concomitant mutation may significantly impact the efficacy of TKI neoadjuvant therapy. In 2019, in another phase II study, intercalated combination of erlotinib and gemcitabine/cisplatin or carboplatin as neoadjuvant therapy with stage IIIA NSCLC gave different results [5▪]. The ORR was 46.15%, and median DFS was 20 months. Patients with EGFR mutations had a higher ORR (85.7%). But median OS was just 25 months, and mutated EGFR was associated with an increased mortality risk versus wild-type EGFR and unknown EGFR mutational status.

Some data of randomized trials showed significant survival benefit of EGFR-TKI as neoadjuvant therapy. In 2019, 31 treatment-naïve Chinese patients with stage IIIA NSCLC were enrolled. Patients without EGFR mutation received cisplatin-based doublet chemotherapy ($n = 16$) whereas EGFR-mutant patients received erlotinib ($n = 15$) as neoadjuvant therapy. Patients who received erlotinib had a marginally better clinical objective response rate (67 versus 19%), pathological response rate (67 versus 38%), and overall survival (51 months versus 20.9 months) compared with those who received chemotherapy. The significant improvement of OS was because of the difference between the two groups, EGFR mutant and wild type patients [6].

In 2018, American Society of Clinical Oncology (ASCO) annual meeting reported a phase II trial of neoadjuvant afatinib (NeoAfat), and a standard-of-care (SOC) curative intent treatment for EGFRm stage III NSCLC began (NCT01553942) [7]. Recently, an interim analysis gave the evolving SOC landscape. NeoAfat ORR was 69%, and 38% patients reduced their dose of NeoAfat. All patients proceeded to CRT with preop median radiotherapy (RT) dose of 54 Gy (range 45–66; $n = 7$) and definitive median dose of 65 Gy. Seventy-one percent of the seven surgical patients had major (four) or complete (one) pathologic response. There were no treatment-related deaths. Median PFS is 34.6 months, and 2-year OS is 85%. Neo-adjuvant afatinib achieves high ORR and major surgical path responses. So far, this clinical trial is continuing to recruit patients.

**Table 1.** Clinical trials about TKI as induction therapy for NSCLC

| TKI | Clinical trial registry number | Patient population | Estimated enrollment | Intervention/treatment | Status |
|---|---|---|---|---|---|
| Erlotinib | CTONG1103/ NCT01407822 | IIIA-N2 | 72 | 6 weeks of erlotinib versus two cycles of gemcitabine plus cisplatin | Active, not recruiting |
| Erlotinib | ESTERN/NCT01217619 | IIIA-N2 | 25 | 8 weeks of erlotinib | Completed |
| Erlotinib | NCT00600587 | IIIA-N2 | 24 | 6 weeks of erlotinib versus three cycles of gemcitabine plus cisplatin | Completed |
| Gefitinib | NCT01833572 | II–IIIA | 35 | 6 weeks of gefitinib | Completed |
| Afatinib | NCT01553942 | III | 30 | 2 months of afatinib 2–4 weeks of sequential radiotherapy | Recruiting |
| Osimertinib | NCT03433469 | I–IIIA | 27 | 1–2 months of osimertinib | Recruiting |
| Crizotinib | NCT03088930 | Stage IA–IIIA | 18 | 6 weeks of crizotinib | Recruiting |

As a third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations, osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of EGFRm advanced NSCLC, with a similar safety profile and lower rates of serious adverse events [8]. A phase II trial is currently evaluating the efficacy of osimertinib as neoadjuvant therapy in patients with surgically resectable EGFR-mutation NSCLC (NCT03433469) [9]. Participants receive 80 mg osimertinib orally on days 1–28. Treatment repeats every 28 days for a minimum of one cycle prior to surgery in the absence of disease progression or unacceptable toxicity. Investigators will have the option to give a second cycle of study drug prior to surgery if clinically indicated. Depending on the timing of the final scans, patients may ultimately receive up to 2 weeks additional therapy with the study drug beyond the end of cycle 1 (or cycle 2) while awaiting surgery. Patients then undergo surgical resection of their cancer. No treatment with the study drug will be given after surgery. This clinical trial aims to produce positive results and confirm the previous predictions.

## ANAPLASTIC LYMPHOMA KINASE TYROSINE KINASE INHIBITORS

Compared with EGFR-mutant NSCLC, ALK-positive NSCLC appears to be more aggressive and resistant to conventional antineoplastic drugs, which generally leads to a poor clinical prognosis. ALK inhibitors can significantly improve the prognoses of patients with advanced ALK-positive NSCLC but it lacks high-level evidence as a neoadjuvant therapy [10]. Zhong's team reviewed the curative effect of neoadjuvant therapy in patients with locally advanced ALK-positive NSCLC [11▪]. All 11 patients showed promising response to induction treatment, allowing for complete resection. In addition, good tolerance of neoadjuvant crizotinib was confirmed in all cases. The study suggests that crizotinib is effective for neoadjuvant therapy. These cases indicate that good radiological and metabolic response may be achieved for salvage surgery after ALK-TKI treatment for about 3 months. Recently, the same team also reported a successful case of the neoadjuvant alectinib [12▪]. Alectinib could be a more optimal choice with its superior efficacy in preventing brain metastasis in advanced disease. Neoadjuvant alectinib may be clinically feasible. Still, a registered real-world study should be set to further assess its clinical implications. The ongoing clinical trials about TKI induction therapy for NSCLC will provide more evidence (Table 1).

## THE RATE OF RADICAL SURGERY OF TYROSINE KINASE INHIBITOR INDUCTION THERAPY AND RECURRENCE RATE

Stage IIIA NSCLC patients are a heterogeneous group with diverse presentations ranging from apparently resectable tumors with occult microscopic nodal metastases to unresectable multistation nodal disease [4]. As mentioned earlier, clinical trial data suggested TKI neoadjuvant therapy could induce tumor downstaging, improving complete resection rate.

EMERGING-CTONG 1103 showed that no pathologic complete response was identified in either erlotinib or GC chemotherapy arms. In a prospective, single-arm, phase II study, the radical resection rate was 68.4% [3▪▪], and MPR was 24.2% in another phase II study [5▪]. The primary endpoint of these trials was ORR, which was 42–67% [3▪▪,4,5▪]. In 2020, a phase II study with gefitinib as neoadjuvant therapy for resectable stage II–IIIA NSCLC cancer showed that ORR was 54.5% and MPR was 24.2%. Median DFS was 33.5 months and median OS was not reached [13]. No patient was reported grade 3 or 4 adverse events.

ADJUVANT CTONG1104 [13] suggested that adjuvant gefitinib led to significantly longer disease-free survival compared with that for vinorelbine

 

with cisplatin in patients with completely resected stage II–IIIA (N1–N2) EGFRm NSCLC. On the basis of the superior disease-free survival, reduced toxicity, and improved quality of life, adjuvant gefitinib could be a potential treatment option compared with adjuvant chemotherapy in these patients. However, the duration of benefit with gefitinib after 24 months might be limited. It must also be noted that the proportion of patients with disease relapse was comparable between the two treatment groups (52% with gefitinib and 50% with vinorelbine with cisplatin). The inference is similar to the RADIANT study; the use of TKI does not prevent a recurrence of the disease but simply delays its onset, which is a challenge when selecting postoperative treatment strategies. Update on ASCO in 2020, median OS of patients receiving subsequent target therapy was 75.5 months and the other arm was 79.2 months ($P = 0.823$) [14▪].

NCT01553942 was a phase II study where neoadjuvant afatinib and standard of care (SOC) curative intent treated EGFRm stage III NSCLC. With median follow-up of 24.1 months (range 5.0–64.2), 6 (46%) patients have recurred, including 4/6 inoperable patients, 2/7 who had surgery, 1/5 with major path response [central nervous system (CNS)-only recurrence]. It is difficult for EGFR TKI as neoadjuvant therapy to reduce postoperative recurrence rates.

## CONCLUSION

Currently, the ORR and safety of EGFR/ALK TKIs as induction treatment of stage II–IIIA NSCLC have been confirmed. TKI induction therapy could induce tumor downstaging, improving complete resection rate. However, there has not been evidence of overall survival benefits and reducing the risk of recurrence. We are looking forward to large-scale randomized controlled trials investigating the role of TKIs in perioperative therapy, combining induction and adjuvant treatments to enhance personalized therapy in the future.

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### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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This was a multicenter, phase II, randomized controlled trial. They found that the erlotinib group achieved significant improvement in progression-free survival.

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This article described the first clinically successful case involving neoadjuvant alectinib. It is the initial evidence that neoadjuvant alectinib may be clinically feasible.

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This is a randomized phase 3 trial that showed adjuvant gefitinib treatment significantly improved DFS versus standard doublet chemotherapy in patients with EGFR mutation-positive resected stage II–IIIA (N1–N2) NSCLC. But the DFS survival advantage did not translate to OS difference in this trial.