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Efficacy and safety of osimertinib in treating EGFR-mutated advanced NSCLC: A meta-analysis

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Osimertinib is the only Food and Drug Administration-approved third-generation epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI). A meta-analysis was performed to aggregate the mixed results of published clinical trials to assess the efficacy and safety of osimertinib. A systematic search of the PubMed, Web of Science, and Cochrane Library electronic databases was performed to identify eligible literature. The primary endpoints were overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and adverse events (AEs). A total of 3,086 advanced nonsmall cell lung cancer (NSCLC) patients from 11 studies have been identified. The aggregate efficacy parameters for treatment-naïve patients with EGFR-TKI-sensitizing mutations are as follows: ORR 79% (95% CI 75–84%), DCR 97% (95% CI 95–99%), 6-month PFS 83% (95% CI 80–87%), and 12-month PFS 64% (95% CI 59–69%). The aggregate efficacy parameters for advanced NSCLC harboring T790M mutations after earlier-generation EGFR-TKI therapy are as follows: ORR 58% (95% CI 46–71%), DCR 80% (95% CI 63–98%), 6-month PFS 63% (95% CI 58–69%), and 12-month PFS 32% (95% CI 17–47%). EGFR-TKI-naïve patients with EGFR-positive mutations tend to have longer median PFS than EGFR-TKI-pretreated counterparts (19.17 *vs.* 10.58 months). The most common AEs were diarrhea and rash, of which the pooled incidences were 44 and 42%, respectively. Generally, osimertinib is a favorable treatment option for previously treated T790M mutation-positive advanced NSCLC as well as a preferable therapy for untreated EGFR mutation-positive advanced NSCLC. Additionally, osimertinib is well tolerated by most patients.

Introduction

Currently, lung cancer is the most common cause of cancer-related death worldwide. Approximately 234,030 new cases and 152,410 deaths are predicted in the United States in 2018.[1] Nonsmall cell lung cancer (NSCLC) is the most common subtype of lung cancer, and more than 50% of patients are in an advanced stage when first diagnosed.[2,3] Systemic treatment is the basic option for advanced cases of NSCLC. Although platinum-based chemotherapies are the cornerstone treatment for advanced NSCLC, they exhibit a modest effect on overall survival (OS).[4] Moreover, due to various adverse events (AEs) related to chemotherapies and increased resistance in tumors, the prognosis of advanced NSCLC remains dismal.[5–7] Therefore, the search for novel therapy strategies is urgent. The recent discovery of new molecular targets and the development of targeted drugs have brought hope for the effective treatment of advanced NSCLC.

Epidermal growth factor receptor (EGFR), a membrane surface receptor with tyrosine-kinase activity, is widely distributed in human epidermal cells and stromal cells and is involved in a variety of intracellular pathways, such as the promotion of the proliferation, invasion, or metastasis of cancer cells and the stimulation of tumor-induced neovascularization.[8–10] A total of 10–40% of NSCLC tumors harbor EGFR-sensitizing mutations, particularly EGFR exon 19 deletions and point mutations in exon 21.[11] Thus, these mutations are considered vital therapeutic targets for

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What's new?

Epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) have shown significant promise in treating advanced non-small-cell lung cancer (NSCLC). In this meta-analysis, the authors found that osimertinib, a third-generation EGFR-TKI, is an especially favorable treatment option. Outcomes were encouraging for previously-treated, advanced NSCLCs that carried T790M mutations. In addition, treatment-naïve patients whose advanced NSCLC had EGFR-TKI-sensitizing mutations tended to have a better response with osimertinib than did previous patients treated with earlier-generation EGFR-TKIs. These results indicate that further clinical trials are warranted for optimizing the use of osimertinib in advanced NSCLC.

advanced NSCLC. EGFR tyrosine-kinase inhibitors (TKIs) inhibit the proliferation of tumor cells *via* binding to EGFR specifically and show favorable therapeutic effects on advanced EGFR-mutated NSCLC. A meta-analysis of randomized controlled trials (RCTs) suggested that EGFR-mutated NSCLC patients treated with first-line first-generation EGFR-TKI (gefitinib or erlotinib) therapy had longer median progression-free survival (PFS) than chemotherapy-treated patients (11.0 *vs.* 5.6 months).[12] Treatment with the second-generation EGFR-TKI afatinib, which irreversibly inhibits EGFR and other ErbB family targets, significantly improved the PFS of untreated EGFR-mutated patients compared to chemotherapy (11.1 *vs.* 6.9 months; $p = 0.001$).[13] The EGFR-TKIs gefitinib, erlotinib, and afatinib have long been recommended as the standard first-line treatment for advanced NSCLC harboring EGFR mutations.

Despite impressive initial response rates, patients treated with first- or second-generation EGFR-TKIs often exhibit progression after 10–14 months.[13,14] The emergence of acquired resistance also limits the long-term efficacy of EGFR-TKIs in EGFR-mutated NSCLC patients. Acquisition of the EGFR-T790M mutation is the most common resistance mechanism, accounting for 50–60% of progression after first-line EGFR-TKIs.[15] The presence of the T790M variant reduces the ability of the reversible EGFR-TKIs, gefitinib and erlotinib, to bind to the adenosinetriphosphate (ATP)-binding pocket of EGFR, which reduces the EGFR-TKI-mediated inhibition of downstream signaling.[16–18] One strategy for overcoming such resistance is the application of irreversible EGFR inhibitors.[15] Preclinical data showed that the irreversible EGFR-TKIs afatinib and dacomitinib could overcome the resistance caused by the T790M mutation.[19,20] However, toxicity-related limitations prevented afatinib and dacomitinib from displaying an anti-resistance effect in clinical trials. The efficacy of afatinib and dacomitinib was less than 10%, and PFS was less than 4 months in patients whose cancer progressed after treatment with first-generation EGFR-TKIs.[21,22] Given the limited efficacy and the toxicity of second-generation EGFR-TKIs used to counter T790M resistance to first-generation EGFR-TKIs therapy, third-generation EGFR-TKIs have been developed.

Osimertinib is an orally taken third-generation EGFR-TKI which can form an irreversible covalent bond *via* the cysteine-797 residue and T790M or other EGFR mutations. Osimertinib selectively targets EGFR-sensitizing and T790M resistance mutations while still sparing wild-type EGFR tyrosine kinase.[18] Osimertinib profoundly induced sustained tumor regression in xenograft and transgenic mouse tumor models in preclinical studies.[18] Osimertinib also displayed impressive central nervous system (CNS) activity in an EGFR mutant mouse brain metastasis model with sustained tumor regression.[23] Recently, several clinical trials have evaluated the effect of osimertinib in treating NSCLC.[24–34] However, these studies were mainly Phase I or II clinical trials and had mixed results. No meta-analysis assessing the efficacy and safety of osimertinib has yet been reported. Our study has synthesized the results of different studies, including the overall response rate (ORR), disease control rate (DCR), PFS, and AEs, to provide more objective data for the optimal clinical use of osimertinib.

Materials and Methods

Search strategy

Our study was carried out according to the preferred reporting items for systematic reviews and meta-analyses statement for reporting systematic reviews.[35] Three databases, namely, PubMed, Web of Science, and the Cochrane Library, were systematically searched to identify relevant studies of patients treated with osimertinib, without any language or date restrictions. The last retrieval was performed on May 4, 2018. For instance, the following retrieval strategy was used on PubMed: ("osimertinib" OR "mereletinib" OR "AZD9291" OR "Tagrisso") AND ("Non-Small Cell Lung Cancer" OR "Non-Small Cell Lung Carcinoma" OR "Non Small Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinoma" OR "Nonsmall Cell Lung Cancer" OR "Non-Small-Cell Lung Carcinomas" OR "Non-Small-Cell Lung Carcinoma" OR "NSCLC"). In addition, the references included were searched manually to avoid omitting any studies that met the inclusion criteria.

Selection criteria

Studies satisfying the following criteria were selected: (1) the patients were histologically diagnosed with advanced NSCLC; (2) the studies were clinical trials performed to evaluate the efficacy and safety of osimertinib in advanced NSCLC patients; (3) no less than 60 advanced NSCLC patients were enrolled; (4) any of the following data: response rate, PFS, and toxicity were provided; (5) the studies were published in English; and (6) the most complete and recent report of the trial was used when the same investigator reported data obtained from the same patients. Duplicate publications, reviews, case reports,

animal or cell experiments, and trials with incomplete data were excluded.

Data extraction

The study selection process was conducted independently by two investigators (LY and JF) based on the inclusion and exclusion criteria. The data collection template was formulated in advance, and the following information was extracted by two investigators: the first author's name, year of publication, country, trial design, sub-category, EGFR mutant (%), study period, treatment line, age (years), sample size, dosage and length of osimertinib, tumor response, median PFS, 6-month PFS (PFS-6), 12-month PFS (PFS-12), and AEs. Any discrepancies were resolved by discussion and consensus during the process of research selection and data extraction or by consulting the third investigator (PL) when necessary.

Quality assessment

The methodological quality of all the included studies was assessed by two reviewers, with discrepancies resolved by consensus. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of single-arm and noncontrolled trials. The overall quality of a study was defined as "poor" if the total NOS score was less than 4, "fair" if the score was 4–6, and "good" with a score of 7–9.[36,37] The methodological quality of the included RCTs was estimated according to the Cochrane Collaboration tool for assessing the risk of bias (ROB).[38] The total ROB of a study was considered "low" when more than four items associated with "low risk" by the Cochrane Collaboration ROB tool were considered applicable, "moderate" when 2–3 items were applicable, and "high" when fewer than two "low risk" items or more than one "high risk" item were considered applicable.

Statistical analysis

All statistical analysis was performed using the Review Manager 5.3 software (Cochrane Library, Oxford, UK) and STATA 12.0 software (Stata Corp., College Station, TX). The chi-square test and I^2 statistic were applied to evaluate the heterogeneity among the retrieved studies. The random effect model was used when there was significant heterogeneity (I^2 value >50%) between studies; otherwise, the fixed effect model was used. The integrated analysis was carried out based on the generic inverse variance method, and the effect size was represented by the 95% confidence interval (CI). The subgroup analyses of ORR, DCR, complete response (CR), partial response (PR), stable disease (SD), median PFS, PFS-6, and PFS-12 were conducted according to treatment lines. The subgroup analyses of ORR and DCR were also conducted according to the dose of osimertinib. AEs of all grades or of grade ≥III were aggregated separately. Additionally, Begg's and Egger's tests, as well as funnel plots, were used to assess the publication bias of the enrolled studies. A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Study selection

A total of 770 references were identified after performing database searches (PubMed 272, Web of Science 448, Cochrane Library 50), and 488 references remained after deduplication. Of these, 452 references that included animal experiments, cell experiments, diagnostic tests, case reports, and other irrelevant studies were excluded according to the inclusion and exclusion criteria. Finally, a total of 11 clinical trials with 3,086 patients were included after reading the full text (Fig. 1).[24–34]

Characteristics of the studies and quality assessment

A total of 11 clinical trials (three RCTs, eight single-arm trials) involving 3,086 patients with advanced NSCLC (632 in the three RCTs, 2,454 in the eight single-arm trials) were included. The patient groups in two of these studies shared partial overlap, and therefore, 90 patients in the group receiving 80 mg osimertinib were removed, leaving 163 patients from the study reported by Janne *et al.* included in our final meta-analysis.[24,31] The eligible studies were published from 2015 to 2017, and the sample size of each study ranged from 60 to 1,217. The proportion of female patients varied from 62 to 69% in each study, apart from three studies for which this information was not available. In the two studies involving first-line treatment, patients with EGFR-TKI-sensitizing mutations accounted for 98.5% (334/339).[33,34] All patients in eight of the nine studies involving second-line treatment or beyond were EGFR T790M-positive. The 80 mg dose of osimertinib was used in 8 of 11 studies. The general characteristics and quality assessment of the included studies are presented in Table 1.

Tumor response

Eleven studies reported the ORR of osimertinb in treating NSCLC. The pooled ORR was 62% (95% CI 50–74%). The ORR was further analyzed according to the line of treatment. Two studies provided data on first-line treatment, and the pooled ORR of patients with EGFR-TKI-sensitizing mutations treated with osimertinib was 79% (95% CI 75–84%), with small heterogeneity (I^2 = 0%, p = 0.58). About 9 of the 11 studies provided data on second-line treatment or beyond, and the combined ORR on EGFR T790M-positive NSCLC patients treated with osimertinib was 58% (95% CI 46–71%), with obvious heterogeneity (I^2 = 98%, p < 0.00001; Fig. 2). Nine studies included usable data on DCR, and the pooled DCR was 84% (95% CI 71–97%). The combined DCR of the first-line treatment group was 97% (95% CI 95–99%), (I^2 = 0%, p = 0.85), while the pooled DCR for second-line treatment or beyond was 80% (95% CI 63–98%), (I^2 = 99%, p < 0.00001; Fig. 3).

The data on CR, PR, and SD were given by six studies. The pooled CR was 3% (95% CI 1–4%). Subgroup analysis showed that the pooled CR values of the first-line group and the

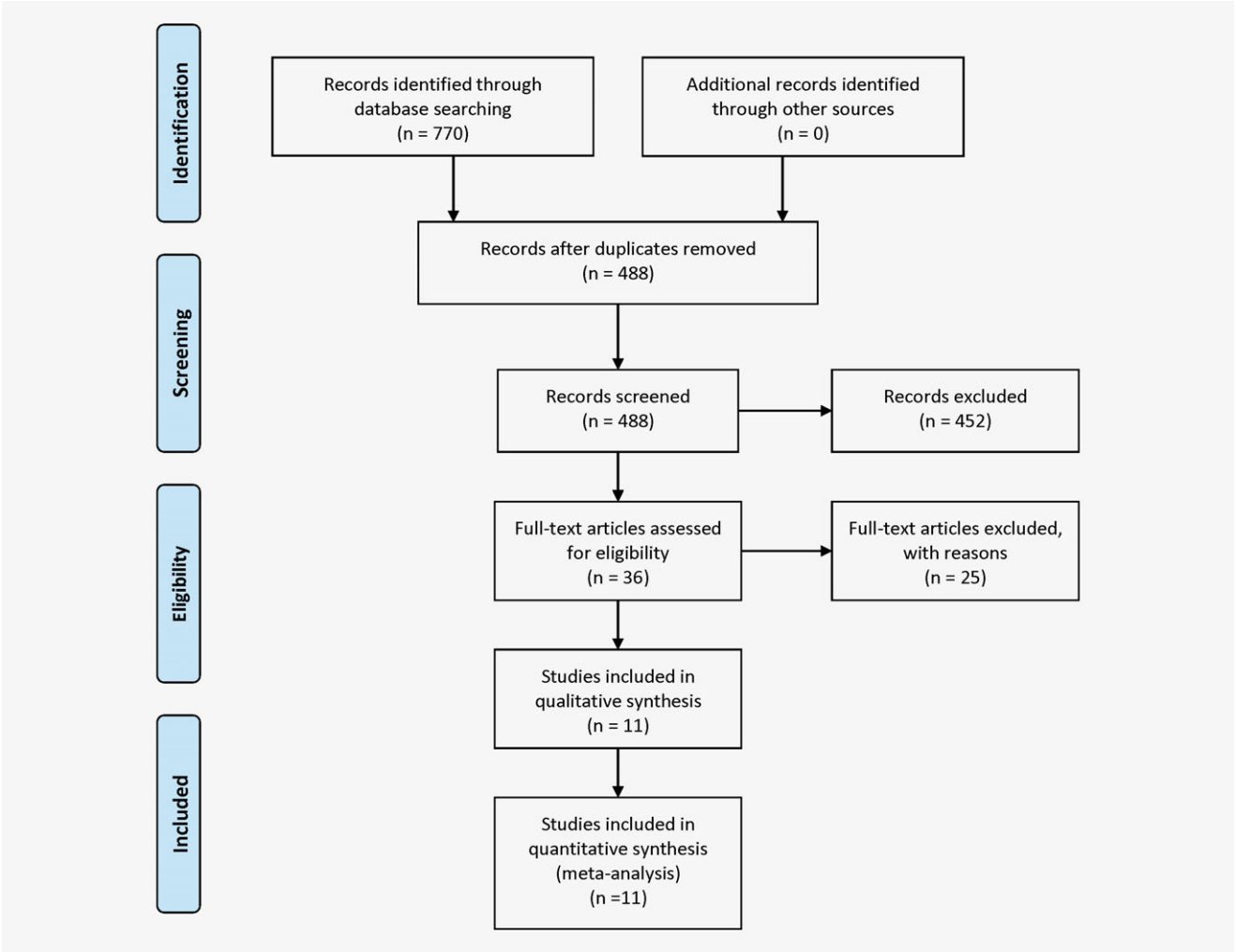

Figure 1. The flowchart of the study selection process for the meta-analysis [Color figure can be viewed at wileyonlinelibrary.com]

second-line or beyond group were 3% (95% CI 1–4%), (I^2 = 0%, P = 0.74) and 3% (95% CI 1–5%), (I^2 = 79%, P = 0.003), respectively (Supporting Information Fig. S1A). The pooled PR was 62% (95% CI 39–84%). Subgroup analysis showed that the pooled PR of the first-line group was 77% (95% CI 72–81%), (I^2 = 0%, p = 0.51), while that of the second-line or beyond group was 55% (95% CI 27–84%), (I^2 = 99%, p < 0.00001; Supporting Information Fig. S1B). The pooled SD was 15% (95% CI 9–21%). Subgroup analysis showed that the pooled SD of the first-line group was 17% (95% CI 13–21%), (I^2 = 0%, p = 0.58), while the pooled SD of the second-line or beyond group was 14% (95% CI 5–22%), (I^2 = 94%, p < 0.00001; Supporting Information Fig. S1C).

In addition, in the subgroup analysis according to the dose of osimertinib, data for the ORR of patients treated with 80 mg of osimertinib were available from eight studies, and the pooled result was 67% (95% CI 56–78%). The group of unknown/other doses included three studies, and the pooled ORR was 49% (95% CI 18–81%; Supporting Information Fig. S2). The combined DCR values of the 80 mg group and the unknown/others group were 91 and 62%, respectively (Supporting Information Fig. S3).

Progression-free survival

The pooled median PFS was 13.06 months (95% CI 10.19–15.93 months; Fig. 4A). Subgroup analysis suggested that the pooled median PFS of patients with EGFR-TKI-sensitizing mutations treated with osimertinib was 19.17 months (95% CI 16.88–21.45 months), (I^2 = 0%, p = 0.61). The pooled median PFS of EGFR T790M-positive patients treated with osimertinib was 10.58 months (95% CI 9.20–11.97 months), (I^2 = 57%, p = 0.07).

The PFS-6 and PFS-12 were analyzed separately based on the available data from five studies. The pooled PFS-6 was 71% (95% CI 60–82%). Subgroup analysis indicated that the pooled PFS-6 of the first-line group was 83% (95% CI 80–87%), with small heterogeneity (I^2 = 0%, p = 0.97). The combined PFS-6 of the second-line or beyond group was 63%

Table 1. Characteristics of the 11 trials included in the meta-analysis

Study (year)	Country	Trial design	Sub-category	EGFR mutant (%)	Treatment line	Age (years)	Sample size (female %)	Dosage and length of osimertinib	Quality assessment
Mok *et al.* (**2017**)	China, America, United Kingdom, Korea, Italy	RCT Phase III	AURA3	T790M (100%)	Second	20–90	279 (62%)	80 mg qd, to PD	Cochrane ROB tool: low risk
Soria *et al.* (**2018**)	America	RCT Phase III	FLAURA	Ex19del/L858R (100%)[1]	First	26–93	279 (64%)	80 mg qd, to PD	Cochrane ROB tool: low risk
Nie *et al.* (**2017**)	China	RCT Phase III	NR	T790M (100%)	Third	18–80	74 (NR)	80 mg qd, to PD	Cochrane ROB tool: medium risk
Janne *et al.* (**2015**)	America, China	Single-arm Phase I	AURA	T790M (NR)	≥Second	28–88	163 (NR)	20–240 mg qd, to PD	NOS: 7
Goss *et al.* (**2016**)	America	Single-arm Phase II	AURA2	T790M (100%)	≥Second	35–88	210 (69%)	80 mg qd, to PD	NOS: 8
Planchard *et al.* (**2016**)	France	NR	NR	T790M (100%)	≥Second	28–92	350 (67%)	NR	NOS: 6
Marinis *et al.* (**2017**)	America	Single-arm Phase III b	ASTRIS	T790M (100%)	Second	27–92	1,217 (67%)	80 mg qd, to PD	NOS: 6
Ramalingam *et al.* (**2018**)	America	Single-arm Phase I	AURA	Ex19del/L858R (92%)[2]	First	38–91	60 (64%)	80 or 160 mg qd, to PD	NOS: 7
Yang *et al.* (**2017**)	China	Single-arm Phase II (extension)	AURA	T790M (100%)	≥Second	37–89	201 (61%)	80 mg qd, to PD	NOS: 7
Zhou *et al.* (**2017**)	China	Single-arm Phase II	AURA17	T790M (100%)	≥Second	26–82	171 (69%)	80 mg qd, to PD	NOS: 5
Hochmair *et al.* (**2017**)	Austria	NR	NR	T790M (100%)	Second	NR	82 (NR)	80 mg qd, to PD	NOS: 4

Abbreviations: EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NOS, Newcastle–Ottawa Scale; NR, not reported; PD, progression disease; RCT, randomized controlled trial; ROB, risk of bias.
[1]T790M (NR)
[2]T790M (8%).

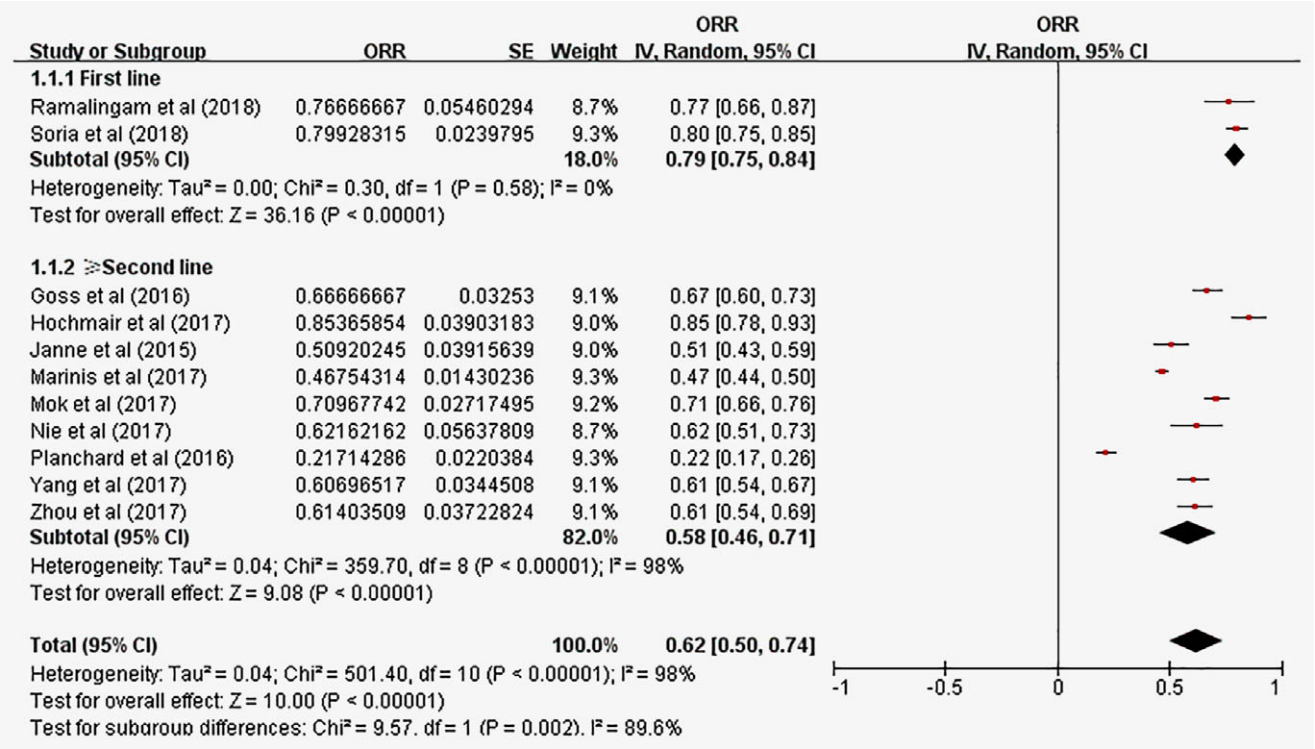

Figure 2. Meta-analysis of the overall response rate (ORR) of EGFR-mutated NSCLC treated with osimertinib [Color figure can be viewed at wileyonlinelibrary.com]

(95% CI 58–69%), with significant heterogeneity (I^2 = 55%, p = 0.11; Fig. 4B).

The combined PFS-12 was 45% (95% CI 26–64%). Subgroup analysis indicated that the pooled PFS-12 of the first-line group was 64% (95% CI 59–69%), with small heterogeneity (I^2 = 0%, p = 0.67). The pooled PFS-12 of the second-line or beyond group was 32% (95% CI 17–47%), with significant heterogeneity (I^2 = 95%, p < 0.00001; Fig. 4C).

In addition, four studies had data for the PFS-6 of patients treated with 80 mg of osimertinib, and the pooled result was 68% (95% CI 56–81%; Supporting Information Fig. S4A). The pooled PFS-12 of patients treated with 80 mg of osimertinib was 40% (95% CI 19–61%; Supporting Information Fig. S4B).

Toxicities

The most common AEs (all grades and grade ≥III) associated with osimertinib in treating advanced NSCLC were shown in Table 2. The highest-incidence AE among AEs of all grades was diarrhea, and the combined rate from a total of six studies (579/1,303) was 44% (95% CI 36–52%). The second was rash, and the pooled rate from a total of six studies (556/1,303) was 42% (95% CI 33–51%). Aggregated analysis based on AEs of grade ≥III indicated that the highest incidence was a prolonged QT interval on ECG, and the combined rate was 2% (95% CI 1–3%), with two studies included in the analysis (10/489). The second was neutropenia, and the combined rate was 2% (95% CI 1–3%), with two studies (9/489) included in the analysis. Furthermore, the pooled rate of diarrhea with grade ≥III was 1% (95% CI 0–1%). Five studies (12/1,132) provided data on rash with grade ≥III, and the pooled rate was 1% (95% CI 0–1%). The details of other common toxicities are presented in Table 2.

Publication bias

The funnel plots for the ORR, DCR, median PFS, PFS-6, PFS-12 of patients in different lines of treatment were roughly symmetric (Supporting Information Fig. S5). The asymmetry of the funnel plots was also further evaluated with Egger's and Begg's tests, but no significantly different results emerged (Supporting Information Table S1).

Discussion

Our study included 11 clinical trials involving 3,086 patients to evaluate the efficacy and safety of osimertinib in treating advanced EGFR-mutated NSCLC. The pooled results showed that the ORR and DCR were 58 and 80%, respectively, and the median PFS was 10.58 months in patients with T790M mutations, which confirmed the efficacy of osimertinib after the failure of previously approved EGFR-TKI therapy. In first-line osimertinib therapy, the pooled ORR and DCR were 79 and 97%, respectively, and the combined median PFS was 19.17 months, suggesting that osimertinib provides well disease control for untreated advanced EGFR-mutated NSCLC. The subgroup analysis by dose indicated that 80 mg of

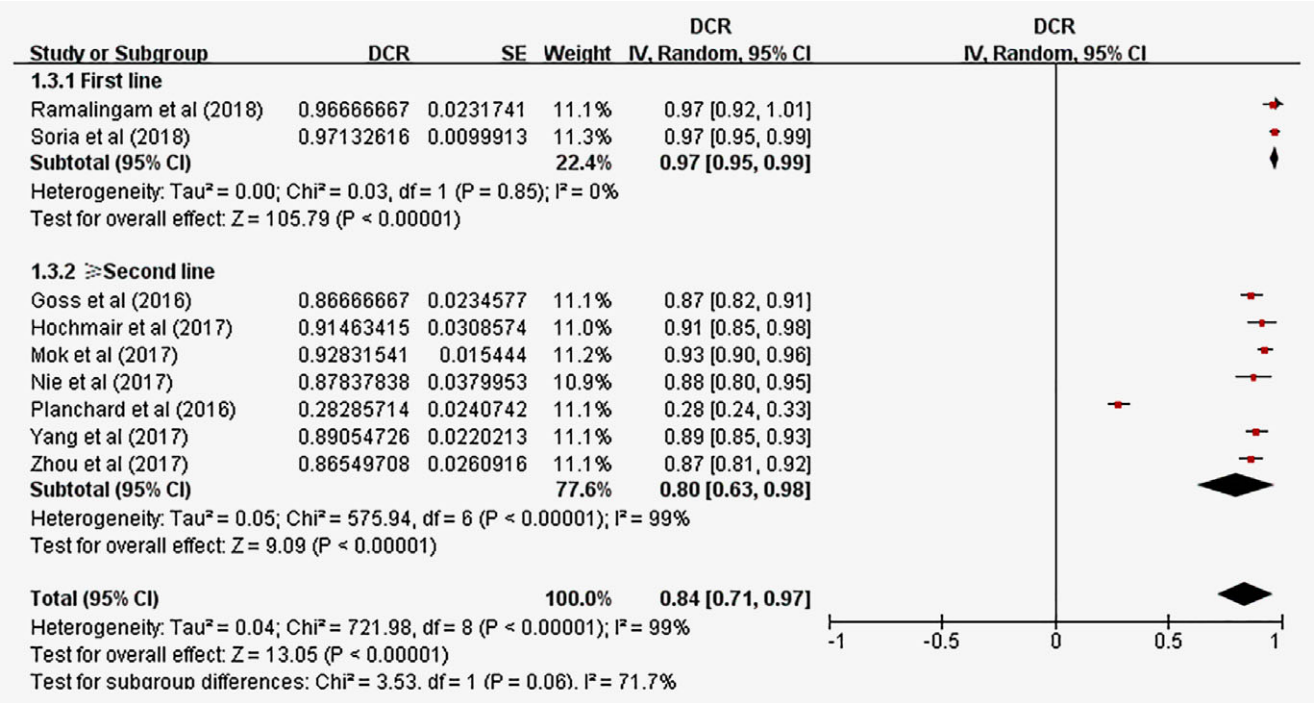

Figure 3. Meta-analysis of the disease control rate (DCR) of EGFR-mutated NSCLC treated with osimertinib [Color figure can be viewed at wileyonlinelibrary.com]

osimertinib once daily had higher ORR and DCR than the other doses (67 *vs.* 49%; 91 *vs.* 62%). Additionally, the most commonly reported AEs with the highest incidence were diarrhea (44%), rash (42%), and dry skin (29%).

Limited subsequent treatment strategies are available for advanced EGFR-mutated NSCLC that has developed resistance to earlier-generation EGFR-TKIs. Chemotherapy is a common treatment option for these patients. A previous study reported that the ORR of these patients with chemotherapy alone was 18%, and the median PFS was 4.2 months, with high hematological and neurological toxicities.[39] Several RCTs showed that EGFR-TKIs combined with chemotherapy had no clinical benefit for patients whose disease progressed after first-generation EGFR-TKI therapy.[40,41] Additionally, the effect of alternating with other first-generation EGFR-TKIs was unsatisfactory in these patients. Currently, osimertinib (AZD9291) is the only approved third-generation EGFR-TKI for clinical use. Compared to earlier-generation EGFR-TKIs, osimertinib shows enhanced EGFR mutant selectivity *in vitro* and in pharmacokinetics studies.[42] In two published RCTs, osimertinib demonstrated superiority over platinum-based chemotherapy in T790M-positive NSCLC.[29,30] A confirmatory Phase III study (AURA3) showed that osimertinib exhibited significant improvements over chemotherapy in ORR (71 *vs.* 31%, $p < 0.001$) and PFS (10.1 *vs.* 4.4 months, $p < 0.001$) in chemotherapy-naïve NSCLC harboring T790M mutations after first-line EGFR-TKI therapy.[29] Based on the above evidence, osimertinib is a preferable drug for advanced NSCLC harboring T790M mutations during or after earlier-generation EGFR-TKI therapy. Furthermore, preclinical data indicated that osimertinib had better blood–brain barrier penetration than gefitinib, rociletinib, or afatinib.[23] Predefined subgroup analysis in the AURA3 study also suggested that osimertinib had a higher CNS response rate (70 *vs.* 31%) and prolonged CNS PFS (11.7 *vs.* 5.6 months) compared to those of chemotherapy.[43] In our study, no aggregate analysis regarding CNS metastases was performed due to insufficient data. Therefore, more relevant clinical trials are warranted to enable further analysis.

With the constant expansion of targeted therapies, a major issue is the optimal sequence of these targeted drugs for the treatment of EGFR-driven NSCLC. The subgroup analysis by line of treatment suggested that treatment-naïve EGFR-mutated NSCLC with osimertinib had a higher ORR and DCR and longer median PFS than advanced NSCLC harboring T790M after earlier-generation EGFR-TKIs. Indeed, osimertinib exhibited superiority over chemotherapy in T790M-positive patients and then was evaluated in EGFR-TKI-naïve advanced NSCLC.[33,34] A recently published Phase III study (FLAURA) showed that in treatment-naïve advanced NSCLC harboring EGFR-TKI-sensitizing mutations, the use of osimertinib instead of first-generation EGFR-TKIs significantly improved the PFS (18.9 *vs.* 10.2 months, $p < 0.0001$).[34] Moreover, the CNS progression was lower in patients treated with osimertinib (6 *vs.* 15%). At present, the OS data on the first-line use of osimertinib compared to geifinib or erlotinib is immature, but osimertinib has displayed a positive trend (HR 0.63, 95% CI 0.45–0.88%; $p = 0.0068$).[44] The efficacy of

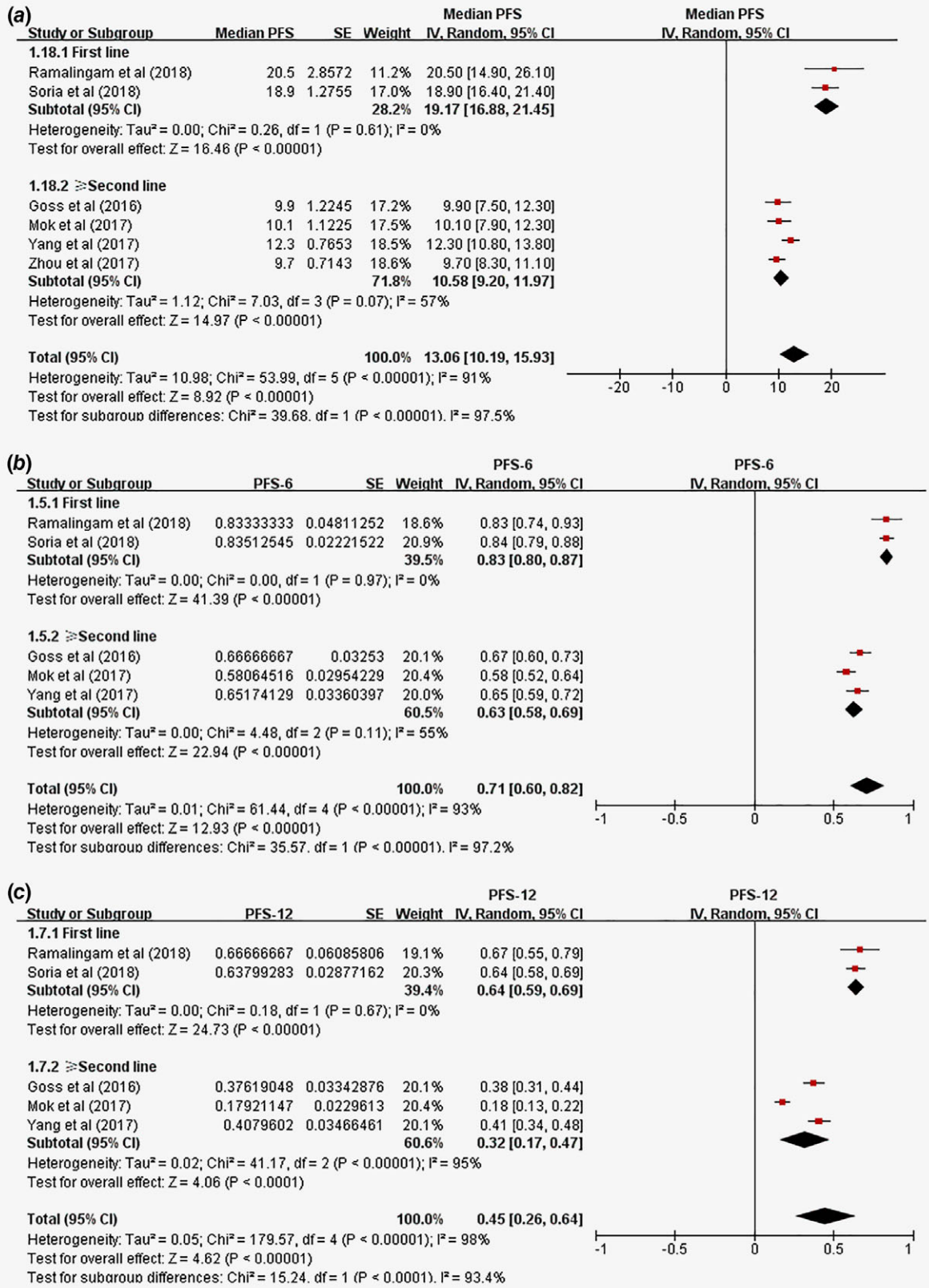

Figure 4. Meta-analysis of the median progression-free survival (PFS), 6-month progression-free survival (PFS-6), and 12-month progression-free survival (PFS-12) of EGFR-mutated NSCLC treated with osimertinib [Color figure can be viewed at wileyonlinelibrary.com]

Table 2. Meta-analysis of the common adverse events

Toxicity	N	Patients	Rates % (95% CI)	Heterogeneity (I^2) (%)
Any grade				
Diarrhea	6	579/1,303	44 (36–52)	89
Rash	6	556/1,303	42 (33–51)	92
Dry skin	5	331/1,132	29 (24–34)	68
Paronychia	5	307/1,132	27 (21–32)	80
Decreased appetite	4	166/922	18 (12–24)	83
Stomatitis	5	193/1,132	16 (10–22)	86
Cough	3	117/721	16 (14–19)	0
Fatigue	3	117/721	16 (12–20)	53
Nausea	4	145/922	16 (11–20)	73
Pruritus	5	170/1,132	15 (12–17)	28
Grade ≥III				
Prolonged QT interval on ECG	2	10/489	2 (1–3)	0
Neutropenia	2	9/489	2 (1–3)	0
Decreased appetite	4	12/922	1 (0–2)	23
Diarrhea	6	16/1,303	1 (0–1)	0
Dyspnea	3	8/721	1 (0–2)	40
Rash	5	12/1,132	1 (0–1)	0
Asthenia	1	3/279	1 (0–2)	–
ALT	3	6/768	1 (0–1)	0
AST	3	6/768	1 (0–1)	0
Fatigue	3	7/721	1 (0–2)	0

Abbreviations: ALT, alanine aminotransferase elevation; AST, aspartate aminotransferase elevation; CI, confidence Interval; ECG, electrocardiogram; *N*, number of included studies.

osimertinib was better than that of first-generation EGFR-TKIs in a first-line setting, this may due to the lower early resistance rate of osimertinib, which delays the emergence of acquired resistance.[34,45,46] In addition, in contrast to prior EGFR-TKIs, first-line osimertinib treatment did not lead to T790M mutation as an acquired resistance mechanism, which was consistent with the preclinical model.[33] Therefore, it seems ideal to consider first-line osimertinib, which is expected to be a new first-line standard of care for EGFR-mutated advanced NSCLC in the future. However, further clinical trials are warranted to clarify whether the sequential use of earlier-generation EGFR-TKIs and osimertinib or first-line osimertinib treatment would lead to longer OS and PFS.

In addition, according to the subgroup analysis of the dose used, osimertinib 80 mg once daily demonstrated a superior therapeutic effect. In a Phase I trial, the exposure dose of osimertinib was not related to efficacy within a dose range of 20–240 mg/day, and increased exposure was associated with a higher rate of AEs.[47] The PFS was similar for the 80 and 160 mg groups in a first-line setting, and low-dose osimertinib was better tolerated.[33] The incidence and severity of AEs, including rashes, dry skin, and diarrhea, were higher at doses of 160 and 240 mg, which may be related to the notable inhibition of wild-type EGFR by osimertinib at this dose.[24] Accordingly, osimertinib 80 mg once daily is recommended as the most appropriate dose based on effectiveness and safety.

Similar to earlier-generation EGFR-TKIs, diarrhea (44%) and rash (42%) were the most frequently reported AEs induced by osimertinib. The rate of diarrhea and rash with prior EGFR-TKI therapy were 53.3 and 66.5%, respectively.[48] Similarly, the incidence of serious AEs diarrhea (1%) and rash (1%) were lower than earlier-generation EGFR-TKIs.[49] Osimertinib attenuated the activity of EGFR T790M while sparing wild-type EGFR, which reduced the epithelial cell toxicities associated with previous EGFR-TKIs.[50] Compared to early-generation EGFR-TKIs, osimertinib showed lower incidences of AEs in treating EGFR-mutated advanced NSCLC. However, the serious AEs caused by osimertinib, namely, prolonged QT interval on ECG and neutropenia, should still be noted. Clinical symptoms of interstitial lung disease (ILD) include cough, dyspnea, chest pain, and systemic symptoms such as fever, fatigue, etc. As for these variables, we have pooled the common AEs in Table 2. Studies of Lee *et al.* and Nie *et al.* reported that ILD is a rare complication with osimertinib, occurring in 1–3% of patients.[51,52] Additionally, it is reported that osimertinib-induced ILD seems to be more common after treatment with anti-PD1 antibody.[53–55] The overall population in our study had not received immunotherapy before osimertinib. Thus, in our study, no such details are available to conduct these analyses for the rare AEs of osimertinib-induced ILD.

Admittedly, our study still has some limitations. First, 1.5% of patients in the first-line subgroup lacked EGFR-sensitizing mutations, which affected the reliability of the results to some extent. Second, the study by Janne *et al.* included a small proportion of T790M-unknown patients. Third, further subgroup analysis of $T790M^+$ and $T790M^-$ was not performed due to the unavailability of stratified data on T790M. Fourth, the combined analysis of PFS and OS was not conducted due to insufficient data. Fifth, most of the studies included were non-controlled trials, and the sample size of some trials was limited. Therefore, more RCTs comparing osimertinib with chemotherapy or earlier-generation EGFR-TKIs are needed to validate the current results. Additionally, the studies we included did not show available details of relapse-site patterns. The baseline of enrolled studies governing specific metastatic sites was not available. Therefore, our current study could not give the pooled data for relapse-site patterns. It is encouraging for further research to exclusively evaluate relapse-site patterns after treatment with osimertinib. It might be interesting if we could see the effect of osimertinib in other minor EGFR mutations or compare differences in effectiveness between the patients diagnosed using tissue and ctDNA, however, due to the limited stratified data of detailed EGFR mutation information, we cannot perform the subgroup analysis.

Conclusions

The results of our study indicate that most patients with advanced NSCLC harboring T790M mutations after earlier-

generation EGFR-TKI therapy would respond to osimertinib treatment or exhibit disease control. Osimertinib has impressive antitumor activity in treatment-naïve advanced NSCLC harboring EGFR-TKI-sensitizing mutations. Additionally, the incidences of AEs such as diarrhea and rash were lower than earlier-generation EGFR-TKIs, and there were no prominent serious AEs. Thus, osimertinib is a drug with favorable efficacy as well as tolerable AEs. Further clinical trials comparing first-line osimertinib treatment with the sequential use of earlier-generation EGFR-TKIs and osimertinib are warranted to update this meta-analysis and provide insight for optimizing the clinical use of osimertinib.

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