A meta-analysis of adjuvant EGFR-TKIs for patients with EGFR mutation of resected non-small cell lung cancer

Ran Cui, MDa, Chun Wei, MDa, Xianyi Li, MDa, Ou Jiang, PhDab,*

Abstract
Background: The role of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKIs) in improving the prognostic outcome of non-small cell lung cancer (NSCLC) cases harboring EGFR mutation following radical surgery is still controversial. This work focused on comparing EGFR-TKIs and adjuvant chemotherapy (ACT) or placebo in treating NSCLC cases, specifically on those with EGFR-mutant, being in the stage of IB-IIIA and possibly gained benefits from the above treatment after radical resection.

Methods: The Cochrane Library, MEDLINE, and Embase databases were searched to identify eligible clinical trials; two authors were responsible for screening the results. The primary outcomes were evaluated by disease-free survival (DFS) and overall survival (OS) based on hazard ratios (HRs) and a relevant 95% confidence interval (CI).

Results: The literature search yielded twelve eligible studies, including four retrospective cohort studies and eight randomized controlled trials (RCTs) that enrolled 1694 cases and were of acceptable quality. In patients receiving adjuvant EGFR-TKIs compared with ACT or placebo treatment, HR regarding DFS was 0.47 (95% CI: 0.40, 0.55), whereas the OS rate was 0.74 (95% CI: 0.58, 0.95). For patients who received adjuvant EGFR-TKIs in combination with conventional chemotherapy compared to chemotherapy, the efficiency was significantly enhanced, with the HR for DFS being 0.29 (95% CI: 0.15, 0.58) and that for OS being 0.51 (95% CI: 0.25, 1.04), separately.

Conclusion: For NSCLC cases who had EGFR mutations and surgery, adjuvant EGFR-TKI combined with chemotherapy achieved superior effect over chemotherapy or placebo with reference to DFS and may prolong the OS up to some extent.

Abbreviations: ACT = adjuvant chemotherapy, CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small cell lung cancer, OS = overall survival, RCTs = randomized controlled trials, TKIs = tyrosine kinase inhibitors.

Keywords: adjuvant therapy, chemotherapy, EGFR tyrosine kinase inhibitor, meta-analysis, non-small-cell lung cancer.

1. Introduction
Lung cancer is one of the most common cancers in the world, with the highest mortality rate (18.0%). NSCLC (non-small cell lung cancer) accounts for 80% of all lung cancers. 5-year survival after radical resection for NSCLC patients in stages IB-IIIA remains 26% to 62%. Postoperative adjuvant therapy is therefore essential. From 2003 to 2008, several large randomized controlled trials (RCTs) were conducted to determine whether adjuvant chemotherapy (ACT) after radical surgery effectively improves long-term survival in this patient population. The studies also showed that in stage IB-IIIA NSCLC cases undergoing radical surgery, cisplatin-based chemotherapy could only increase 5-year survival by 5% (40–45%).

Adjuvant therapy after radical surgery has become a rational approach to lowering the risk of recurrence and improving overall survival (OS) outcomes. According to some studies, adjuvant epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKIs) can significantly improve the survival of NSCLC patients with EGFR mutations after radical resection compared to standard chemotherapy. The studies CTONG1104 and EVIDENCE, disease-free survival (DFS) was improved when Adjuvant EGFR-TKIs were compared with standard of care chemotherapy in patients with NSCLC and EGFR mutation, with hazard ratio (HR) = 0.60, 95% CI: 0.42, 0.87; Phet = 0.0054)
and HR = 0.36 [95% CI: 0.24, 0.55]; Phet < 0.0001], respectively. Furthermore, the recently updated ADAURA study found that, regardless of disease stage, patients who received osimertinib after radical surgery had a better DFS than those who received adjuvant chemotherapy (HR = 0.16, 95% confidence interval: 0.10, 0.26). While those studies did not show a significant difference in OS due to DFS advantage. Simultaneously, some studies yielded negative results. The IMPACT study found no statistically significant differences in DFS or OS, with HR = 0.92 [95% CI: 0.67, 1.28] and HR = 1.03 [95% CI: 0.65, 1.65], respectively, in patients with completely resected pathologic stage II-III non-small-cell lung cancer harboring EGFR mutations receiving gefitinib. Therefore, the use of EGFR-TKI after surgery is still debatable.

Because recent studies have reached conflicting conclusions, we conducted this meta-analysis to compare adjuvant EGFR-TKI with conventional chemotherapy in NSCLC cases undergoing radical surgery, with the goal of determining the best treatment for patients with stage IB-IIIA EGFR mutations.

2. Methods

2.1. Strategy for literature search

This study systemically searched Embase, PubMed, Cochrane, and Web of Science databases for identifying related studies that compared EGFR-TKI with chemotherapy among NSCLC cases harboring EGFR mutation and received radical surgery from inception to March 10, 2022. The keywords included non-small cell lung cancer, EGFR, TKI, postoperative, and chemotherapy. The search terms included (“Non-small cell lung cancer” or “lung tumor” or “lung cancer”) and (“EGFR-TKI” or “EGFR-tyrosine kinase inhibitor” or “erlotinib” or “gefitinib” or “afatinib” or “icotinib” or “neratinib” or “vandetanib” or “dacomitinib” or “osimertinib” or “canertinib” and (“Adjuvant” or “auxiliary” or “accessory” OR “adjunct” or “intercalated” or “alternative”).

2.2. Study selection

Study inclusion criteria were shown below:

1. Studies, including adult cases with the diagnosis of NSCLC (pathological stage IB-IIIa) who could receive ACT;
2. Those evaluating the effect of EGFR-TKIs-ACT compared with placebo or chemotherapy, or TKIs-ACT compared with chemotherapy;
3. Those that reported one or more related clinical outcomes like overall survival (OS) and DFS and had available long-time follow-up data; and
4. Those with adequate raw data to calculate HRs and P-values. All the enrolled articles were published in English, and the publication type was not restricted.

Studies conforming to the following criteria were excluded:

1. Single-arm articles that reported outcomes of EGFR-TKI-ACT;
2. Articles that had inadequate data to carry out statistical analysis;
3. Duplicate studies;
4. No available full texts in the original studies.

2.3. Outcomes and data extraction

Basic information from all the enrolled articles was collected by two researchers (CW and XY). Any disagreements between them regarding study screening and data collection were settled down through mutual negotiation or by the opinion of a third researcher (RC). Furthermore, we recorded the available data like first author, publication year, case numbers and baseline features, clinical stage, tumor histology, interventions, EGFR status, outcomes, study design and phase, OS, and DFS for comparing the benefits of EGFR-TKI-ACT and traditional chemotherapy for NSCLC cases receiving radical surgery. Those original and acquired data were imported into the standard tables.

2.4. Quality assessment

The bias risk approach (Cochrane Handbook for Systematic Reviews of Interventions) was implemented by two reviewers for the independent assessment of study quality. This meta-analysis also assessed the generation of sequences, concealment of allocation, missing data, blinding, selective reporting, as well as additional biased sources. Any disagreement was settled down through mutual negotiation or the opinion of a third investigator.

This work utilized the Newcastle–Ottawa Scale (NOS) in non-RCTs, including three categories, selection, outcome, and comparability. Our enrolled RCTs quality was evaluated following Cochrane Collaboration’s approach to evaluating bias risk (5.3.0) by the methodological items below, generation of random sequences, concealment of allocation, outcome assessment, selective reporting, insufficient outcome data, as well as additional possible bias sources. The items were categorized into low, high, or unclear risk, and together they determined the general quality. Figures 1 and 2 display the risk-of-bias graph and summary. Table 1 display the Newcastle–Ottawa scale for quality assessment of non-randomized cohort studies. The opinion of a third researcher settled down disagreements.

2.5. Statistical analysis

This meta-analysis was carried out by integrating survival data from articles conducted by Parmar and Tierney. Log (HR) and standard error data of enrolled RCTs were collected to analyze the time-to-event data.

The F² test was applied to analyze heterogeneity, where F < 50% and P > 0.1 indicated no heterogeneity, and the fixed-effects model was applied, whereas F > 50% stood for significant heterogeneity, and the random-effects model should thereby be utilized. P < 0.05 denotes statistical significance. Review Manager Software, version 5.3 (Cochrane Collaboration, Oxford, UK), was employed for statistical analysis.

DFS was considered the primary endpoint, and it characterized the duration between randomization and disease recurrence or death. OS was regarded as the secondary endpoint.

3. Results

Figure 3 represents the study screening flowchart. Among those 4135 studies obtained from the literature review, just 12 articles were qualified for our meta-analysis. Of which eight were RCTs, and four were RCSs. Table 2 displays enrolled study features.

This work enrolled 1694 cases for meta-analysis altogether; among them, 926 received adjuvant EGFR-TKI, whereas 768 received placebo. In four studies (5, 25, 23, 18), not all patients have EGFR mutation, but these studies analyzed the data from cases harboring EGFR-mutation, in which the analyzed got positive results. All the patients included in the other eight studies had EGFR mutations.

3.1. Effects of adjuvant TKIs versus placebo or chemotherapy on DFS and OS

In eight RCTs and four RCSs, DFS was analyzed. As a result, EGFR-TKI-ACT improved patient DFS (HR, 0.47; 95% CI: 0.40, 0.55) (Fig. 4). There was obvious heterogeneity among enrolled articles by using the random-effects model
Also, our analysis showed that the OS (HR,0.74; 95% CI: 0.58, 0.95) (Fig. 5) after adjuvant EGFR-TKIs was better than chemotherapy, in which five RCTs (7, 8, 10, 11,23) and four RCSs (5, 20, 26, 28) were included. While there was obvious heterogeneity among those involved articles (Phet < 0.00001, $I^2 = 80\%$), the significant heterogeneity mainly comes from the study ADAURA2017 according to the sensitivity analyses. No significant publication bias was found.

## 3.2. Effects of adjuvant TKIs versus chemotherapy on DFS and OS

Four RCTs (7, 8, 10, and 23) and one RCS (20) were included in this analysis to assess DFS and OS. Adjuvant TKIs significantly improved DFS (HR,0.43; 95% CI: 0.26, 0.72) (Fig. 6) among EGFR-mutation cases. Significant heterogeneity was noted (Phet < 0.00001, $I^2 = 85\%$). At the same time, there is no

![Figure 1. Study screening flowchart. EGFR = epidermal growth factor receptor, TKIs = tyrosine kinase inhibitors.](image)

![Figure 2. Forest plots showing HR regarding DFS for adjuvant EGFR-TKI compared with placebo among NSCLC cases receiving radical surgery. CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.](image)

**Table 1**

Newcastle–Ottawa quality assessment scale.

| Study        | Selection | Comparability | Exposure |
|--------------|-----------|---------------|----------|
|              | 1 | 2 | 3 | 4 | 1 | 2 | 3 |
| Angelo 2012  | b | a | a | b | ab | a | a | a |
| Yelena 2011  | b | a | a | a | ab | a | a | b |
| lv2015       | b | a | a | b | a | a | a | a |
| Pan2021      | b | a | a | a | ab | a | a | b |
Figure 3. Forest plots showing HR regarding OS for adjuvant EGFR-TKI compared with placebo among NSCLC cases receiving radical surgery. CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, OS = overall survival, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.

Table 2

| Study      | Intervention                        | Size | EGFR mutation (%) | TKI vs Control arm number | Stage       | Median follow up (mo) | Design  | Primary endpoint |
|------------|-------------------------------------|------|-------------------|---------------------------|-------------|-----------------------|---------|------------------|
| CTONG1104  | gefitinib chemotherapy               | 222  | 100%              | 111                       | 0 74 148 36.5 | RCT DFS/OS            |         |                  |
| 2018[17]   |                                     |      |                   |                           |             |                       |         |                  |
| EVIDENCE   | icotinib chemotherapy                | 322  | 100%              | 161                       | 88 14 181 25 | RCT DFS               |         |                  |
| 2021[18]   |                                     |      |                   |                           |             |                       |         |                  |
| IMPACT2021 | gefitinib chemotherapy               | 232  | 100%              | 116                       | 74 9 144 70 | RCT DFS/OS            |         |                  |
| 2021[18]   | erlotinib chemotherapy               | 102  | 100%              | 51                        | 0 0 102 33  | RCT DFS/OS            |         |                  |
| EVAN2018   | osimertinib + chemotherapy           | 682  | 100%              | 203                       | 216 231 235 22 | RCT DFS               |         |                  |
| ADURA2017  | placebo + chemotherapy osimertinib   | 207  | 100%              | 135                       |             |                       |         |                  |
| 2017[18]   |                                     |      |                   |                           |             |                       |         |                  |
| lv2015     | erlotinib/gefitinib/icotinib Placebo| 257  | 138 (53.6%)       | 30                        | 126 48 83 31 | RCS DFS/OS            |         | DFS/OS           |
| Angelo 2012| erlotinib or gefitinib placebo       | 1118 | 284 (25.4%)       | 84                        | 718 166 167 27 | RCS DFS/OS            |         | DFS/OS           |
| BR19 2012  | gefitinib placebo                    | 503  | 15 (4%)           | 7                         | 260 175 67 56.4 | RCT DFS/OS            |         | DFS/OS           |
| Yelena 2011| erlotinib or gefitinib               | 167  | 100%              | 56                        | 117 25 25 20 | RCS DFS/OS            |         | DFS/OS           |
| Li 2014    | gefitinib + chemotherapy             | 60   | 100%              | 111                       | 0 0 60 30.6 | RCT DFS/OS            |         | DFS/OS           |
| Feng2015   | icotinib + chemotherapy               | 39   | 100%              | 21                        | 17 10 12 46.4 | RCT DFS               |         | DFS/OS           |
| Pan 2021   | icotinib chemotherapy                | 43   | 100%              | 22                        | 0 43 0 35.5 | RCS DFS/OS            |         | DFS/OS           |

DFS = disease-free survival, OS = overall survival, RCTs = randomized controlled trials.

Figure 4. Forest plots showing HR regarding DFS for adjuvant EGFR-TKI compared with chemotherapy among NSCLC cases receiving radical surgery. CI = confidence interval, DFS = disease-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = non-small-cell lung cancer, SE = standard error, TKI = tyrosine kinase inhibitor.
significant beneficial effect of TKI treatment on OS (HR, 0.79; 95% CI: 0.59, 1.05) (Fig. 7) compared with chemotherapy in the patients with NSCLC. The heterogeneity mostly comes from study Pan2021 with no significant publication bias.

3.3. Effects of adjuvant TKIs plus chemotherapy versus chemotherapy alone on DFS and OS

The analysis included three RCTs (11, 25, 29) and one RCS (26), showing that TKIs plus chemotherapy were superior to those of chemotherapy in both DFS (HR, 0.29; 95% CI: 0.15, 0.58) (Fig. 8) as well as OS (HR, 0.51; 95% CI: 0.25, 1.04) (Fig. 9). Upon sensitivity analysis, the combined results were not significantly affected by any study, despite the apparent heterogeneity (Phet = 0.001, $I^2 = 79\%$) regarding DFS. And no significant publication bias was found.

3.4. Ongoing clinical trials

According to Table 3, seven ongoing RCTs enrolling 1819 cases were conducted using the intervention model, including...
2 (NCT02264210, NCT05120349) that collected early cases; the others involved the treatment of patients at different stages.

4. Discussion

The continuous innovation and research progress of EGFR-TKIs in recent years has provided clinical researchers with novel therapies and application ideas. Although TKIs have increased efficacy in EGFR mutation advanced NSCLC compared with chemotherapy,[17] whether TKI should be used in NSCLC cases receiving radical surgery remains controversial. According to our findings, adjuvant EGFR-TKIs enhanced DFS among cases with EGFR mutation after radical resection compared with chemotherapy, whereas OS was not significant. The adjuvant EGFR-TKIs plus chemotherapy demonstrated a significant beneficial effect on DFS and OS. The meta-analyze may support these results, showing that TKIs plus chemotherapy, the first-line therapy, significantly increase ORR while improving OS and DFS for advanced NSCLC cases with EGFR mutation.[18]

EGFR-TKIs have been recommended as first-line therapies for patients with EGFR-mutant NSCLC, and patients tend to benefit from adjuvant EGFR-TKI treatment in terms of DFS and OS. The ability of adjuvant EGFR-TKI treatment, however, remains unsatisfactory. According to some studies[7,8,23] EGFR-TKI DFS is superior to chemotherapy in EGFR mutation NSCLC patients. However, TKI cannot effectively prolong patients’ survival when compared to chemotherapy.[7,8,23] The recent IMPACT study found that gefitinib as postoperative adjuvant therapy for patients did not improve DFS or OS.[10] The reason why TKI can only prolong DFS but not show DFS advantage translate to a significant OS difference in those studies (even in IMPACT both DFS and OS were not positive) may be that previous studies’ follow-up time (The median follow-up time for most experiments was no more than 40 months) were shorter than IMPACT (70 months), and the performance of TKI’s DFS was more superior in the early stage, while the DFS of TKI gradually decreased to the same level as the placebo.

Chemotherapy remains the guideline-recommended adjuvant treatment, despite having limited benefits for patients. EGFR-TKIs may inhibit sensitive mutant cancer cell growth, while chemotherapy may eliminate tumor cells and prevent micrometastasis.[22,23] Noronha et al recently discovered that TKI combined with chemotherapy can significantly improve DFS and OS in resected NSCLCs.[34,25] Furthermore, the percentage of patients receiving EGFR-TKI combined with chemotherapy who were alive and disease-free at 24 months was 89% (95% CI 95%, 99%), while the placebo arm had only 58% (95% CI 80%, 89%) in the ADAURA[11] study. A subgroup analysis was also performed in this study for patients after resection who received TKI combined with chemotherapy versus those who received

| Table 3 |
|---------|
| Patient features among ongoing research. |
| Study (ClinicalTrials.gov) | Study type | Estimated enrollment | Allocation | Intervention mode | Stage | Actual study start date | Estimated primary completion date |
| NCT02193282 | Interventional | 450 | Randomized | Parallel assignment | IB-IIIA | 2014/7/17 | 2026/10/10 |
| NCT02264210 | Interventional | 128 | Randomized | Parallel assignment | IB | 2014/10/15 | 2025/12/1 |
| NCT02448797 | Interventional | 320 | Randomized | Parallel assignment | II-IIIA | 2015/5/19 | 2023/12/1 |
| NCT04351555 | Interventional | 328 | Randomized | Parallel assignment | II - IIIB N2 | 2020/4/17 | 2029/3/29 |
| NCT05132985 | Interventional | 45 | Randomized | Parallel assignment | II-IIIB N2 | 2021/11/24 | 2028/1/1 |
| NCT04455594 | Interventional | 168 | Randomized | Parallel assignment | IIIA-N2 | 2020/7/2 | 2025/10/1 |
| NCT05120349 | Interventional | 380 | Randomized | Parallel assignment | IIA-I A3 | 2021/11/15 | 2032/11/2 |
Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIA non-small cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.

Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA non-small-cell lung cancer harboring positive EGFR mutations: a single-center retrospective study. Clin Lung Cancer. 2015;16:173–81.

Xie H, Wang H, Xu L, et al. Gefitinib versus adjuvant chemotherapy in patients with stage II-IIIA non-small-cell lung cancer harboring positive EGFR mutations: a single-center retrospective study. Clin Lung Cancer. 2018;19:484–92.

Zhong W-Z, Wang Q, Mao W-M, et al. ADJUVANT investigators. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CITONG1104): a randomised, open-label, phase 3 study. Lancet Oncol. 2018;19:139–48.

Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage II-IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med. 2018;6:863–73.

Tsoubi M, Kato H, Nagai K, et al. Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer. Anticancer Drugs. 2005;16:1123–8.

He J, Su C, Liang W, et al. Icotinib versus chemotherapy as adjuvant treatment at stage II-IIIA EGFR-mutant non-small-cell lung cancer (evidence): a randomised, open-label, phase 3 trial. Lancet Respir Med. 2021;9:1021–9.

Wu YL, John T, Grohe C, et al. Postoperative chemotherapy use and outcomes from ADAURA: osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC. J Thorac Oncol. 2022;17:423–33.

Kelly K, Altoroki NA, Eberhardt WE. Adjuvant erlotinib versus placebo in patients with stage IIb-IIIA non-small-cell lung cancer (radiant): a randomized, double-blind, phase III trial. J Clin Oncol. 2015;33:44007–14.

Tada H, Mitsudomi T, Misumi T, et al. Randomized phase iii study of gefitinib versus cisplatin plus vinorelbine for patients with stage I-IIIA non-small-cell lung cancer with EGFR mutation (impact). J Clin Oncol. 2022;40:231–41.

Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343.

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17:2815–34.

Tierney JF, Stewart LA, Gersdorff S, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:1–16.

Shi Q, Guan M, Wang Y, et al. Survival analysis of patients with advanced non-small cell lung cancer receiving tyrosine kinase inhibitor (TKI) treatment: a multi-center retrospective study. Thor Cancer. 2018;9:278–83.

Wu Q, Luo W, Li W, Wang T, Huang L, Xu F. First-generation EGFR-TKI plus chemotherapy versus EGFR-TKI alone as first-line treatment in advanced NSCLC with EGFR activating mutation: a systematic review and meta-analysis of randomized controlled trials. Front Oncol. 2021;11:1883.

Wu Y-L, Tsuobi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383:1711–23.

Pan S, Wang S, Li W, Chai Y. Icotinib versus cisplatin plus docetaxel as adjuvant chemotherapy in patients with stage II (n1) non-small cell lung cancer harboring positive EGFR mutations: a single-center retrospective study. Oncol Targets Ther. 2021;14:1083–91.

Hosomi Y, Morita S, Sugawara S, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: Nej009 study. J Clin Oncol. 2020;38:1115–23.

Peng S, Wang R, Zhang X, et al. EGFR-TKI resistance promotes immune escape in lung cancer via increased PD-L1 expression. Mol Cancer. 2019;18:165.

Eguchi T, Kodera Y, Nakashima H, et al. The effect of chemotherapy against micrometastases and isolated tumor cells in lymph nodes: an in vivo study. In Vivo. 2008;22:707–12.

Noronha V, Patil VM, Joshi A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. J Clin Oncol. 2020;38:124–36.

Li N, Ou W, Ye X, et al. Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIa-N2 non-small cell lung cancer harbouring EGFR mutations: a randomized, phase II study. Ann Surg Oncol. 2014;21:2091–6.
[26] D’Angelo SP, Janjigian YY, Ahye N, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol. 2012;7:1815-22.

[27] Goss GD, O’Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol. 2013;31: 3320-6.

[28] Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. J Thorac Oncol. 2011;6:569-75.

[29] Feng S, Wang Y, Cai K, et al. Randomized adjuvant chemotherapy of EGFR-mutated non-small cell lung cancer patients with or without Icotinib consolidation therapy. PLoS One. 2015;10:e0140794.