ORIGINAL ARTICLE

Overall Survival Benefits of First-Line Treatments for Asian Patients With Advanced EGFR-Mutated NSCLC Harboring L858R Mutation: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction: Randomized controlled trials have investigated different first-line treatments for patients with advanced *EGFR*-mutated NSCLC. Nevertheless, their efficacy, in particular, the long-term overall survival (OS) benefit in Asian patients with L858R mutation, remains unclear.

Methods: We performed a systematic review and frequentist network meta-analysis by retrieving relevant literature from PubMed/MEDLINE, Ovid, EMBASE, Cochrane Library, trial registries, and other sources. We included randomized controlled trials comparing two or more treatments in the first-line setting for Asian patients with L858R mutation. This study was registered in the Prospective Register of Systematic Reviews (CRD 42022295897).

Results: There were a total of 18 trials that involved 1852 Asian patients and 12 treatments, including the following: *EGFR* tyrosine kinase inhibitors (TKIs) (osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, and icotinib), pemetrexed-based chemotherapy, pemetrexed-free chemotherapy, and combination treatments (gefitinib plus apatinib, erlotinib plus ramucirumab, erlotinib plus bevacizumab and gefitinib plus pemetrexed-based chemotherapy). Asian patients with L858R mutation had no significant OS benefits from all these treatments. Gefitinib plus pemetrexed-based chemotherapy, dacomitinib, osimertinib, and erlotinib plus bevacizumab were found to be consistent in yielding the best progression-free survival benefit (p scores = 93%, 79%, 77%, and 70%). Combination treatments caused more toxicity, especially erlotinib plus bevacizumab and gefitinib plus pemetrexed-based chemotherapy, resulting in the greatest incidence of grade greater than or equal to 3 adverse events.

Conclusions: In Asian patients harboring L858R mutation, *EGFR* TKIs and combination treatments had no OS benefit when compared with conventional chemotherapies. Further studies are warranted to investigate the resistance mechanism with TKIs and potential combination strategies in patients with this common but less favorable mutation.

Keywords: Non–small-cell lung cancer; Epidermal growth factor receptor; L858R mutation; Tyrosine kinase inhibitors; Asian

Introduction

Lung cancer is the most common type of cancer globally, claiming an estimated 1.8 million lives in 2018.[1]

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Approximately 60% of the world's lung cancer cases occur in Asia and most lung cancers are NSCLC.[2–4] Mutation of the *EGFR* is more often encountered in Asian population (30%–40%) than in those in the United States and Europe (10%–15%).[5–8] Among the *EGFR*-mutated NSCLCs, exon 19 deletion and exon 21 L858R mutation are the most common activating mutations.[9,10]

In the past two decades, *EGFR* tyrosine kinase inhibitors (TKIs) were found to have clinical responsiveness and survival benefits by potentially blocking the cell signaling pathways responsible for mutated *EGFR*-mediated tumor proliferation.[11] Three generations of *EGFR* TKIs have been developed so far, including erlotinib, gefitinib, and icotinib (first generation), dacomitinib and afatinib (second generation), and osimertinib (third generation), and they have established themselves as standard first-line treatments.[12] Biologically, synergistic combinations of *EGFR* TKIs with other treatments that possess different mechanisms of anticancer activity, including systemic chemotherapy, monoclonal antibodies, and some other growth pathway inhibitors, have been investigated as concurrent first-line treatment to overcome resistance and prolong survival.[13] Despite the positive results found in the overall study population in various randomized controlled trials (RCTs) and meta-analyses,[14–40] their efficacy, in particular, the long-term overall survival (OS) benefit for Asian patients with L858R mutation, remains controversial.

Patients with L858R mutation seem to have a worse sensitivity and duration of response to *EGFR* TKIs and shortened survival when compared with those with exon 19 deletion.[41–43] To the best of our knowledge, no head-to-head study or meta-analysis has yet been conducted that allows for direct comparison of OS benefits among different *EGFR* TKIs and combination treatments in patients with L858R mutation. We therefore performed this network meta-analysis (NMA) to investigate the efficacy of all first-line treatments in Asian patients with advanced *EGFR*-mutated NSCLC harboring L858R mutation.

Materials and Methods

Selection Criteria

We included published and unpublished phase 2/3 RCTs that met the following criteria: (1) clinical trials that enrolled patients with histologically or cytologically confirmed advanced (stage III/IV/recurrent) NSCLC with *EGFR*-activating mutations; (2) clinical trials that compared any two or more different arms of first-line treatments for patients with *EGFR*-mutated NSCLC; (3) clinical trials that enrolled Asian patients or contained Asian subset analysis; and (4) clinical trials that reported on at least one of the following clinical outcome measures in patients with the L858R mutation: (1) OS, (2) progression-free survival (PFS), and (3) toxicity. All study periods and durations of follow-up were eligible, and some updated data from mature or long-term follow-up of an original article were also used.

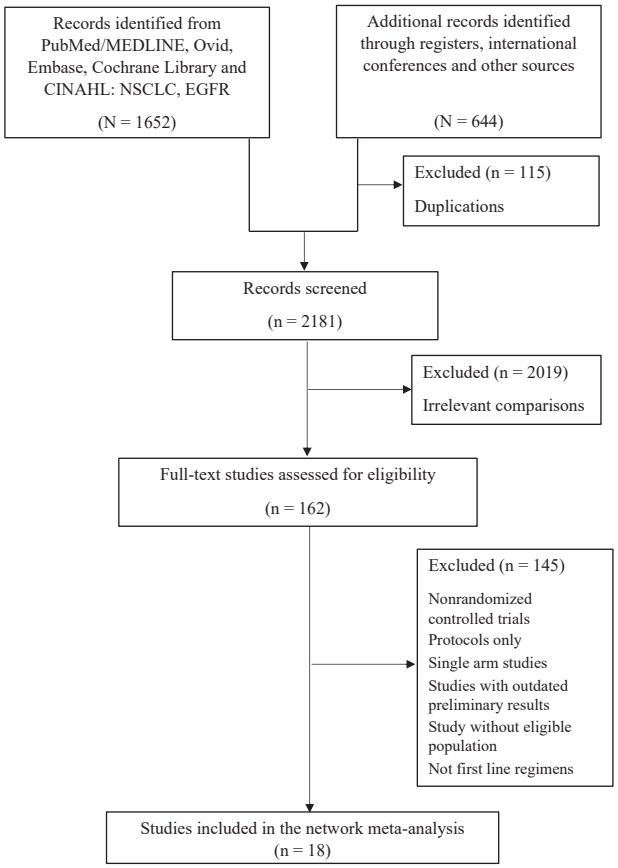

Figure 1. Study flowchart illustrating the results of systematic review identified from PubMed/MEDLINE, Ovid, Embase, Cochrane Library, CINAHL Databases, trial registries, and other sources.

Data Sources and Search Strategy

We performed a systematic literature search using PubMed/MEDLINE, Ovid, EMBASE, Cochrane Library, CINAHL Databases, trial registries, and other sources, in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines for publications from inception to November 30, 2021, in all languages using a combination of the main search terms "NSCLC" and "*EGFR*" within the restriction limit of "randomised/randomized controlled trial" (Fig. 1 and Supplementary Table 1). Titles and abstracts were screened, and the full texts of potentially eligible articles were sequentially assessed for final inclusion. Abstracts and presentations of ongoing RCTs on NSCLC from major international conferences were also inspected (e.g., American Society of Clinical Oncology, World Conference

on Lung Cancer, and European Society of Medical Oncology) to include the most updated outcomes. Manual search through reference lists of pertinent reviews and relevant studies was performed for additional articles. The detailed search strategy is presented in Supplementary Methods 1 of Supplemental Digital Content. The protocol was registered in the Prospective Register of Systematic Reviews (CRD 42022295897).

Data Extraction and Quality Assessment

Data extraction was performed by two authors (SC and HC) independently. Reported data for any relevant variable for which analysis was conducted were extracted. These included the following: (1) study characteristics, including country, year of publication, and phase; (2) number of patients in each arm within the subset of L858R mutation, regimens compared, and treatment protocol; (3) reported hazard ratio (HR) and 95% confidence interval (CI) for OS and PFS in the subgroup of L858R mutation; and (4) incidence of adverse events (AEs) of any grade or severe AEs (grade $\geq$ 3), which were defined and graded according to the National Cancer Institute Common Terminology Criteria for AEs. Because of the absence of subgroup analysis of AEs, we assumed that L858R mutation subgroup in each trial had comparable toxicity profile with the overall study cohort. We also preferred to extract treatment-related AE, but we included all AEs if it not specified as treatment related.

The primary end point for this NMA was OS, defined as the time from the date of randomization to the date of death from any cause. The secondary end points were PFS (the time from the date of randomization to the date of first disease progression (locoregional or distant) or death from any cause, whichever occurred earlier) and AEs of grade greater than or equal to 3.

The Cochrane Collaboration tool was used by two authors (SC and HC) to assess risk of bias for each trial based on seven domains associated with biased estimates of treatment effect (i.e., random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias).[44] Items were scored as low, high, or unclear risk of bias. A third author (VL) resolved the differences in opinions.

We considered pemetrexed-free and pemetrexed-based chemotherapies (PbCT) separately in comparison arms in our network because the latter yields significantly higher efficacy than other third-generation chemotherapy drugs in nonsquamous cell carcinoma, which is a dominant histologic type of *EGFR*-mutated NSCLC.[45–47] Nevertheless, the FLAURA Asia study grouped gefitinib and erlotinib together in the control arm of standard *EGFR* TKIs.[48] Therefore, we assumed that these two regimens had the same outcomes in terms of efficacy in this trial when compared with the experimental arm osimertinib, similar to a recently published NMA.[47]

Statistical Analysis

We synthesized all direct and indirect evidence to compare different treatments in terms of efficacy and safety, reported as HRs for survival outcomes (OS and PFS) and ORs for binary outcomes (AEs of grade $\geq$3) along with corresponding 95% CIs. We performed this NMA using a frequentist approach with the R package netmeta (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria) for its advantages of easier interpretation of the estimates and computation and programming.[49,50] The I^2 and Q statistic were used to quantify the heterogeneity among different trials for the same regimen.[50] Fixed-effects model was used in this study, whereas random-effects model was planned in the case of important heterogeneity if I^2 greater than 50% or significant Q statistic at p value less than 0.1. The regimens were ranked using the p score where regimens having higher p score represent better performance.[51] Results from the NMA were compared with standard pairwise meta-analysis to evaluate if there was inconsistency. The net-splitting analysis was applied to evaluate inconsistency for closed loops in the network.[52–54] Significant inconsistency was indicated if the net-splitting analysis derived p value less than 0.05 of disagreement between direct and indirect evidence.

We did not use funnel plots to assess the publication bias and small study effects given the small number of trials included in each comparison. Nevertheless, we conducted several sensitivity analyses to assess the robustness and reliability of the results. We reanalyzed the data using Bayesian approach in the first sensitivity analysis (details in Supplementary Methods 2 of Supplemental Digital Content). The second sensitivity analysis restricted phase 3 RCTs. The third analysis for PFS and AEs of grade 3 or above excluded FLAURA Asia study, to check the effect of the adjustments made for synthesis of unspecified data on the results, together with FLAURA China study, which contained a few number of overlapping patients with FLAURA Asia so as to ensure more fair comparison.[47,48,55] Furthermore, we conducted exploratory analyses to evaluate the intervention effects in different contexts with reduced treatment heterogeneity stratified by the generations and the reversibility of different treatment regimens and to compare the intervention effects in L858R mutation with the cohort of exon 19 deletion in the studies included in this NMA.[40]

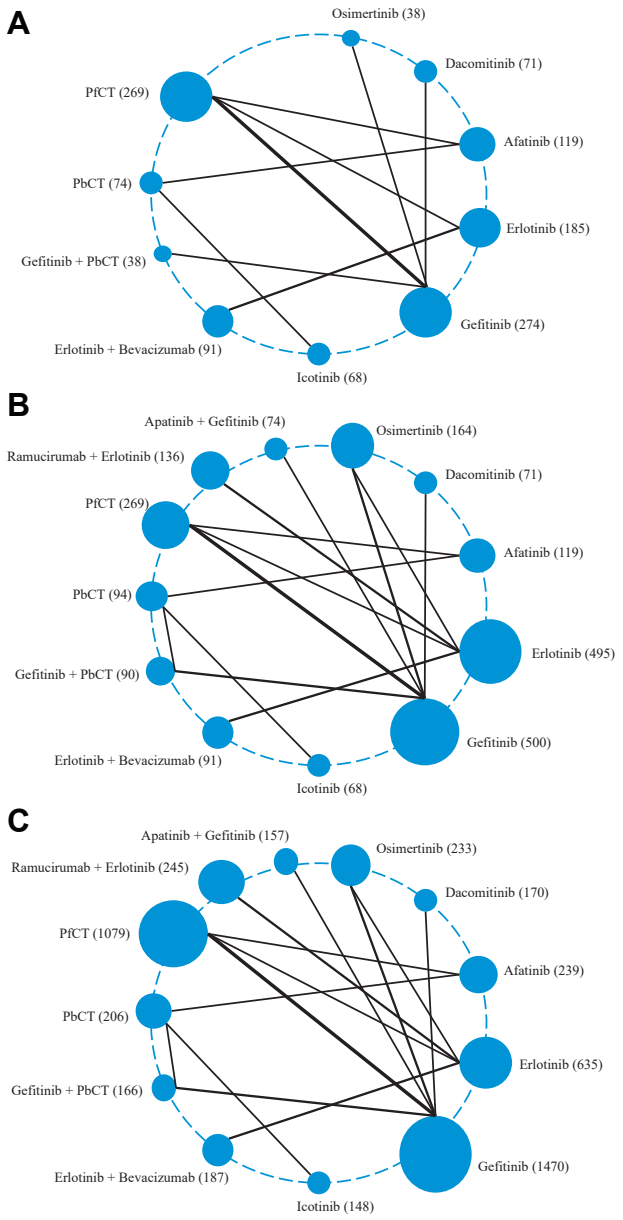

Figure 2. Network diagrams of comparisons on different outcomes of treatments in Asian patients with advanced *EGFR*-mutated NSCLC harboring L858R mutation. (*A*) Comparisons on overall survival. (*B*) Comparisons on progression-free survival. (*C*) Comparisons on adverse events of grade 3 or higher. Each circular node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment (in brackets). Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy.

Results

Systematic Review and Characteristics of the Included Studies

We identified 2296 records from the initial title and abstract screening and retrieved and reviewed 162 reports in full text (Fig. 1). Finally, 18 studies were deemed eligible for inclusion with a total of 1852 Asian patients with L858R mutation enrolled to receive 12 different treatments, including *EGFR* TKIs (osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, and icotinib), pemetrexed-based chemotherapy, pemetrexed-free chemotherapy, and combination treatments (gefitinib plus apatinib, erlotinib plus ramucirumab, erlotinib plus bevacizumab, gefitinib plus pemetrexed-based chemotherapy).[17–20,23,24,26–34,36,48,55–59] The networks are displayed in Figure 2*A-C*. Detailed information on all the included studies has been presented in Table 1. The assessment of risk of bias is also presented in Supplementary Figure 1*A* and 1B.

Comparison of OS and Ranking

There were 13 trials of 1257 Asian patients with L858R mutation in this analysis.[17–20,24,26,28,29,31,34,55–57] There was no significant heterogeneity observed (I^2 = 0%, p = 0.644 for Q statistic), and fixed-effects model was used. Asian patients with L858R mutation had no significant OS benefits from all *EGFR* TKIs or combination treatments over chemotherapies (Fig. 3*A* and Supplementary Fig. 2*A*). Gefitinib plus pemetrexed-based chemotherapy, dacomitinib, and erlotinib plus bevacizumab ranked better with their respective p scores of 89%, 82%, and 68%, respectively, although no significant statistical difference was observed when compared with most other treatments. Dacomitinib had possible increased efficacy when compared with gefitinib (HR = 0.62, 95% CI: 0.41–0.93).

Exploratory analyses revealed that there was no significant OS difference among TKIs of different generations, combination treatments, and chemotherapies (Supplementary Fig. 3*A*). Similar efficacy was also found among treatments when stratified by their reversibility (Supplementary Fig. 3*B*). In addition, no significant OS benefits from all treatments over chemotherapies were observed in Asian patients with exon 19 deletion though afatinib, osimertinib, and gefitinib plus PbCT ranked better (p scores = 77%, 76%, and 75%, respectively) (Supplementary Fig. 3*C*).

Comparison of PFS and Ranking

There were 18 studies of 1852 Asian patients with L858R mutation in the PFS meta-analysis.[17–20,23,26,27,29–33,36,48,55,57–59] No significant heterogeneity was observed (I^2 = 31.4%, p = 0.227 for Q statistic). Net-splitting analysis did not reveal significant inconsistency between direct and indirect estimates (Supplementary Table 2). Most of the regimens had substantial PFS benefits when compared with pemetrexed-free chemotherapy

Table 1. Baseline Characteristics of Studies Included in the Network Meta-Analysis

Study	Phase	Sample Size (No.)	Intervention Arm	Control Arm	Reported OS (HR, 95% CI)	Reported PFS (HR, 95% CI)
NEJ026[30,56]	III	56/57	Erlotinib 150 mg once a day + bevacizumab 15 mg/kg every 3 wk	Erlotinib 150 mg once a day	0.79 (0.46-1.36)	0.57 (0.33-0.97)
FLAURA Asia[48]	III	129	Osimertinib 80 mg once a day	Gefitinib 250 mg once a day or erlotinib 150 mg once a day	NR	0.48 (0.31-0.74)
FLAURA China[55]	III	35/32	Osimertinib 80 mg once a day	Gefitinib 250 mg once a day	1.02 (0.59-1.78)	0.69 (0.39-1.21)
ARCHER Asia[57]	III	71/73	Dacomitinib 45 mg once a day	Gefitinib 250 mg once a day	0.62 (0.42-0.93)	0.51 (0.34-0.76)
COVINCE[17]	III	68/63	Icotinib 125 mg three times a day	PbCT (cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 every 3 wk (4 cycles) + pemetrexed 500 mg/m^2 every 3 wk)	1.14 (0.74-1.76)	0.64 (0.40-1.03)
Han et al.[31]	II	19/20	Gefitinib 250 mg once a day + PbCT (carboplatin AUC = 5 + pemetrexed 500 mg/m^2 every 4 wk (6 cycles) + pemetrexed 500 mg/m^2 every 4 wk)	Gefitinib 250 mg once a day	0.50 (0.25-1.00)	0.31 (0.15-0.66)
		19/20	Gefitinib 250 mg once a day + PbCT (carboplatin AUC = 5 + pemetrexed 500 mg/m^2 every 4 wk (6 cycles) + pemetrexed 500 mg/m^2 every 4 wk)	PbCT (carboplatin AUC = 5 + pemetrexed 500 mg/m^2 every 4 wk (6 cycles) + pemetrexed 500 mg/m^2 every 4 wk)	NR	0.11 (0.04-0.28)
JMIT[32]	II	52/23	Gefitinib 250 mg once a day + pemetrexed 500 mg/m^2 every 3 wk	Gefitinib 250 mg once a day	NR	0.58 (0.33-1.01)
ENSURE[18]	III	52/46	Erlotinib 150 mg once a day	PfCT (gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2 every 3 wk (≤4 cycles))	1.05 (0.60-1.84)	0.57 (0.31-1.05)
JO25567[33,34]	II	35/37	Erlotinib 150 mg once a day + bevacizumab 15 mg/kg every 3 wk	Erlotinib 150 mg once a day	0.83 (0.46-1.49)	0.57 (0.33-0.97)
LUX-Lung 6[20]	III	92/46	Afatinib 40 mg once a day	PfCT (gemcitabine 1000 mg/m^2 + cisplatin 75 mg/m^2 every 3 wk [≤6 cycles])	1.22 (0.81-1.83)	0.32 (0.19-0.52)

(continued)

Table 1. Continued

Study	Phase	Sample Size (No.)	Intervention Arm	Control Arm	Reported OS (HR, 95% CI)	Reported PFS (HR, 95% CI)
LUX-Lung 3[19]	III	91/47	Afatinib 40 mg once a day	PbCT (cisplatin 75 mg/m^2 + pemetrexed 500mg/m^2 every 3 wk [≤6 cycles])	1.30 (0.80-2.11)	0.76 (0.46-1.17)
OPTIMAL[23,24]	III	39/33	Erlotinib 150 mg once a day	PfCT (gemcitabine 1000 mg/m^2 + cisplatin AUC = 5 every 3 wk [≤4 cycles])	0.92 (0.55-1.54)	0.26 (0.14-0.49)
NEJ002[26]	III	49/48	Gefitinib 250 mg once a day	PfCT (paclitaxel 200 mg/m^2 + carboplatin AUC = 6 every 3 wk [≥3 cycles])	0.82 (0.49-1.38)	0.32 (0.23-0.45)
WJTOG[27,28]	III	36/49	Gefitinib 250 mg once a day	PfCT (cisplatin 80 mg/m^2 + docetaxel 60 mg/m^2 every 3 wk [3-6 cycles])	1.09 (0.66-1.80)	0.51 (0.29-0.90)
RELAY (East Asian)[58]	III	80/86	Ramucirumab 10 mg/kg every 2 wk + erlotinib 150 mg once a day	Erlotinib 150 mg once a day	NR	0.64 (0.44-0.95)
RELAY (Japanese)[59]	III	56/54	Ramucirumab 10 mg/kg every 2 wk + erlotinib 150 mg once a day	Erlotinib 150 mg once a day	NR	0.51 (0.32-0.84)
IPASS[29]	III	64/47	Gefitinib 250 mg once a day	PfCT (paclitaxel 200 mg/m^2 + carboplatin AUC=5/6 every 3 wk [3-6 cycles])	0.79 (0.46-1.36)	0.55 (0.35-0.87)
CTONG1706[36]	III	74/73	Apatinib 500 mg + Gefitinib 250 mg once a day	Gefitinib 250 mg once a day	NR	0.72 (0.48-1.09)

AUC, area under the concentration-time curve; CI, confidence interval; HR, hazard ratio; No., number; NR, not reported; OS, overall survival; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; PFS, progression-free survival.

(Fig. 3*A* and Supplementary Fig. 2*B*). Gefitinib plus PbCT, dacomitinib, osimertinib, and erlotinib plus bevacizumab were found to be consistent in yielding the best benefit of all regimens in terms of PFS, with their corresponding *p* scores of 93%, 79%, 77%, and 70%.

Exploratory analyses revealed that first-generation TKI plus chemotherapy provided the highest efficacy in terms of PFS (versus second-generation TKIs [HR = 0.41, 95% CI: 0.21–0.81], first-generation TKIs [0.39, 0.23–0.66], and chemotherapies [0.18, 0.10–0.32]) (*p* score = 95%) (Supplementary Fig. 3*A*). Third-generation TKIs and first-generation TKI plus anti-angiogenic agents were found to be consistent with first-generation TKIs plus chemotherapy in providing the best PFS with their *p* scores of 77% and 67%, respectively. Moreover, combination treatments and irreversible TKIs had statistically significant PFS benefits in patients with L858R mutation (Supplementary Fig. 3*B*). In patients with exon 19 deletion, erlotinib plus bevacizumab (*p* score = 94%), erlotinib plus ramucirumab (*p* score = 84%), and osimertinib (*p* score = 80%) were the top three regimens with the highest probabilities of PFS benefits (Supplementary Fig. 3*C*).

Safety and Toxicity

A total of 4989 patients from the overall cohort of 18 studies were enrolled in the analysis of toxicity given the reasons aforementioned.[17–20,23,26,27,29–33,36,48,55,57–59] Fixed-effects model was adopted given its insignificant heterogeneity (I^2 = 46.3%, p = 0.164 for Q statistic). No inconsistency between direct and indirect estimates was observed in the net-splitting analysis (Supplementary Table 2). We observed fewer toxicities related to *EGFR* TKIs among the comparable treatments, in particular, icotinib and osimertinib,

A

Progression-free survival

Overall survival

Osimertinib (34%; 77%)	0.98 (0.52–2.19)	0.51 (0.24–1.06)	**0.51 (0.32–0.83)**	**0.54 (0.36–0.81)**	0.48 (0.17–1.37)	0.90 (0.45–1.79)	0.88 (0.46–1.68)	1.42 (0.74–2.72)	0.76 (0.36–1.54)	**0.30 (0.13–0.70)**	**0.21 (0.13–0.34)**
0.61 (0.31–1.21)	**Dacomitinib (82%; 79%)**	**0.48 (0.20–0.97)**	0.48 (0.22–1.04)	**0.50 (0.29–0.91)**	0.45 (0.14–1.41)	0.85 (0.34–2.10)	0.83 (0.34–1.99)	1.33 (0.61–2.91)	0.70 (0.30–1.62)	**0.29 (0.11–0.74)**	**0.20 (0.10–0.39)**
1.12 (0.54–2.31)	1.83 (0.99–3.41)	**Afatinib (19%; 36%)**	1.01 (0.48–2.12)	1.06 (0.55–2.03)	0.94 (0.40–2.22)	1.78 (0.73–4.30)	1.74 (0.74–4.08)	**2.81 (1.34–5.86)**	1.47 (0.61–3.55)	0.60 (0.34–1.07)	**0.41 (0.23–0.75)**
0.90 (0.44–1.82)	1.47 (0.80–2.68)	0.80 (0.46–1.40)	**Erlotinib (44%; 33%)**	1.05 (0.64–1.71)	0.93 (0.32–2.67)	**1.75 (1.08–2.85)**	**1.72 (1.12–2.64)**	**2.77 (1.39–5.53)**	1.45 (0.67–3.14)	0.59 (0.25–1.38)	**0.41 (0.26–0.64)**
0.98 (0.56–1.70)	**1.61 (1.07–2.41)**	0.88 (0.55–1.40)	1.09 (0.70–1.71)	**Gefitinib (32%; 36%)**	0.88 (0.33–2.37)	1.67 (0.84–3.34)	1.64 (0.85–3.14)	**2.64 (1.34–5.86)**	1.39 (0.77–2.51)	0.57 (0.27–1.20)	**0.39 (0.28–0.54)**
0.98 (0.37–2.60)	1.61 (0.65–3.95)	0.88 (0.46–1.68)	1.09 (0.47–2.58)	1.00 (0.45–2.23)	**Icotinib (37%; 36%)**	1.90 (0.59–6.09)	1.85 (0.59–5.82)	**2.99 (1.10–8.13)**	1.57 (0.50–4.98)	0.64 (0.34–1.21)	0.44 (0.17–1.17)
0.72 (0.32–1.63)	1.19 (0.58–2.44)	0.65 (0.33–1.28)	0.81 (0.54–1.20)	0.74 (0.41–1.34)	0.74 (0.29–1.90)	**Erlotinib + Bevacizumab (68%; 70%)**	0.98 (0.51–1.97)	1.58 (0.68–3.68)	0.83 (0.33–2.06)	**0.34 (0.13–0.90)**	**0.23 (0.12–0.45)**
NA	NA	NA	NA	NA	NA	NA	**Ramucirumab + Erlotinib (NA; 69%)**	1.61 (0.71–3.64)	0.85 (0.35–2.05)	**0.35 (0.13–0.89)**	**0.24 (0.13–0.44)**
0.49 (0.20–1.19)	0.80 (0.36–1.79)	0.44 (0.19–1.01)	0.55 (0.24–1.25)	1.00 (0.45–2.23)	0.50 (0.17–1.44)	0.68 (0.27–1.69)	NA	**Gefitinib + PbCT (89%; 93%)**	0.53 (0.24–1.15)	**0.21 (0.10–0.46)**	**0.15 (0.08–2.26)**
NA	NA	NA	NA	NA	NA	NA	NA	NA	**Apatinib + Gefitinib (NA; 58%)**	0.60 (0.34–1.07)	**0.28 (0.14–0.55)**
0.86 (0.36–2.06)	1.41 (0.64–3.10)	0.77 (0.47–1.25)	0.96 (0.46–2.01)	0.74 (0.41–1.34)	0.88 (0.57–1.35)	1.19 (0.51–2.75)	NA	1.75 (0.67–4.62)	NA	**PbCT (52%; 11%)**	0.69 (0.33–1.44)
0.92 (0.50–1.67)	1.50 (0.94–2.40)	0.82 (0.55–1.23)	1.02 (0.70–1.49)	0.94 (0.74–1.19)	0.93 (0.43–2.01)	1.27 (0.73–2.19)	NA	1.87 (0.90–3.89)	NA	1.07 (0.57–1.01)	**PfCT (43%; 2%)**

B

Adverse events of grade 3 or above

Osimertinib (80%)											
1.23 (0.47–3.21)	**Dacomitinib (71%)**										
2.09 (0.80–2.49)	1.71 (0.53–5.49)	**Afatinib (49%)**									
1.01 (0.54–1.89)	0.82 (0.29–2.34)	0.48 (0.18–1.28)	**Erlotinib (79%)**								
1.10 (0.64–1.88)	0.89 (0.40–1.98)	0.52 (0.22–1.23)	1.08 (0.55–2.14)	**Gefitinib (77%)**							
0.36 (0.07–1.85)	0.29 (0.05–1.70)	**0.17 (0.04–0.7)**	0.36 (0.07–1.86)	0.33 (0.07–1.58)	**Icotinib (94%)**						
8.33 (3.28–21.19)	**6.79 (1.94–23.77)**	**3.98 (1.20–13.18)**	**8.25 (4.12–16.49)**	**7.61 (2.88–20.05)**	**23.01 (3.86–137.1)**	**Erlotinib + Bevacizumab (10%)**					
2.36 (1.02–5.47)	1.92 (0.58–6.29)	1.13 (0.36–3.47)	**2.33 (1.33–4.1)**	2.15 (0.89–5.19)	**6.51 (1.14–37)**	**0.28 (0.12–0.69)**	**Ramucirumab + Erlotinib (47%)**				
3.02 (0.62–14.49)	2.46 (0.45–13.49)	1.44 (0.33–6.3)	2.99 (0.6–14.94)	**2.76 (1.00–12.42)**	**8.33 (1.7–40.97)**	0.36 (0.06–2.09)	1.28 (0.23–7.05)	**Gefitinib + PbCT (25%)**			
9.42 (3.42–25.87)	**7.79 (2.39–25.37)**	**4.13 (1.24–13.83)**	**9.30 (3.11–27.83)**	**8.73 (3.76–20.26)**	**20.85 (3.72–116.9)**	1.13 (0.30–4.17)	**3.99 (1.15–13.84)**	1.99 (0.54–7.35)	**Apatinib + Gefitinib (7%)**		
2.55 (0.66–9.87)	2.07 (0.46–9.31)	1.22 (0.42–3.51)	2.52 (0.64–9.94)	2.32 (0.65–8.31)	**7.03 (2.84–17.39)**	0.31 (0.07–1.42)	1.08 (0.25–4.76)	0.84 (0.23–3.12)	2.97 (0.70–12.62)	**PbCT (38%)**	
5.10 (2.69–9.66)	**4.15 (1.65–10.45)**	**2.43 (1.17–5.08)**	**5.04 (2.63–99.67)**	**4.65 (2.91–7.43)**	**14.07 (3.07–64.56)**	0.61 (0.24–1.58)	2.16 (0.91–5.11)	1.69 (0.38–7.58)	1.82 (0.69–4.81)	2.00 (0.59–6.81)	**PfCT (22%)**

Figure 3. Pooled estimates of the network meta-analysis. (*A*) Pooled hazard ratios (95% confidence intervals) for overall survival (upper triangle) and progression-free survival (lower triangle). *p* scores for overall survival (left) and progression-free survival (right) are indicated under each treatment. (*B*) Pooled ORs (95% confidence intervals) for adverse events of grade 3 or higher. *p* scores are indicated under each treatment. Data in each cell are hazard or ORs (95% confidence intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios or OR less than one favor row-defining treatment. Significant results are in bold. NA, not available; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy.

which had the fewest and second fewest grade $\geq$ 3 AEs) (*p* scores = 94% and 80%, respectively) (Fig. 3*B*). Afatinib was noted with the most grade greater than or equal to 3 AEs when compared with other *EGFR* TKIs. It is also revealed that combination treatments were associated with a higher risk of grade greater than or equal to 3 AEs (Supplementary Fig. 4), whereas gefitinib plus apatinib and erlotinib plus bevacizumab were likely to produce the most grade greater than or equal to 3 AEs (Fig. 3*B*).

There are more than 100 types of AEs reported in the studies included in this NMA, of which 16 were selected as a representation of the most clinically relevant in the current real-world practice.[47] The toxicity profiles of

EGFR TKIs and combination treatments were different from those of conventional chemotherapies as the former had the more frequently reported AEs of rash, diarrhea, stomatitis, and interstitial lung disease (Supplementary Fig. 5).

Sensitivity Analysis

The analyses of OS, PFS, and safety were reconducted using Bayesian approach in the first sensitivity analysis. The results did not reveal relevant deviations compared with the original NMA (Supplementary Figs. 6 and 7*A-C*). Bayesian ranking profiles of the studied treatments are summarized in Supplementary Table 3. Inconsistency between direct and indirect estimates from the node splitting analyses did not reveal significant differences in comparisons in PFS and grade greater than or equal to 3 AEs (Supplementary Table 4). The robustness of the study results was also detected after restricting phase 3 RCTs in the second sensitivity analysis, and in the comparisons of the remaining treatments in PFS and AEs after the removal of the FLAURA studies in the third analysis (Supplementary Figs. 8 and 9).[48,55]

Discussion

Principal Findings

Several scores of RCTs and traditional pairwise meta-analyses have been conducted to investigate the comparative efficacy of first-line treatments for patients with advanced *EGFR*-mutated NSCLC.[14–40] Nevertheless, these were based on the direct comparison model only which failed to explore the relative efficacy between any two of the multiple first-line treatments. It is almost impractical and impossible to conduct a well-designed phase 3, multicenter, RCT directly comparing all different first-line treatments owing to the constraints of resources and a very long event follow-up duration. NMA is therefore needed to evaluate the available treatments which yields summary estimates for the relative effectiveness between all different intervention pairs from direct and indirect comparisons.[60,61] Previous NMAs, however, have not incorporated the most recent trials and have not been specific enough to Asian patients with L858R mutation only.[47,62–65] To the best of our knowledge, this NMA is the first to evaluate various first-line treatments in Asian patients with advanced *EGFR*-mutated NSCLC harboring L858R mutation.

The major findings of our NMA can be summarized as follows. First, Asian patients with L858R mutation had no OS benefit under all available *EGFR* TKIs and combination treatments despite significant PFS benefits. Second, combination treatments and irreversible TKIs provided the best PFS, and gefitinib plus pemetrexed-based chemotherapy, dacomitinib, osimertinib and erlotinib plus bevacizumab were the most promising treatments. Third, combination treatments caused more toxicities and *EGFR* TKIs were associated with different toxicity spectrums. Sensitivity analyses revealed that our results remained robust in general.

In line with other similar meta-analyses and NMAs,[40,47] our work, with a focus on Asian patients and with the most updated trials incorporated such as RELAY and FLAURA, reveals no OS benefit with TKIs and combination treatments in the L858R-mutated subgroup.[48,55,58,59] The reduced response of the L858R mutated NSCLCs toward TKIs and combination treatments might be attributed to its intrinsic biological activities and autophosphorylation and its suboptimal binding affinity with TKIs.[66–68] The relatively high prevalence of co-existing pretreatment T790M mutation which is associated with acquired resistance to TKIs may also help explain this phenomenon.[47,69–71] Another hypothesis is that L858R may form a complex with other atypical mutations, such as C797S and G719S (termed "complex mutation"), which further affects its sensitivity to TKIs.[72–75] Oncogenic driver alterations in several other genes (TP53, PIK3CA, BRAF, MET, MYC, CDK6, and CTNNB1) might also lower the efficacy of these treatments in the L858R-mutated subgroup given it has a higher chance of such comutations.[76–80] The performance of *EGFR* TKIs and combination treatments in terms of PFS and safety in this study is consistent with those in the two previous reviews.[39,47] Despite the effectiveness in prolonging PFS, combination strategies, that is, the addition of other treatments to an *EGFR* TKI, imply additional AEs for either combined drug. Clinicians should be more cautious about the increased toxicities when prescribing combination treatments. Knowledge of the toxicity profile of each treatment is crucial for clinical decision and better management because safety is of equal importance in the treatment evaluation. Although we tried our best to summarize the major acute toxicities here with an assumption that the L858R-mutated subgroup is having comparable toxicity profile with the overall study population, further studies are warranted to generate a complete and potent toxicity spectrum of each treatment which is specific to Asian patients with L858R mutation.

Implications

Our NMA incorporating all evidences from RCTs provides crucial information for clinicians to evaluate the efficacy and safety of different *EGFR* TKI treatment options for Asian patients with NSCLC with L858R mutation. Nevertheless, several issues need to be addressed in future studies. First of all, the mechanism of the poor response toward TKIs and combination treatments in

L858R mutation is currently not fully understood. It is highly expected that further studies on the resistance mechanism with TKIs and potential combination strategies in the L858R subgroup may help delay resistance and provide therapeutic benefits in particular prolonging OS. Some preclinical studies exploring the fourth-generation *EGFR* TKIs targeting complex mutations comprising L858R could help gain a more complete picture.[81–83] Furthermore, co-existing mutations alongside *EGFR* might be an important predictor of clinical outcomes following treatment with *EGFR* TKIs as aforementioned.[76–80] A typical example is co-existing TP53 exon 8 mutation that limits treatment response to gefitinib.[36,79,84–86] This highlights the importance of comprehensive genomic profiling with next-generation sequencing to identify comutations early in the treatment planning to devise more personalized treatment strategies, instead of just offering TKIs alone.[80,87,88] It would also be interesting to await the results of the ongoing phase 3 TOP study (NCT04695925) investigating the combination of osimertinib and chemotherapy for patients with concurrent *EGFR* and TP53 mutations.[89] As a whole, L858R mutation should be regarded as a distinct group albeit unclear resistance mechanism, although the current international guidelines grouping L858R and exon 19 deletion into one category and recommending the same treatment strategy for both are far from the aims of precision medicine.[12] Our exploratory analyses in this NMA revealed their difference in the most efficacious treatment. Further studies are warranted to investigate the most optimal treatment strategy for Asian patients with L858R mutation.

Strengths and Limitations

Compared with other reported meta-analyses and NMAs for patients with advanced *EGFR*-mutated NSCLC, we believe that our present NMA has several strengths.[36–40,47,62–65] Our work represents the most updated study that incorporated comparisons among all existing EGFR TKI monotherapies with other combination treatments and systemic chemotherapy as first-line treatment specifically for Asian patients with L858R mutation. We comprehensively analyzed all major efficacy, including OS and PFS, and toxicity outcomes with the rigorous methodology and the most extensive and updated data including the previously unpublished or recently updated results. The OS data of RELAY and CTONG1706 remain immature, which are eagerly awaited.[36,58,59] Furthermore, trials such as FLAURA2 (NCT04035486) assessing the efficacy of osimertinib plus chemotherapy, RAMOSE (NCT03909334) and TORG1833 (JPRN-JapicCTI-184146) evaluating the combination of osimertinib and ramucirumab, and MARIPOSA (NCT04487080) evaluating the combination of lazertinib and amivantamab, are still ongoing.[90–93] The REVOL858R (WJOG14420L) study comparing erlotinib plus ramucirumab with osimertinib specifically for patients with NSCLC positive for the L858R mutation is also underway.[94]

Nonetheless, there are a few drawbacks in our work. Although NMA is now widely accepted by various public health bodies as a strategy to evaluate health care interventions,[60,61] its use of indirect comparisons has certain unavoidable limitations.[95] Although regimens in this study were usefully ranked with respect to OS, PFS, and grade greater than or equal to 3 AEs, they were primarily calculated using point estimates, which in this study were HRs and ORs.[51] Therefore, to accurately and critically assess the evidence and the superiority of one regimen, more emphasis should be placed on the HR or OR estimates and their corresponding CIs, including their consistency across a variety of end points. Second, the inclusion of some studies into our NMA may potentially lead to less precise estimates, for example, FLAURA studies grouping gefitinib and erlotinib together in the same control arm. Sensitivity analyses excluding FLAURA studies were however conducted and robust results were ensured. Third, OS as the primary end point might be potentially confounded by subsequent lines of systemic treatment or the nature of crossing over to the experimental arm in some trials, but this effect could not be accurately assessed in this NMA because of lack of such specific information in the L858R subgroup. Besides, some trials have not reported the mature OS at their interim analysis or did not have survival data for Asian patients with L858R mutation. Nevertheless, we also reported PFS as the secondary outcome measure for a more comprehensive review of the treatment efficacy. Fourth, we did not compare the treatment efficacy between Asians and whites in this NMA. It may not be possible to conduct a NMA here on whites owing to data scarcity because so far only EURTAC (with OS and PFS data) and RELAY Europe/U.S. subset analysis (with PFS data only) reported the treatment outcomes in whites with L858R mutation, which are however all negative.[96,97] Last, whether patients in the L858R subgroup were randomized and balanced optimally in their original clinical trials is questionable, and transitivity could not be evaluated owing to the absence of the reported descriptive statistics for study baselines in the L858R subgroup, such as age, sex, and performance status. Further studies, for example, individual patient data NMA, should investigate the relative treatment efficacy in the L858R subgroup in a more precise way although this was not possible in the present NMA owing to the data unavailability from the existing publications.

In conclusion, patients with advanced NSCLC harboring L858R mutation had no OS benefit under first-line *EGFR* TKI use in this NMA. Clinical judgment with comprehensive evaluation of risk of disease progression and potential treatment-related toxicities should be carefully exercised in this setting. Additional data and more clinical studies which help devise more personalized treatment for this subgroup are highly warranted.

CRediT Authorship Contribution Statement

Sik-Kwan Chan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing.

Horace Cheuk-Wai Choi: Data curation, Formal analysis, Investigation, Software, Validation, Visualization, Writing - original draft, Writing - review & editing.

Victor Ho-Fun Lee: Conceptualization, Data curation, Visualization, Investigation, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing.

Informed Consent Statement

No informed consent is required. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design and implementation of the study. No patients were asked to advice on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100322.

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