First-line therapeutic strategy for patients with advanced non–small cell lung cancer with Leu858Arg epidermal growth factor receptor mutations: a Bayesian network meta-analysis

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Abstract

Aim: The objective of this network meta-analysis was to determine the most useful first-line therapeutic strategy for patients with advanced (IIIB/IV or relapsed) non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Leu858Arg or EGFR 19del mutations.

Methods: PubMed, the Web of Science, Medline, and reports of the top three world cancer conferences (WCLC, ESMO, and ASCO) were searched for appropriated randomized controlled studies (RCTs) discussing the use of various generations of tyrosine kinase inhibitors (TKIs; gefitinib, erlotinib, icotinib, afatinib, dacomitinib, osimertinib, aumolertinib), chemotherapy [pemetrexed-based chemotherapy (PC), non-pemetrexed-based chemotherapy (NPC)], and different combined therapies (osimertinib plus bevacizumab, afatinib plus cetuximab, erlotinib plus bevacizumab, erlotinib plus ramucirumab, gefitinib plus apatinib, gefitinib plus PC, and gefitinib plus pemetrexed) to treat patients with advanced NSCLC with EGFR Leu858Arg or 19del mutations. OpenBugs and Stata software were used to analyze the data.

Results: We included 21 studies with 16 arms (including 2479 cases with EGFR Leu858Arg mutations and 3325 cases with EGFR 19del mutations). Among patients with NSCLC with EGFR Leu858Arg mutations, compared with the first-generation TKIs (such as gefitinib), the second- or third-generation TKIs [dacomitinib: hazard ratio (HR) = 0.63; 95% confidence index (CI) = (0.45, 0.89); osimertinib: HR = 0.63; 95% CI = [0.42, 0.97]] showed significant benefits in improving progression-free survival (PFS), as did afatinib plus cetuximab [HR = 1.98; 95% CI = [1.01, 3.95]], erlotinib plus bevacizumab [HR = 1.79; 95% CI = [1.22, 2.62]], and erlotinib plus ramucirumab [HR = 1.62; 95% CI = [1.07, 2.48]]. In terms of overall survival (OS), these 16 arms showed no significant differences between each other (p > 0.05). Among patients with NSCLC with EGFR 19del mutations, compared with the first- or second-generation TKIs (such as gefitinib and afatinib), aumolertinib [versus gefitinib: HR = 0.39; 95% CI = [0.28, 0.55]] versus afatinib: HR = 0.53; 95% CI = [0.36, 0.81]] and osimertinib [versus gefitinib: HR = 0.49; 95% CI = [0.30, 0.71]] versus afatinib: HR = 0.53; 95% CI = [0.36, 0.79]] showed significantly beneficial effects. Among these first-line therapeutic strategies for patients with EGFR Leu858Arg mutations, the combination of afatinib and cetuximab ranked as the best to prolong PFS (33.0%). For NSCLC patients with 19del mutations, however, osimertinib plus bevacizumab was the best at prolonging PFS (84.3%).

Conclusion: For NSCLC patients with EGFR Leu858Arg mutations, the second-generation TKIs, the third-generation TKIs, and the combined treatments showed better efficacy than the first-generation TKIs for PFS. There were, however, no significant differences between each group for OS.

Keywords: epidermal growth factor receptor, meta-analysis, non–small cell lung cancer, tyrosine kinase inhibitors

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Introduction
Lung cancer contributed to over 130,000 deaths in 2020. The use of targeted therapies and immunotherapies has increased the 5-year survival rate of non–small cell lung cancer (NSCLC) to over 15%, even reaching 50%. The overall prevalence of epidermal growth factor receptor (EGFR) mutations is 49.1% for Asian patients and 12.8% among European patients with NSCLC. For patients with EGFR-mutant NSCLC, the standard treatment is tyrosine kinase inhibitors (TKIs; first generation (gefitinib, erlotinib, and icotinib), second generation (afatinib and dacomitinib), and third generation (osimertinib and aumolertinib)), which improved overall survival (OS) and were recommended by the National Comprehensive Cancer Network (NCCN) NSCLC guidelines. Furthermore, the combination of TKIs with other therapies (e.g. chemotherapy, bevacizumab, ramucirumab, and apatinib) also showed beneficial results for survival.

Among patients with EGFR mutations, 42% are Leu858Arg mutations. Rosell et al. reported that erlotinib significantly improved progression-free survival (PFS) compared with chemotherapy in EGFR 19del-mutated NSCLC instead of the Leu858Arg-mutated subgroup. Studies also proved that when treated using various generations of EGFR TKIs, patients with NSCLC with EGFR Leu858Arg mutations experienced worse clinical outcomes than those with 19del mutations.

In 2019, Zhao et al. conducted a network meta-analysis and performed a subgroup analysis of Leu858Arg mutations. The result showed that among the Leu858Arg subgroup, gefitinib plus pemetrexed-based chemotherapy (PC) was the best strategy to improve PFS, and dacomitinib was the most promising regimen to prolong OS. To date, several multicenter studies (including ACTIVE, SWOG 1403, BEVERLY, WJOG9717L, and AENEAS) have shown impressive results. In this study, we collected data from patients with Leu858Arg or 19del mutations and clarified the efficacy of different antitumor agents among them.

Methods
This meta-analysis follows the PRISMA reporting guidelines. Two investigators independently searched PubMed, Web of Science, MEDLINE, and the latest reports from world lung cancer conferences [World Conference of Lung Cancer (WCLC), European Society for Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO)] for appropriate studies about using various EGFR TKIs and combined therapies in NSCLC with EGFR Leu858Arg mutations. For example, in PubMed, we used the following keywords: ‘EGFR’ and ‘NSCLC’, and the study type was restricted as ‘randomized controlled trial’ or ‘clinical trial.’ Up to 29 November 2021, we found 1491 studies after deleting duplicates, and we finally included 21 randomized controlled trials (RCTs; including 2479 cases with EGFR Leu858Arg mutations and 3325 cases with EGFR 19del mutations). These enrolled studies contained 16 therapeutic arms [aumolertinib, osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, icotinib, osimertinib plus bevacizumab, afatinib plus cetuximab, erlotinib plus bevacizumab, erlotinib plus ramucirumab, gefitinib plus apatinib, gefitinib plus PC, gefitinib plus pemetrexed, PC, and non-pemetrexed-based chemotherapy (NPC)] (Figure 1).

Inclusion and exclusion criteria
The inclusion criteria comprised the following: (1) RCTs discussing first-line therapeutic strategies for patients with advanced NSCLC with EGFR Leu858Arg or EGFR 19del mutations, (2) primary outcome: PFS, and (3) only published in English. The exclusion criteria comprised the following: (1) review, retrospective research, case report, study with nonrandomized controlled designs; (2) single-arm studies; and (3) insufficient data in the articles.

Data extraction and risk of bias assessment
Two authors independently reviewed the identified abstracts and selected articles for full review. The third reviewer addressed the discrepancies. For each selected publication, the following baseline and study characteristics were extracted: first author, publication year, country, participant characteristics, total number of patients in the experiment and control groups, age of the patients in each group, other baseline characteristics, and the treatment dose of each group in these studies (Table 1). The primary outcome was PFS of selected NSCLC patients with EGFR Leu858Arg mutations. The secondary outcomes included OS of EGFR Leu858Arg mutations and PFS and OS of EGFR 19del mutations.
Statistical analysis

We pooled the data and used the hazard ratio (HR) and its associated confidence interval (CI) for the dichotomy outcome: PFS and OS of selected patients with EGFR Leu858Arg- or 19del-mutated NSCLC. All statistical analyses were performed using OpenBugs (version 3.2.3) and Stata (version 15.1; StataCorp LLC, College Station, Texas, USA). The results were calculated based on Bayesian algorithm.

Results

This study included 21 studies (2479 subjects with EGFR Leu858Arg mutations and 3325 subjects with EGFR 19del mutations).8–11,13,15,20–35 The network maps of the various therapeutic arms for the results of PFS and OS of EGFR Leu858Arg mutations are shown in Figures 2 and 3, respectively.

For the PFS of patients with NSCLC with EGFR Leu858Arg mutations, compared with the first-generation TKIs (such as gefitinib and erlotinib), some of the second- or third-generation TKIs, such as dacomitinib [versus gefitinib: HR = 0.63; 95% CI = (0.45, 0.89) versus erlotinib: HR = 0.63; 95% CI = (0.41, 0.98)], osimertinib [versus gefitinib: HR = 0.51; 95% CI = (0.39, 0.67) versus erlotinib: HR = 0.51; 95% CI = (0.39, 0.67)], and aumolertinib [versus gefitinib: HR = 0.60; 95% CI = (0.40, 0.90) versus erlotinib: HR = 0.60; 95% CI = (0.38, 0.98)], showed significantly better beneficial effects. In addition, compared with gefitinib, afatinib plus cetuximab [HR = 1.98; 95% CI = (1.01, 3.90)], erlotinib plus bevacizumab [HR = 1.69; 95% CI = (1.18, 2.41)], and erlotinib plus ramucirumab [HR = 1.62; 95% CI = (1.06, 2.47)] also showed increased PFS. Compared with NPC, the other therapeutic strategies showed significantly improved PFS. For OS, however, none of the first-line therapeutic strategies showed significant differences between each of the groups (Table 2).

For the PFS of patients with EGFR 19del-mutated NSCLC, compared with the first- and second-generation TKIs (such as gefitinib, erlotinib, icotinib, and afatinib), the third-generation TKIs such as aumolertinib [versus gefitinib: HR = 0.39; 95% CI = (0.28, 0.55) versus erlotinib: HR = 0.45; 95% CI = (0.30, 0.68) versus icotinib:
Table 1. Baseline characteristics of the enrolled studies.

| Study       | Country and participants | Number of subjects (group A versus group B) | Age (group A versus group B) | Sex (group A versus group B) | Group A | Group B | Histopathological classification |
|-------------|--------------------------|---------------------------------------------|-------------------------------|-------------------------------|---------|---------|----------------------------------|
| AENEAS      | China, multicenter       | 214 versus 215 [all] 74 versus 74 [Leu858Arg] | 59 [32–78] versus 62 [25–81] | 37.4% versus 37.2% [all]     | Aumolertinib 110 mg/d  | Gefitinib 250 mg/d | Adenocarcinoma [98.1% versus 98.1%] |
| WJOG9717L   | Japan, multicenter       | 61 versus 61 [all] 26 versus 25 [Leu858Arg] | 67 [41–86] versus 66 [29–85] | 39.4% versus 37.7% [all]     | Osimertinib 80 mg/d  | Bevacizumab 15 mg/kg, q3w | Nonsquamous NSCLC |
| BEVERLY     | Italy, multicenter       | 80 versus 80 [all] 34 versus 32 [Leu858Arg] | 65.9 [57.9–71.8] versus 67.7 [60.7–73.6] | 35% versus 37.5% [all] | Erlotinib 150 mg/d plus bevacizumab 15 mg/kg, q3w | Erlotinib 150 mg/d | Nonsquamous NSCLC |
| NEJ009      | Japan, multicenter [47 centers] | 170 versus 172 [all] 69 versus 67 [Leu858Arg] | 64.8 ± 7.8 versus 64.0 ± 8.4 [all] | 32.9% versus 37.2% [all] | Gefitinib 250 mg/d combined with carboplatin AUC 5 and pemetrexed 500 mg/m² | Gefitinib 250 mg/d | Adenocarcinoma [98.8% versus 98.8%] |
| NEJ026      | Japan, multicenter [69 centers] | 114 versus 114 [all] | 67 [61–73] versus 68 [62–73] [all] | 37.0% versus 35.0% [all] | Erlotinib 150 mg/d plus bevacizumab 15 mg/kg | Erlotinib 150 mg/d | Adenocarcinoma [98% versus 100%] Large-cell carcinoma [1% versus 0%] Other [1% versus 0%] |
| WJTOG3405   | Japan, multicenter [36 centers] | 86 versus 86 [all] [Leu858Arg] | 64.0 [34–74] versus 64.0 [41–75] | 31.4% versus 30.2% [all] | Gefitinib 250 mg/d | Docetaxel [60 mg/m²] and cisplatin [80 mg/m²] for 28 days | Adenocarcinoma [96.5% versus 97.7%] Adenosquamous carcinoma [0% versus 1.2%] Squamous-cell carcinoma [1.2% versus 0%] Non-small cell lung cancer; not otherwise specified [2.3% versus 1.2%] |
| Archer 1050 | China, multicenter [71 centers] | 227 versus 225 [all] [Leu858Arg] | 62 [53–68] versus 61 [54–68] [all] | 36% versus 44% [all] | Dacomitinib 45 mg/d | Gefitinib 250 mg/d | / |
| RELAY       | Japan, multicenter [100 centers in 13 countries] | 224 versus 225 [all] [Leu858Arg] | 65 [57–71] versus 64 [56–70] [all] | 37% versus 37% [all] | Ramucirumab 10 mg/kg/2 weeks and erlotinib 150 mg/d | Erlotinib 150 mg/d | Adenocarcinoma [96% versus 97%] NSCLC not otherwise specified [4% versus 3%] |
| LUX-Lung 3  | China, multicenter [133 centers in 25 countries] | 230 versus 115 [all] 91 versus 47 [Leu858Arg] | 61.5 [28–86] versus 61 [31–83] | 36.1% versus 33.0% [all] | Arafatinib 40 mg/d | Cisplatin [75 mg/m²] plus pemetrexed [500 mg/m²] | Adenocarcinoma [100% versus 100%] |

(Continued)
| Study       | Country and participants                                                                 | Number of subjects (group A versus group B) | Age (group A versus group B) | Sex (group A versus group B) | Group A                  | Group B                  | Histopathological classification                                                                 |
|-------------|------------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------|-----------------------------|--------------------------|--------------------------|---------------------------------------------------------------------------------------------|
| LUX-Lung 7  | South Korea, multicenter [64 centers in 13 countries]                                    | 160 versus 159 [all]                       | 63 [30–84] versus 63 [32–89] | 43% versus 33% [all]        | Afatinib 40 mg/d          | Gefitinib 250 mg/d          | /                                                                           |
| FLAURA      | USA, multicenter                                                                          | 279 versus 277 [all]                       | 64 [26–85] versus 64 [35–93] | 36% versus 38% [all]        | Osimertinib 80 mg/d      | Gefitinib 250 mg/d or erlotinib 150 mg/d                                               | Adenocarcinoma [99% versus 98%] Others [1% versus 2%]                                       |
| EURTAC      | Spain, multicenter                                                                         | 86 versus 87 [all]                         | 63.4 ± 11.0 versus 64.2 ± 9.2 | 33% versus 22% [all]        | Erlotinib 150 mg/d        | Cisplatin 75 mg/ m² [carboplatin AUC 6] on day 1 plus docetaxel [75 mg/m² on day 1] or gemcitabine [1250 mg/m² on days 1 and 8] | Adenocarcinoma [95% versus 90%] Bronchoalveolar adenocarcinoma [0% versus 2%] Large-cell carcinoma [3% versus 1%] Squamous-cell carcinoma [11% versus 0%] Other [0% versus 7%] |
| LUX-Lung 6  | China, multicenter [36 centers]                                                           | 242 versus 122 [all]                       | 58 [49–65] versus 58 [49–62] | 36% versus 32% [all]        | Afatinib 40 mg            | Gemcitabine 1000 mg/m² on days 1 and 8 plus cisplatin 75 mg/m² on day 1 [3-week schedule for up to 6 cycles] | Adenocarcinoma [100% versus 100%]                                                        |
| ACTIVE      | China, multicenter [36 centers]                                                           | 157 versus 156 [all]                       | 57 [51–65] versus 60 [51–65] | 42% versus 39.7% [all]      | Gefitinib 250 mg/d plus apatinib 500 mg/d | Gefitinib 250 mg/d          | Adenocarcinoma [98.1% versus 99.4%]                                                       |
| CTONG-0802  | China, multicenter [22 centers]                                                            | 83 versus 82 [all]                         | 57 [31–74] versus 59 [36–78] | 41% versus 40% [all]        | Erlotinib 150 mg/d        | Up to 4 cycles of gemcitabine plus carboplatin                                           | Adenocarcinoma [88% versus 86%] Non-adenocarcinoma [12% versus 14%]                         |
| CTONG-1509  | China, multicenter                                                                         | 157 versus 154 [all]                       | 57 [33–78] versus 59 [27–77] | 38.2% versus 37.7% [all]    | Bevacizumab plus erlotinib | Erlotinib                 | Adenocarcinoma [100% versus 100%]                                                        |
| SWOG 1403   | Canada, multicenter                                                                       | 83 versus 85 [all]                         | 65.5 [27.9–90.5] versus 66.3 [39.3–93.0] | 29% versus 38%             | Afatinib 40 mg orally daily plus cetuximab intravenously (IV) 500 mg/m            | Afatinib 40 mg orally daily                                                               | Adenocarcinoma [96% versus 95%] Large-cell carcinoma [0% versus 1%] Squamous-cell carcinoma [4% versus 0%] Mixed [0% versus 2%] |
| Country and participants | Number of subjects (group A versus group B) | Age (group A versus group B) | Sex (group A versus group B) | Histopathological classification |
|--------------------------|--------------------------------------------|-----------------------------|-----------------------------|--------------------------------|
| Cheng 2016, NCT01469000 | China, multicenter 126 versus 65 (all) | 62.0 ± 9.4 versus 61.0 ± 9.5 | 35% versus 37% (all) | Adenocarcinoma (99%) versus Adenocarcinoma (100%) |
| JO 25567 Japan, multicenter | 75 versus 77 (all) | 67.0 (59–73) versus 67.0 (59–73) | 40% versus 34% | Adenocarcinoma (99%) versus Adenocarcinoma (100%) |
| COVINCE China, multicenter | 148 versus 137 (all) | 66.35–73.7 versus 67.0–73.1 | 29.1% versus 30.8% | Adenocarcinoma (100%) versus Adenocarcinoma (100%) |
| WJOG5108L Japan, multicenter | 279 versus 280 (all) | 68.34–91 versus 67.39–85 | 45.5% versus 45.7% | Adenocarcinoma (100%) versus Adenocarcinoma (100%) |

For EGFR Leu858Arg-mutated NSCLC, the first-line therapeutic strategies to prolong PFS were ranked as follows: afatinib plus cetuximab was the best (33.1%), followed by gefitinib plus PC (30.1%), and NPC (0%). To prolong OS, the first-line therapeutic strategies were ranked as follows: afatinib plus cetuximab was the best (27.7%), followed by gefitinib plus PC (30.1%), NPC (0%).
Figure 2. Network evidence of the comparisons for the different treatment strategies for patients with the EGFR LeuL858Arg mutation in terms of PFS.

Figure 3. Network evidence of the comparisons for the different treatment strategies for patients with the EGFR LeuL858Arg mutation in terms of OS.
### Table 2. The pooled comparisons shown as hazard ratios (with 95% confidence intervals) for progression-free survival (upper triangle) and overall survival (lower triangle) in patients with NSCLC with E0FR Leu859Arg mutations.

| Overall survival | Aum | Osi | Osi + Bev | Gef + Apa | Gef + Cet | Erl + Bev | Erl + Ram |
|------------------|-----|-----|-----------|-----------|----------|----------|----------|
| Aum              | 1.17| 0.95| 0.82      | 0.69      | 1.18     | 1.01     | 0.83     |
|                  | [0.73, 1.93] | [0.56, 1.62] | [0.49, 1.41] | [0.38, 0.98] | [0.54, 2.24] | [0.59, 1.73] | [0.47, 1.98] |
| Overall survival | NA  | Osi | Osi + Bev | Gef + Apa | Gef + Cet | Erl + Bev | Erl + Ram |
| Osi              | 0.81| 0.70| 0.51      | 0.51      | 0.80     | 1.00     | 0.82     |
|                  | [0.52, 1.26] | [0.46, 1.07] | [0.39, 0.67] | [0.39, 0.67] | [0.59, 2.08] | [0.59, 2.15] | [0.53, 2.18] |
| Overall survival | NA  | Osi | Gef + Apa | Gef + Cet | Gef + Cet | Gef + Apa | Gef + Cet |
| Gef + Apa        | 1.23| 0.97| 0.83      | 1.03     | 0.97     | 0.83     | 1.03     |
|                  | [0.54, 1.92] | [0.47, 1.73] | [0.47, 1.75] | [0.47, 2.07] | [0.54, 1.73] | [0.47, 1.75] | [0.47, 1.73] |
| Overall survival | NA  | Gef + Cet | Gef + Cet | Gef + Apa | Gef + Cet | Gef + Apa | Gef + Cet |
| Gef + Cet        | 1.03| 0.75| 0.60      | 1.03     | 0.75     | 1.03     | 0.75     |
|                  | [0.39, 2.18] | [0.31, 1.48] | [0.31, 1.48] | [0.31, 1.48] | [0.31, 1.48] | [0.31, 1.48] | [0.31, 1.48] |
| Overall survival | NA  | Gef + Apa | Gef + Cet | Gef + Apa | Gef + Apa | Gef + Apa | Gef + Apa |
| Gef + Apa        | 1.06| 0.70| 0.60      | 1.06     | 0.70     | 1.06     | 0.70     |
|                  | [0.43, 1.38] | [0.31, 1.94] | [0.31, 1.94] | [0.31, 1.94] | [0.31, 1.94] | [0.31, 1.94] | [0.31, 1.94] |

(Continued)
Progression-free survival

| Gef | Gef + P | Gef + PC | Gef + PC | Gef + PC |
|-----|---------|----------|----------|----------|
| NA | 0.73    | 0.25     | 0.25     | 0.25     |
| 0.59 | 0.59    | 0.81     | 0.81     | 0.81     |
| 0.57 | 0.57    | 0.57     | 0.57     | 0.57     |
| 1.03 | 1.03    | 1.03     | 1.03     | 1.03     |
| 1.30 | 1.30    | 1.30     | 1.30     | 1.30     |

**Table 2.** (Continued)

(18.8%), osimertinib (13.3%), dacomitinib (2.0%), afatinib (1.5%), icotinib (0.7%), erlotinib plus bevacizumab (0.5%), erlotinib (0%), gefitinib (0%), and PC (0%) (Table 4).

**Discussion**

The results of this study demonstrated that compared with the first-generation EGFR TKIs, the second-generation EGFR TKI (dacomitinib) and the third-generation EGFR TKIs (osimertinib and aumolertinib) showed significantly improved PFS in patients with NSCLC with EGFR Leu858Arg mutations. In addition, afatinib plus cetuximab was the best first-line therapeutic strategy for patients with NSCLC with EGFR Leu858Arg mutations. For patients with NSCLC with EGFR 19del mutations, the third-generation EGFR TKIs (osimertinib and aumolertinib) showed significantly improved PFS compared with that of the first- and second-generation EGFR TKIs (gefitinib, erlotinib, icotinib, and afatinib). In addition, to prolong PFS, osimertinib plus bevacizumab was the best first-line therapeutic strategy for patients with NSCLC with EGFR 19del mutations.

We assumed that using the third-generation TKIs combined with other therapies would be more beneficial than the other treatments for patients with NSCLC with EGFR Leu858Arg mutations. The results of the WJOG9717L study, however, showed that the combination of osimertinib and bevacizumab did not achieve a better PFS than osimertinib alone in patients with NSCLC with EGFR Leu858Arg mutations. Apart from chemotherapy, various agents have been attempted in the dual therapy strategy, such as bevacizumab, ramucirumab, apatinib, and cetuximab.

Most tumor tissues show high expression of vascular endothelial growth factor (VEGF), which is associated with increased risk of metastasis and death. Bevacizumab and ramucirumab are recombinant humanized monoclonal anti-VEGF antibodies. Previous studies demonstrated that bevacizumab plus chemotherapy could improve the PFS and OS in patients with NSCLC. Apatinib, as a VEGFR2 TKI, targets the intracellular domain of the receptor and blocks signal transduction and can be orally administrated. The theoretical basis of the combinations of TKIs and antivascular treatment was that the antivascular treatment could inhibit
Table 3. The pooled comparisons shown as hazard ratios (with 95% confidence intervals) for progression-free survival (upper triangle) and overall survival (lower triangle) in patients with NSCLC with EGFR 19del mutations.

| Progression-free survival | Overall survival | Aum | [0.65, 1.16] | [0.43, 0.84] | [0.28, 0.55] | [0.10, 0.50] | [0.70, 1.20] | [0.47, 0.81] | [0.35, 0.81] | [0.33, 0.68] | [0.36, 0.80] | [0.08, 0.33] | [0.07, 0.18] |
|---------------------------|-----------------|-----|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| NA                        | Osi             | 0.78| [0.79, 1.00] | [0.55, 0.93] | [0.41, 0.69] | [0.14, 0.69] | [0.01, 0.69] | [0.68, 1.67] | [0.59, 1.61] | [0.34, 1.61] | [0.48, 1.36] | [0.11, 0.25] | [0.10, 0.25] |
| NA                        | Dac             | 0.75| [0.55, 0.95] | [0.33, 1.18] | [0.08, 0.51] | [0.01, 0.51] | [0.01, 0.51] | [0.69, 1.61] | [0.36, 1.36] | [0.40, 1.36] | [0.40, 1.36] | [0.40, 1.36] | [0.40, 1.36] |
| NA                        | Afa             | 0.67| [0.52, 1.33] | [0.49, 1.33] | [0.24, 1.06] | [0.69, 1.33] | [0.69, 1.33] | [0.72, 1.33] | [0.72, 1.33] | [0.72, 1.33] | [0.72, 1.33] | [0.72, 1.33] | [0.72, 1.33] |
| NA                        | Erl             | 0.69| [0.61, 1.25] | [0.58, 1.17] | [0.72, 1.44] | [0.02, 1.19] | [0.01, 1.19] | [0.81, 1.39] | [0.47, 2.69] | [0.18, 2.69] | [0.23, 2.69] | [0.23, 2.69] | [0.23, 2.69] |
| NA                        | Gef             | 0.59| [0.37, 1.15] | [0.44, 1.18] | [0.47, 1.58] | [1.90, 2.42] | [1.58, 2.42] | [1.90, 2.42] | [1.58, 2.42] | [1.58, 2.42] | [1.58, 2.42] | [1.58, 2.42] | [1.58, 2.42] |
| NA                        | Ic + Afa        | 0.99| [0.45, 2.22] | [0.29, 2.34] | [0.33, 3.33] | [0.68, 3.06] | [0.74, 3.06] | [0.97, 3.18] | [0.70, 2.56] | [0.68, 2.56] | [0.73, 2.56] | [0.19, 0.64] | [0.46, 0.46] |
| NA                        | Er + Gef       | 0.47| [0.23, 1.04] | [0.16, 0.92] | [0.09, 0.92] | [0.72, 0.84] | [0.72, 0.84] | [0.48, 1.48] | [0.48, 1.54] | [0.50, 1.54] | [0.50, 1.54] | [0.11, 0.26] | [0.26, 0.26] |
| NA                        | Er + Ic        | 0.37| [0.16, 0.92] | [0.17, 0.92] | [0.16, 0.92] | [0.48, 1.54] | [0.50, 1.54] | [0.48, 1.54] | [0.48, 1.54] | [0.48, 1.54] | [0.48, 1.54] | [0.37, 0.23] | [0.23, 0.23] |
| NA                        | Gef + Ap         | 0.09| [0.04, 0.26] | [0.04, 0.26] | [0.04, 0.26] | [0.17, 0.26] | [0.17, 0.26] | [0.17, 0.26] | [0.17, 0.26] | [0.17, 0.26] | [0.17, 0.26] | [0.04, 0.17] | [0.04, 0.17] |

(Continued)
Table 3. (Continued)

**Progression-free survival**

| NA  | NA  | NA  | NA  | NA  | NA  | NA  | NA  | NA  | NA  | Gef + P |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------|
|     |     |     |     |     |     |     |     |     |     | 1.03    |
|     |     |     |     |     |     |     |     |     |     | [0.57, 1.86] |
| Gef + PC | 0.25 | [0.13, 0.34] |

Afa, afatinib; Apa, apatinib; Aum, aumolertinib; Bev, bevacizumab; Cet, cetuximab; Dac, dacomitinib; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; NPC, non-pemetrexed-based chemotherapy; Osi, osimertinib; PC, pemetrexed-based chemotherapy; Ram, ramucirumab.

Table 4. Estimated probabilities of each treatment being the best for PFS and OS in patients with 21L858R and 19del mutations.

| Amu | Osi | Dac | Afa | Erl | Gef | Ico | Osi + Bev | Gef + P |
|-----|-----|-----|-----|-----|-----|-----|-----------|--------|
| PFS [21L858R] | 0.061 | 0.124 | 0.027 | 4.0E-4 | 0 | 0 | 0.128 | 0.129 | 0.303 | 0.036 | 0.043 | 0.010 | 0.136 | 0.003 | 6.667E-5 | 0 |
| OS [21L858R] | NA | 0.001 | 0.189 | 8.333E-4 | 7.667E-4 | 0 | 0.086 | NA | 0.277 | 0.234 | NA | NA | NA | 0.086 | 0.119 | 0.007 |
| PFS [19del] | 0.110 | 0.036 | 0.002 | 3.333E-5 | 0 | 0 | 0 | 0.8425 | 6.667E-5 | 0.004 | 0.003 | 6.0E-4 | 0.001 | 8.0E-4 | 0 | 0 |
| OS [19del] | NA | 0.133 | 0.020 | 0.015 | 0 | 0 | 0.007 | NA | 0.331 | 0.005 | NA | NA | NA | 0.301 | 0 | 0.188 |

Afa, afatinib; Apa, apatinib; Aum, aumolertinib; Bev, bevacizumab; Cet, cetuximab; Dac, dacomitinib; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; NPC, non-pemetrexed-based chemotherapy; Osi, osimertinib; PC, pemetrexed-based chemotherapy; Ram, ramucirumab.
tumor angiogenesis, thus improving the delivery of EGFR TKIs by vascular normalization.41

Anti-EGFR therapy resistant tumors contain T790M, exon 20 insertion, and EGFR amplification mutations. Using dual therapy comprising afatinib and cetuximab, Janjigian et al.42 showed that patients with EGFR-mutant NSCLC with acquired resistance could achieve a response rate of about 30%, regardless of their T790M status. This demonstrated that the combination was beneficial to patients with T790M mutations. Second, Hasegawa et al.43 demonstrated that EGFR exon 20 insertion mutations (typically resistant to EGFR TKIs) might respond well to the same combination. Mechanistically, dual inhibition of EGFR is probably useful in tumors that are dependent on signaling through the receptor, as EGFR TKIs bind to the intracellular domain of the receptor, whereas cetuximab binds extracellularly.

In addition, exon 21Leu858Arg mutations have a lower incidence of T790M mutations than 19del mutations. In some real-world studies, the authors reported that the frequency of the T790M mutation among patients with initial exon 19 deletion mutation was almost twice that in patients with 21Leu858Arg mutation,44,45 which could benefit from using the third-generation TKIs. Therefore, therapies containing the third-generation EGFR TKIs are probably the best to treat patients with NSCLC with EGFR 19del mutations, but not those with 21Leu858Arg mutations.

There were, however, several limitations in our study. First, we could not identify some comutated genes (such as TP53 mutation) in the subjects included in our study, which contributes to a shorter PFS than in patients with wild-type TP53.46 Second, the number of enrolled patients in some therapeutic arms was relatively small, which might have led to bias. Moreover, some updated studies included in our research were not published formally.

**Conclusion**

For patients with NSCLC with EGFR Leu858Arg mutations, afatinib plus cetuximab ranked as the best to prolong PFS. For patients with NSCLC with EGFR 19del mutations, however, osimertinib plus bevacizumab was the best to improve PFS. In the future, combined therapy containing the second-generation TKIs and other drugs (such as anti-VEGFR monoclonal antibodies) could be further tested to treat patients with NSCLC with EGFR Leu858Arg mutations.

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Author contributions**

Chongxiang Chen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Chunning Zhang: Formal analysis; Software.

Huaming Lin: Formal analysis; Investigation; Validation.

Qianying Liu: Formal analysis; Investigation; Software.

Limian Wu: Validation; Writing – review & editing.

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**Competing interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Availability of data and materials**

The datasets used and/or analyzed in this study are available from the corresponding author upon request.
Data availability
All data generated or analyzed during this study are included in this published article.

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References
1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7–33.
2. Nadal E, Massuti B, Dómine M, et al. Immunotherapy with checkpoint inhibitors in non-small cell lung cancer: insights from long-term survivors. Cancer Immunol Immunother 2019; 68: 341–352.
3. Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced non-small-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. J Clin Oncol 2019; 37: 2518–2527.
4. Lin JJ, Cardarella S, Lydon CA, et al. Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. J Thorac Oncol 2016; 11: 556–565.
5. Pacheco JM, Gao D, Smith D, et al. Natural history and factors associated with overall survival in stage IV ALK-rearranged non-small cell lung cancer. J Thorac Oncol 2019; 14: 691–700.
6. Melosky B, Kambartel K, Hantschel M, et al. Worldwide prevalence of epidermal growth factor receptor mutations in non-small cell lung cancer: a meta-analysis. Mol Diagn Ther 2022; 26: 7–18.
7. Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, version 2.2021. J Natl Compr Canc Ne 2021; 19: 254–266.
8. Zhao H, Yao W, Min X, et al. Apatinib plus gefitinib as first-line treatment in advanced EGFR-mutant NSCLC. The phase III ACTIVE study (CTONG1706). J Thorac Oncol 2021; 16: 1533–1546.
9. Zhou Q, Xu CR, Cheng Y, et al. Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study. Cancer Cell 2021; 39: 1279–1291.e3.
10. Seto T, Kato T, Nishio M, 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. Lancet Oncol 2014; 15: 1236–1244.
11. Saito H, Fukuhara T, Furuya N, 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. Lancet Oncol 2019; 20: 625–635.
12. Kawashima Y, Fukuhara T, Saito H, et al. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Respir Med 2022; 10: 72–82.
13. Nakagawa K, Garon EB, Seto T, 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. Lancet Oncol 2019; 20: 1655–1669.
14. Karachaliou N, Mayo-de las Casas C, Queralt C, et al. Association of EGFR L858R mutation in circulating free DNA with survival in the EURTAC trial. JAMA Oncol 2015; 1: 149–157.
15. Rosell R, Carcereny E, Gervais R, 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. Lancet Oncol 2012; 13: 239–246.
16. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol 2005; 23: 2513–2520.
17. Paz-Ares L, Tan E-H, O’Byrne K, et al. Aftabinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase Ib LUX-Lung 7 trial. Ann Oncol 2017; 28: 270–277.
18. Ramalingam SS, Vansteenkiste J, Panchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. New Engl J Med 2020; 382: 41–50.
19. Zhao Y, Liu J, Cai X, 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) 2019; 367: i5460.

20. Goldberg SB, Redman MW, Lilenbaum R, et al. Randomized trial of afatinib plus cetuximab versus afatinib alone for first-line treatment of EGFR-mutant non-small-cell lung cancer: final results from SWOG S1403. J Clin Oncol 2020; 38: 4076–4085.

21. Piccirillo MC, Bonanno L, Garassino MCC, et al. Bevacizumab plus erlotinib vs erlotinib alone as first-line treatment of pts with EGFR mutated advanced non squamous NSCLC: Final analysis of the multicenter, randomized, phase III BEVERLY trial. Ann Oncol 2021; 32: S950–S950.

22. Kenmotsu H, Wakuda K, Mori K, et al. Primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small cell lung cancer harboring EGFR mutations: WJOG9717L study. Ann Oncol 2021; 32: S1322–S1323.

23. Lu S, Dong X, Jian H, et al. AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic Non-small-cell lung cancer with egfr exon 19 deletion or L858R Mutations. J Clin Oncol 2022; 40: 3162–3171.

24. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTQG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121–128.

25. Cheng Y, Murakami H, Yang PC, et al. Randomized phase II trial of gefitinib with and without pemetrexed as first-line therapy in patients with advanced nonsquamous non-small-cell lung cancer with activating epidermal growth factor mutations. J Clin Oncol 2016; 34: 3258–3266.

26. Wu YL, Cheng Y, Zhou X, 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. Lancet Oncol 2017; 18: 1454–1466.

27. Park K, Tan EH, O’Byrne K, et al. Afatinib 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. Lancet Oncol 2016; 17: 577–589.

28. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327–3334.

29. Shi YK, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol 2017; 28: 2443–2450.

30. Urata Y, Katakami N, Morita S, et al. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. J Clin Oncol 2016; 34: 3248–3257.

31. Wu YL, Zhou C, Hu CP, 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. Lancet Oncol 2014; 15: 213–222.

32. Zhou C, Wu YL, Chen G, 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. Lancet Oncol 2011; 12: 735–742.

33. Cheng Y, He Y, Li W, et al. Osimertinib versus comparator EGFR TKI as first-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, a randomized study. Target Oncol 2021; 16: 165–176.

34. 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: 115–123.

35. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. New Engl J Med 2018; 378: 113–125.

36. Toi M, Matsumoto T and Bando H. Vascular endothelial growth factor: its prognostic, predictive, and therapeutic implications. Lancet Oncol 2001; 2: 667–673.

37. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in...
38. Zhou C, Wu YL, Chen G, et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; 33: 2197–2204.

39. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New Engl J Med* 2006; 355: 2542–2550.

40. Fontanella C, Ongaro E, Bolzonello S, et al. Clinical advances in the development of novel VEGFR2 inhibitors. *Ann Transl Med* 2014; 2: 123.

41. Khan KA and Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. *Nat Rev Clin Oncol* 2018; 15: 310–324.

42. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov* 2014; 4: 1036–1045.

43. Hasegawa H, Yasuda H, Hamamoto J, et al. Efficacy of afatinib or osimertinib plus cetuximab combination therapy for non-small-cell lung cancer with EGFR exon 20 insertion mutations. *Lung Cancer (Amsterdam, Netherlands)* 2019; 127: 146–152.

44. Li H, Wang J, Zhang G, et al. Detection of plasma T790M mutation after the first generation EGFR-TKI resistance of non-small cell lung cancer in the real world. *J Thorac Dis* 2020; 12: 550–557.

45. Liang H, Pan Z, Wang W, et al. The alteration of T790M between 19 del and L858R in NSCLC in the course of EGFR-TKIs therapy: a literature-based pooled analysis. *J Thorac Dis* 2018; 10: 2311–2320.

46. Tan J, Hu C, Deng P, et al. The predictive values of advanced non-small cell lung cancer patients harboring uncommon EGFR mutations: the mutation patterns, use of different generations of EGFR-TKIs, and concurrent genetic alterations. *Front Oncol* 2021; 11: 646577.