Systematic Review and Meta-Analysis

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The efficacy and safety of osimertinib in treating nonsmall cell lung cancer

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is the primary treatment in treating with EGFR mutant nonsmall cell lung cancer (NSCLC). This systematic review and meta-analysis aimed to evaluate the efficacy and safety of the third-generation EGFR-TKI, osimertinib, and summarize the risk factors associating with outcome after osimertinib treatment.

Method: The Ovid Medline, Embase, Cochrane Library, and Pubmed were systematically searched due to December 10, 2019. All the studies that mentioned the overall survival (OS), progression-free survival (PFS), treatment response, and adverse events (AEs) of osimertinib were involved in our study. Hazard ratio (HR) with 95% confidence intervals was used for comparing OS and PFS.

Result: A total of 47 studies were included in the systematic review, of which 14 studies were used to compare the efficacy between osimertinib and other EGFR-TKI or chemotherapy. Patients treating with osimertinib favors a higher OS and PFS in all the patients (HR = 0.56 and 0.38, $P < .001$, respectively), and in subgroup analysis, compared with other treatments. Median 55% T790 mutant NSCLC patients might experience partial response, and 25% of patients remained as stable disease. The incidence of severe AE ranged from 0% to 5%, and the most common severe AE was pneumonia (3%). Patients with the T858R mutation may have a better OS than Del 19 mutation (HR = 0.55, $P = .037$), while patients who have a smoking history may have a higher risk of progression than never-smoker patients (HR = 1.47, $P = .028$).

Conclusion: Osimertinib has an impressive antitumor activity compared with prior EGFR-TKI and chemotherapy with an acceptable response and tolerable AEs. EGFR mutation type and smoking status were the risk factors for mortality and progression in NSCLC patients.

Abbreviations: AE = adverse event, CI = confidence intervals, CNS = central nervous system, CR = complete response, DCR = disease control rate, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = nonsmall cell lung cancer, ORR = overall response rate, OS = overall survival, PD = progression disease, PFS = progression-free survival, PR = partial response, RCT = randomized control study, SD = stable disease, TKI = tyrosine kinase inhibitor.

Keywords: EGFR-TKI, nonsmall cell lung cancer, osimertinib, toxicity

1. Introduction

Lung cancer is the most common cancer globally, and its incidence is still increasing.[1] Most recently, the research report shows that 222,500 new lung cancer cases occurred in the United States in 2017, accounting for 13.3% of all new tumors.[2] In China, more than 800,000 lung cancer patients were newly diagnosed each year, and the mortality rate ranks first in malignant tumors.[3] Nonsmall cell lung cancer (NSCLC) accounts for about 80% of the total number of lung cancers, and the epidermal growth factor receptor (EGFR) is one of the most common driver genes of NSCLC.[4] Paez, Lynch, and other studies confirmed that EGFR mutations are related to the efficacy of gefitinib, and further revealed the molecular mechanism of NSCLC's sensitivity to EGFR tyrosine kinase inhibitor (EGFR-TKI).[5] Subsequently, several prospective clinical studies have confirmed that EGFR-sensitive mutations play a pivotal role in screening TKIs predominant populations (such as Asian, female, adenocarcinoma, and nonsmoking).[6,7] Currently, the first-generation EGFR-TKI, gefitinib and erlotinib, and second-generation EGFR-TKI afatinib and dacotinib were widely used in treating EGFR-positive mutations.[8] A large number of randomized phase III clinical trials have concluded that gefitinib,

Editor: Robert Chen.

This study was waived from our local ethical committee due to the data from the publication studies.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Liu J, Li X, Shao Y, Guo X, He J. The efficacy and safety of osimertinib in treating non-small cell lung cancer: A PRISMA-compliant systematic review and meta-analysis. Medicine 2020;99:34(e21826).

Received: 24 March 2020 / Received in final form: 27 June 2020 / Accepted: 18 July 2020

http://dx.doi.org/10.1097/MD.0000000000021826

erlotinib, and afatinib are more effective when applied to untreated advanced NSCLC with mutations in the EGFR gene, with longer survival rate and lower toxicity than standard platinum 2-drug combination chemotherapy.[9,10] As a result, EGFR-TKI is currently recommended as a first-line treatment for patients with advanced EGFR-mutant NSCLC.[11,12] Unfortunately, most patients undergoing initial EGFR-TKI treatment will progress within 10 to 12 months after initial treatment and develop resistance, and several mechanisms of first-generation EGFR-TKI acquired resistance have been reported.[13] In more than half of the cases, a common drug resistance mechanism is a unique missense mutation in exon 20, the so-called T790 M mutation, in which threonine at 790th is replaced by methionine.[14] Compared with reversible EGFR-TKIs such as gefitinib and erlotinib, it has an increased affinity for ATP, and ATP competes for alternative drugs in the binding site, thus making the tumor resistant to the reversible EGFR-TKI inhibition.[15]

Osimertinib is an oral, selective third-generation EGFR-TKI inhibitor, which has an excellent inhibitory effect on the T790 M mutation. It can selectively and irreversibly target mutant EGFR and T790 while retaining wild-type EGFR tyrosine kinase, and targeting EGFR gene catalysis through the formation of covalent bonds. The C797 of the ATP-binding site of the domain forms a covalent bond, thereby irreversibly binding to a specific EGFR mutant form, inhibiting downstream signal pathway activity, and exerting a role in inhibiting tumor cell proliferation and promoting apoptosis.[16] The third-generation EGFR-TKI osimertinib has achieved significant results in patients with NSCLC who have progressed to T790 M mutation after treatment with EGFR-TKIs.[17,18] The AURA3 study showed that it reached 71% overall response rate (ORR) and 10.1 month progression-free survival (PFS) in treating T790 M mutant NSCLC patients.[19] Moreover, in terms of adverse reactions, osimertinib has a lower rate of grade 3 adverse events (AEs) than the first-generation TKIs, especially for the patients with central nervous system (CNS) metastasis.[20] Due to the excellent efficacy of the AURA series, osimertinib is currently the standard treatment protocol for obtaining T790 M mutation after the first-line application of EGFR-TKIs in patients with advanced NSCLC with EGFR mutations.[21] Based on the results of the FLAURA study in October 2017, osimertinib is recommended as a first-line treatment for patients with advanced NSCLC with EGFR mutations, and it is listed as a priority recommendation by the National Comprehensive Cancer Network guidelines in 2019.[20] Although some meta-analysis showed the efficacy of osimertinib was superior to other treatments in treating NSCLC, the safety and the outcome evaluation of osimertinib itself had not fully reported yet. Moreover, due to the strict criteria that the randomized control studies (RCT) involved, the results seemed contrarious with mixed results with the real-world trial data. Thus, we designed this systematic review and meta-analysis, aiming to evaluate the response rate, AEs, and survival outcome in NSCLC patients treating with osimertinib. In this study, we included observational, real-world, cohort, and RCT to summarize the risk factors associated with outcome after osimertinib treatment.

2. Methods

This study was designed following the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[22]

2.1. Search strategy

A systematic review and meta-analysis was designed to compare the effectiveness of osimertinib with other EGFR-TKI or chemotherapy and to evaluate the efficacy and safety of osimertinib in treating NSCLC. The Ovid Medline, Embase, Cochrane Library, and Pubmed were systematically searched due to December 10, 2019. Besides, the gray literature was undertaken using important related conferences (European Society of Medical Oncology, European Cancer Conference, American Society of Clinical Oncology, and World Conference on Lung Cancer) and Google Scholar. The key words were designed by an experienced librarian. In brief, the keywords included "osimertinib" OR "AZD9291" OR "third-generation EGFR-TKI," and "nonsmall cell lung cancer." All the studies containing abstracts and titles were imported into Endnote X7 to find duplicate studies and then for literature screening.

2.2. Inclusion and exclusion criteria

All the studies mentioned the overall survival (OS), PFS, treatment response, and AEs of osimertinib were involved in our study. The inclusion criteria were: The studies enrolled patients with histologically diagnosed as NSCLC with EGFR activating mutation; The studies reported the survival outcome, treatment response rate, or toxicity rate at least in osimertinib treatment group and the data of the outcome could be extracted. The meta-analysis, reviews, conference abstracts, and comments were recorded for the further inclusion of the papers. Only English written papers were involved in systematic reviews.

The exclusion criteria were: in vitro or in vivo experiment; case reports, case series, or the case less than 10; non-English written studies. Data from the same project or center will be selected as one for further meta-analysis.

2.3. Literature screening and data extraction

Two researchers (JL and XM L) independently screened the titles and abstracts based on the inclusion and exclusion criteria. The full text was further evaluated if the abstracts could not be determined and the data could not be extracted. The third investigator (JGH) was adapted for discussion if any disagreement existed.

A standard form was designed for data extraction and the data were collected according to the following information: the study characteristics (author, publish year, country, institution, recruitment period, study design, subcategory, etc.), patient characteristics (treatment, total sample, median age, gender, smoking status, Eastern Cooperative Oncology Group Performance status etc.), and outcome assessment (treatment response, toxicity, and survival status). The treatment response, including ORR, disease control rate (DCR), complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD), was assessed in accordance with the Response Evaluation Criteria in Solid Tumors.[23] PFS was defined as the time from randomization to first progression or death. OS was defined as the time from treatment until death from any cause.

2.4. Quality assessment

Two researchers (JL and YHS) independently assess the quality of the including papers. Generally speaking, a modified Jadad scale was used to evaluate the quality of the randomized control studies. The scores of low-quality studies ranged from 0 to 3,

whereas those of high-quality studies ranged from 4 to 8. For nonrandomized studies, the quality was assessed based on the Newcastle-Ottawa Quality Assessment Scale, with a high quality of 6 to 9, whereas low quality was scored as 0 to 5.[24]

2.5. Statistical analysis

The statistical analysis was performed by Stata 15.0 software (Stata Corporation, College Station, TX). P value $< .05$ was set as significant difference. When comparing the outcome between 2 different treatments or risk factors, the hazard ratio (HR) with 95% confidence intervals (CIs) was extracted. For 1 study, the single proportion, such as AEs rate and response rate, was derived using the Wilson score method.[25] The I^2 statistic and χ^2 test were used for heterogeneity assessment ($I^2 \geq 50\%$ indicating the presence of heterogeneity). When the heterogeneity not existed, the fix-effects model was used while the random-effect model was used in the opposite way. Finally, the forest plots were drawn, and funnel plots were used for evaluating the publication bias.

3. Results

3.1. Literature selection

A total of 4051 studies were found according to the search strategy. The literature screening process was shown in the flowchart (Fig. 1). After screening the abstracts and titles, 236 studies were scanned in full-text. After excluding the incompatible studies, a total of 47 studies were included in the systematic review, in which 14 studies were used to compare the efficacy between osimertinib and other EGFR-TKI or chemotherapy,[19,20,26–37] and 40 studies were used to evaluate the treatment response and AEs.[16,20,21,26,28,30,31,34,35,38–68]

3.2. The comparison of efficacy between osimertinib and other treatments

The characteristics of the studies comparing osimertinib and other treatments were summarized in Table 1. A total of 4229 patients were included. However, 7 studies were from the FLAURA program and 4 studies were from the AURA3 program. The median age was 62 years old, while 62% were female, and 67% were never-smoking patients. FLAURA trial was mainly compared with osimertinib with other EGFR-TKI, AURA3, AURA, and IMPRESS were mainly compared with chemotherapy, and CAURAL study was mainly compared with combining the use of Durvalumab. The quality of the RCTs was evaluated as low risk

The meta-analysis comparing OS and PFS was shown in Fig. 2. In terms of OS, the patients treating with osimertinib favors a higher survival rate compared with other treatments (HR 0.56,

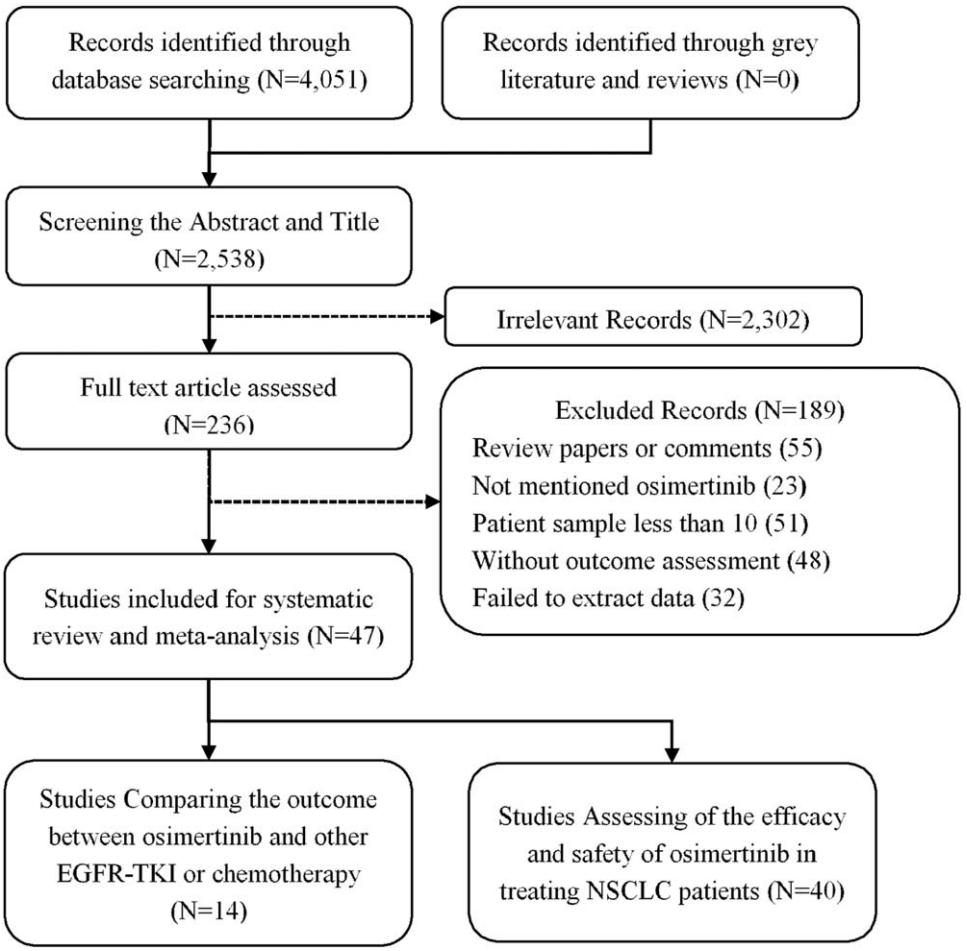

Figure 1. Flowchart of literature screening of the meta-analysis.

Table 1

Characteristics of studies comparing osimertinib with EGFR-TKI/chemotherapy in treating NSCLC.

Name	Publication year	Study design	Subcategory	Quality assessment	Treatment regimen	Patients	Median age	Female,%	Never smoking,%	ORR,%	DCR,%
Akamatsu et al	2018	RCT	AURA3	Low risk	Osimertinib	41	69.0	63.0	68.0	70.7	95.1
					Chemotherapy	22	67.0	64.0	59.0	36.4	86.4
Chih-Hsin Yang et al	2019	RCT	CAURAL	Median risk	osimertinib	17	65.0	76.5	76.5	—	—
					Durvalumab + osimertinib	12	56.0	50.0	66.7	—	—
Cho et al	2019	RCT	FLAURA	Low risk	Osimertinib	160	63.5	63.1	65.0	—	—
					Gefitinib/erlotinib	160	64.0	56.9	59.4	—	—
Gray et al	2019	RCT	FLAURA	Low risk	Osimertinib	145	—	—	—	—	—
					Gefitinib/erlotinib	144	—	—	—	—	—
Mann et al	2018	RCT	AURA IMPRESS	Median risk	Osimertinib	405	62.0	47.4	71.6	—	—
					Chemotherapy	61	55.0	54.1	65.6	—	—
Mok et al	2017	RCT	AURA3	Low risk	Osimertinib	279	62.0	61.6	67.7	71.0	93.0
					Chemotherapy	140	63.0	69.3	67.1	31.0	74.0
Nie et al	2018	RCT	NG	Median risk	Osimertinib	74	49.0	71.6	82.4	61.6	87.7
					Docetaxel-bevacizumab	73	49.0	69.9	80.8	8.3	43.1
Odogwu et al	2018	RCT	AURA3	Low risk	Osimertinib	279	62.0	62.0	68.0	—	—
					Chemotherapy	140	63.0	69.0	67.0	—	—
Ohe et al	2019	RCT	FLAURA	Low risk	Osimertinib	65	67.0	66.2	53.8	75.4	96.9
					Gefitinib/erlotinib	55	67.0	50.9	52.7	76.4	96.4
Planchard et al	2019	RCT	FLAURA	Low risk	Osimertinib	279	—	—	—	—	—
					Gefitinib/erlotinib	277	—	—	—	—	—
Ramalingam et al	2019	RCT	FLAURA	Low risk	Osimertinib	279	—	—	—	—	—
					Gefitinib/erlotinib	277	—	—	—	—	—
Reungwetwattana et al	2018	RCT	FLAURA	Low risk	Osimertinib	61	63.0	62.0	—	91.0	90.0
					Gefitinib/erlotinib	67	63.0	61.0	—	68.0	84.0
Sebastian et al	2018	RCT	AURA3	Low risk	Osimertinib	102	63.7	63.7	—	—	—
					Chemotherapy	59	64.5	61.0	—	—	—
Soria et al	2018	RCT	FLAURA	Low risk	Osimertinib	279	64.0	63.8	65.2	80.0	97.0
					Gefitinib/erlotinib	277	64.0	62.1	63.2	76.0	92.0

DCR = disease control rate, NG = not given, ORR = overall response rate;

95% CI 0.44–0.71, $P < .001$). Similarly, osimertinib increased the PFS in comparison with other treatments (HR 0.38, 95% CI 0.33–0.44, $P < .001$). Moreover, osimertinib was superior in PFS than other treatments in the subgroup analysis, such as gender, age, smoking status, and EGFR driving mutation (all $P < .05$, Supplement Figure, http://links.lww.com/MD/E723).

3.3. The characteristics and treatment response of patients treating with osimertinib

A total of 6900 patients in 40 studies were involved in assessing the safety and efficacy of osimertinib (Table 2). The recruitment year was between 2013 and 2018, and the median age was 64.1 years old. 64.9% of patients were female, 71.4% of patients had no smoking history, and 60.9% of patients (range from 35.1% to 84.1%) were positive Del 19 mutation. In terms of the prior EGFR-TKI treatment, 63.1% of patients were treated with gefitinib, and 32.6% were treated with erlotinib previously. The median ORR was 54.7%, and the median DCR was 86.0%. The treatment response was shown in Figure 3. The median CR was 3% (95% CI = 1%–4%), while 55% of patients might experience PR when treating with osimertinib (95% CI = 46%–64%). Twenty-five percent of patients had SD experience (95% CI = 18%–32%), but 11% of patients may have a progression response eventually (95% CI = 9%–14%).

3.4. Toxicities

The common AEs, including all grades and grades≥III, associated with osimertinib were listed in Table 3. The highest incidence of all-grade AEs was rash, occupying 42% patients (95% CI 34%–50%). The second common was diarrhea, occupying 35% of patients (95% CI 22%–49%). Besides, the incidence of all grade paronychia, dry skin, stomatitis was higher than 20%. The prevalence of headache, nausea, anorexia, headache, vomiting, anemia, pruritus, constipation, fatigue, and cough was between 10% and 20%. However, most of the results presented a higher heterogeneity (median $I^2 = 64.9\%$, range from 0% to 99.0%). The increasing number of involved studies was related to a higher I^2 ($r^2 = 0.566$, $P = .001$).

In terms of the grade ≥III AE, the result indicated that the highest common AE was pneumonia, which was 3% (95% CI 0%–5%, $I^2 = 58.6\%$). The second common was anorexia, which was 2% (95% CI 1%–3%, $I^2 = 60.0\%$). The incidence of other AE was 0% to 1%, with an acceptable heterogeneity.

3.5. Risk factors associated with survival outcome in treating with osimertinib

The risk factors associated with the survival outcome were presented in Figure 4 OS and Figure 5 PFS. Age and ECOG performance status were not the significant risk factor associated with survival outcomes in patients treating with osimertinib.

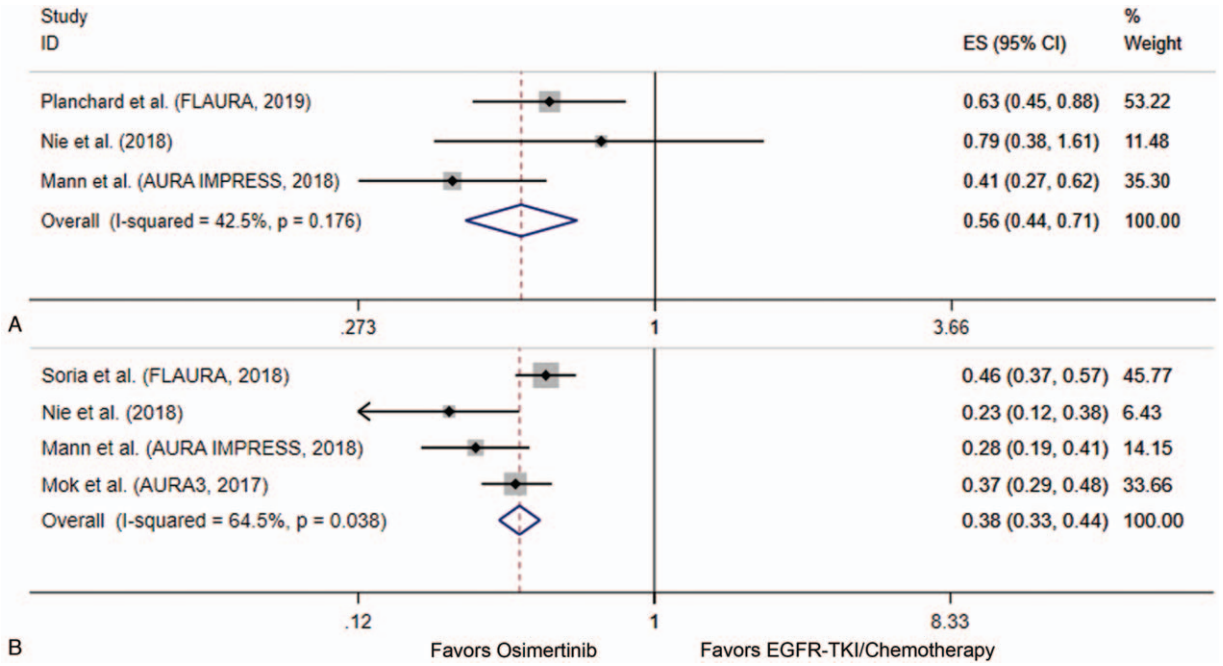

Figure 2. The forest plot comparing of overall survival (A) and progression-free survival (B) between osimertinib and other treatments.

Table 2

Characteristics of involved studies evaluating the efficacy and safety of osimertinib.

Author	Year	Recruitment year	Subcategory	Total sample	Median age	Female, %	19DEL mutation, %	Never smoking, %	Prior treatment, gefitinib / erlotinib / afatinib	ORR, %	DCR, %
Zhao et al	2019	2014–2016	NG	31	—	51.6	—	74.2	25/6/-	29.0	87.1
Yoshimura et al	2019	2014–2018	NG	27	78.0	66.7	74.1	74.1	—		
Yang et al*	2019	2015–2017	BLOOM	41	59.0	70.7	—	73.2	31/7/-	41.0	
Xing et al	2019	2017	NG	22	59.4	59.1	50.0	90.9	13/7/-	40.9	86.4
Xie et al	2019	2015–2016	NG	40	63.0	82.5	47.5	82.5	25/7/14		
Su et al	2019	2016–2018	NG	46	—	—	—	—	—		
Ramalingam et al	2019	2014–2017	FLAURA	279	—	—	—	—	—		
Park et al	2019	2016–2017	LiquidLung-O-Cohort 2	19	—	—	—	—	—	66.7	100.0
Ono et al	2019	2017–2018	NG	47	73.0	—	—	—	—	57.4	
Ohe et al	2019	2014–2017	FLAURA	65	—	66.2	50.8	53.8	—	76.8	96.9
Nakashima et al	2019	2016–2017	NG	30	66.0	73.3	53.3	66.7	17/17/6	53.0	80.0
Nakao et al	2019	NG	NG	36	79.9	—	—	—	—		
Mu et al	2019	2017–2018	NG	94	59.0	59.6	35.1	79.8	48/25/5	47.3	90.1
Mu et al	2019	2017–2018	NG	65	59.0	58.5	41.5	75.4	—		
Marinis et al	2019	2015–2018	ASTRIS	3,015	62.0	63.9	—	—	1721/905/294		
Kuo et al	2019	2016	NG	57	63.0	59.6	63.2	66.7	—		
Kawamura et al	2019	2016–2018	NG	90	—	75.6	62.2	61.1	—	43.0	72.0
Kato et al	2019	2016–2018	NG	31	72.0	77.4	61.3	67.7	24/5/2	53.3	
Jaiswal et al	2019	2016–2018	NG	90	59.0	48.9	71.1	92.2	65/12/13		
Igawa et al	2019	2017–2018	NG	51	71.0	—	—	—	—	58.8	
Ichihara et al	2019	2016–2018	NG	15	68.0	73.3	60.0	—	—	33.0	
Hirashima et al.	2019	2014	AURA	81	66.0	66.7	69.1	70.4	65/41/1		
Cho et al	2019	2016–2017	KCSG-LU15-09	36	60.0	38.9	—	44.4	—		
Cho et al	2019	2015–2017	ASTRIS	466		66.3	60.7		323/145/48	71.0	
Cho et al	2019	2014–2017	FLAURA	162	63.5	62.3	—	64.2	—		
Chih-Hsin Yang et al	2019	NG	CAURAL	17	65.0	76.5	—	76.5	—		
Cao et al	2019	2016–2018	NG	74	58.0	66.2	—	89.2	—		

(*continued*)

Table 2

(continued).

Author	Year	Recruitment year	Subcategory	Total sample	Median age	Female, %	19DEL mutation, %	Never smoking, %	Prior treatment, gefitinib / erlotinib / afatinib	ORR, %	DCR, %
Ahn et al	2019	2014–2016	AURA AURA2	411	62.0	67.6	67.9	71.5	239/235/74		
Stratmann et al	2018	NG	NG	51	66.0	66.7	80.4	56.9	—		
Soria et al	2018	2014–2017	FLAURA	279	64.0	63.8	56.6	65.2	—		
Odogwu et al	2018	2014–2015	AURA3	279	62.0	62.0	—	68.1	—	65.0	
Nie et al	2018	2015–2016	NG	74	49.0	71.6	55.4	82.4	46/28/-	61.6	87.7
Lee et al	2018	2014–2017	AURA AURA3 AURA17	74	58.0	59.5	55.4	68.9	36/26/1	68.0	
Furuta et al	2018	2014–2017	NG	77	66.0	68.8	57.1	77.9	52/19/6	56.0	
Buder et al	2018	2015–2016	NG	91	67.0	50.5	56.0	—	38/7/29	64.0	74.0
Yang et al	2017	2014–2015	AURA	201	61.4	66.2	70.6	66.7	117/116/4		
Remon et al	2017	2015–2016	NG	18	—	77.8	77.8	—	—		
Fujiwara et al	2017	2015–2016	NG	18	—	55.6	72.2	66.7	—		
Goss et al	2016	2014	AURA2	210	64.0	69.0	65.2	76.2	122/119/38		
Janne et al	2015	2013–2014	NG	90	—	—	—	—	—		

DCR = disease control rate, NG = not given, ORR = overall response rate.

* Means the patients were treating with Osimertinib 160 mg/d, otherwise treating with 80 mg/d.

Patients with the T858R mutation may have a better OS than Del 19 mutation (HR = 0.55, 95% CI = 0.31–0.96, $P = .037$, $I^2 = 10.4\%$), but no significant statistical difference in PFS (HR = 0.64, 95% CI = 0.37–1.09, $P = .103$, $I^2 = 67.8\%$). Patients who have a smoking history may have a higher risk of progression than never-smoker patients (HR = 1.47, 95% CI = 1.04–2.08, $P = .028$, $I^2 = 3.5\%$), with no significant difference in mortality (HR = 1.29, 95% CI = 0.78–2.14, $P = .313$, $I^2 = 0\%$).

Table 3

Meta-analysis of the common adverse events.

Toxicity	Studies	Events	Total patients	Rate, % (95% CI)	Heterogeneity (I^2) (%)
All grade					
Rash	21	1094	2421	42 (34–50)	94.3
Diarrhea	21	1104	5389	35 (22–49)	99.0
Nausea	15	307	4699	18 (12–24)	96.0
Dry skin	17	696	2277	28 (22–33)	88.8
Paronychia	14	515	1628	30 (24–35)	82.4
Anorexia	13	307	1442	18 (14–22)	66.2
Headache	6	97	747	13 (10–15)	0
Vomiting	11	169	4253	10 (5–14)	93.0
Anemia	10	144	1164	12 (8–15)	64.6
Pruritus	9	233	1516	15 (13–17)	0
Constipation	12	201	1345	14 (10–17)	61.7
Fatigue	9	233	1206	16 (13–19)	44.3
Stomatitis	15	432	2124	21 (16–26)	86.5
Cough	7	133	890	14 (11–17)	19.7
Pneumonia	8	79	3400	3 (1–5)	78.4
Grade ≥III					
Rash	20	21	2403	1 (0–1)	0
Diarrhea	20	40	2822	1 (0–1)	14.1
Nausea	14	12	1684	1 (0–2)	34.9
Dry skin	15	3	2169	0 (0–1)	0
Paronychia	13	2	1799	0 (0–1)	0
Anorexia	13	32	1442	2 (1–3)	60.0
Headache	6	6	747	1 (0–2)	0
Vomiting	10	3	1238	0 (0–1)	0
Anemia	11	20	1194	1 (0–2)	28.3
Fatigue	9	19	1206	1 (0–2)	49.4
Stomatitis	14	5	2106	0 (0–1)	0
Pneumonia	8	22	851	3 (0–5)	58.6

4. Discussion

This is the largest-scale systematic review to evaluate the efficacy and safety of osimertinib in treating EGFR-mutated NSCLC patients. Our meta-analysis suggested that osimertinib presented a better long-term survival outcome compared with other EGFR-TKI treatments and chemotherapy, with an acceptable AE. The EGFR mutation and smoking status were the risk factors associated with outcome in patients treating with osimertinib. More RCTs and real-world data analysis need to be performed to demonstrate its efficacy in different regions and populations.

Osimertinib, also named as AZD9291, has a distinctive and unique chemical structure. Compared with wild-type EGFR, osimertinib has a nearly 200-fold potency in resistance to L858R/T790 M, which confirm its selectivity to the mutant EGFR NSCLC.[69] In establishing in vitro models to evaluate the specificity of different EGFR TKI mutations, osimertinib has shown a full therapeutic window of resistance to EGFR T790 M mutations.[70] It has also demonstrated minimal off-target kinase activity when studying a variety of other kinases, thus demonstrating the overall selectivity of osimertinib. Interestingly, osimertinib did not show activity on insulin-like growth factor receptor 1, and insulin receptors in vitro and this observation was confirmed in vivo studies, indicating that osimertinib was associated with low risk of hyperglycemia-related dose-limiting toxicity.[69] Unlike the first-generation TKI, osimertinib is more effective to inhibit phosphorylation in T790 M mutant cell lines (H1975 and PC −9), can also more effectively inhibit downstream signal transduction substrates (pAKT, pERK). Based on the encouraging results of preclinical studies, osimertinib has mostly demonstrated its continued antitumor activity as a selective inhibitor of EGFR mutations.[69,70]

In terms of clinical trials, the phase I/II AURA trials were designed to determine the safety and effectiveness of osimertinib in the progression of disease after receiving EGFR TKI in patients

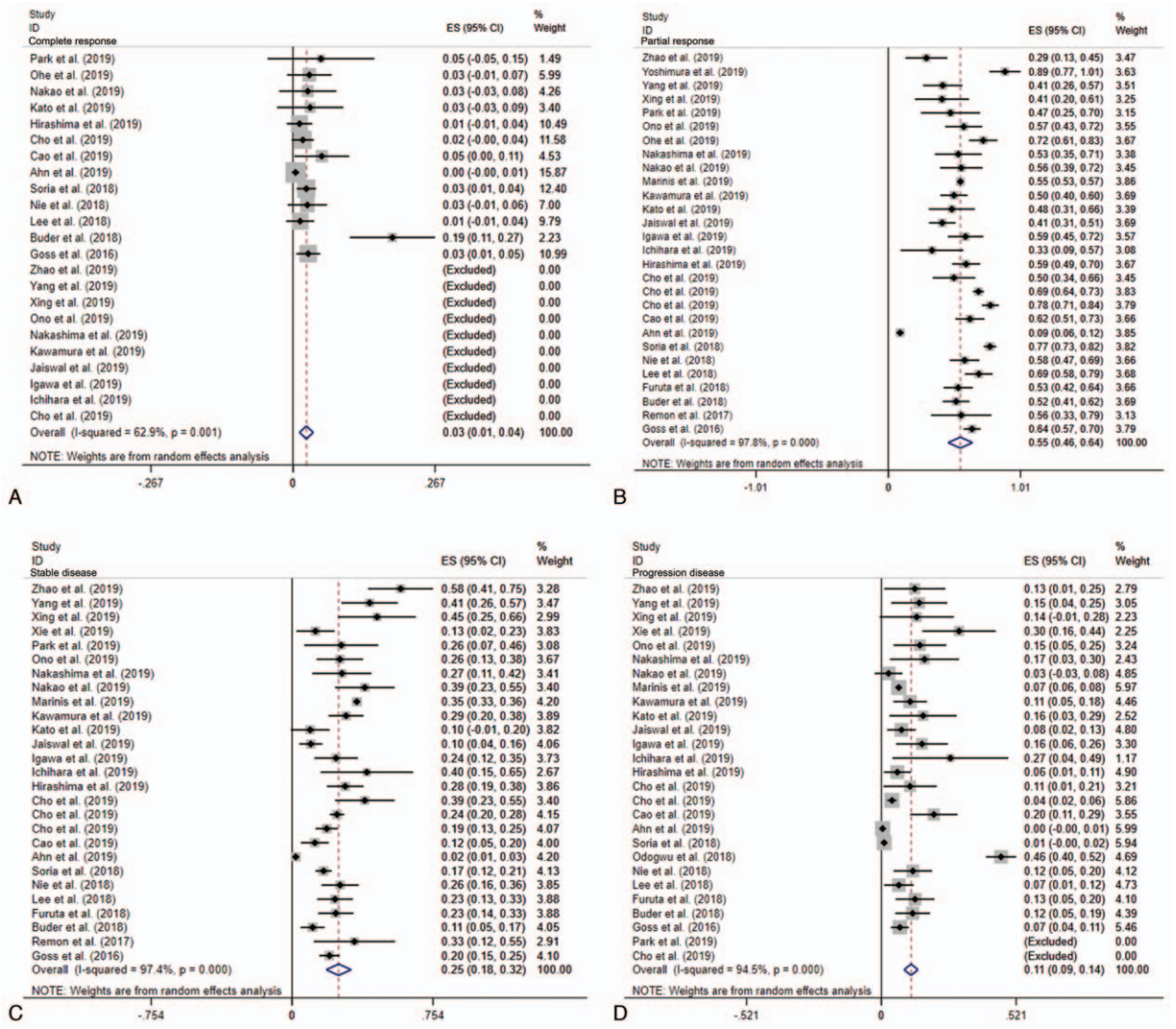

Figure 3. The forest plot of single proportion in evaluating complete response (A), partial response (B), stable disease (C), and progression disease (D) after osimertinib treatment.

with advanced NSCLC.[16] In this study, a total of 253 patients with known EGFR sensitization mutations or those who have benefited from the clinical treatment of EGFR-TKI and have significant disease progression during treatment were included: a total of 31 patients in a dose-escalation cohort.[5] There were 222 patients in the extended queue. In the expanded cohort, tumor biopsies were performed on all patients to determine the mutation status of EGFR T790 M, of which 138 (62%) were mutation-positive. Of the 239 evaluable patients, 123 (51%) had a clear objective response, including 122 patients with PR and 1 CR with a DCR of 84%, and the median PFS duration was 8.2 months. The results and safety of the AURA I/II were encouraging, and the subsequent phase II AURA also presented an inspiring result in multicenter, single-course analysis. A total of 210 patients with EGFR T790 M mutation-positive locally advanced or metastatic NSCLC were enrolled and received 80 mg orally daily osimertinib treatment.[68] As of the data deadline (January 1, 2015), the median follow-up time was 13 months, and 58% of patients were still receiving treatment. Of the 199 evaluable patients, the ORR was 70%, of which CR was 3% and, DCR was 92%. The high proportion of objective responses was consistent across all subgroups, including patients with CNS metastases. Subsequent phase II AURA extended studies also confirmed that after EGFR TKI treatment, patients with EGFR-sensitive and T790M-positive NSCLC benefited from osimertinib treatment.[21] Afterward, a randomized phase III clinical trial (AURA3) was designed to demonstrate that osimertinib is superior to platinum in patients with EGFR mutations and T790M-positive NSCLC who have disease progression after first-line EGFR-TKI and chemotherapy with Pemetrexed. Patients with EGFR mutations and T790M-positive NSCLC after disease progression after TKI treatment are superior to standard chemotherapy with platinum and Pemetrexed.[19] Compared with the control group, the median PFS and ORR in the osimertinib group were significantly improved. FLAURA is a phase III, double-blind, international multicenter study that assessed the safety and efficacy of first-line treatment of osimertinib and early EGFR TKI in locally advanced or metastatic EGFR-positive NSCLC. The risk of disease progression or death was significantly reduced by 54% in the osimertinib group (HR = 0.46), and this advantage was observed in all subgroups, includes patients with CNS metastases at baseline.[20] These were the most extensive and analytical studies

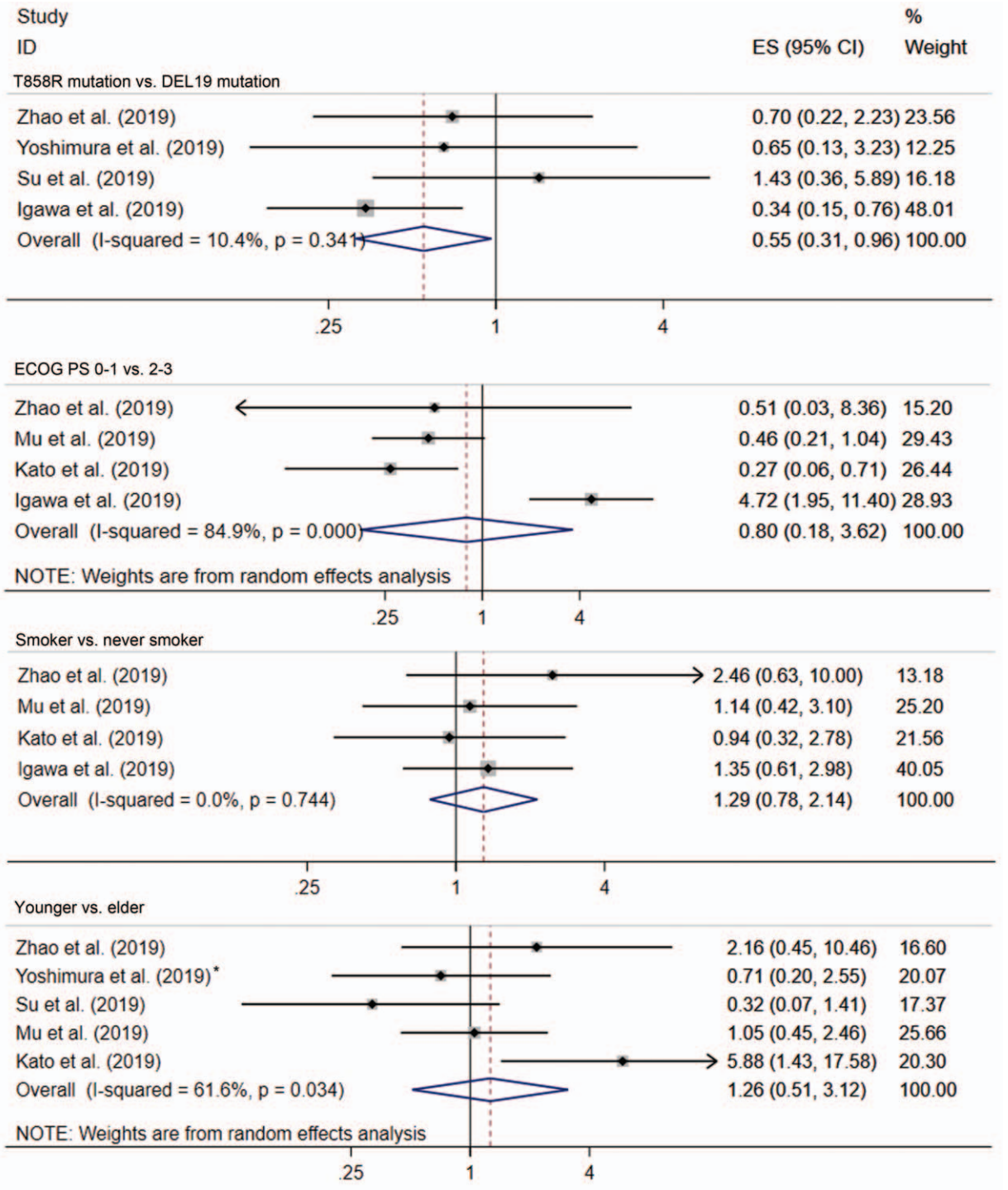

Figure 4. The forest plot indicating the risk factors, including EGFR mutation, ECOG PS, smoking status and age, for overall survival after osimertinib treatment. EGFR = epidermal growth factor receptor, ECOG PS = Eastern Cooperative Oncology Group Performance status.

comparing osimertinib and other treatments up to now. After combining the results of the clinical studies, our meta-analysis still demonstrated that osimertinib has superior efficacy than other treatments in treating with EGFR mutation NSCLC patients.

Rash and diarrhea were the most common AEs in patients treating with osimertinib, among which only 1% patients will have severe toxicity. Interstitial pneumonia is one of the severe AEs that causes discontinuation of treatment with osimertinib. Our meta-analysis summarized 22 patients had severe pneumonia occupying 3% of the patients. Some clinical trials also stated that the incidence of these AEs is 3.3%, of which 0.5% is life-threatening.[59] The results of the geographical distribution study showed that the impact of pneumonia in the Japanese population was relatively high, reaching 9%, while the impact in the non-Japanese Asian population was comparable to that of Whites, approximately 4%.[21] Also, some studies have pointed out the

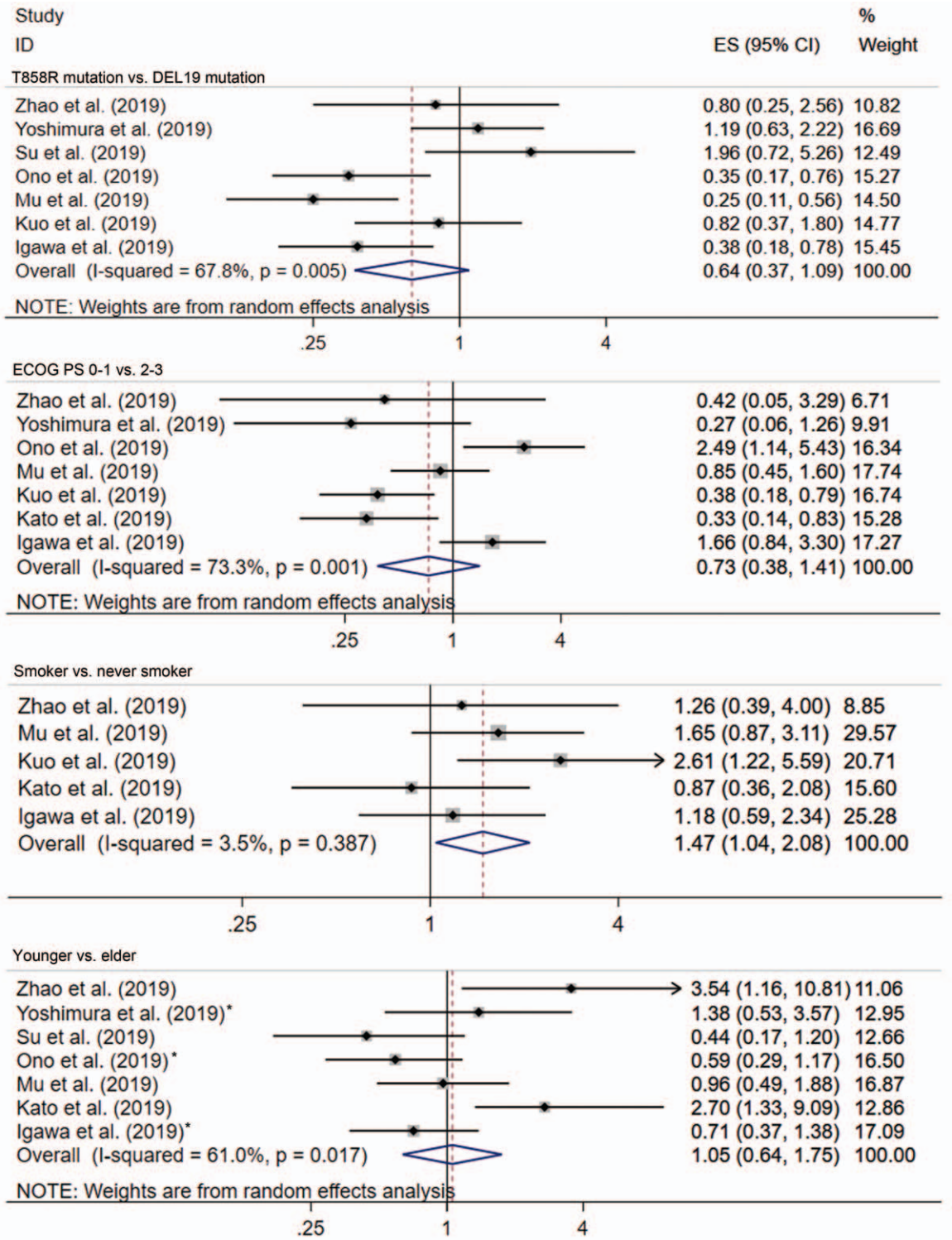

Figure 5. The forest plot indicating the risk factors, including EGFR mutation, ECOG PS, smoking status and age, for progression-free survival after osimertinib treatment. EGFR = epidermal growth factor receptor, ECOG PS = Eastern Cooperative Oncology Group Performance status.

use of programmed death receptor-1 (PD-1) inhibitors or both at the same time as the risk factors for interstitial pneumonia.[71] Ahn et al[72] reported that the incidence of interstitial pneumonia was as high as 38% in patients who used both osimertinib and duvazumab, which may be related to the enhanced immunological activity of lymphocyte T cells CD8 + by PD-1 inhibitors. The median time to interstitial pneumonia after using osimertinib was 34.5 days (4–114 days). After the occurrence of interstitial pneumonia, it is generally necessary to discontinue osimertinib and receive supportive care, including glucocorticoids.[21] In our meta-analysis, the heterogeneity remained higher, which was related to the increasing number of involved studies.

There were some limitations to our study. First, almost all the RCTs were from the AURA3 or FLAURA studies, and most of the studies were not controlled studies, which may decrease the quality of the meta-analysis. Therefore, more RCTs comparing osimertinib and other therapy are needed to validate the current result. Second, the subgroup analysis of T790 positive and negative, first-line use, and second use of osimertinib was not performed due to the insufficient data. Third, although we included a large scale of NSCLC patients treated with osimertinib, this study was not a meta-analysis based on the "individual patients," thus much of essential data were lost when reviewing from each manuscript. While due to the lower incidence of the AEs, the rate remains heterogeneity, which could not be avoided in our current meta-analysis. Further efforts need to be made in individual patient meta-analyses and regressions to discuss the efficacy and safety in patients treating with osimertinib.

5. Conclusion

Our systematic review and meta-analysis indicated that osimertinib has an impressive antitumor activity compared with prior EGFR-TKI and chemotherapy. The sequential use of osimertinib could achieve an acceptable response with tolerable AEs. EGFR mutation type and smoking status were the risk factors for mortality and progression in NSCLC patients. Further clinical trials, real-world data are needed to update this meta-analysis and investigate the role of osimertinib in treating NSCLC patients.

Author contributions

Design of the meta-analysis: Jing Liu and Jinggui He
Literature screening: Jing Liu and Xuemei Li
Quality assessment: Yinghong Shao and Jing Liu
Statistics analysis: Xiyun Guo
Write and revise: Jing Liu, Xuemei Li, Yinghong Shao, Xiyun Guo, and Jinggui He

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:
[3] Chen W, Zheng R, Zhang S, et al. Cancer incidence and mortality in China, 2013. Cancer Lett 2017;401:63–71.
[4] Molina JR, Yang P, Cassivi SD, et al, editors. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clinic Proceedings; 2008: Elsevier.
[5] Haber D, Bell D, Sordella R, et al, editors. Molecular targeted therapy of lung cancer: EGFR mutations and response to EGFR inhibitors. Cold Spring Harbor symposia on quantitative biology; 2005: Cold Spring Harbor Laboratory Press.
[6] Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non–small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866–74.
[7] Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin–paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2012;24:54–9.
[8] Mitsudomi T. Erlotinib, gefitinib, or chemotherapy for EGFR mutation-positive lung cancer? Lancet Oncol 2011;12:710–1.
[9] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.
[10] Han J-Y, Park K, Kim S-W, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012;30:1122–8.
[11] Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3488–515.
[12] Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(suppl_3):iii27–39.
[13] Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Soc 2014;23:356–66.
[14] Helena AY, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240–7.
[15] Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26–175ra.
[16] Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689–99.
[17] Helena AY, Tian SK, Drilon AE, et al. Acquired resistance of EGFR-mutant lung cancer to a T790M-specific EGFR inhibitor: emergence of a third mutation (C797S) in the EGFR tyrosine kinase domain. JAMA Oncol 2015;1:982–4.
[18] Watanabe S, Sone T, Matsui T, et al. Transformation to small-cell lung cancer following treatment with EGFR tyrosine kinase inhibitors in a patient with lung adenocarcinoma. Lung Cancer 2013;82:370–2.
[19] Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629–40.
[20] Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113–25.
[21] Yang JC, Ahn MJ, Kim DW, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. J Clin Oncol 2017;35:1288–96.
[22] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[23] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[24] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[25] Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857–72.
[26] Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2019;382:41–50.
[27] Planchard D, Boyer MJ, Lee JS, et al. Postprogression outcomes for osimertinib versus standard-of-Care EGFR-TKI in patients with previously untreated EGFR-mutated advanced non-small cell lung cancer. Clin Cancer Res 2019;25:2058–63.
[28] Ohe Y, Imamura F, Nogami N, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. Jpn J Clin Oncol 2019;49:29–36.
[29] Gray JE, Okamoto I, Sriuranpong V, et al. Tissue and plasma EGFR mutation analysis in the FLAURA trial: osimertinib versus comparator EGFR tyrosine kinase inhibitor as first-line treatment in patients with EGFR-mutated advanced non-small cell lung cancer. Clin Cancer Res 2019;25:6644–52.
[30] Cho BC, Chewaskulyong B, Lee KH, et al. Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian Subset. J Thorac Oncol 2019;14:99–106.
[31] Chih-Hsin Yang J, Shepherd FA, Kim DW, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. J Thorac Oncol 2019;14:933–9.
[32] Sebastian M, Ryden A, Walding A, et al. Patient-reported symptoms possibly related to treatment with osimertinib or chemotherapy for advanced non-small cell lung cancer. Lung Cancer 2018;122:100–6.

[33] Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol 2018;JCO2018783118.
[34] Odogwu L, Mathieu L, Goldberg KB, et al. FDA benefit-risk assessment of osimertinib for the treatment of metastatic non-small cell lung cancer harboring epidermal growth factor receptor T790 M mutation. Oncologist 2018;23:353–9.
[35] Nie K, Zhang Z, Zhang C, et al. Osimertinib compared docetaxel-bevacizumab as third-line treatment in EGFR T790 M mutated non-small-cell lung cancer. Lung Cancer 2018;121:5–11.
[36] Mann H, Andersohn F, Bodnar C, et al. Adjusted indirect comparison using propensity score matching of osimertinib to platinum-based doublet chemotherapy in patients with EGFRm T790 M NSCLC who have progressed after EGFR-TKI. Clin Drug Investig 2018;38:319–31.
[37] Akamatsu H, Katakami N, Okamoto I, et al. Osimertinib in Japanese patients with EGFR T790 M mutation-positive advanced non-small-cell lung cancer: AURA3 trial. Cancer Sci 2018;109:1930–8.
[38] Zhao S, Li X, Zhao C, et al. Loss of T790 M mutation is associated with early progression to osimertinib in Chinese patients with advanced NSCLC who are harboring EGFR T790 M. Lung Cancer 2019;128:33–9.
[39] Yoshimura A, Yamada T, Okura N, et al. Clinical characteristics of osimertinib responder in non-small cell lung cancer patients with EGFR-T790 M mutation. Cancers 2019;11:
[40] Yang JCH, Kim SW, Kim DW, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study. J Clin Oncol 2019;38:538–47.
[41] Xing P, Mu Y, Hao X, et al. Data from real world to evaluate the efficacy of osimertinib in non-small cell lung cancer patients with central nervous system metastasis. Clin Transl Oncol 2019;21:1424–31.
[42] Xie L, Nagpal S, Wakelee HA, et al. Osimertinib for EGFR-mutant lung cancer with brain metastases: results from a single-center retrospective study. Oncologist 2019;24:836–43.
[43] Su PL, Yang SC, Chen YL, et al. Real-world outcomes of NSCLC patients receiving tissue or circulating tumor DNA-guided osimertinib treatment. Cancer Med 2019;8:5939–47.
[44] Park CK, Cho HJ, Choi YD, et al. A phase II trial of osimertinib in the second-line treatment of non-small cell lung cancer with the EGFR T790 M mutation, detected from circulating tumor DNA: LiquidLung-O-Cohort 2. Cancer Res Treat 2019;51:777–87.
[45] Ono T, Igawa S, Ozawa T, et al. Evaluation of osimertinib efficacy according to body surface area and body mass index in patients with non-small cell lung cancer harboring an EGFR mutation: a prospective observational study. Thorac Cancer 2019;10:880–9.
[46] Nakashima K, Kimura M, Akamatsu H, et al. Osimertinib for patients with EGFR T790 M mutation-positive non-small-cell lung cancer and a poor performance status. Jpn J Clin Oncol 2019;49:671–5.
[47] Nakao A, Hiranuma O, Uchino J, et al. Osimertinib in elderly patients with epidermal growth factor receptor T790M-positive non-small-cell lung cancer who progressed during prior treatment: a phase II trial. Oncologist 2019;24:593–e170.
[48] Mu Y, Xing P, Hao X, et al. Real-world data of osimertinib in patients with pretreated non-small cell lung cancer: a retrospective study. Cancer Manag Res 2019;11:9243–51.
[49] Mu Y, Hao X, Yang K, et al. Clinical modality of resistance and subsequent management of patients with advanced non-small cell lung cancer failing treatment with osimertinib. Target Oncol 2019;14:335–42.
[50] Marinis F, Wu YL, de Castro GJr, et al. ASTRIS: a global real-world study of osimertinib in >3000 patients with EGFR T790 M positive non-small-cell lung cancer. Future Oncol 2019;15:3003–14.
[51] Kuo CS, Huang CH, Liu CY, et al. Prior EGFR-TKI Treatment in EGFR-Mutated NSCLC affects the allele frequency fraction of acquired T790 M and the subsequent efficacy of osimertinib. Target Oncol 2019;14:433–40.
[52] Kawamura T, Kenmotsu H, Kobayashi H, et al. Negative impact of malignant effusion on osimertinib treatment for non-small cell lung cancer harboring EGFR mutation. Invest New Drugs 2019;38:194–201.
[53] Kato Y, Hosomi Y, Watanabe K, et al. Impact of clinical features on the efficacy of osimertinib therapy in patients with T790M-positive non-small cell lung cancer and acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors. J Thorac Dis 2019;11:2350–60.
[54] Jaiswal R, Pinninti R, Krishna MM, et al. T790 M mutation and clinical outcomes with osimertinib in patients with epidermal growth factor receptor-mutant nonsmall cell lung cancer. Indian J Med Paediatr Oncol 2019;40:73–8.
[55] Igawa S, Ono T, Kasajima M, et al. Impact of EGFR genotype on the efficacy of osimertinib in EGFR tyrosine kinase inhibitor-resistant patients with non-small cell lung cancer: a prospective observational study. Cancer Manag Res 2019;11:4883–92.
[56] Ichihara E, Hotta K, Ninomiya K, et al. Re-administration of osimertinib in osimertinib-acquired resistant non-small-cell lung cancer. Lung Cancer 2019;132:54–8.
[57] Hirashima T, Satouchi M, Hida T, et al. Osimertinib for Japanese patients with T790M-positive advanced non-small-cell lung cancer: a pooled subgroup analysis. Cancer Sci 2019;110:2884–93.
[58] Cho JH, Lim SH, An HJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09). J Clin Oncol 2019;38:488–95.
[59] Cho BC, Kim DW, Park K, et al. Real-world use of osimertinib in non-small cell lung cancer: ASTRIS study Korean subgroup analysis. Curr Med Res Opin 2019;36:477–82.
[60] Cao Y, Qiu X, Xiao G, et al. Effectiveness and safety of osimertinib in patients with metastatic EGFR T790M-positive NSCLC: an observational real-world study. PLoS One 2019;14:e0221575.
[61] Ahn MJ, Tsai CM, Shepherd FA, et al. Osimertinib in patients with T790 M mutation-positive, advanced non-small cell lung cancer: long-term follow-up from a pooled analysis of 2 phase 2 studies. Cancer 2019;125:892–901.
[62] Stratmann JA, Michels S, Hornetz S, et al. Efficacy and safety analysis of the German expanded access program of osimertinib in patients with advanced, T790M-positive non-small cell lung cancer. J Cancer Res Clin Oncol 2018;144:2457–63.
[63] Lee H, Lee HY, Sun JM, et al. Transient asymptomatic pulmonary opacities during osimertinib treatment and its clinical implication. J Thorac Oncol 2018;13:1106–12.
[64] Furuta H, Uemura T, Yoshida T, et al. Efficacy and safety data of osimertinib in elderly patients with NSCLC who Harbor the EGFR T790 M mutation after failure of initial EGFR-TKI treatment. Anticancer Res 2018;38:5231–7.
[65] Buder A, Hochmair MJ, Schwab S, et al. Cell-free plasma DNA-guided treatment with osimertinib in patients with advanced EGFR-mutated NSCLC. J Thorac Oncol 2018;13:821–30.
[66] Remon J, Caramella C, Jovelet C, et al. Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. Ann Oncol 2017;28:784–90.
[67] Fujiwara Y, Goto Y, Kanda S, et al. Efficacy and safety of osimertinib in a Japanese compassionate use program. Jpn J Clin Oncol 2017;47:625–9.
[68] Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2016;17:1643–52.
[69] Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046–61.
[70] Hirano T, Yasuda H, Tani T, et al. In vitro modeling to determine mutation specificity of EGFR tyrosine kinase inhibitors against clinically relevant EGFR mutants in non-small-cell lung cancer. Oncotarget 2015;6:38789–803.
[71] Mamesaya N, Kenmotsu H, Katsumata M, et al. Osimertinib-induced interstitial lung disease after treatment with anti-PD1 antibody. Invest New Drugs 2017;35:105–7.
[72] Ahn M-J, Yang J, Yu H, et al. Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TATTON phase Ib trial. J Thorac Oncol 2016;11:S115.