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ORIGINAL ARTICLE

Efficacy and safety of osimertinib for patients with EGFR-mutated NSCLC: a systematic review and meta-analysis of randomized controlled studies

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ABSTRACT

Background: Osimertinib is a recently approved third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR-T790M resistance mutations. The aim of the present meta-analysis was to investigate the efficacy and safety of osimertinib for patients with EGFR-mutated non-small-cell lung cancer (NSCLC).

Materials and methods: Databases were searched for randomized controlled studies that reported the efficacy and safety of osimertinib versus other treatments (chemotherapy, other EGFR-TKIs, etc.) in treating EGFR-mutated NSCLC. The measured effects included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), central nervous system progression-free survival (CNS-PFS), and overall survival (OS). Additional outcome was the incidence of adverse event. Relative risk (RR) for incidence and hazard ratio (HR) for survival outcomes were pooled.

Results: Seven studies containing 3335 participants were finally included. Osimertinib tended to improve ORR and DCR (RRs >1) as compared with other treatments. Osimertinib was also a significant protective factor for PFS, CNS-PFS, and OS (HRs <1 and $p < .05$). Osimertinib showed similar advantages in improving tumor response and patient survival when used as first-line, second-line, and third-line/adjuvant therapy, respectively, as compared with other treatments (RRs >1 for ORR and DCR; HRs <1 for PFS, CNS-PFS, and OS). Osimertinib also had better therapeutic effects as compared with chemotherapy, other EGFR TKIs, docetaxel + bevacizumab, and placebo, respectively. The five most common adverse events with pooled incidence $>$ 20% were diarrhea, rash, nail effects, dry skin, and stomatitis, yet the pooled incidence of serious adverse events was less than 2%.

Conclusions: This meta-analysis suggests that osimertinib has a positive effect in disease control and survival for patients with EGFR-mutated NSCLC with acceptable toxicities.

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KEYWORDS
Osimertinib; EGFR; TKI; chemotherapy; NSCLC

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the standard first-line treatment for patients with EGFR-mutated advanced non-small-cell lung cancer (NSCLC) [1,2]. Although a favorable proportion of patients show response, diseases progresses in a majority of patients after a year of first-line EGFR-TKIs treatment [3–6]. Regardless of race or ethnic background, more than a half of patients are found to present with a p.Thr790Met point mutation (T790M) in the gene encoding EGFR at the time of progression [7,8]. The mutation of T790M can reduce the binding of ATP-binding pocket of EGFR to the first- and second-generation EGFR-TKIs. Thus, the inhibition of downstream signaling by EGFR-TKI is reduced, which might contribute to the disease progression [8–10].

Thereafter, the third-generation EGFR-TKI, osimertinib has emerged as an alternative standard of care for patients with centrally confirmed T790M-positive advanced NSCLC after first-line EGFR-TKI therapy. Osimertinib is an oral, irreversible EGFR-TKI with activity in the central nervous system (CNS), and is selective for both EGFR and T790M resistance mutations [11]. Osimertinib showed an objective response rate (ORR) of 61% and median progression-free survival (PFS) of 9.6 months in patients with T790M-positive NSCLC in the phase I component of AURA, a phase I/II trial (ClinicalTrials.gov number, NCT01802632) [12]. Similar result was observed in a pooled analysis of two subsequent phase II researches of osimertinib in 411 patients with T790M-positive NSCLC, with an ORR of 66% and median PFS of 11 months. Based on the current evidence, the FDA approved osimertinib under the Breakthrough Therapy Designation Program. Thereafter, a randomized, international, open-label, phase 3 trial included 419 patients with T790M-positive NSCLC that had progressed during first-line EGFR-TKI therapy and compared the efficacy of osimertinib versus intravenous intravenous pemetrexed plus carboplatin/cisplatin [13]. Osimertinib showed better efficacy with an odds ratio (OR)

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for ORR of 5.39 (95% confidence interval (CI), 3.47–8.48; $p < .001$), and the hazard ratio (HR) of median duration of PFS was 0.32 (95% CI: 0.21–0.49)[13].

Several subsequent studies also compared the therapeutic effects of osimertinib with other treatments including chemotherapy, bevacizumab, and other EGFR-TKI such as gefitinib, erlotinib, and afatinib. Most of the studies have revealed better treatment benefits of osimertinib, but there was also indefinite result. For instance, the study by Zhou *et al.* included 813 patients to compare osimertinib versus first-generation EGFR-TKIs for patients with EGFR-mutant advanced NSCLC without baseline CNS metastasis [14]. At approximately 3 years of follow-up, the cumulative incidence of CNS metastasis was not different in the two groups (11.8 versus 15.6%). Moreover, there was a higher tendency of CNS metastasis of osimertinib in patients with 19del mutation ($p = .744$) but a lower tendency in patients with L858R mutation ($p = .053$) [14]. The therapeutic superiority of osimertinib upon other treatments remains undetermined.

We therefore conducted this meta-analysis and systematic review to compare the efficacy and safety of osimertinib versus other treatments for patients with EGFR-mutated NSCLC. To our knowledge, this is the first analysis that systematically compared osimertinib against other treatments for EGFR-mutated NSCLC.

Materials and methods

Literature search

We searched all articles focusing on the comparison of osimertinib versus other treatments in patients with EGFR-mutated NSCLC in the following databases: Web of Science, PubMed, Embase and the Cochrane Library. The following key words were used for literature search: osimertinib or OSI or TAGRISSO or AstraZeneca for identifying the articles of osimertinib treatment; versus or vs or compared or comparison or comparing or compare for identifying the articles that compared osimertinib with other treatments; lung or pulmonary or NSCLC or SCC for identifying the articles of lung cancer. To avoid the missed articles searched *via* keywords, we also obtained additional articles by reviewing the citation list of the articles included and recent reviews. Two authors independently assessed the eligibility of articles for inclusion. If there was dissonance of the result, further discussion with the third author was conducted to resolve the dissonance.

The articles were included if they met the following inclusion criteria:

I. Participants were patients with EGFR-mutated NSCLC;
II. Study design was randomized controlled trials that compared osimertinib with other treatment;
III. At least one of the following outcomes were reported: ORR, disease control rate (DCR), PFS, central nervous system progression-free survival (CNS-PFS), overall survival (OS), and the incidence of adverse event (AE).

During the screening process, articles were excluded for the following reasons:

I. Duplicate records;
II. Specific types of paper without available data such as letter, comment, editorial, protocol, reply, review, meta-analysis, guideline, *etc.*;
III. Studies with less than 10 patients;
IV. Basic research;
V. Case report or case series with limited number of patients;
VI. In the full text review, no available data were found.

The articles were managed by using Endnotes (version X9) throughout the literature screening process. The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42022319480).

Data extraction

The following information in the included articles was collected: first author, year of publication, study location, type of cancer of the study population, stage of cancer, previous treatment, type of treatment in the control group, the total sample size of the study population, the type of subgroups in the subgroup analysis. For data synthesis, the following raw statistics were collected: ORR (alternatively, the number of complete response (CR) and partial response (PR)), DCR (alternatively, the number of CR, PR, and stable disease (SD)), the value of HR and 95% CI for PFS, CNS-PFS, and OS, and the number of AEs in the experimental group (osimertinib) and control group (other treatment), respectively. Raw data were extracted by two authors independently from each article and recorded by the software Excel. The dissonance of the results was resolved with the third author in the similar method as described in the literature search section. All extracted data are summarized in a Word file which is available in the Supplementary Table S1.

Definitions

ORR and DCR

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. ORR was defined as the overall rate of CR + PR, while DCR was defined as the overall rate of CR + PR + SD.

PFS, CNS-PFS, and OS

To incorporate the HR of all included studies with subtle differences of definitions of PFS and OS, the following definitions were used in this meta-analysis: PFS was defined as the duration from the time of the baseline assessment or therapy begin to the time of subjective disease deterioration or death, objective disease progression whichever was recorded first. CNS-PFS was defined as the duration from the time of the baseline assessment or therapy begin to the time of CNS

disease progression. OS was defined as the duration from the time of treatment start or the baseline assessment to the date of death. Follow up was censored on the date of the last cancer assessment of patients if the cancer had not progressed or patients had not died or lost follow up.

Adverse event

The AEs occurred during treatment in both groups were evaluated and recorded according to the Common Terminology Criteria Adverse Events (CTCAE) version 5.0. Serious adverse event (SAE) was defined as CTCAE grade 3 or worse AE.

Data synthesis and statistical analysis

To guarantee the reliability of the result, data synthesis was performed by the two authors independently as described. If there was mismatch of calculation by the two authors, a third author would preside over a re-calculation and discussion until consensus was reached. The STATA software, version 15 (Stata Corporation, College Station, TX, USA) was used for data synthesis and overall effect calculation.

The *metan* module of STATA was used for the pooled estimation and comparison of ORR, DCR, PFS, CNS-PFS, OS, and AEs following the random effects model. The results were presented as pooled estimate with 95% CI and plotted as forest plot. Statistical significance of difference ($p < .05$) was determined by the Z test. Heterogeneity of included studies was evaluated *via* the I^2 statistic and p value.

Subgroup analysis

Subgroup analysis was performed according to the line of osimertinib (first, second, and other), comparator arm (chemotherapy, other EGFR TKIs, docetaxel plus bevacizumab, and placebo), and study location (international or in China).

Sub-population analysis for PFS and OS

Sub-population analysis was performed according to the available data of subgroups in the included studies: sex (male and female), age ($\geq$65 and $<$65), race (Asian and non-Asian), smoking history (yes and no), CNS metastases (yes and no), EGFR-TKI-sensitizing mutation status (Exon 19 deletion and L858R).

Results

Search results and study characteristics

As shown in Figure 1, a total of 380 articles were initially identified from database searching and the citation list of specific papers, of which 68 were duplicates and excluded. After screening by reviewing title, abstract and full-text, seven studies containing 3335 participants with EGFR-mutated NSCLC were considered eligible and finally included in this meta-analysis [13,15–20].

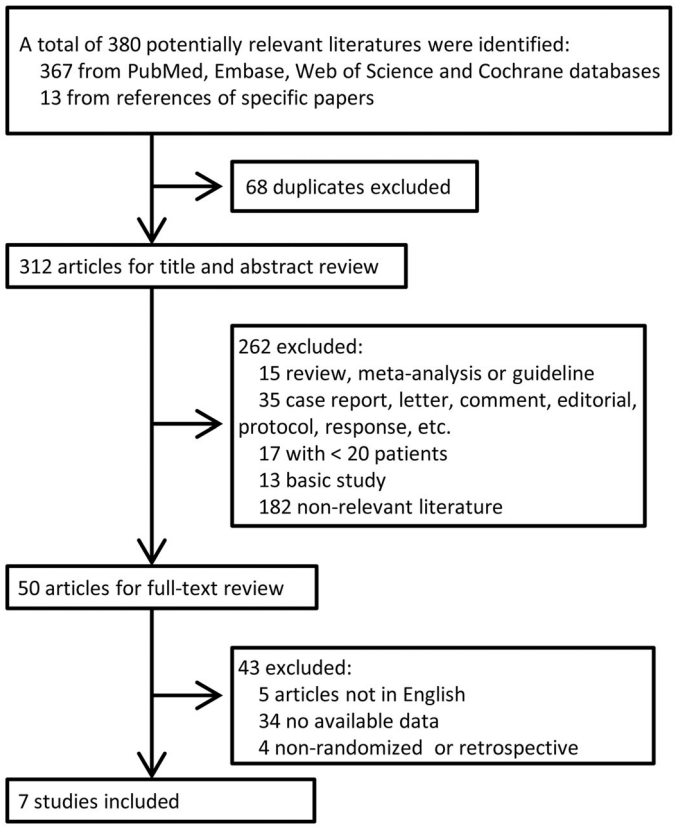

Figure 1. Flow chart of literature searching and screening.

The characteristics of included studies were listed in Table 1. Six studies were conducted across international regions and one study was in China. Most of the tumors were locally advanced or metastatic. The participants underwent previous treatment including first-line EGFR-TKI therapy, EGFR-TKI + chemotherapy and resection in 2, 1, and 1 studies, respectively. The patients in the other three studies were treatment-naive. Osimertinib was used as first, second, third-line, and adjuvant therapy in 3, 2, 1, and 1 studies, respectively. Osimertinib was compared with chemotherapy, docetaxel + bevacizumab, other EGFR-TKIs and placebo in 2, 1, 3, and 1 studies, respectively. There were more than 100 patients in all studies.

The results of quality assessment are shown in Figure 2. Most studies ($n = 6$ of 7) did not provide available data for the assessment of selection bias (random sequence generation and allocation concealment). While three studies showed high risk in the performance bias due to the lack of blinding of participants and personnel. Other types of bias were low risk.

Overall comparisons

In total (Figure 3), osimertinib tended to induce a higher ORR with RR = 2.42 (95% CI: 0.92–6.39; $p = .075$), higher DCR with RR = 1.36 (95% CI: 0.93–1.98; $p = .114$), significantly longer PFS with HR = 0.28 (95% CI: 0.18–0.44; $p < .001$), significantly longer CNS-PFS with HR = 0.29 (95% CI: 0.11–0.77;

Table 1. Characteristics of included studies.

Study ID	Study location	Stage of NSCLC	Previous treatment	Line of osimertinib	Type of study	Control treatment	Total sample size
Mok 2017 [13]	International	Locally advanced or metastatic	First-line EGFR-TKI	Second	Randomized, open-label, phase 3	Pemetrexed plus carboplatin/cisplatin	419
Soria 2018 [15]	International	Locally advanced or metastatic	None	First	Randomized, double-blind, phase 3	Gefitinib or erlotinib	556
Nie 2018 [16]	China	Locally advanced or metastatic	EGFR-TKI + chemotherapy	Third	Randomized, open-label, phase 3	Docetaxel + bevacizumab	147
Reungwetwattana 2018 [17]	International	Locally advanced or metastatic	None	First	Randomized, double-blind, phase 3	Gefitinib or erlotinib	556
Ramalingam 2020 [18]	International	Locally advanced or metastatic	None	First	Randomized, double-blind, phase 3	Gefitinib or erlotinib	556
Papadimitrakopoulou 2020 [19]	International	Locally advanced or metastatic	First-line EGFR-TKI	Second	Randomized, open-label, phase 3	Pemetrexed plus carboplatin/cisplatin	419
Wu 2020 [20]	International	Postsurgical pathological stage IB, II, or IIIA	Complete resection	Adjuvant	Randomized, double-blind, phase 3	Placebo	682

NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.

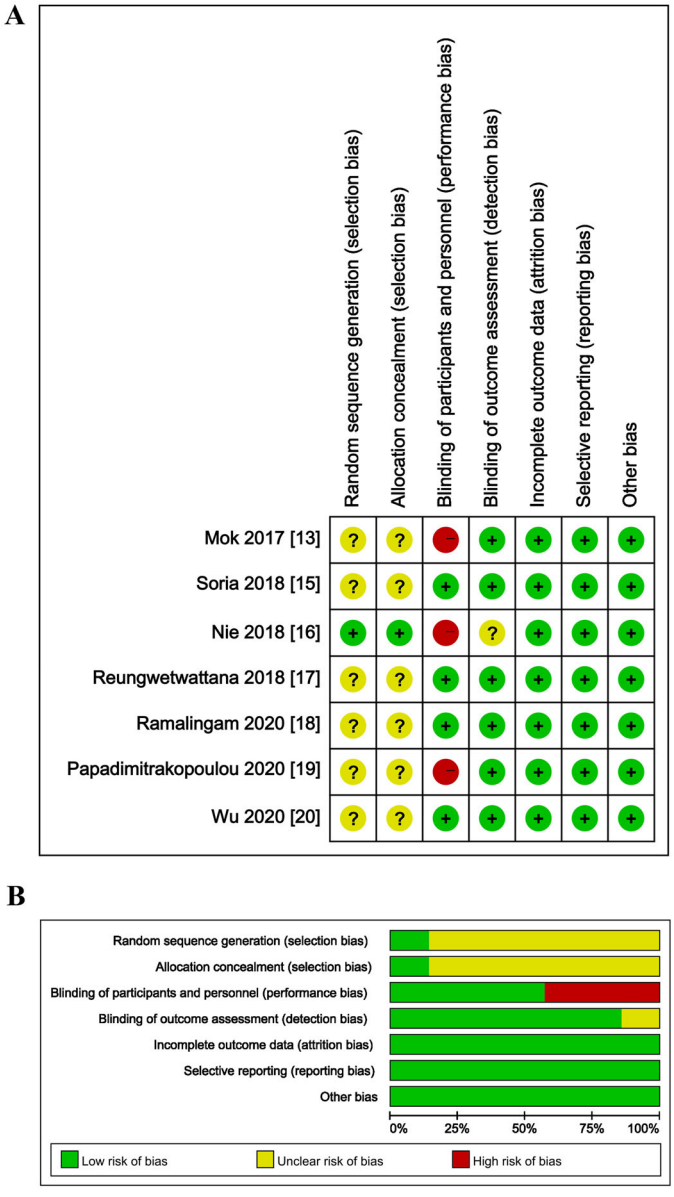

Figure 2. Quality assessment of included studies. (A) The figure shows the authors' judgments about each aspect of quality item for each included study. (B) The results are also presented as percentages across all included studies.

$p = .013$), and significantly longer OS with HR = 0.78 (95% CI: 0.68–0.91; $p = .001$).

Subgroup analysis

As shown in Table 2, subgroup analysis was performed according to the line of osimertinib (first, second, and other), comparator arm (chemotherapy, other EGFR-TKIs, docetaxel plus bevacizumab, and placebo) and study location (international or in China). The number of studies in each group was relatively limited ($n = 1$ or 2 in most subgroups). When used as first, second, and other lines of therapy, respectively, osimertinib induced higher ORR and DCR (RR >1) as well as longer PFS, CNS-PFS, and OS (HR <1). Similar results were observed when osimertinib was compared with chemotherapy, other EGFR-TKIs, docetaxel plus bevacizumab, and placebo, respectively. In the subgroups including different stages of NSCLC and study location, the results were also consistent.

Sub-population analysis for PFS and OS

We also evaluated the efficacy of osimertinib in different sub-populations for PFS and OS (Supplementary Table S2). Three studies provided the data of PFS and OS in the following sub-populations: sex (male and female), age (≥65 and < 65), race (Asian and non-Asian), smoking history (yes and no), CNS metastases (yes and no), EGFR-TKI-sensitizing mutation status (Exon 19 deletion and L858R). The pooled HRs for PFS were <1 in all subgroups with all p<.01, suggesting that osimertinib treatment was also a significant protective factor in different sub-populations of patients against disease progression as compared with other treatments. As for OS (Supplementary Table S2), the pooled HRs were <1 in all sub-populations, while the p values were <.05 in 4 of these 12 sub-populations. The benefit of osimertinib treatment for OS was not as significant as PFS in the other eight sub-populations.

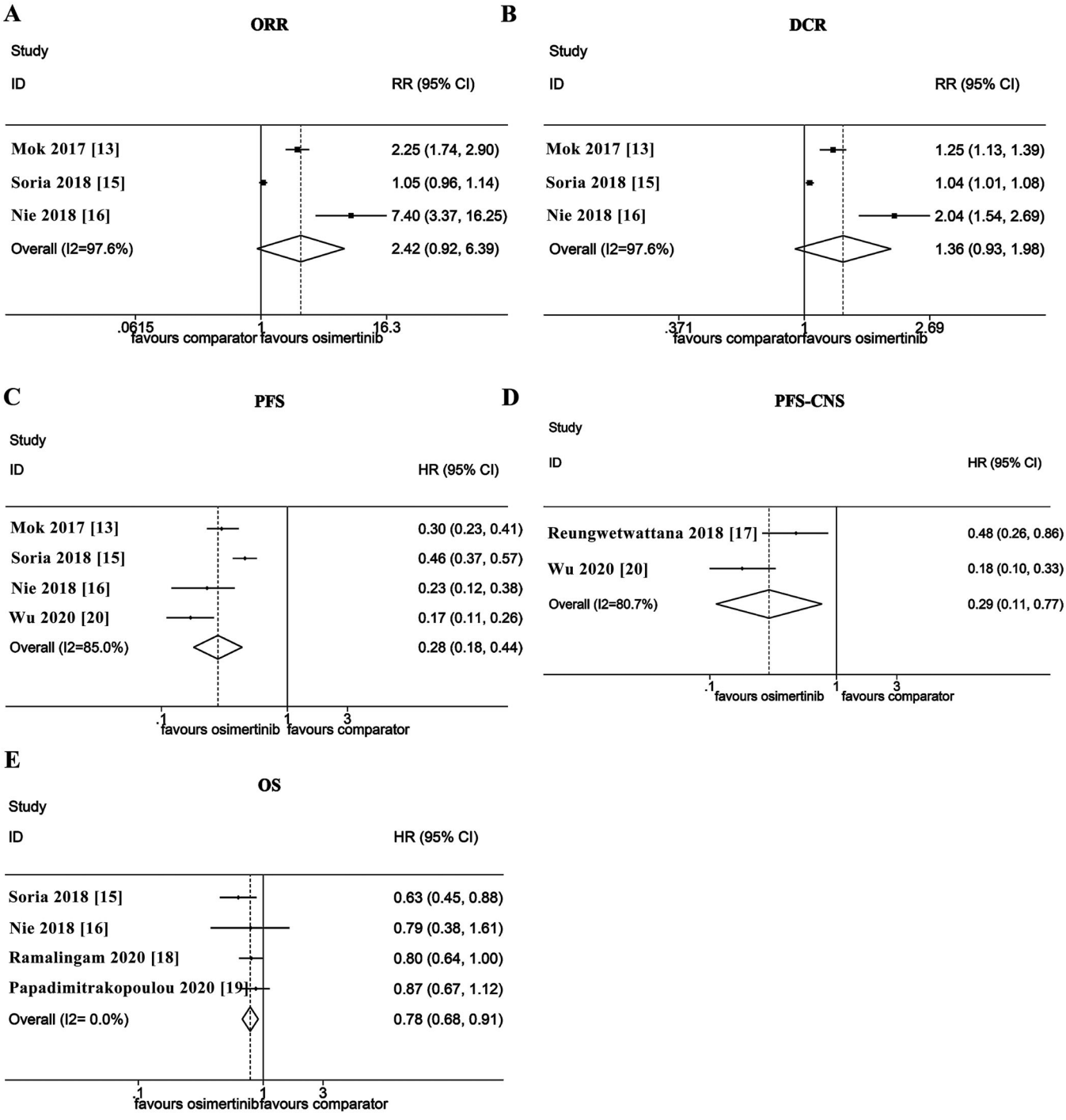

Figure 3. The pooled efficacy comparisons of (A) ORR, (B) DCR, (C) PFS, (D) CNS-PFS, and (E) OS. ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; CNS-PFS: central nervous system progression-free survival; OS: overall survival; RR: relative risk; HR: hazard ratio.

AEs of osimertinib

As listed in Supplementary Table S3, the most common five AEs of osimertinib with pooled incidence >20% were diarrhea, rash, nail effects, dry skin, and stomatitis. The AEs with pooled incidence 10–20% were decreased appetite, cough, nausea, pruritus, fatigue, constipation, back pain, upper respiratory tract infection, dyspnea, nasopharyngitis, headache, vomiting, insomnia, and leukopenia. All the pooled incidences of SAEs were less than 2%.

Discussion

In the case of NSCLC, complete resection of the cancer is usually followed by relapse, for instance in the form of distant metastases. The patients might need to receive chemotherapy, which is often unable to curtail the metastases and unsuitable per se for other patients. In these circumstances, the so-called tyrosine kinase inhibitor can be used, which is directed against the epidermal growth factor receptor that is altered or produced excessively in the affected patients. A

Table 2. Subgroup analysis.

Subgroup	RR of ORR	RR of DCR	HR of PFS	HR of CNS-PFS	HR of OS
Line of osimertinib					
First	RR = 1.05 $p = .258$ N* = 1	RR = 1.043 $p = .007$ $N = 1$	HR = 0.46 $p < .001$ $N = 1$	HR = 0.48 $p = .016$ $N = 1$	HR = 0.735 $p = .007$ $N = 2$
Second	RR = 2.247 $p < .001$ $N = 1$	RR = 1.254 $p < .001$ $N = 1$	HR = 0.3 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$	HR = 0.87 $p = .288$ $N = 1$
Other (third or adjuvant)	RR = 7.397 $p < .001$ $N = 1$	RR = 2.036 $p < .001$ $N = 1$	HR = 0.189 $p < .001$ $N = 2$	HR = 0.18 $p < .001$ $N = 1$	HR = 0.79 $p = .522$ $N = 1$
Comparator arm					
Chemotherapy (pemetrexed plus carboplatin/cisplatin)	RR = 2.247 $p < .001$ $N = 1$	RR = 1.254 $p < .001$ $N = 1$	HR = 0.3 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$	HR = 0.87 $p = .288$ $N = 1$
EGFR TKIs (gefitinib or erlotinib)	RR = 1.05 $p = .258$ $N = 1$	RR = 1.043 $p = .007$ $N = 1$	HR = 0.46 $p < .001$ $N = 1$	HR = 0.48 $p = .016$ $N = 1$	HR = 0.735 $p = .007$ $N = 2$
Docetaxel plus bevacizumab	RR = 7.397 $p < .001$ $N = 1$	RR = 2.036 $p < .001$ $N = 1$	HR = 0.23 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$	HR = 0.79 $p = .522$ $N = 1$
Placebo	RR = NA P = NA $N = 0$	RR = NA P = NA $N = 0$	HR = 0.17 $p < .001$ $N = 1$	HR = 0.18 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$
Stage of NSCLC					
Locally advanced or metastatic	RR = 2.419 $p = .075$ $N = 3$	RR = 1.357 $p = .114$ $N = 3$	HR = 0.335 $p < .001$ $N = 3$	HR = 0.48 $p = .016$ $N = 1$	HR = 0.785 $p = .001$ $N = 4$
Postsurgical pathological stage IB, II, or IIIA	RR = NA P = NA $N = 0$	RR = NA P = NA $N = 0$	HR = 0.17 $p < .001$ $N = 1$	HR = 0.18 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$
Study location					
International	RR = 1.525 $p = .35$ $N = 2$	RR = 1.14 $p = .328$ $N = 2$	HR = 0.294 $p < .001$ $N = 3$	HR = 0.294 $p = .013$ $N = 2$	HR = 0.782 $p = .003$ $N = 3$
China	RR = 7.397 $p < .001$ $N = 1$	RR = 2.036 $p < .001$ $N = 1$	HR = 0.23 $p < .001$ $N = 1$	HR = NA P = NA $N = 0$	HR = 0.79 $p = .522$ $N = 1$

N: number of studies that had available data for synthesis;
RR: relative risk; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; HR: hazard ratio; CNS-PFS: central nervous system progression-free survival; OS: overall survival; NA: not available; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; NSCLC: non-small cell lung cancer.

drug from this substance class, osimertinib, has recently been approved for such use. Currently, osimertinib is the standard of care for advanced EGFR-mutation-positive NSCLC due to its improvement of PFS and OS [15,18] over the first-generation EGFR TKIs from the FLAURA trial as well as for EGFR T790M-positive NSCLC which fails from the first- or second-generation EGFR TKIs [12,21,22]. Within approximately 5 years, osimertinib progressed from the beginning of phase I study in 2013 and report of preliminary treatment effect data on 60 patients with NSCLC in the same year on the ESMO/ECCO congress with clinical efficacy upon EGFR T790M-positive NSCLC observed at the first dose cohort (20 mg daily) to acquiring approval for two indications. In the phase 3 FLAURA trial, for patients with newly diagnosed EGFR-mutant advanced NSCLC, osimertinib presented with an obvious survival benefit of OS and PFS as compared with erlotinib (Tarceva) and gefitinib (Iressa), irrespective of the presence of brain metastases. Results from the study served as one of the bases for the agent's approval in this setting in 2018. Thereafter, quite a few studies have compared the efficacy and safety of osimertinib versus other treatments, such as chemotherapy, other EGFR TKIs and vascular endothelial growth factor A monoclonal antibody bevacizumab.

In the included studies in this meta-analysis, the most commonly compared treatment is chemotherapy and other EGFR-TKIs. Osimertinib has showed greater benefit upon ORR, DCR, PFS, CNS-PFS, and OS as compared with these treatments. It should be noted that the heterogeneity in most comparisons ranges from moderate to substantial. The major reason of observed heterogeneity might be the limited number of studies. Since osimertinib has just been applied in the recent 7 years in clinical practice, the number of comparative investigations are quite limited and the study populations are very different. Therefore, such heterogeneity is inevitable to conduct the meta-analysis of this theme in the current era. Despite the heterogeneity in these comparisons, it might have little impact on the final conclusion, given that most comparisons in each study have suggested the superiority of osimertinib over other therapies. In brief, the results of the meta-analysis provided preliminary evidence for the efficacy of osimertinib.

The third-generation EGFR-TKI is specifically designed to selectively inhibit the T790M mutation by covalent binding to the C797 residue and possess the effect to also restrain EGFR activating mutations while sparing wild-type EGFR. Thus, it is expected to have less side effects than wild-type EGFR blockade in the skin and gastrointestinal tract. Despite that the AEs such as diarrhea and rash are commonly observed in the present meta-analysis, they rarely lead to severe outcomes. The well-tolerant feature of osimertinib

might also offer the possibility of combination with other therapy such as chemotherapy. The unresolved issues on osimertinib still need further investigation.

Conclusion

In summary, this meta-analysis suggested that osimertinib was associated with improved disease response and patient survival as compared with other treatments including chemotherapy, other EGFR TKIs, and placebo in patients with EGFR mutation-positive NSCLC and had an acceptable safety profile.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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