A network meta-analysis of nonsmall-cell lung cancer patients with an activating EGFR mutation
Should osimertinib be the first-line treatment?

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Abstract

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the preferred first-line treatment for nonsmall-cell lung cancer (NSCLC) patients with an activating EGFR mutation. Osimertinib, compared with erlotinib or gefitinib, showed an improvement in progression-free survival (PFS) in a recent trial. The authors compared EGFR TKIs in terms of PFS in a network meta-analysis.

Methods: The PubMed and Embase databases and meeting abstracts were screened for relevant studies between January 2009 and November 2017. A random-effect frequentist network meta-analysis model was conducted to assess PFS. P-score was used to rank treatment effects.

Results: Eleven trials with 3145 patients and 5 TKIs (gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib) were included. Heterogeneity and inconsistency existed in the network analysis. Gefitinib and erlotinib had similar effects (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.76–1.15). For all patients, the 3 TKIs with the highest probability of benefit were osimertinib, dacomitinib, and afatinib, with P-scores of 91%, 78%, and 46%, respectively. Compared with erlotinib or gefitinib, osimertinib was associated with improvement in men (HR = 0.79, 95% CI, 0.68–0.92), non-Asians (HR = 0.63, 95% CI, 0.40–0.98), smokers (HR = 0.73, 95% CI, 0.56–0.95), and those with a Del19 mutation (HR = 0.69, 95% CI, 0.54–0.90); dacomitinib and afatinib showed no improvement. Toxicity profiles mostly overlapped in all the EGFR TKIs. Toxicity-related death was rare.

Conclusions: Osimertinib was shown to be the best agent to achieve the longest PFS in NSCLC patients with an activating EGFR mutation. However, the benefit of osimertinib might be restricted to certain subgroups.

Abbreviations: CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = nonsmall-cell lung cancer, PFS = progression-free survival, SoC = standard of care, TKIs = tyrosine kinase inhibitors.

Keywords: EGFR, meta-analysis, nonsmall-cell lung cancer, targeted therapy

1. Introduction

The incidence of an activating epidermal growth factor receptor (EGFR) mutation in patients with nonsmall-cell lung cancer (NSCLC) is 15% to 50%, depending on race, gender, and smoking status.[1] As first-generation tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib have consistently shown a greater response, longer progression-free survival (PFS), and improved quality of life compared to chemotherapy in patients who have a driver mutation in the EGFR gene for first-line treatment.[16-18] These results have established either of the 2 TKIs as the standard of care (SoC).

Unlike the reversible first-generation EGFR TKIs, second-generation TKIs (afatinib and dacomitinib) irreversibly bind to ErbB receptors.[6] Two prospective trials have confirmed the superiority of afatinib over chemotherapy, and the extent of the benefit of PFS was similar to that observed in trials comparing first-generation TKIs with chemotherapy.[7,8] A subsequent head-to-head study compared afatinib with gefitinib as first-line treatments and showed a statistically significant improvement in PFS with afatinib,[9] but the difference was not clinically meaningful (median PFS of 11.0 and 10.9 months for afatinib and gefitinib, respectively). By contrast, in another head-to-head trial, the irreversible EGFR blocker dacomitinib was associated with an absolute difference of 5.5 months in PFS compared with gefitinib, though at the cost of increased toxicity.[10]

Osimertinib, a third generation, irreversible EGFR TKI that targets primary activating EGFR mutations and secondary T790M mutations, has been approved as a preferred second-line therapy in patients who developed the T790M mutation after first-line TKI treatment.[11-13] Then, osimertinib was used as a first-line treatment to maximize its effect on delaying progression. In the FLAURA study, compared with SoC, osimertinib showed remarkably improved PFS and more favorable tolerability.[14]

We performed a network meta-analysis by including relevant trials investigating EGFR TKIs to compare efficacy in terms of PFS and toxicity and focused primarily on whether osimertinib was superior to first-generation EGFR TKIs.

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2. Methods

2.1. Study search and identification

The following terms were used for the search: NSCLC, EGFR, gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, rociletinib, system review, meta-analysis, randomized, and trials. Studies were prospective phase II and III randomized controlled trials that compared EGFR TKIs with standard platinum-based chemotherapy or compared different first-line EGFR TKIs in patients with newly pathologically confirmed advanced NSCLC with actionable EGFR mutations. The PubMed and Embase databases and the Cochrane Central Register of Controlled Trials were searched for published randomized controlled trials. We also searched the references of the included publications and related systemic reviews for potential publications. The search was limited to trials published between January 2009 and November 2017. Abstracts were also searched from meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Lung Cancer Conference. The study adhered to the recommendations of the PRISMA protocol.

2.2. Data extraction and quality assessment

The data extracted from the trials were as follows: name of the study, publication year, trial phase, sample size, treatments, patients’ clinical and pathological characteristics, response rates, adverse events, PFS, hazard ratio (HR), and overall survival. The subsequent subgroup analyses were performed according to sex (female vs male), ethnicity (Asian vs non-Asian), smoking status (nonsmokers vs current or former smokers), and EGFR mutation type (Del19 vs L858R). The P value, HRs, and 95% confidence intervals (CIs) were directly extracted for overall and subgroup analyses. Data extraction was conducted by 2 reviewers independently. Disagreement between reviewers was resolved by a third reviewer. The quantitative Jadad scale was used to assess study quality.\[15\]

2.3. Statistical analysis

We used a frequentist weighted least-squares approach described by Rücker\[16,17\] and implemented in the R package netmeta instead of Bayesian modeling because of easier computation and programming. Both approaches were considered to produce instead of Bayesian modeling because of easier computation and programming. First, we compared gefitinib with erlotinib in terms of PFS. Six were included. Both gefitinib and erlotinib were associated with a reduction in disease progression compared with chemotherapy. Erlotinib had a similar effect compared with gefitinib (HR 0.94, 95% CI 0.76–1.15). On this basis, treatment with erlotinib or gefitinib through all the trials was considered identical and was denoted as the SoC. This SoC arm was used as a mutual arm to connect other treatments for indirect comparison (Fig. 2).

A statistical test with \( P < .05 \) was considered significant. All 95% CIs were 2-sided. Network meta-analysis was performed with R software, version i386 3.3.2.

3. Results

According to the flow chart in Fig. 1, after titles and abstracts were screened, 20 potential studies were evaluated further. Nine studies were excluded, namely, 2 for enrolling patients without a confirmed EGFR mutation status,\[21,22\] 1 for providing therapy with double targeted agents,\[23\] 3 for duplicate publications,\[24–26\] and 3 for combining TKIs with chemotherapy.\[27–29\] The remaining 11 trials were finally included in the network analysis.\[12,5–7,10,14,30,31\] Five TKIs were evaluated: first-generation gefitinib and erlotinib, second-generation afatinib and dacomitinib, and third-generation osimertinib. The study characteristics are shown in Table 1. The Chinese CTONG 0901 study allowed 91 (35.5%) patients to receive gefitinib or erlotinib as second-line treatment,\[31\] and these 91 patients were excluded, resulting in a total of 3145 patients in the final analysis. All patients harbored sensitive EGFR mutations, with 2 types of mutations (19Del and L858R) accounting for over 90% of the population in the analysis. The quality of included trials was high (Jadad \( \geq 3 \)).

The main outcomes of included studies, including response rates, PFS, and overall survival, are presented in Table 2. Overall, TKIs had significantly higher response rates and longer PFS than chemotherapy. The second (afatinib and dacomitinib) and third (osimertinib) generations of TKIs were superior to gefitinib in PFS, though they were not accompanied by a higher response rate. No significant survival differences were demonstrated in all the comparisons among the trials.

The whole network showed significant heterogeneity (\( Q_{total} = 21.72, P = .001 \)). The \( Q_{total} \) statistics were further deconstructed to assess the heterogeneity within and between study designs, and the results showed significant heterogeneity within designs (\( Q = 18.57, P = .001 \)) but not between designs (\( Q = 3.15, P = .26 \)). After deconstructing the within-designs heterogeneity, all 3 designs of TKIs (gefitinib, erlotinib, and afatinib) versus chemotherapy were identified as the source of heterogeneity. A random-effects frequentist network model was applied to assess PFS.

First, we compared gefitinib with erlotinib in terms of PFS. Six were included. Both gefitinib and erlotinib were associated with a reduction in disease progression compared with chemotherapy. Erlotinib had a similar effect compared with gefitinib (HR 0.94, 95% CI 0.76–1.15). On this basis, treatment with erlotinib or gefitinib through all the trials was considered identical and was denoted as the SoC. This SoC arm was used as a mutual arm to connect other treatments for indirect comparison (Fig. 2).

Regarding PFS, compared with SoC, the 3 TKIs with the highest probability of benefit were osimertinib, dacomitinib, and afatinib, with HRs (95% CI) of 0.71 (0.54–0.93), 0.80 (0.60–1.06), and 0.96 (0.86–1.17), respectively. The corresponding P-scores were 91%, 78%, 46%, and 33% for osimertinib, dacomitinib, afatinib, and SoC, respectively. This rank remained unchanged in females, males, non-Asians, never smokers, ever or current smokers, and those with 19Del and L858R mutations but not in the Asian subgroup. HRs and 95% CIs of direct and indirect comparisons in this network analysis are shown in Fig. 2.

Compared with SoC, osimertinib was associated with improvement in men (HR = 0.79, 95% CI, 0.68–0.92), non-Asians (HR = 0.63, 95% CI, 0.40–0.98), smokers (HR = 0.73,
Table 1
Baseline characteristics of included trials.

| Study year, phase | Comparison  | N  | Median age | Female, % | Asian race, % | Never smoker, % | PS 0–1, % | Adenocarcinoma, % | 19Del/L858R/other, % |
|-------------------|------------|----|------------|-----------|---------------|----------------|-----------|-------------------|---------------------|
| WJOG3405          | Gefitinib  | 86 | 64         | 69        | 100           | 71             | 100       | 97                | 58/42/0             |
| 2010, III         | Chemotherapy | 86 | 64         | 70        | 100           | 66             | 100       | 98                | 43/57/0             |
| NEJ002            | Gefitinib  | 114 | 63.9       | 63.2      | 100           | 65.8           | 99.1      | 90.4              | 50.9/43/6.1         |
| 2010, III         | Gefitinib  | 114 | 62.6       | 64        | 100           | 57.9           | 98.2      | 96.5              | 51.8/42/16.1        |
| EURTAC            | Erlotinib  | 86  | 63         | 67        | 0             | 66             | 86        | 95                | 66/34/0             |
| 2011, III         | Chemotherapy | 87 | 64         | 78        | 0             | 72             | 86        | 90                | 67/33/0             |
| OPTIMAL           | Erlotinib  | 82  | 57         | 59        | 100           | 72             | 91        | 88                | 52/48/0             |
| 2011, III         | Chemotherapy | 72 | 59         | 60        | 100           | 69             | 96        | 86                | 54/46/0             |
| ENSURE            | Erlotinib  | 110 | 57.5       | 61.8      | 100           | 71.8           | 93.6      | 94.5              | 52.3/47.7/0         |
| 2015, III         | Chemotherapy | 107 | 56        | 60.7      | 100           | 69.2           | 94.2      | 94.4              | 57/43/0             |
| Lux-lung3         | Afatinib   | 230 | 61.5       | 63.9      | 71.7          | 67.4           | 100       | 100               | 49.1/39.6/11.3      |
| 2013, III         | Chemotherapy | 115 | 61        | 67        | 72.7          | 70.4           | 99.1      | 100               | 49.6/40.9/9.6       |
| Lux-lung6         | Afatinib   | 242 | 58         | 64        | 100           | 74.8           | 100       | 100               | 51.2/38/10.7        |
| 2014, III         | Chemotherapy | 122 | 58        | 68        | 100           | 81.1           | 100       | 100               | 50.8/37.7/11.5      |
| Lux-lung7         | Afatinib   | 160 | 63         | 57        | 59            | 66             | 100       | 99                | 42/58/0             |
| 2016, II          | Gefitinib  | 159 | 63         | 67        | 55            | 67             | 100       | 99                | 42/58/0             |
| ARCHER1050        | Dacomitinib | 227 | 62        | 64        | 75            | 65             | 100       | —                 | 59/41/0             |
| 2017, III         | Gefitinib  | 225 | 61         | 56        | 78            | 64             | 100       | —                 | 59/41/0             |
| CTONG00901        | Erlotinib  | 128 | —          | 53.1      | 100           | 82             | 98.4      | 96.1              | 57.8/42.2           |
| 2017, III         | Gefitinib  | 128 | —          | 53.9      | 100           | 72.7           | 96.9      | 96.1              | 57.8/42.2           |
| FLAURA            | Osimertinib | 279 | 64        | 64        | 62            | 65             | 100       | 99                | 57/35/0             |
| 2017, III         | SoC        | 277 | 64         | 62        | 62            | 63             | 100       | 98                | 56/32/0             |

*PS = performance status, SoC = standard of care (Erlotinib or Gefitinib).*

Figure 1. The search strategy. EGFR = epidermal growth factor receptor; RCTs = randomized controlled trials; TKI = tyrosine kinase inhibitor.
95% CI, 0.56–0.95), and those with the Del19 mutation (HR = 0.69, 95% CI, 0.54–0.90). Dacomitinib and afatinib were not associated with improvement in all subgroups. The results of the rank and P-scores are presented in Table 3.

After excluding the 2 studies that reported longer median PFS than 6 months in the chemotherapy arm, the sensitivity analysis showed consistent results with the primary results.

Table 2: Response rates, PFS, and OS for included trials.

| Study        | Comparison  | Object response, % | PFS, mo; HR (95% CI) | OS, mo; HR (95% CI) |
|--------------|-------------|--------------------|----------------------|--------------------|
| WJTOG3405    | Gefitinib   | 62.1               | 9.2                  | 30.9               |
|              | Chemotherapy| 32.2               | 6.3                  | Not reach          |
| NEJ002       | Gefitinib   | 73.7               | 10.8                 | 27.7               |
|              | Chemotherapy| 30.7               | 5.4                  | 26.6               |
| EURTAC       | Erlotinib   | 56                 | 9.7                  | 19.3               |
|              | Chemotherapy| 15                 | 5.2                  | 19.5               |
| OPTIMAL      | Erlotinib   | 83                 | 13.1                 | 22.8               |
|              | Chemotherapy| 36                 | 4.6                  | 27.2               |
| ENSURE       | Erlotinib   | 62.7               | 11.0                 | 26.3               |
|              | Chemotherapy| 33.6               | 5.6                  | 25.5               |
| Lux-lung3    | Afatinib    | 56                 | 11.1                 | 28.2               |
|              | Chemotherapy| 23                 | 6.9                  | 28.2               |
| Lux-lung6    | Afatinib    | 74.4               | 11.0                 | 23.1               |
|              | Chemotherapy| 31.1               | 5.6                  | 23.5               |
| Lux-lung7    | Afatinib    | 70                 | 11.0                 | 27.9               |
|              | Gefitinib   | 56                 | 10.9                 | 24.5               |
|              |              |                    | 0.73 (0.57–0.95)      | 0.88 (0.66–1.12)    |
| ARCHER1050   | Dacomitinib | 75                 | 14.7                 | Not reach          |
|              | Gefitinib   | 72                 | 9.2                  | Not reach          |
|              |              |                    | 0.59 (0.47–0.74)      | —                  |
| CTONG0901    | Erlotinib   | 58.0               | 13.2                 | 22.4               |
|              | Gefitinib   | 52.4               | 11.1                 | 20.7               |
|              |              |                    | 0.96 (0.69–1.35)      | 0.98 (0.67–1.42)    |
| FLAURA       | Osimertinib | 80                 | 18.9                 | Not reach          |
|              | SoC         | 76                 | 10.2                 | Not reach          |
|              |              |                    | 0.46 (0.37–0.57)      | 0.63 (0.45–0.88)    |

CI = confidence interval, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, SoC = standard of care (Erlotinib or Gefitinib).

Figure 2: Network of comparisons. Solid lines indicate direct comparisons, and dashed lines indicate indirect comparisons. For each comparison, the arrows point to the reference arm. The hazard ratio and 95% confidence interval are presented.
The main toxicities of different TKIs in each trial are summarized in Table 4. The first- and second-generation TKIs share similar common adverse events, predominately rash and diarrhea, but the third-generation TKI was not associated with a significant incidence of rash. The permanent discontinuation rate due to toxicity was low for all EGFR TKIs. Toxicity-related death was rare.

### Table 3

**Rank and P-scores of subgroups.**

| N     | Rank 1 | Rank 2 | Rank 3 | Rank 4 |
|-------|--------|--------|--------|--------|
|       | P-score, % | P-score, % | P-score, % | P-score, % |
|       | HR (95% CI) | HR (95% CI) | HR (95% CI) | Reference |
| Total | 3145   | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 91     | 78      | 46      | 35 |
|       | 0.71 (0.54–0.95) | 0.80 (0.60–1.06) | 0.96 (0.86–1.17) | 1 |
| Subgroups | | | | |
| Female | 1749   | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 79     | 86      | 44      | 37 |
|       | 0.67 (0.46–1.00) | 0.74 (0.50–1.09) | 0.97 (0.75–1.26) | 1 |
| Male   | 1003   | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 94     | 75      | 45      | 33 |
|       | 0.79 (0.68–0.92) | 0.87 (0.75–1.01) | 0.97 (0.85–1.11) | 1 |
| Asian  | 2421   | Dacomitinib | Osimertinib | Afatinib | SoC |
|       | 75     | 84      | 65      | 36 |
|       | 0.75 (0.43–1.29) | 0.77 (0.45–1.34) | 0.84 (0.60–1.17) | 1 |
| Non-Asian | 721   | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 95     | 52      | 49      | 46 |
|       | 0.63 (0.40–0.98) | 0.95 (0.60–1.50) | 0.99 (0.68–1.43) | 1 |
| Nonsmoker | 1876  | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 87     | 81      | 40      | 40 |
|       | 0.71 (0.50–1.01) | 0.75 (0.52–1.06) | 1.01 (0.79–1.29) | 1 |
| Smoker | 876    | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 93     | 66      | 57      | 33 |
|       | 0.73 (0.56–0.95) | 0.87 (0.66–1.14) | 0.91 (0.76–1.10) | 1 |
| Del19  | 1560   | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 91     | 78      | 49      | 30 |
|       | 0.69 (0.54–0.90) | 0.77 (0.59–1.00) | 0.92 (0.77–1.11) | 1 |
| Lc858Arg | 1114  | Osimertinib | Dacomitinib | Afatinib | SoC |
|       | 74     | 86      | 56      | 37 |
|       | 0.75 (0.53–1.05) | 0.87 (0.66–1.14) | 0.82 (0.58–1.15) | 1 |

CI = confidence interval, HR = hazard ratio, SoC = standard of care (Erlotinib or Gefitinib).

The main toxicities of different TKIs in each trial are summarized in Table 4. The first- and second-generation TKIs shared similar common adverse events, predominately rash and diarrhea, but the third-generation TKI was not associated with a significant incidence of rash. The permanent discontinuation rate due to toxicity was low for all EGFR TKIs. Toxicity-related death was rare.

### Table 4

**The most common adverse events reported in each study.**

| AE-related withdrawal, n (%) | AE-related death |
|-----------------------------|------------------|
| Most common AE              |                  |
| Gefitinib                   | Sigmoid colon diverticulitis |
| WJTOG3405 Skin rash, elevated ALT/AST, diarrhea | Not report | 1 Interstitial lung disease |
| NEJ002 Skin rash, elevated ALT/AST | Not report | 1 Interstitial lung disease |
| ARCHER1050 Diarrhea, elevated ALT/AST | 15 (7) | 1 |
| Lux-lung7 Increased ALT/AST, rash or acne | 10 (6) | 1 Hepatic and renal failure |
| CTONG0901 Skin rash, diarrhea, elevated ALT/AST | Not report | None |
| Erlotinib                   | Sigmoid colon diverticulitis |
| EURTAC Rash, elevated ALT/AST | 5 (6) | 1 Hepatotoxicity |
| OPTIMAL Skin rash, diarrhea | None | None |
| ENSURE Skin rash, diarrhea | 3 (2.7) | 1 Pulmonary embolism |
| CTONG0901 Skin rash, diarrhea | Not report | None |
| Afatinib                    | Respiratory decompositions 1 sepsis |
| Lux-lung3 Diarrhea, rash, mucositis, nails change | 18 (8) | 2 |
| Lux-lung6 Diarrhea, rash or acne, mucositis | 14 (5.9) | 1 Sudden death |
| Lux-lung7 Diarrhea, rash or acne, fatigue | 10 (6) | None |
| Dacomitinib                 | None |
| ARCHER1050 Diarrhea, paronychia, dermatitis, acneiform, stomatitis | 22 (10) | 1 Diarrhea |
| Osimertinib                 | Cholestasis |
| FLALRA Rash or acne, diarrhea, dry skin | 37 (13) | None |

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase.
4. Discussion

For patients with advanced EGFR-mutant NSCLC, 3 currently approved TKIs (gefitinib, erlotinib, and afatinib) led to dramatic tumor shrinkage and prolonged PFS compared with platinum-based chemotherapy.\[12,30,32,33\] Afatinib, dacomitinib, and osimertinib all have been evaluated against gefitinib or erlotinib in a first-line setting. Osimertinib was concluded to be the most potent TKI in terms of PFS based on results from the FLAURA study.\[14\] The primary results of this network meta-analysis further supported the conclusion.

Patient characteristics influenced outcomes in patients receiving TKIs.\[20\] We performed subgroup analysis by using treatment with gefitinib or erlotinib (SoC) as a comparison. Women, Asians, and nonsmokers tended to derive greater benefit from TKIs than men, non-Asians, and current or former smokers.\[20\] According to our subgroup analysis, substituting osimertinib for SoC did not show more favorable HRs in subpopulations of women, Asians, and nonsmokers, which suggested that these patients might be inherently sensitive to all EGFR TKIs. However, for men, non-Asians, or current or former smokers who seemed to derive less benefit, switching from SoC to osimertinib led to a significant improvement in PFS, which implied a treatment shift. Neither dacomitinib nor afatinib demonstrated superiority over SoC in all subgroups.

Specific EGFR mutations might potentially separate patients into different biological entities. Del19 and L858R mutations in EGFR have different predictive and prognostic impacts.\[14,34\] In a combined analysis of the Lux-lung 3 and 6 trials investigating afatinib versus chemotherapy, overall survival was improved in patients with the Del19 mutation but not in patients with the L858R mutation.\[26\] However, utilizing the del19 mutation to guide treatment decisions has not yet gained solid supporting evidence.\[35\] In the present subgroup analysis, osimertinib led to a favorable HR in patients with the del19 mutation but showed no difference in patients with the L858R mutation. A retrospective study showed that the prevalence of the secondary T790M mutation was significantly higher in del19-positive disease than in the L858R-positive disease.\[17,37\] This was probably the underlying reason for the results in this subgroup analysis.

EGFR TKIs had a favorable toxicity profile. EGFR TKIs were better tolerated than chemotherapy. Treatment-related death was not common. Dose reductions were more common for erlotinib, afatinib, and dacomitinib. In addition to its advantage in disease control, treatment with osimertinib was better tolerated than treatment with SoC.\[14\]

Based on the findings of this network meta-analysis, osimertinib seems to be a better option than the other EGFR TKIs. There were more merits for osimertinib. First, the activity of osimertinib in the central nervous system should lend weight to its uptake in a first-line setting. In the FLAURA study, osimertinib produced longer PFS than SoC in patients with CNS metastasis (15.2 months with osimertinib vs 9.6 months with SoC, HR = 0.47, P = .0009).\[14\] Responses in the cranium were not different between 2 treatments, but the median duration of response favored osimertinib (13.8 months vs 8.3 months).\[14\] It should be noted that the ARCHER1050 study excluded patients with central nervous system metastasis.\[10\] Second, only up to 60% of patients who would develop T790M mutations after first-line gefitinib and erlotinib were appropriate candidates for osimertinib treatment.\[13\] The remaining 40% of patients did not receive treatment with osimertinib. Only when osimertinib was introduced in front-line therapy did all patients have the chance of receiving osimertinib. In addition, confirming the T790M mutation before second-line osimertinib spared patients from re-biopsy.

However, several questions remain to be answered. First, the unquestionable effect of first-line osimertinib on overall survival outcome is still unclear from the AURA 3 study\[31\] and the FLAURA study.\[14\] There was a trend toward improvement in overall survival for osimertinib in the FLAURA study, but it was not statistically significant.\[14\] Second, patients who developed the T790M mutation during first-line SoC clearly benefited from second-line osimertinib. The total PFS of first-line SoC (9–13 months) plus second-line osimertinib (~10 months) in this population was numerically equivalent to the value in the FLAURA study. Such patients did not necessarily require first-line osimertinib; however, no markers are currently available for identification.

Third, the mechanisms of resistance to first-line osimertinib were unknown. From the AURA1 study, potential resistance mechanisms included the amplification of MET and KRAS; mutations in MEK1, KRAS, PIK3CA, and EGFRc797S; and HER2 exon 20 insertion.\[34\] There was no evidence of an acquired EGFR T790M mutation.\[39\] For now, most of these mutations had no targeted agents; thus, clinicians would face the uncertainty of subsequent therapy after exhausting osimertinib in first-line treatment.

Finally, the Japanese study showed that the addition of bevacizumab to first-line erlotinib improved PFS from 9.7 to 16 months in EGFR mutation-positive patients without brain metastasis.\[21\] Relevant phase III trials are being investigated. This finding suggested that erlotinib with bevacizumab might provide a similar extent of PFS benefit as that of osimertinib in this population and push osimertinib to second-line treatment for up to 60% of patients. Such treatment sequencing might maximize the effects of currently available agents. However, the improvement was at the expense of increased toxicity.\[23\]

Several limitations existed in this network meta-analysis. First, heterogeneity was evident in the whole and subgroup analyses. Races, chemotherapy regimens, EGFR mutation types, and between-trial designs were intrinsic sources of heterogeneity. Heterogeneity was difficult to resolve even using the individual patient data. We used the random-effect model for the analysis and performed a sensitivity analysis. Second, the number of trials was relatively low, and data were not based on individual data. Lastly, overall survival was not assessed in our study. However, most of the included trials showed no difference in comparisons, and some overall survival results were immature.

In summary, our study supported osimertinib as a first-line treatment for NSCLC patients with an activating EGFR mutation. The analysis suggested that only some subgroups (men, non-Asians, and smokers) would really benefit from osimertinib compared with gefitinib or erlotinib.

Author contributions

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