Review Article

Front-Line Therapy in EGFR Exon 19 Deletion and 21 Leu858Arg Mutations in Advanced Non-Small Cell Lung Cancer: A Network Meta-Analysis

Tongji Xie,1 Zihua Zou,1 Chengcheng Liu,2 Yixiang Zhu,1 Ziyi Xu,1 Le Wang,3 Junling Li,1 and Puyuan Xing1

1National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
2Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
3Department of Cancer Prevention, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China

Correspondence should be addressed to Puyuan Xing; xingpuyuan@cicams.ac.cn

Received 29 June 2021; Accepted 10 November 2021; Published 13 December 2021

Academic Editor: Woon-Man Kung

Copyright © 2021 Tongji Xie et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. This study aimed to compare the efficacy of different first-line strategies based on different EGFR mutation types (19 deletion and 21 Leu858Arg mutations).

Methods. We conducted a systematic review and network meta-analysis (NMA) by searching and analyzing RCTs on PubMed, Embase, Cochrane Library, ASCO.org, and ESMO.org, from inception to September 30th, 2020.

Results. Nineteen RCTs involving 5450 patients were finally included in this study, covering 10 different treatment strategies. The Bayesian ranking results suggested that, in terms of PFS, in the overall population and in patients with 19del mutation, osimertinib was most likely to rank the first, with the cumulative probabilities of 41.89% and 45.73%, respectively, while for patients with 21 Leu858Arg mutation, standard of care (SoC, represents first-generation EGFR-TKIs in this NMA) + chemotherapy was most likely to rank the first, with the cumulative probabilities of 30.81% in PFS. Moreover, SoC + chemotherapy provided the best overall survival benefit for the overall population and patients with 19del, with the cumulative probabilities of 57.85% and 33.51%, respectively. In contrast, for patients with 21 Leu858Arg mutation, dacomitinib showed the most favorable overall survival, with the cumulative probabilities of 36.73%. Conclusions. In this NMA, osimertinib and SoC combined with chemotherapy would be the optimal first-line treatment options for advanced NSCLC patients harboring EGFR 19 deletion mutation and 21 Leu858Arg mutation, respectively. This finding is likely to be adopted in clinical practice and provide guidance for future clinical study design. Systematic review registration: INPLASY2020100059.

1. Introduction

Lung cancer leads to the highest cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of overall lung cancer cases [1]. Due to the great progress in molecular diagnostic technology, several driven genes have been identified in lung adenocarcinoma, resulting in shifting the treatment for these patients from chemotherapy to targeted therapy [2]. Because numerous clinical trials demonstrated the superiority of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) over platinum-based doublet chemotherapy in overall response rate (ORR) and progression-free survival (PFS), multiple generations of EGFR-TKIs became standard treatments in the first-line setting, including first-generation TKI gefitinib, erlotinib and icotinib, second-generation TKI dacomitinib and afatinib, and third-generation TKI osimertinib [3]. Furthermore, some synergistic combination
strategies such as chemotherapy plus EGFR-TKIs or anti-angiogenic drugs plus EGFR-TKIs were also investigated in some clinical trials to overcome the acquired resistance of targeted therapy [4].

What is more, the advanced NSCLC patients harboring EGFR mutation are different, including race, gender, age, smoking status, and EGFR mutation status. In terms of EGFR gene mutation, there are two common types (19 deletion mutation and 21 Leu858Arg mutation) [5] and other rare types (such as 18 Gly719Cys mutation) [6]. Data in multiple trials have shown that the efficiency of different treatment strategies might differ in various kinds of EGFR mutation statuses, especially between 19 deletion and 21 Leu858Arg mutations [7–13].

Although many previous network meta-analyses analyzed some preferable choices for EGFR-mutated advanced NSCLC based on different mutation statuses via indirect comparisons [14], some important data were still unavailable, such as final overall survival (OS) for FLAURA and NEJ026 study and PFS for CTONG-1509, RELAY, and ACTIVe study [7, 8, 15–18]. Thus, we conducted this network meta-analysis (NMA) which is widely used in the absence of head-to-head trial data [19] to further integrate the latest outcomes of randomized controlled trials and synthesize direct and indirect evidence to draw a more potent conclusion.

2. Method

2.1. Participants and Methods. This systematic review was conducted and reported under the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. The protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) and is available in full at inplasy.com (https://inplasy.com/inplasy-2020-10-0059/) or in Table S1.

2.2. Systematic Literature Review. This systematic literature review was conducted to identify clinical trials assessing the efficacy of EGFR-TKIs, including PFS and OS. The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched from inception to September 30th, 2020. Under the guidelines of PICOs, combinations of MeSH terms and keywords related to “NSCLC,” “EGFR,” “TKI,” “PFS,” “OS,” and “Randomized Controlled Trial (RCT)” were applied in the literature search. Besides, literature was further supplemented in conferences of the American Society of Clinical Oncology, European Society of Medical Oncology, European Cancer Conference, and World Conference on Lung Cancer. Detailed search strategies are available in Table S2.

2.3. Outcome Definition. The primary outcome was PFS, defined as the time from randomization to the first documented disease progression or death from any cause. The secondary outcome was OS, which was defined as the time from date of randomization to death from any cause.

2.4. Selection of Studies for the NMA. Eligible studies need to meet all the following inclusion criteria: (1) study population: patients with advanced NSCLC harboring EGFR mutation; (2) interventions: EGFR-TKIs with or without antivascular endothelial growth factor (VEGF); (3) comparators: EGFR-TKIs or chemotherapy; (4) outcomes: OS, PFS; and (5) study design: RCTs.

Studies were excluded if they met any of the following exclusion criteria: (1) no EGFR mutation patients; (2) no intervention of EGFR-TKIs; (3) EGFR-TKIs not as first-line treatment; (4) no survival data; (5) duplicated studies; and (6) review, comment, editor opinion, or protocol.

2.5. Data Extraction and Risk of Bias Assessment. According to predefined eligibility criteria by the research working group, the titles and abstracts of all identified records were initially screened. Then, potentially eligible studies were assessed by full text. For the final included studies, data extraction and risk of assessment were further performed. The above contents were conducted by Tongji Xie and Zihua Zou independently, and a third expert (Puyuan Xing) was invited to arbitrate until reaching a consensus in case of any disagreement.

A proform designed by the review working group was done for data extraction, including the following information: (1) basic information: name of the study, year of publication, country; (2) trials design: design type, patient characteristics, sample size, therapies in intervention, and control group; and (3) outcomes: data on PFS and OS.

The Cochrane risk-of-bias tool [21] was used to assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases.

2.6. Network Meta-Analyses. For both survival outcomes, the natural log hazard ratio (HR) versus the reference arm and its associated standard error (SE) were used as inputs for the NMAs. The network plots were drawn using Stata software (version 15.0) to show the interaction of different treatment regimens in the included studies [22]. Heterogeneity across included studies was assessed by Q test and I². Heterogeneity was considered low, moderate, or high for estimated I² values under 25%, between 25% and 50%, and over 50%, respectively [23].

Bayesian network meta-analysis was applied due to its advantages of accommodating complex situations (accounting for the effect of study-specific covariates, resulting in exact estimates in the presence of limited information) and providing a more straightforward method for conducting probabilistic statements and predictions on the treatment effects. The Bayesian framework was performed by a Markov Chain Monte Carlo simulation technique in R software (version 3.6.3). We utilized the "gemtc" and "rjags" packages and chose the random effect model, using the odds ratio (OR) as the effect quantity and 95% credible interval (CI) to compare the intervention measures [24].
Based on the previous experience and published literature, we chose the fixed model in the registration for this NMA. When we conducted the analysis, most NMAs showed low heterogeneities because most evaluated interventions were from only one or two studies with almost identical population characteristics. However, for PFS in all patients, high heterogeneities could be found in the comparisons between Chemotherapy and Afatinib ($I^2 = 75.7\%$), standard of care (SoC, represents first-generation EGFR-TKIs in this NMA), and chemotherapy ($I^2 = 74.8\%$). For PFS in patients with 19del mutation, comparisons of SoC and chemotherapy ($I^2 = 70.9\%$) showed high heterogeneities. In addition, for PFS in patients with 21 Leu858Arg mutation, comparisons of chemotherapy and afatinib ($I^2 = 65.6\%$), SoC and chemotherapy ($I^2 = 55.2\%$), and SoC + chemotherapy and SoC+Afatinib ($I^2 = 53.7\%$) showed high heterogeneities. For OS in all patients, high heterogeneities could be found in the comparisons between chemotherapy and afatinib ($I^2 = 70.7\%$), and SoC and osimertinib ($I^2 = 65.4\%$). For OS in patients with 19del mutation, comparisons of SoC and Afatinib ($I^2 = 64.1\%$), and SoC and chemotherapy ($I^2 = 54.6\%$) also showed high heterogeneities (data were not shown). Finally, given the high heterogeneities mentioned above, the random effects consistency model was used to guarantee the model’s robustness.

There are four different sets of initial values to fit the model. For both the PFS and OS, 10,000 sample iterations were generated with 5,000 burn-ins and a thinning interval of 5. We evaluated convergence of iterations by visual inspection of the four chains to establish homogenous parameter estimates in accordance with the density plot (Figure S1) [25]. Under the Bayesian framework, NMA estimated the overall rankings of treatments based on the surface under the cumulative ranking curve for each, which equals 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst.

More importantly, two key assumptions in support of the NMA are transitivity (the exchangeability across included studies to compare two treatments via a third one) and consistency (that the direct and indirect estimates are statistically similar). To guarantee the transitivity, we identified randomized controlled trials with strict patient allocation and optimized the same condition for all evaluated treatments. Inconsistency was evaluated by comparing the fit of consistency and inconsistency models [26]. If a direct comparison existed simultaneously between the 2 interventions, a node splitting technique was used to evaluate the network consistency by determining the difference between the indirect and direct estimates.

3. Results

3.1. Characteristics of Included Studies. A total of 19 randomized controlled trials were finally included in this study, covering 10 different treatments. Detailed information for inclusion and exclusion is shown in Figure 1.

Table 1 summarizes studies included in this meta-analysis [7–13, 15–18, 27–45]. The range of median PFS follow-up time was between 2.7 and 45.0 months. The range of median OS follow-up time was between 27.0 and 59.1 months. The mean sample size was 287 patients (range, 81 to 556 patients).

3.2. Quality of Reporting Evidence. The quality assessment for included studies was mainly based on the Cochrane handbook. The overall quality is of low-to-medium bias risk.

All included studies described the method used to generate the allocation sequence, conceal the allocation sequence, and report the related outcomes based on the trial’s protocol. No serious census data could be found in most studies, except for the trial NCT01466660 [27, 28] with high incomplete outcome bias: 34 patients recruited in this trial did not have their ethnic origin recorded [27]. However, these 34 patients were sorted into a non-Asian group when the OS of the trial was reported [28]. Although we do not analyze the ethnic information of patients, the bias of the trial NCT01466660 [27, 28] adversely affects the reliability of its results. More importantly, most studies did not state the method for blending in both the intervention and outcome. Details for the quality evaluation of the included literature are listed in Figure 2.

3.3. Network Meta-Analysis. Network meta-analysis included all treatments for PFS, while there were 16 studies with the outcome of OS. For patients with 19del mutation, all identified literature reported PFS (Figure 3(a)), while 11 had the outcome of OS (Figure 3(b)). For patients with 21 Leu858Arg mutation, 18 included studies reported PFS (Figure 3(c)), while 11 studies reported the outcome of OS (Figure 3(d)).

3.4. Progression-Free Survival: Overall and Results Specific to Mutation Type. For PFS for all patients (Figure 4(a)), chemotherapy had lowest efficacy, when compared with osimertinib (HR 0.19, 95% CI 0.12–0.32), SoC+chemotherapy (HR 0.20, 95% CI 0.14–0.29), SoC+bevacizumab (HR 0.24, 95% CI 0.16–0.34), dacomitinib (HR 0.24, 95% CI 0.14–0.40), SoC+monochemotherapy (HR 0.26, 95% CI 0.15–0.45), SoC+ramucirumab (HR 0.26, 95% CI 0.16–0.44), SoC+apatinib (HR 0.29, 95% CI 0.17–0.48), afatinib (HR 0.32, 95% CI 0.24–0.44), and SoC (HR 0.41, 95% CI 0.33–0.52). In addition, compared with osimertinib (HR 0.47, 95% CI 0.30–0.74), SoC+chemotherapy (HR 0.49, 95%CI 0.35–0.67), SoC+bevacizumab (HR 0.57, 95% CI 0.42–0.77), and dacomitinib (HR 0.59, 95% CI 0.37–0.93), SoC had lower efficacy. What is more, afatinib (HR 0.62, 95% CI 0.39–0.96) was inferior to SoC+chemotherapy. As for other comparisons, no significant difference could be found. In terms of PFS for patients with 19del mutation (Figure 4(b)), compared with chemotherapy, osimertinib (HR 0.13, 95% CI 0.06–0.28), SoC+chemotherapy (HR 0.15, 95% CI 0.09–0.26), dacomitinib (HR 0.17, 95% CI 0.08–0.36), SoC+bevacizumab (HR 0.18, 95% CI 0.10–0.30), SoC+ramucirumab (HR 0.20, 95% CI 0.09–0.43), SoC+apatinib (HR 0.21, 95% CI 0.09–0.45), SoC+monochemotherapy (HR 0.21, 95% CI 0.09–0.47),
afatinib (HR 0.24, 95% CI 0.15–0.37), and SoC (HR 0.31, 95% CI 0.21–0.42) showed superior efficacy. Additionally, compared with osimertinib (HR 0.43, 95% CI 0.21–0.86), SoC+chemotherapy (HR 0.50, 95% CI 0.33–0.79), and SoC+bevacizumab (HR 0.57, 95% CI 0.36–0.92), SoC had poorer PFS. For other interventions, no distinguished differences could be found.

For PFS in patients with 21 Leu858Arg mutation (Figure 4(c)), in comparison with SoC, SoC+chemotherapy (HR 0.46, 95% CI 0.23–0.86) and SoC+bevacizumab (HR 0.57, 95% CI 0.33–0.97) demonstrated more favorable prognosis. Particularly, chemotherapy showed the worst results in PFS, compared with SoC + chemotherapy (HR 0.26, 95% CI 0.12–0.54), osimertinib (HR 0.29, 95% CI 0.11–0.72), SoC + bevacizumab (HR 0.32, 95% CI 0.16–0.61), SoC + monochemotherapy (HR 0.33, 95% CI 0.12–0.90), SoC + ramucirumab (HR 0.35, 95% CI 0.14–0.89), dacomitinib (HR 0.36, 95% CI 0.14–0.88), afatinib (HR 0.46, 95% CI 0.27–0.78), and SoC (HR 0.56, 95% CI 0.37–0.81). From the available comparisons, no other significant differences could be found.

For OS in all patients (Figure 4(d)), SoC had lower efficacy than SoC + chemotherapy (HR 0.66, 95% CI 0.47–0.92). No superior treatment could be found among SoC+chemotherapy, dacomitinib, afatinib, osimertinib, chemotherapy, SoC, and SoC+bevacizumab for patients with mutations of 19del (Figure 4(e)) or 21 Leu858Arg (Figure 4(f)).

3.6. Rank Probabilities. Bayesian ranking profiles of evaluated treatments in different populations could be found in Figure S2. In general, the Bayesian ranking results were almost in line with the pooled analysis using HR. In terms of PFS, in the overall population (Figure 5(a)) and patients with 19del mutation (Figure 5(b)), osimertinib was most likely to rank first, with the cumulative probabilities of 41.89% and 45.73%, respectively. Nonetheless, for patients with 21 Leu858Arg mutation (Figure 5(c)), SoC + chemotherapy demonstrated the most favorable PFS (30.81%). For OS, SoC+chemotherapy ranked at the top of the list for the overall population (Figure 5(d)) and patients with 19del mutation (Figure 5(e)), with the cumulative probabilities of 57.85% and 33.51%, respectively. For patients with 21 Leu858Arg mutation (Figure 5(f)), dacomitinib provided the best OS (36.73%).

3.5. Overall Survival: Overall and Results Specific to Mutation Type. For OS in all patients (Figure 4(d)), SoC had lower efficacy than SoC+chemotherapy (HR 0.66, 95% CI 0.47–0.92). No superior treatment could be found among SoC+chemotherapy, dacomitinib, afatinib, osimertinib, chemotherapy, SoC, and SoC+bevacizumab for patients with mutations of 19del (Figure 4(e)) or 21 Leu858Arg (Figure 4(f)).

3.7. Inconsistency Assessment. The fit of the consistency model was similar to or better than that of the inconsistency model (Table S3). No significant differences in comparisons
| Study                  | Region                | Year (enrollment of patients) | Phase     | Clinical trial number | Sample size (no) | Median age | Female (%) | Adenocarcinoma (%) | BM status | Ethnicity          | Nonsmoking (%) | EGFR mutation type | Intervention Arm | Control Arm | Outcome |
|-----------------------|-----------------------|------------------------------|-----------|-----------------------|------------------|------------|------------|-------------------|-----------|-------------------|----------------|-------------------|-----------------|-------------|---------|
| ELSASIA [7–9]         | Global (multicenter)  | 2014-2016                    | III (dual-blind) | NCT01854215           | 276/277          | 64.9±6.0   | 63.9±6.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| ARCHER1050 [10, 11]   | Global (multicenter)  | 2013                          | III (open-label) | NCT01774721           | 227/225          | 62.0±7.2   | 63.8±7.2   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Leu858Arg       | Dacomitinib     | Yes         | Yes     |
| LUX LUNG-3 [12, 13]   | Global (multicenter)  | 2011                          | II (dual-blind)  | NCT01084844           | 184/185          | 63.0±7.0   | 64.8±7.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | PFS OS           | Afatinib        | Yes         | Yes     |
| CONVINCE [36]         | China (multicenter)   | 2013                          | III (dual-blind) | NCT01854215           | 276/277          | 64.9±6.0   | 63.9±6.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| LUX-LUNG-6 [44, 45]   | East-Asia (multicenter) | 2010                      | III (open-label) | NCT01121393           | 242/122          | 58.0±7.0   | 59.9±7.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Leu858Arg       | Afatinib        | Yes         | Yes     |
| JMIT [30, 31]         | India (monocenter)    | 2012                          | II (open-label)  | NCT01469000           | 126/65           | 58.0±7.0   | 59.9±7.0   | 70.1±17.1         | BM and non-BM | Asian                | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| NEJ009 [32]           | Japan (multicenter)   | 2011                          | III (open-label) | NCT00000000           | 170/172          | 64.8±7.2   | 64.8±7.2   | 70.1±17.1         | BM and non-BM | Asian                | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| CONVOCLE [36]         | China (multicenter)   | 2013                          | III (dual-blind) | NCT01854215           | 276/277          | 64.9±6.0   | 63.9±6.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| INFORM [40]           | China (multicenter)   | 2008-2009                     | III (open-label) | NCT00849850           | 138/145          | 56.5±7.0   | 56.5±7.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| EURTAC [38]           | Europe (multicenter)  | 2007-2011                     | III (open-label) | NCT00446225           | 86/87            | 67.4±7.2   | 67.4±7.2   | 70.1±17.1         | BM and non-BM | Non-Asian           | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| OPTIMAL [40]          | China (multicenter)   | 2008-2009                     | III (open-label) | NCT00849850           | 138/145          | 56.5±7.0   | 56.5±7.0   | 70.1±17.1         | BM and non-BM | Asian and non-Asian | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |
| WJTOG3405 [41, 42]    | Japan (multicenter)   | 2006-2009                     | III (open-label) | NCT00000000           | 86/87            | 64.8±7.2   | 64.8±7.2   | 70.1±17.1         | BM and non-BM | Asian                | 82/81±7.7       | Exon 19 deletion | Osimertinib     | Yes         | Yes     |

Data are expressed as intervention/control unless indicated otherwise. NA: not available; BM: brain metastases; SoC: standard of care, representing first-generation epidermal growth factor receptor tyrosine kinase inhibitors in this network meta-analysis (including gefitinib, erlotinib, and icotinib). *Median age is not given, so the mean age is shown here.
could be found between direct and indirect estimates in the node splitting analysis \((P > 0.05)\) (Table S4).

### 4. Discussion

Compared with previous studies, our NMA showed the following advantages. Firstly, our study ensured the homogeneity of the study population. Because some patients harboring uncommon EGFR mutations were included in some clinical trials, such as Lux-Lung-3 [43, 44] and Lux-Lung-6 [44, 45], we ruled out this part of patients and only included patients with common EGFR mutations in the final analysis. Secondly, data extracted from some RCTs served as a bridge to systematically explore the optimal treatment drugs among six commonly used EGFR-TKIs and three antivascular agents for patients with 19 deletion and 21...
Leu858Arg mutations, respectively. Thirdly, although many previous NMAs analyzed some preferable choices for EGFR-mutated advanced NSCLC based on different mutation status [14], some important data were not available at that time (these include final OS for FLAURA and NEJ026 study, PFS for CTONG-1509, RELAY, and ACTIVE study) [7, 8, 15–18]. We conducted this NMA by further integrating the latest information of RCTs in order to draw a more compelling conclusion. Fourth, our NMA systematically compared multiple therapeutic strategies, including three different anti-VEGF agents, bevacizumab [12, 13, 15, 16, 29], ramucirumab [17], and apatinib [18], not available in other NMAs.

In NMA, we comprehensively compared the efficacy of multiple first-line treatments, including all available EGFR-TKIs, cytotoxic agents, and combination strategies for advanced NSCLC patients harboring two different common EGFR mutations. The results suggested that osimertinib was considered the optimal treatment strategy for all patients and patients with EGFR exon 19 deletion in providing the best PFS. First-generation EGFR-TKIs plus chemotherapy was regarded as the best treatment strategy for patients with EGFR exon 21 Leu858Arg mutation with the best PFS. Combination treatment of first-generation EGFR-TKIs with chemotherapy showed the best efficiency in terms of OS for all patients and patients harboring EGFR exon 19 deletion. As for the best choice for patients with EGFR exon 21 Leu858Arg mutation in providing the best OS, two methods employed by our NMA provided slightly different conclusions: in pooled analysis (Figure 4(f)), first-generation EGFR-TKIs plus chemotherapy was the best choice, but in Bayesian ranking profiles (Figure 5(f)), dacomitinib was considered the best. Given that the HR/OR for SoC+chemotherapy versus dacomitinib was equal to 1 and the

![Figure 3](image_url)
### Table 1: Medication Comparison

| Medication | Chemotherapy | Osimertinib | Afatinib | Apatinib | Bevacizumab |
|------------|--------------|-------------|---------|----------|-------------|
| Osimertinib| 0.96 (0.51-1.68) | 0.82 (0.42-1.55) | 0.80 (0.34-1.84) | 0.74 (0.39-1.37) | 0.67 (0.35-1.33) |
| SoC Chemotherapy | 0.83 (0.47-1.46) | 0.83 (0.42-1.44) | 0.77 (0.43-1.30) | 0.70 (0.46-1.48) | 0.62 (0.39-0.96) |
| Bevacizumab | 0.97 (0.56-1.72) | 0.97 (0.52-1.52) | 0.90 (0.57-1.41) | 0.85 (0.54-1.43) | 0.79 (0.53-1.19) |
| Afatinib | 1.28 (0.69-2.20) | 1.03 (0.60-1.80) | 0.94 (0.46-1.87) | 0.85 (0.44-1.85) | 0.75 (0.37-1.53) |
| Apatinib | 0.91 (0.56-1.48) | 0.91 (0.51-1.60) | 0.82 (0.45-1.53) | 0.73 (0.39-1.35) | 0.57 (0.31-1.05) |
| SoC+ Chemotherapy | 0.89 (0.49-1.68) | 0.89 (0.44-1.73) | 0.81 (0.43-1.53) | 0.75 (0.44-1.44) | 0.59 (0.30-1.16) |
| Bevacizumab | 0.71 (0.39-1.31) | 0.71 (0.37-1.41) | 0.63 (0.35-1.17) | 0.57 (0.31-1.05) | 0.41 (0.22-0.76) |

### Table 2: Additional Medication Comparison

| Medication | Chemotherapy | Osimertinib | Afatinib | Apatinib | Bevacizumab |
|------------|--------------|-------------|---------|----------|-------------|
| Osimertinib| 0.98 (0.52-1.84) | 0.82 (0.42-1.60) | 0.80 (0.34-1.84) | 0.74 (0.39-1.37) | 0.67 (0.35-1.33) |
| SoC Chemotherapy | 0.83 (0.47-1.46) | 0.83 (0.42-1.44) | 0.77 (0.43-1.30) | 0.70 (0.46-1.48) | 0.62 (0.39-0.96) |
| Bevacizumab | 0.97 (0.56-1.72) | 0.97 (0.52-1.52) | 0.90 (0.57-1.41) | 0.85 (0.54-1.43) | 0.79 (0.53-1.19) |
| Afatinib | 1.28 (0.69-2.20) | 1.03 (0.60-1.80) | 0.94 (0.46-1.87) | 0.85 (0.44-1.85) | 0.75 (0.37-1.53) |
| Apatinib | 0.91 (0.56-1.48) | 0.91 (0.51-1.60) | 0.82 (0.45-1.53) | 0.73 (0.39-1.35) | 0.57 (0.31-1.05) |
| SoC+ Chemotherapy | 0.89 (0.49-1.68) | 0.89 (0.44-1.73) | 0.81 (0.43-1.53) | 0.75 (0.44-1.44) | 0.59 (0.30-1.16) |
| Bevacizumab | 0.71 (0.39-1.31) | 0.71 (0.37-1.41) | 0.63 (0.35-1.17) | 0.57 (0.31-1.05) | 0.41 (0.22-0.76) |

### Table 3: Further Medication Comparison

| Medication | Chemotherapy | Osimertinib | Afatinib | Apatinib | Bevacizumab |
|------------|--------------|-------------|---------|----------|-------------|
| Osimertinib| 0.98 (0.52-1.84) | 0.82 (0.42-1.60) | 0.80 (0.34-1.84) | 0.74 (0.39-1.37) | 0.67 (0.35-1.33) |
| SoC Chemotherapy | 0.83 (0.47-1.46) | 0.83 (0.42-1.44) | 0.77 (0.43-1.30) | 0.70 (0.46-1.48) | 0.62 (0.39-0.96) |
| Bevacizumab | 0.97 (0.56-1.72) | 0.97 (0.52-1.52) | 0.90 (0.57-1.41) | 0.85 (0.54-1.43) | 0.79 (0.53-1.19) |
| Afatinib | 1.28 (0.69-2.20) | 1.03 (0.60-1.80) | 0.94 (0.46-1.87) | 0.85 (0.44-1.85) | 0.75 (0.37-1.53) |
| Apatinib | 0.91 (0.56-1.48) | 0.91 (0.51-1.60) | 0.82 (0.45-1.53) | 0.73 (0.39-1.35) | 0.57 (0.31-1.05) |
| SoC+ Chemotherapy | 0.89 (0.49-1.68) | 0.89 (0.44-1.73) | 0.81 (0.43-1.53) | 0.75 (0.44-1.44) | 0.59 (0.30-1.16) |
| Bevacizumab | 0.71 (0.39-1.31) | 0.71 (0.37-1.41) | 0.63 (0.35-1.17) | 0.57 (0.31-1.05) | 0.41 (0.22-0.76) |

### Table 4: Continued

| Medication | Chemotherapy | Osimertinib | Afatinib | Apatinib | Bevacizumab |
|------------|--------------|-------------|---------|----------|-------------|
| Osimertinib| 0.98 (0.52-1.84) | 0.82 (0.42-1.60) | 0.80 (0.34-1.84) | 0.74 (0.39-1.37) | 0.67 (0.35-1.33) |
| SoC Chemotherapy | 0.83 (0.47-1.46) | 0.83 (0.42-1.44) | 0.77 (0.43-1.30) | 0.70 (0.46-1.48) | 0.62 (0.39-0.96) |
| Bevacizumab | 0.97 (0.56-1.72) | 0.97 (0.52-1.52) | 0.90 (0.57-1.41) | 0.85 (0.54-1.43) | 0.79 (0.53-1.19) |
| Afatinib | 1.28 (0.69-2.20) | 1.03 (0.60-1.80) | 0.94 (0.46-1.87) | 0.85 (0.44-1.85) | 0.75 (0.37-1.53) |
| Apatinib | 0.91 (0.56-1.48) | 0.91 (0.51-1.60) | 0.82 (0.45-1.53) | 0.73 (0.39-1.35) | 0.57 (0.31-1.05) |
| SoC+ Chemotherapy | 0.89 (0.49-1.68) | 0.89 (0.44-1.73) | 0.81 (0.43-1.53) | 0.75 (0.44-1.44) | 0.59 (0.30-1.16) |
| Bevacizumab | 0.71 (0.39-1.31) | 0.71 (0.37-1.41) | 0.63 (0.35-1.17) | 0.57 (0.31-1.05) | 0.41 (0.22-0.76) |

---

**Figure 4:** Continued.
cumulative probabilities of dacomitinib (36.73%) and SoC+ chemotherapy (32.56%) to rank the first were close, we deduced that dacomitinib and SoC+ chemotherapy could demonstrate similar performance in prolonging OS for patients with EGFR exon 21 Leu858Arg mutation. Combination treatments of first-generation EGFR-TKIs with different anti-VEGF agents showed the identical tendency of the EGFR exon 20 _whr790Met_ mutation or epithelial to mesenchymal transition [48]. On the other hand, the combination of erlotinib or gefitinib with pemetrexed can prolong the benefits of patients with acquired resistance to erlotinib or gefitinib [49]. Furthermore, gefitinib could reverse the chemotherapy resistance in the NSCLC cell line [50]. Therefore, whether osimertinib or the combination of the first-line EGFR-TKIs with chemotherapy can be considered the optimized treatment strategy for advanced EGFR mutated NSCLC patients.

As a secondary endpoint in most studies, OS is impacted by multiple factors, and thus we mainly analyzed the difference of PFS in this NMA. Different statuses of EGFR mutation might influence the choice of treatment strategies for advanced EGFR mutated NSCLC patients in acquiring the best PFS. Some studies imply that EGFR-TKIs are more efficient in patients with 19del mutation than with 21_Leu858Arg_ mutation [51, 52]. A possible explanation might be that the EGFR exon 21 _Leu858Arg_ mutation is accompanied by a more frequent appearance of EGFR exon 20

![Figure 4: Pooled estimates of the network meta-analysis. Pooled odds ratios (95% credible intervals). Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios less than 1 followed by ramucirumab and apatinib.](image-url)

| SoC+ Chemotherapy | Dacomitinib | Afatinib | SoC+ Bevacizumab | Osimertinib | Chemotherapy | Osimertinib | Chemotherapy | Osimertinib | Chemotherapy | Osimertinib | Chemotherapy |
|--------------------|-------------|----------|-----------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|
| SoC+ Chemotherapy  | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |
| Afatinib           | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |
| Dacomitinib        | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |
| SoC+ Bevacizumab   | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |
| Osimertinib        | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |
| Chemotherapy       | 1.00        | 0.95     | 0.99            | 0.97        | 0.94         | 1.00        | 0.94         | 1.00        | 0.99         | 1.00        | 0.99         |

The heterogeneity and inconsistency assessment suggested that minor heterogeneities could be found in most comparisons from one or two studies. The quality assessment for included studies showed low-to-medium bias risk. On the whole, the Bayesian ranking results were almost in line with the pooled analysis using hazard and odds ratios. Therefore, the results we got could be considered robust.

Osimertinib can provide long PFS and translate PFS in all patients; (b) PFS in patients with 19del mutation; (c) PFS in patients with 21_Leu858Arg_ mutation; (d) OS in all patients; (e) OS in patients harboring different common mutations in providing better PFS for all patients (Figure 4(a)) and patients harboring different common mutations (Figures 4(b) and 4(c)) compared to SoC and chemotherapy: first-generation EGFR-TKIs with bevacizumab was the best, followed by ramucirumab and apatinib.

![Figure 4: Pooled estimates of the network meta-analysis. Pooled odds ratios (95% credible intervals). Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios less than 1 followed by ramucirumab and apatinib.](image-url)

As a secondary endpoint in most studies, OS is impacted by multiple factors, and thus we mainly analyzed the difference of PFS in this NMA. Different statuses of EGFR mutation might influence the choice of treatment strategies for advanced EGFR mutated NSCLC patients in acquiring the best PFS. Some studies imply that EGFR-TKIs are more efficient in patients with 19del mutation than with 21_Leu858Arg_ mutation [51, 52]. A possible explanation might be that the EGFR exon 21 _Leu858Arg_ mutation is accompanied by a more frequent appearance of EGFR exon 20

![Figure 4: Pooled estimates of the network meta-analysis. Pooled odds ratios (95% credible intervals). Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios less than 1 followed by ramucirumab and apatinib.](image-url)
PFS in all patients

(a)

PFS in patients with 19del mutation

(b)

PFS in patients with 21L858R mutation

(c)

OS in all patients

(d)

Figure 5: Continued.
Thr790Met mutations [53, 54] and concomitant mutations (such as TP53, PIK3CA, BRAF) [55], which are associated with higher resistance and worse response of EGFR-TKIs [56–59], compared with EGFR exon 19del mutation [59]. Therefore, the third-generation EGFR-TKI osimertinib should be more efficient in patients harboring 19del mutation because of its irreversible inhibition of EGFR, which is consistent with our results (pooled odds ratio of osimertinib versus SoC + chemotherapy is 0.86, 0.36–1.91 in Figure 4(b), and in Figure 5(b), osimertinib was most likely to rank the first in 19del mutated patients). First-generation EGFR-TKIs plus chemotherapy should be more efficient in 21 Leu858Arg mutated patients who are liable to show drug resistance due to its effectively preventing patients from multimechanism resistance to first-generation EGFR-TKIs [48], which is also in accordance with our results (pooled odds ratio of SoC + chemotherapy versus osimertinib is 0.90, 0.31–2.47 in Figure 4(c), and in Figure 5(c), SoC + chemotherapy was most likely to rank the first in 21 Leu858Arg mutated patients). Additionally, the optimized choice for all patients in providing longer PFS is osimertinib, which might owe to the amount of 19del mutated patients is larger than 21 Leu858Arg mutated patients in most selected RCTs (pooled odds ratio of osimertinib versus SoC + chemotherapy is 0.96, 0.55–1.68 in Figure 4(a), and in Figure 5(a), osimertinib was most likely to rank the first in all patients).

In terms of OS, the first-generation EGFR-TKIs plus chemotherapy shows the best efficiency for all patients and patients harboring different mutation types, which might be associated with the activation of chemotherapy to the immune system (eliminating immunosuppression cells [60, 61], generating memory T cells [62], etc.) and activated immune system.

Our results were similar to previous findings. In terms of PFS, Zhao et al. found that osimertinib and gefitinib plus pemetrexed based chemotherapy were considered the best treatment options for 19del mutated patients and 21 Leu858Arg mutated patients, respectively, which was in consistent with our results [14]. As for OS, Zhao et al. considered afatinib and dacomitinib were the most favorable treatments for 19del mutated patients and 21 Leu858Arg mutated patients respectively [14]. Zhao et al.’s result of OS was slightly different from ours’ which could be attributed to immature subgroup results of NEJ009 study at that time [32]. In Alanazi et al.’s NMA, osimertinib and dacomitinib ranked first in all patients in terms of PFS and OS respectively, which was in congruent with our findings [63]. It should be noted that combination treatment strategies were not included in their research.

We have also found that the combination treatment of first-generation EGFR-TKIs with different anti-VEGF agents show the identical tendency in providing better PFS for all patients and patients harboring different common mutations: first-generation EGFR-TKIs with bevacizumab is the best, with ramucirumab is the next and with apatinib is the least effective.
the worst. The reasons for this tendency might be as follows: (1) all selected RCTs about first-generation EGFR-TKIs plus bevacizumab [12, 13, 15, 16, 29] are open-label, while the RCTs about the combination with ramucirumab [17] or apatinib [18] are double-blind, which might lead to overestimating the benefits of bevacizumab; (2) the molecular structure of these anti-VEGF agents and their targets are different. Bevacizumab is a VEGF targeted IgG1 monoclonal antibody; ramucirumab is a VEGFR targeted IgG1 monoclonal antibody; apatinib is a VEGFR-TKIs, which might have some influences on their efficacy (monoclonal antibody could mediate antibody-dependent cell-mediated cytotoxicity and opsonization, which could increase the apoptosis of vascular endothelial and the elimination of VEGF, respectively).

There are still some limitations in this study. Firstly, this NMA uses some data from the experimental group or control group in some studies as a “bridge” to indirectly compare the advantages and disadvantages of different treatment strategies. However, the most direct evidence should come from a direct comparison of two or more agents, and the indirect comparison results may be distorted. Secondly, although our NMA suggests first-generation EGFR-TKIs combined with chemotherapy are the optimal first-line treatment option for advanced NSCLC patients harboring EGFR 21 Leu858Arg mutation, there is no RCT comparing the second- or third-generation EGFR-TKIs plus chemotherapy with chemotherapy or other treatments, and whether chemotherapy combining the second- or third-generation EGFR-TKIs would be more effective than the first-generation, EGFR-TKI should be further investigated. Thirdly, heterogeneity might be influenced by the complexity of subsequent treatment options in different trials when OS was considered the endpoint for evaluating the efficacy of various treatment strategies. Therefore, PFS was taken as the primary endpoint in this meta-analysis. Finally, NSCLC patients, with other driver gene changes or EGFR uncommon mutations, or patients of other kinds of cancer with gene mutations also have the problem of “optimal treatment,” which needs to be further studied by clinical workers and researchers.

5. Conclusions

This NMA suggests that osimertinib and first-generation EGFR-TKIs combined with chemotherapy would be the optimal first-line treatment option for advanced NSCLC patients harboring EGFR 19 deletion mutation and 21 Leu858Arg mutation, respectively.

Data Availability

The data were extracted from published articles or abstracts.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

Tongji Xie and Zihua Zou contributed equally to this work and should be considered co-first authors. Tongji Xie and Puyuan Xing were responsible for conception and design. Junling Li was responsible for administrative support. Yixiang Zhu and Ziyi Xu were responsible for literature research. Tongji Xie, Zihua Zou, and Puyuan Xing were responsible for data extraction and risk of bias assessment. Chengcheng Liu and Le Wang were responsible for data analysis and interpretation. Tongji Xie and Zihua Zou were responsible for manuscript writing. All the authors read and approved the final manuscript.

Supplementary Materials

There are 4 supplementary tables and 2 supplementary figures for this paper. (Supplementary Materials)

References

[1] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, “Global cancer statistics, 2012,” CA: A Cancer Journal for Clinicians, vol. 65, no. 2, pp. 87–108, 2015.
[2] J. Greenhalgh, K. Dwan, A. Boland et al., “First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer,” Cochrane Database System Review, vol. 25, no. 5, Article ID CD010383, 2016.
[3] NCCN, Clinical Practice Guidelines in Oncology for Non-small Cell Lung Cancer. Version 2, 2019, https://www.nccn.org/patients.
[4] S. G. Wu and J. Y. Shih, “Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer,” Molecular Cancer, vol. 17, no. 1, p. 38, 2018.
[5] S. V. Sharma, D. W. Bell, J. Settleman, and D. A. Haber, “Epidermal growth factor receptor mutations in lung cancer,” Nature Reviews Cancer, vol. 7, no. 3, pp. 169–181, 2007.
[6] P. T. Harrison, S. Vyse, and P. H. Huang, “Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer,” Seminars in Cancer Biology, vol. 61, pp. 167–179, 2020.
[7] B. C. Cho, B. Chewaskulyong, K. H. Lee et al., “Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA asian subset,” Journal of Thoracic Oncology, vol. 14, no. 1, pp. 99–106, 2019.
[8] S. S. Ramalingam, J. Vansteenkiste, D. Planchar et al., “Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC,” New England Journal of Medicine, vol. 382, no. 1, pp. 41–50, 2020.
[9] J.-C. Soria, Y. Ohe, J. Vansteenkiste et al., “Osimertinib in UntreatedEGFR-mutated advanced non-small-cell lung cancer,” New England Journal of Medicine, vol. 378, no. 2, pp. 113–125, 2018.
[10] Y.-L. Wu, Y. Cheng, X. Zhou et al., “Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial,” The Lancet Oncology, vol. 18, no. 11, pp. 1454–1466, 2017.
[11] T. S. Mok, Y. Cheng, X. Zhou et al., “Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung
cancer and EGFR-activating mutations,” *Journal of Clinical Oncology*, vol. 36, no. 22, pp. 2244–2250, 2018.

[12] T. Seto, T. Kato, M. Nishio et al., “Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study,” *The Lancet Oncology*, vol. 15, no. 11, pp. 1236–1244, 2014.

[13] N. Yamamoto, T. Seto, M. Nishio et al., “Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer (NSCLC): survival follow-up results of JO25567,” *Journal of Clinical Oncology*, vol. 36, no. 15_suppl, Article ID 9007, 2018.

[14] Y. Zhao, J. Liu, X. Cai et al., “Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis,” *BMJ (Clinical Research ed.*)*, vol. 367, Article ID 75460, 2019.

[15] M. Maemondo, T. Fukuhara, H. Saito et al., “NEJ026:Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations,” *Journal of Clinical Oncology*, vol. 38, no. 15_suppl, Article ID 9506, 2020.

[16] Q. Zhou, Y.-L. Wu, Y. Cheng et al., “CTONG 1509: phase III study of bevacizumab with or without erlotinib in untreated Chinese patients with advanced EGFR-mutated NSCLC,” *Annals of Oncology*, vol. 30, no. 5_suppl, Article ID 14800, 2019.

[17] K. Nakagawa, E. B. Garon, T. Seto et al., “Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial,” *The Lancet. Oncology*, vol. 20, no. 12, pp. 1655–1669, 2019.

[18] L. Zhang, H. Zhao, Z. Zhang et al., “ACTIVE: apatinib plus gefitinib versus placebo plus gefitinib as first-line treatment for advanced epidermal growth factor receptor-mutant (EGFRm) non-small-cell lung cancer (NSCLC): a multi-centered, randomized, double-blind, placebo-controlled phase III trial (CTONG1706),” *Annals of Oncology*, vol. 31, no. 4_suppl, Article ID LBA50, 2020.

[19] J. P. Jansen, R. Fluereuse, B. Devine et al., “Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1,” *Value in Health*, vol. 14, no. 4, pp. 417–428, 2011.

[20] K. Knobloch, U. Yoon, and P. M. Vogt, “Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias,” *Journal of Cranio-Maxillofacial Surgery*, vol. 39, no. 2, pp. 91-92, 2011.

[21] J. P. T. Higgins, J. Thomas, and J. Chandler, *Cochrane Handbook for Systematic Reviews of Interventions version 6.1*, 2020.

[22] A. Chaimani, J. P. Higgins, D. Mavridis, P. Spyridonos, and G. Salanti, “Graphical tools for network meta-analysis in STATA,” *PLoS One*, vol. 8, no. 10, Article ID e76654, 2013.

[23] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, “Measuring inconsistency in meta-analyses,” *Bmj*, vol. 327, no. 7414, pp. 557–560, 2003.

[24] G. Lu and A. E. Ades, “Combination of direct and indirect evidence in mixed treatment comparisons,” *Statistics in Medicine*, vol. 23, no. 20, pp. 3105–3124, 2004.

[25] S. P. Brooks and A. GelMan, “General methods for monitoring convergence of iterative simulations,” *Journal of Computational and Graphical Statistics*, vol. 7, no. 4, pp. 434–455, 1998.

[26] G. Salanti, A. E. Ades, and J. P. A. Ioannidis, “Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial,” *Journal of Clinical Epidemiology*, vol. 64, no. 2, pp. 163–171, 2011.

[27] K. Park, E.-H. Tan, K. O’Byrne et al., “Afinitin versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial,” *The Lancet Oncology*, vol. 17, no. 5, pp. 577–589, 2016.

[28] L. Paz-Ares, E.-H. Tan, K. O’Byrne et al., “Afinitin versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial,” *Annals of Oncology*, vol. 28, no. 2, pp. 270–277, 2017.

[29] H. Saito, T. Fukuhara, N. Furuya et al., “Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial,” *The Lancet Oncology*, vol. 20, no. 5, pp. 625–635, 2019.

[30] J. C.-H. Yang, Y. Cheng, H. Murakami et al., “A randomized phase 2 study of gefitinib with or without pemetrexed as first-line treatment in nonsquamous NSCLC with EGFR mutation: final overall survival and biomarker analysis,” *Journal of Thoracic Oncology*, vol. 15, no. 1, pp. 91–100, 2020.

[31] Y. Cheng, H. Murakami, P.-C. Yang et al., “Randomized phase II trial of gefitinib with and without pemetrexed as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer with activating epidermal growth factor receptor mutations,” *Journal of Clinical Oncology*, vol. 34, no. 27, pp. 3258–3266, 2016.

[32] Y. Hosomi, S. Morita, T. Kato et al., “Gefitinib alone versus gefitinib plus chemotherapy for non–small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study,” *Journal of Clinical Oncology*, vol. 38, no. 2, pp. 115–123, 2019.

[33] V. Noronha, V. M. Pati, A. Josh et al., “Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer,” *Journal of Clinical Oncology*, vol. 38, no. 2, pp. 124–136, 2019.

[34] Y. Lou, J. Xu, Y. Zhang et al., “Chemotherapy plus EGFR-TKI as first-line treatment provides better survival for advanced EGFR-positive lung adenocarcinoma patients: updated data and exploratory in vitro study,” *Targeted Oncology*, vol. 15, no. 2, pp. 175–184, 2020.

[35] B. Han, B. Jin, T. Chu et al., “Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: a randomized controlled trial,” *International Journal of Cancer*, vol. 141, no. 6, pp. 1249–1256, 2017.

[36] Y. K. Shi, L. Wang, B. H. Han et al., “First-line icotinib versus gefitinib in first-line treatment of patients with EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study,” *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, vol. 28, no. 10, pp. 2443–2450, 2017.
[37] Y.-L. Wu, C. Zhou, C.-K. Liam et al., “First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study,” *Annals of Oncology*, vol. 26, no. 9, pp. 1883–1889, 2015.

[38] R. Rosell, E. Carcereny, R. Gervais et al., “Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial,” *The Lancet Oncology*, vol. 13, no. 3, pp. 239–246, 2012.

[39] C. Zhou, Y.-L. Wu, G. Chen et al., “Final overall survival results from a randomised, Phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802),” *Annals of Oncology*, vol. 26, no. 9, pp. 1877–1883, 2015.

[40] C. Zhou, Y.-L. Wu, G. Chen et al., “Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study,” *The Lancet Oncology*, vol. 12, no. 8, pp. 735–742, 2011.

[41] H. Yoshioka, M. Shimokawa, T. Seto et al., “Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer,” *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, vol. 30, no. 12, pp. 1978–1984, 2019.

[42] T. Mitsudomi, S. Morita, Y. Yatabe et al., “Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial,” *The Lancet Oncology*, vol. 11, no. 2, pp. 121–128, 2010.

[43] L. V. Sequist, J. C.-H. Yang, N. Yamamoto et al., “Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations,” *Journal of Clinical Oncology*, vol. 31, no. 27, pp. 3327–3334, 2013.

[44] J. C.-H. Yang, Y.-L. Wu, M. Schuler et al., “Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials,” *The Lancet Oncology*, vol. 16, no. 2, pp. 141–151, 2015.

[45] Y.-L. Wu, C. Zhou, C.-P. Hu et al., “Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial,” *The Lancet Oncology*, vol. 15, no. 2, pp. 213–222, 2014.

[46] H. A. Yu, M. E. Arcila, N. Rekhtman et al., “Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers,” *Clinical Cancer Research*, vol. 19, no. 8, pp. 2240–2247, 2013.

[47] L. V. Sequist, B. A. Waltham, and D. Dias-Santagata, “Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors,” *Science Translational Medicine*, vol. 3, no. 75, Article ID 75ra26, 2011.

[48] S. La Monica, D. Madeddu, M. Tiseo et al., “Combination of gefitinib and pemetrexed prevents the acquisition of TKI resistance in NSCLC cell lines carrying EGFR-activating mutation,” *Journal of Thoracic Oncology*, vol. 11, no. 7, pp. 1051–1063, 2016.

[49] N. Yoshimura, K. Okishio, S. Mitsuoka et al., “Prospective assessment of continuation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of pemetrexed,” *Journal of Thoracic Oncology*, vol. 8, no. 1, pp. 99–101, 2013.

[50] C.-H. Yang, C.-J. Huang, C.-S. Yang et al., “Gefitinib reverses chemotherapy resistance in gefitinib-insensitive multidrug resistant cancer cells expressing ATP-binding cassette family protein,” *Cancer Research*, vol. 65, no. 15, pp. 6943–6949, 2005.

[51] C. K. Lee, Y.-L. Wu, P. N. Ding et al., “Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: a meta-analysis,” *Journal of Clinical Oncology*, vol. 33, no. 17, pp. 1958–1965, 2015.

[52] G. J. Riely, W. Pao, D. Pham et al., “Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib,” *Clinical Cancer Research*, vol. 12, no. 3, pp. 839–844, 2006.

[53] D. M. Jackman, B. Y. Yeap, L. V. Sequist et al., “Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib,” *Clinical Cancer Research*, vol. 12, no. 13, pp. 3908–3914, 2006.

[54] J.-Q. Zhu, W.-Z. Zhong, G.-C. Zhang et al., “Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals,” *Cancer Letters*, vol. 265, no. 2, pp. 307–317, 2008.

[55] C. M. Blakely, T. B. K. Watkins, W. Wu et al., “Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers,” *Nature Genetics*, vol. 49, no. 12, pp. 1693–1704, 2017.

[56] T. De Pas, F. Toffalorio, M. Manzotti et al., “Activity of afatinib or gemcitabine plus pemetrexed for first-line treatment of Asian patients with non-small cell lung cancer harboring rare EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring rare epidermal growth factor receptor mutations,” *Journal of Thoracic Oncology*, vol. 6, no. 11, pp. 1895–1901, 2011.

[57] E. Massarelli, F. M. Johnson, H. S. Erickson, I. I. Wistuba, and V. Papadimitrakopoulou, “Uncommon epidermal growth factor receptor mutations in non-small cell lung cancer and their mechanisms of EGFR tyrosine kinase inhibitors sensitivity and resistance,” *Lung Cancer*, vol. 80, no. 3, pp. 235–241, 2013.

[58] M. B. Barnet, S. O’Toole, L. G. Horvath et al., “EGFR-CoMutated advanced NSCLC and response to EGFR tyrosine kinase inhibitors,” *Journal of Thoracic Oncology*, vol. 12, no. 3, pp. 585–590, 2017.

[59] S. Hong, F. Gao, S. Fu et al., “Concomitant genetic alterations with response to treatment and epidermal growth factor receptor tyrosine kinase inhibitors in patients with EGFR-mutant advanced non-small cell lung cancer,” *JAMA Oncology*, vol. 4, no. 5, pp. 739–742, 2018.

[60] W. J. Lesterhuis, C. J. A. Punt, S. V. Hato et al., “Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice,” *Journal of Clinical Investigation*, vol. 121, no. 8, pp. 3100–3108, 2011.

[61] F. Ghiringhelli, C. Menard, P. E. Puig et al., “Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients,” *Cancer Immunology, Immunotherapy*, vol. 56, no. 5, pp. 641–648, 2007.
[62] P. Nisticò, I. Capone, B. Palermo et al., “Chemotherapy enhances vaccine-induced antitumor immunity in melanoma patients,” *International Journal of Cancer*, vol. 124, no. 1, pp. 130–139, 2009.

[63] A. Alanazi, I. Yunusa, K. Elenizi, and A. I. Alzarea, “Efficacy and safety of tyrosine kinase inhibitors in advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutation: a network meta-analysis,” *Lung Cancer Management*, vol. 10, no. 1, Article ID LMT43, 2020.