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Efficacy and safety of osimertinib plus bevacizumab versus osimertinib alone for advanced non–small-cell lung cancer with EGFR mutations

A meta-analysis of randomized controlled trials

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Abstract

Background: To systematically evaluate the efficacy and safety of osimertinib plus bevacizumab in treating advanced non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.

Methods: Up to May 26, 2024, the databases of PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure, Chinese Biomedical Literature, China Science and Technology Journal, and Wanfang were searched, and the randomized controlled clinical trials (RCTs) of osimertinib plus bevacizumab in the treatment of advanced EGFR-mutant NSCLC were included. Two researchers independently screened the literature, assessed the quality of the included literature, and extracted the literature data. Revman5.4 software was used for meta-analysis.

Results: A total of 824 patients were included in 10 RCTs. The results of meta-analysis showed that compared with the control group (osimertinib alone), the experimental group (osimertinib plus bevacizumab) had a higher objective response rate (ORR) (relative risk [RR] = 1.23, 95% confidence interval [CI] = 1.03–1.47, $P = .02$), and the experimental group could significantly reduce the expression levels of carcinoembryonic antigen (mean difference [SMD] = 0.82, 95% CI = 0.30–1.35, $P = .002$), vascular endothelial growth factor (SMD = 0.43, 95% CI = 0.13–0.73, $P = .005$), neuron-specific enolase (SMD = 0.88, 95% CI = 0.60–1.17, $P < .00001$), cytokeratin 19 fragments (SMD = 1.33, 95% CI = 0.34–2.33, $P = .009$), and carbohydrate antigen 125 (SMD = 0.46, 95% CI = 0.15–0.77, $P = .004$) in serum. However, the experimental group did not significantly improve the disease control rate (DCR) (RR = 1.17, 95% CI = 1.00–1.36, $P = .05$), 1- and 2-year progression-free survival (PFS) rates (RR = 1.15, 95% CI = 1.00–1.33, $P = .05$; RR = 1.02, 95% CI = 0.74–1.40, $P = .92$), 1- and 2-year overall survival (OS) rates (RR = 1.11, 95% CI = 0.92–1.36, $P = .28$; RR = 0.99, 95% CI = 0.84–1.18, $P = .95$). Interestingly, the results of subgroup analysis showed that the experimental group significantly improved ORR, DCR, 1-year PFS, and OS rates in the Chinese population and patients under 65 years old ($P < .05$). In addition, when the dose of bevacizumab was 7.5 mg/kg q3w in the experimental group, ORR, DCR, 1-year PFS, and OS rates were significantly better than those in the control group ($P < .05$). In terms of adverse events of drugs, the incidence of proteinuria, hypertension, oral mucositis, bleeding, nausea, and vomiting in the experimental group was higher than that in the control group ($P < .05$).

Conclusion: For patients with advanced EGFR-mutant NSCLC, osimertinib plus bevacizumab has some clinical benefit compared with osimertinib alone. Still, it does not provide additional long-term survival benefits and has higher toxicity. More well-designed, multicenter RCTs are needed to identify the subgroups of patients most likely to benefit from this combination regimen and to validate the optimal dose of this combination regimen.

Abbreviations: AZD= osimertinib, BEV= bevacizumab, CA125 = carbohydrate antigen 125, CEA = carcinoembryonic antigen, CI= confidence interval, CR = complete response, Cyfra21-1 = cytokeratin 19 fragments, DCR = disease control rate, EGFR = epidermal growth factor receptor, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, NSCLC = non–small-cell lung cancer, NSE = neuron-specific enolase, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, q3w= every 3 weeks, qd= once daily, RCTs = randomized controlled clinical trials, RR = relative risk, SMD = standard mean difference, VEGF = vascular endothelial growth factor.

Keywords: bevacizumab, meta-analysis, non–small-cell lung cancer, osimertinib

LY, CZ, and DL contributed equally to this work.

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

Ethical approval was not necessary, because this article is a meta-analysis and it does not involve the participation of ethics committee.

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1. Introduction

According to the annual statistics of GLOBOCAN 2022, lung cancer is still the malignant tumor with the highest mortality in the world.[1] Non–small-cell lung cancer (NSCLC) is the most common pathological type of lung cancer, accounting for about 85% of all lung cancer patients.[2] As the early clinical symptoms of lung cancer are not obvious and the disease progresses rapidly, most patients are diagnosed with advanced lung cancer, losing the best opportunity for surgical treatment, and the 5-year survival rate is less than 15%.[3] Epidermal growth factor receptor (EGFR)–sensitive mutations are present in approximately 50% of Asian NSCLC patients.[4] EGFR tyrosine kinase inhibitor (EGFR-TKI) is the first-line treatment for advanced NSCLC with EGFR mutation.[5] Osimertinib is a third-generation EGFR-TKI, which is sensitive to EGFR and selectively inhibits T790M mutation caused by resistance to the first- and second-generation EGFR-TKI.[6] Osimertinib has a higher penetration rate in the central nervous system,[7] but drug resistance is still inevitable after long-term use. Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, which can inhibit tumor growth by inhibiting neovascularization.[8] In addition, some scholars have found that bevacizumab can eliminate EGFR-TKI resistance.[9,10] To explore whether the addition of bevacizumab based on osimertinib can delay the emergence of secondary drug resistance, there have been many relevant clinical studies in recent years, but the conclusions are not completely consistent. Therefore, in this study, meta-analysis was used to systematically evaluate the efficacy and safety of osimertinib plus bevacizumab versus osimertinib alone in the treatment of advanced NSCLC patients with EGFR mutation, to provide a higher level of evidence-based medicine evidence for clinical rational drug use.

2. Materials and methods

2.1. Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[11] The systematic literature search was performed through PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure, Chinese Biomedical Literature, China Science and Technology Journal, and Wanfang, covering all articles published up to May 26, 2024. The following keywords were used to retrieve articles: Non-small cell lung cancer, NSCLC, Osimertinib, Tagrisso, AZD-9291, Bevacizumab, Avastin. References of the retrieved publications were also screened. The search strategy for PubMed is described as follows:

#1 "Carcinoma, Non-Small-Cell Lung" [Mesh]
#2 "Non small Cell Lung Cancer" OR "Non-Small Cell Lung Cancer" OR "Non-Small Cell Lung Carcinoma" OR "Carcinoma, Non-Small Cell Lung" OR "Non Small Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinomas" OR "Lung Carcinomas, Non-Small-Cell" OR "Lung Carcinoma, Non-Small-Cell" OR "Carcinomas, NonSmall-Cell Lung" OR "Carcinoma, Non Small Cell Lung" [Title/ Abstract]
#3 #1 OR #2
#4 "Osimertinib" OR "Tagrisso" OR "AZD-9291" [Title/ Abstract]
#5 "Bevacizumab" OR "Avastin" OR "Mvasi" [Title/ Abstract]
#6 #3 AND #4 AND #5

Other database databases use similar search formulas.

2.2. Literature inclusion and exclusion criteria

2.2.1. Inclusion criteria.

1 Participants: Patients with advanced EGFR-mutant NSCLC.
2 Type of study: Randomized controlled clinical trials (RCTs).
3 Intervention: The experimental group received osimertinib plus bevacizumab, and the control group received osimertinib alone.
4 Outcome indicators: At least one of the following outcomes was reported: Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) rate, overall survival (OS) rate, pre- and post-treatment tumor marker (carcinoembryonic antigen [CEA], carbohydrate antigen 125 [CA125], neuron-specific enolase [NSE], cytokeratin 19 fragments [Cyfra21-1], and VEGF) levels, and incidence of adverse events. The results were divided into complete response (CR), partial response (PR), stable disease, and progressive disease according to the Response Evaluation Criteria in Solid Tumors v1.1. The ORR was calculated as the sum of the CR and PR rates. The DCR was calculated as the sum of the CR, PR, and stable disease rates.

2.2.2. Exclusion criteria. Non-RCTs; reviews, case reports, conference summaries, and repeated studies; literature with no available outcome indicators, incomplete data, and no access to original data.

2.3. Data extraction and literature quality evaluation

Data were independently screened, extracted, and cross-checked by 2 reviewers. If there is any disagreement in the process, the decision will be made through discussion or by referring to the opinions of the third reviewer. The extracted data mainly include first author name, country, year of publication, sample size, age, treatment regimen, EGFR mutation type, and outcome indicators. If there is a lack of important information in the study, try to contact the first author or corresponding author by email to further obtain unpublished data. The Cochrane risk of bias tool[12] was used to evaluate the quality of each RCTs included. The risk of bias was evaluated from 7 items: selection bias (random sequence generation, allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other biases. Each item was classified as "low risk of bias," "unclear risk of bias," and "high risk of bias."

2.4. Statistical analysis

The Review Manager version 5.4 software was used to perform the meta-analysis. For dichotomous data, relative risk (RR) and 95% confidence intervals (CI) were used as evaluation indexes. For continuous variables, standard mean difference (SMD) and 95% CI were used for effect pooled analysis. All P values were 2-sided, and $P < .05$ was considered statistically significant. The heterogeneity was tested by Q and I^2 tests. When the heterogeneity exists ($I^2 > 50\%$ or $P < .1$), the random-effect model was used for a meta-analysis, otherwise, the fixed-effect model was used. A leave-one-out sensitivity analysis was performed to test the possibly substantial impact of individual studies on the synthesized result. Publication bias was evaluated by funnel plot.

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3. Results

3.1. Literature search and study characteristics

A total of 616 articles were retrieved, and 195 repeated articles were excluded by title, year of publication, and author information. Then after reading abstracts and full-text screening, 411 articles that did not meet the criteria were excluded and finally included 10 studies[13–22] (Fig. 1). There were 824 patients with advanced EGFR-mutant NSCLC, of which 412 patients received osimertinib plus bevacizumab (experimental group) and 412 patients received osimertinib alone (control group). The quality evaluation of the included studies is shown in Table 1. The key baseline characteristics of the included studies are shown in Table 2.

3.2. Objective response rate

Ten studies[13–22] provided ORR data, and heterogeneity test results showed significant heterogeneity among studies ($P = .03$, $I^2 = 51\%$). Random-effects model analysis showed that the ORR of the experimental group was significantly higher than

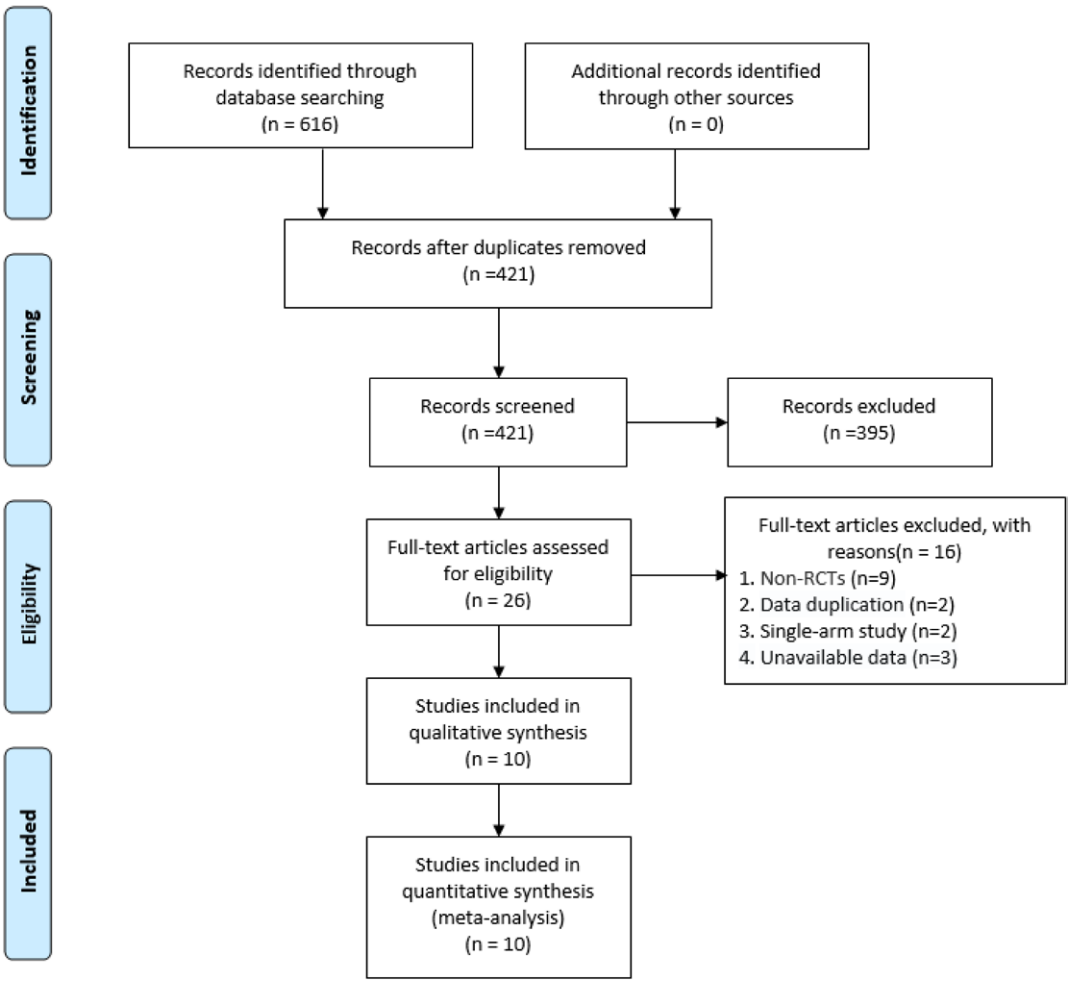

Figure 1. Literature screening flowchart. RCT = randomized controlled clinical trials.

Table 1

The methodological quality of the included randomized controlled trials was assessed using the Cochrane "Risk of Bias" tool.

	Selection bias						
Study	**Random sequence generation**	**Allocation concealment**	**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
Akamatsu et al 2021[13]	+	?	?	?	+	+	?
Chen 2023[14]	+	?	?	?	+	+	?
Feng et al 2022[15]	+	?	?	?	+	+	?
Kenmotsu et al 2022[16]	+	-	?	?	+	+	?
Pan et al 2023[17]	+	?	?	?	+	+	?
Ren 2021[18]	?	?	?	?	+	+	?
Soo et al 2022[19]	+	-	?	?	+	+	?
Su et al 2022[20]	+	?	?	?	+	+	?
Wang et al 2024[21]	+	?	?	?	+	+	?
Zhang 2022[22]	+	?	?	?	+	+	?

? = unclear risk of bias; + = low risk of bias; - = high risk of bias.

Table 2

Basic characteristics of the included literature.

Study	Country	Number of patients		Male/female		Age (yr)		Types of EGFR mutations	Treatment scheme		Treatment line	Outcome indicators
		Experimental group	Control group	Experimental group	Control group	Experimental group	Control group		Experimental group	Control group		
Akamatsu et al 2021[13]	Japan	40	41	16/24	17/24	68 (43–82)	70 (41–82)	T790M/ Ex19del/ L858R	AZD 80 mg qd + BEV (15 mg/kg q3w)	AZD 80 mg qd	Second-line treatment	①②③④⑥
Chen 2023[14]	China	40	41	26/14	28/13	59.36 (40–75)	59.25 (40–72)	-	AZD 80 mg qd + BEV (5 mg/kg q3w)	AZD 80 mg qd	-	①②⑤⑥
Feng et al 2022[15]	China	16	16	12/4	10/6	-	-	-	AZD 80 mg qd + BEV (7.5 mg/kg q3w)	AZD 80 mg qd	First-line treatment	①②③⑤⑥
Kenmotsu et al 2022[16]	Japan	61	61	24/37	23/38	67 (59–74)	66 (60–74)	Ex19del/ L858R	AZD 80 mg qd + BEV (15 mg/kg q3w)	AZD 80 mg qd	First-line treatment	①②③④⑥
Pan et al 2023[17]	China	42	41	25/17	23/18	60 (48–77)	60 (47–77)	T790M	AZD 80 mg qd + BEV (15 mg/kg q3w)	AZD 80 mg qd	First-line treatment	①②④⑤⑥
Ren 2021[18]	China	32	32	15/17	11/21	-	-	-	AZD 80 mg qd + BEV (7.5 mg/kg q3w)	AZD 80 mg qd	-	①②⑥
Soo et al 2022[19]	Global multicenter	78	77	31/47	28/49	68 (34–85)	66 (41–83)	T790M	AZD 80 mg qd + BEV (15 mg/kg q3w)	AZD 80 mg qd	Second-line treatment	①②③④⑥
Su et al 2022[20]	China	32	32	18/14	20/12	66.11 ± 5.28	65.28 ± 4.63	T790M	AZD 80 mg qd + BEV (7.5 mg/kg q3w)	AZD 80 mg qd	-	①②⑤⑥
Wang et al 2024[21]	China	51	51	27/24	29/22	61.56 (32–77)	62.31 (35–79)	T790M	AZD 80 mg qd + BEV (7.5 mg/kg q3w)	AZD 80 mg qd	First-line treatment	①②③④⑤⑥
Zhang 2022[22]	China	20	20	12/8	15/5	64.53 (48–72)	64.18 (46–70)	-	AZD 80 mg qd + BEV (7.5 mg/kg q3w)	AZD 80 mg qd	-	①②⑤⑥

① = objective response rate; ② = disease control rate; ③ = progression-free survival; ④ = overall survival; ⑤ = tumor markers; ⑥ = adverse events.
AZD = osimertinib, BEV = bevacizumab, EGFR = epidermal growth factor receptor, q3w = every 3 weeks, qd = once daily.

that of the control group (RR = 1.23, 95% CI = 1.03–1.47, P = .02; Fig. 2).

3.3. Disease control rate

Ten studies[13–22] provided DCR data, and heterogeneity test results showed significant heterogeneity among studies (P < .00001, I^2 = 90%). Random-effects model analysis showed that there was no significant difference in DCR between the experimental group and the control group (RR = 1.17, 95% CI = 1.00–1.36, P = .05; Fig. 3).

3.4. Progression-free survival

Five studies[13,15,16,19,21] and 2 studies[16,19] provided 1- and 2-year PFS rate data, respectively, and the results of heterogeneity test showed no significant heterogeneity among the studies (1-year PFS: P = .18, I^2 = 36%; 2-year PFS: P = .51, I^2 = 0%). Fixed-effects model analysis showed that there was no significant difference in 1- and 2-year PFS rate between the 2 groups (RR = 1.15, 95% CI = 1.00–1.33, P = .05; RR = 1.02, 95% CI = 0.74–1.40, P = .92; Fig. 4).

3.5. Overall survival

Five studies[13,16,17,19,21] and 2 studies[16,19] provided 1- and 2-year OS rate data, respectively, according to the results of the heterogeneity test (1-year OS: P = .0001, I^2 = 83%; 2-year OS: P = .37, I^2 = 0%). The random-effect model was used for 1-year OS, and the fixed-effect model was used for 2-year OS. The results showed that there were no significant differences in 1- and 2-year OS rates between the 2 groups (RR = 1.11, 95% CI = 0.92–1.36, P = .28; RR = 0.99, 95% CI = 0.84–1.18, P = .95; Fig. 5).

3.6. Tumor markers

Four studies[15,17,20,21] reported the levels of serum CEA before and after treatment in the experimental group and the control group, and heterogeneity test results showed significant heterogeneity among studies (P = .005, I^2 = 76%). Random-effects model analysis showed that the experimental group could significantly reduce the expression level of serum CEA compared with the control group (SMD = 0.82, 95% CI = 0.30–1.35, P = .002). Three studies[14,17,22] reported NSE expression levels in the serum of the experimental and control groups before and after treatment. Based on the results of heterogeneity test (P = .97, I^2 = 0%), the fixed-effect model analysis showed that the experimental group could significantly reduce the expression level of NSE in the serum of patients compared with the control group (SMD = 0.88, 95% CI = 0.60–1.17, P < .00001). Three studies[14,20,22] reported the expression levels of Cyfra21-1 in the serum of the experimental and control groups before and after treatment. Based on the results of heterogeneity test (P = .0001, I^2 = 89%), the random-effect model analysis showed

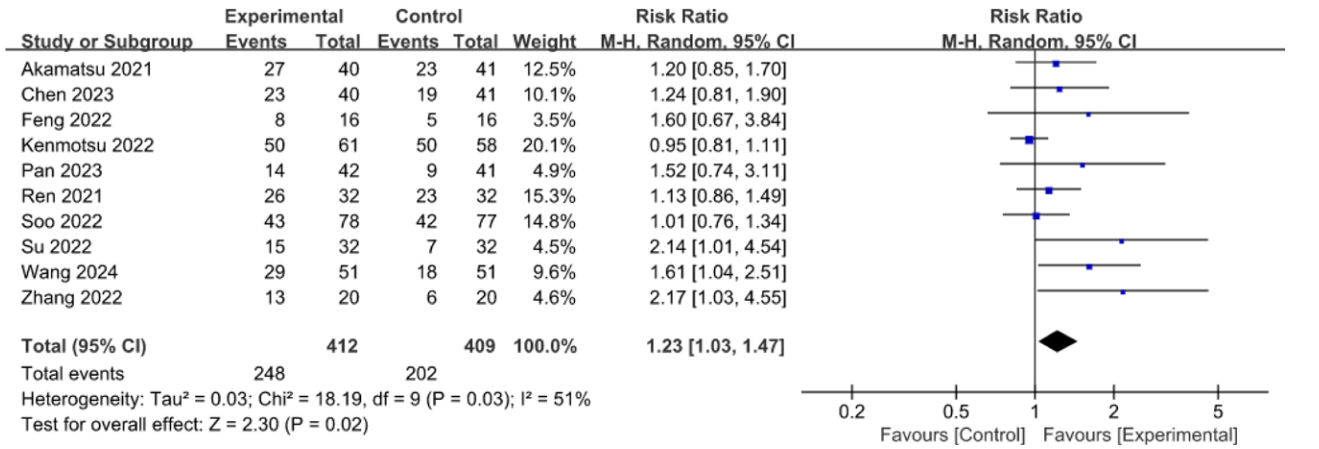

Figure 2. ORR forest plot of osimertinib plus bevacizumab versus osimertinib alone. CI = confidence interval, ORR = objective response rate.

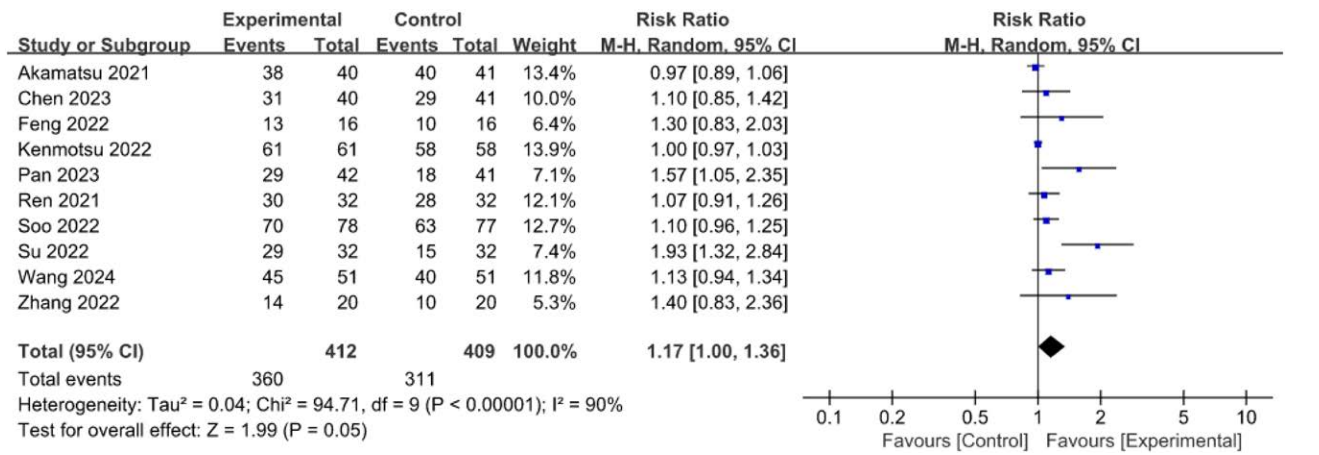

Figure 3. DCR forest plot of osimertinib plus bevacizumab versus osimertinib alone. CI = confidence interval, DCR = disease control rate.

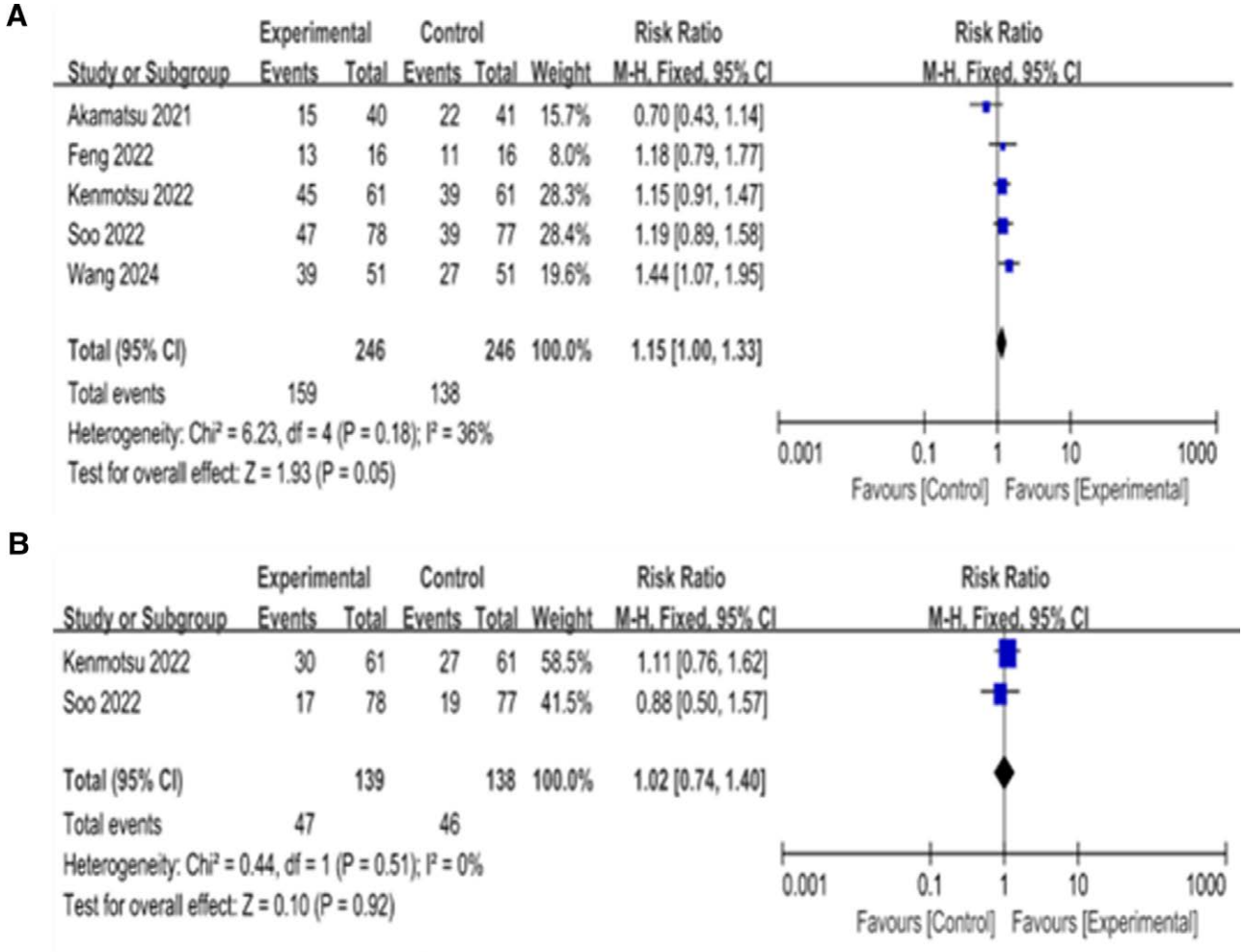

Figure 4. PFS rate forest plot of osimertinib plus bevacizumab versus osimertinib alone. (A) 1-yr PFS rate, (B) 2-yr PFS rate. CI = confidence interval, PFS = progression-free survival.

that the experimental group could significantly reduce the expression level of serum Cyfra21-1 compared with the control group (SMD = 1.33, 95% CI = 0.34–2.33, $P = .009$). Two studies[20,21] reported the expression levels of CA125 in the serum of the experimental and control groups before and after treatment. Based on the results of heterogeneity test ($P = .35$, $I^2 = 0\%$), the fixed-effect model analysis showed that the experimental group could significantly reduce the expression level of CA125 in the serum of patients compared with the control group (SMD = 0.46, 95% CI = 0.15–0.77, $P = .004$). Three studies[15,21,22] reported serum VEGF expression levels before and after treatment in the experimental and control groups. Based on the results of heterogeneity test ($P = .67$, $I^2 = 0\%$), the fixed-effect model analysis showed that the experimental group could significantly reduce the expression level of VEGF in the serum of patients compared with the control group (SMD = 0.43, 95% CI = 0.13–0.73, $P = .005$; Fig. 6).

3.7. Adverse events

In terms of adverse events of drugs, the incidence of proteinuria, hypertension, oral mucositis, bleeding, nausea, and vomiting in the experimental group was higher than that in the control group ($P < .05$). There was no significant difference in the incidence of thrombocytopenia, leukopenia, neutropenia, diarrhea, liver function damage, creatinine elevated, rash, anemia, decreased appetite, fatigue, paronychia, interstitial pneumonia, pruritus, and dry skin between the 2 groups ($P > .05$), as shown in Table 3.

3.8. Sensitivity analysis and publication bias

Sensitivity analysis was performed for each meta-analysis, and each included study was excluded one by one before effect size was pooled. The RR and SMD values and 95% CI obtained did not change significantly, indicating that the results were stable. Subgroup analyses were performed to examine sources of heterogeneity in ORR, DCR, 1-year PFS, and 1-year OS according to country, age, dose of regimen, and number of lines of therapy. As shown in Table 4, subjects from different countries may be a source of heterogeneity. In addition, the results of subgroup analysis showed that the experimental group significantly improved ORR, DCR, 1-year PFS, and OS rates in the Chinese population and patients under 65 years old ($P < .05$). The ORR, DCR, 1-year PFS, and OS rates in the experimental group were significantly better than those in the control group when the dose of bevacizumab was 7.5 mg/kg q3w ($P < .05$). The funnel plots with ORR and DCR as indicators were basically symmetric, suggesting no significant publication bias (Fig. 7). The number of studies for the remaining outcome indicators was less than 10, so funnel plots and bias tests were not performed.

4. Discussion

Osimertinib is an irreversible third-generation EGFR inhibitor, which belongs to a monoaniline pyrimidine small molecule.[23] The propionamide group of osimertinib forms covalent binding to C797 at the ATP-binding site of the catalytic domain of the EGFR gene, thereby irreversibly binding to EGFR mutation, and

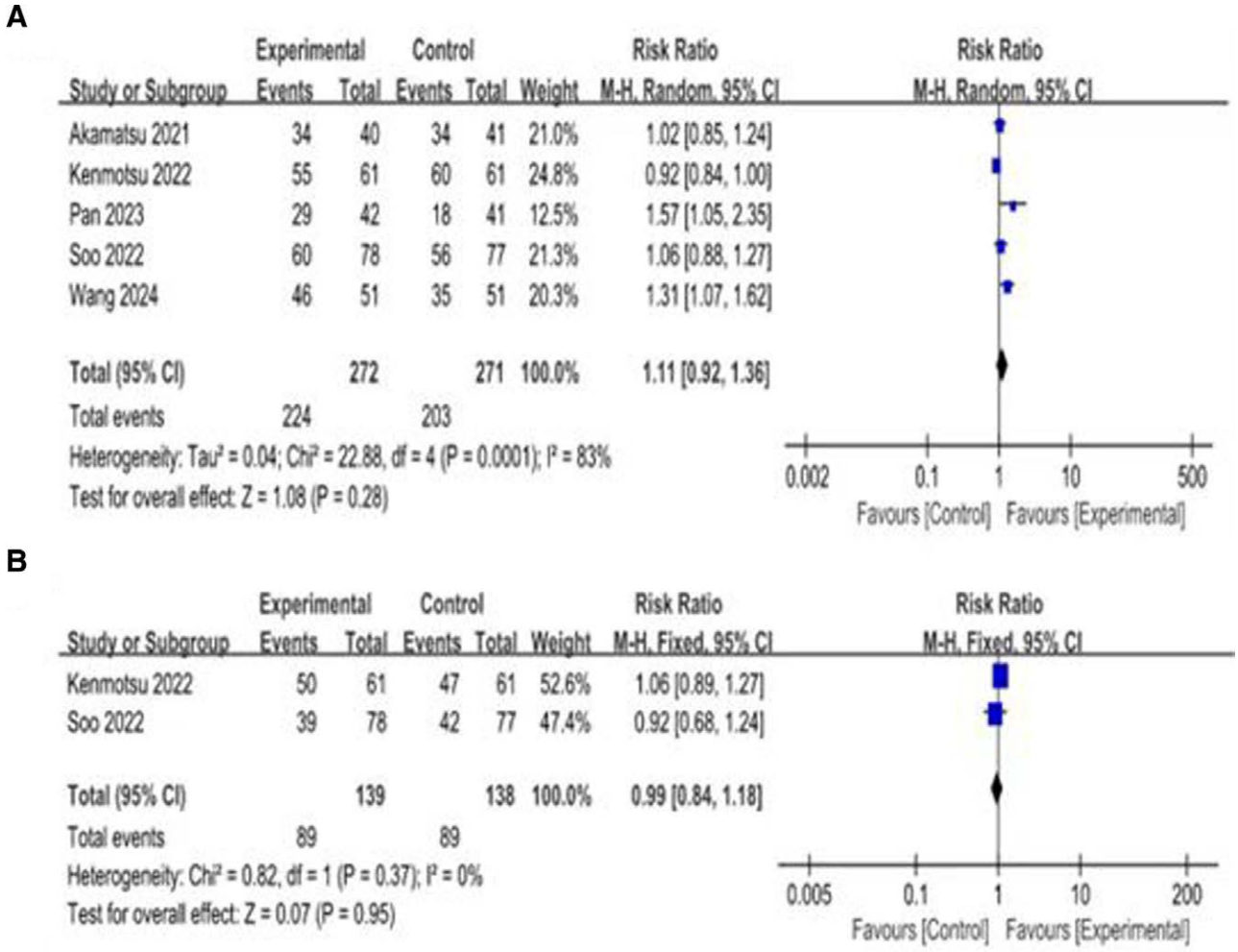

Figure 5. OS rate forest plot of osimertinib plus bevacizumab versus osimertinib alone. (A) 1-yr OS rate, (B) 2-yr OS rate. CI = confidence interval, OS = overall survival.

inhibiting tumor cell proliferation and promoting apoptosis.[24] Osimertinib can selectively inhibit EGFR-positive sensitive mutations and T790M positive resistance mutations, especially can significantly prolong the survival time of advanced NSCLC patients with confirmed EGFR and acquired T790M mutations.[25] However, due to the fixed nature of its binding target, with the extension of the treatment cycle, acquired resistance and disease progression inevitably occur.[26] Based on the successful experience of erlotinib (the first-generation EGFR-TKI) combined with bevacizumab,[27,28] clinical studies of osimertinib (the third-generation EGFR-TKI) combined with bevacizumab in the treatment of advanced EGFR-mutant NSCLC have been emerging. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, that can combine with VEGF to block its biological activity, inhibit angiogenesis, and normalize tumor blood vessels, to achieve the effect of tumor treatment.[29] Studies[30,31] have shown that the synergistic effect of bevacizumab and osimertinib is achieved by reducing the expression level of VEGF in tumor tissues, improving the tumor microenvironment, and enhancing the signaling pathways that inhibit the growth of tumor cells. Compared with increasing the dose of osimertinib alone, combination therapy with appropriate doses may bring more significant survival benefits to patients.

To systematically evaluate the efficacy and safety of osimertinib plus bevacizumab in the treatment of advanced EGFR-mutant NSCLC patients, a total of 10 RCTs were included for meta-analysis after screening according to the inclusion and exclusion criteria. In terms of drug efficacy, it was divided into short-term efficacy (ORR, DCR) and long-term efficacy (OS, PFS). In terms of short-term efficacy, the ORR of the experimental group was significantly higher than that of the control group, and the DCR was slightly higher, suggesting that the experimental group had better short-term efficacy than the control group. However, as far as the long-term efficacy indicators of OS and PFS are concerned, the combination therapy does not seem to effectively improve the long-term survival rate of patients and reduce the risk of death. This is basically consistent with the results of Zhou et al,[32] but Zhou et al's[32] meta-analysis included only 4 RCTs and did not conduct subgroup analysis based on the age of the subjects, country, dose of the treatment regimen, and treatment line, which may screen out the population that can truly benefit from the combination therapy and the optimal mode of treatment. The results of our subgroup analysis showed that the experimental group had significantly improved ORR, DCR, 1-year PFS, and OS rates compared with the control group in the Chinese population and patients under 65 years old. In addition, according to the dose of bevacizumab, the experimental group could be divided into high-dose group (15 mg/kg q3w), medium-dose group (7.5 mg/kg q3w), and low-dose group (5 mg/kg q3w). The results of subgroup analysis showed that the ORR, DCR, 1-year PFS, and OS rates of the experimental group were significantly better than those of the control group when the experimental group was given the dose of osimertinib (80 mg qd) plus bevacizumab (7.5 mg/kg q3w).

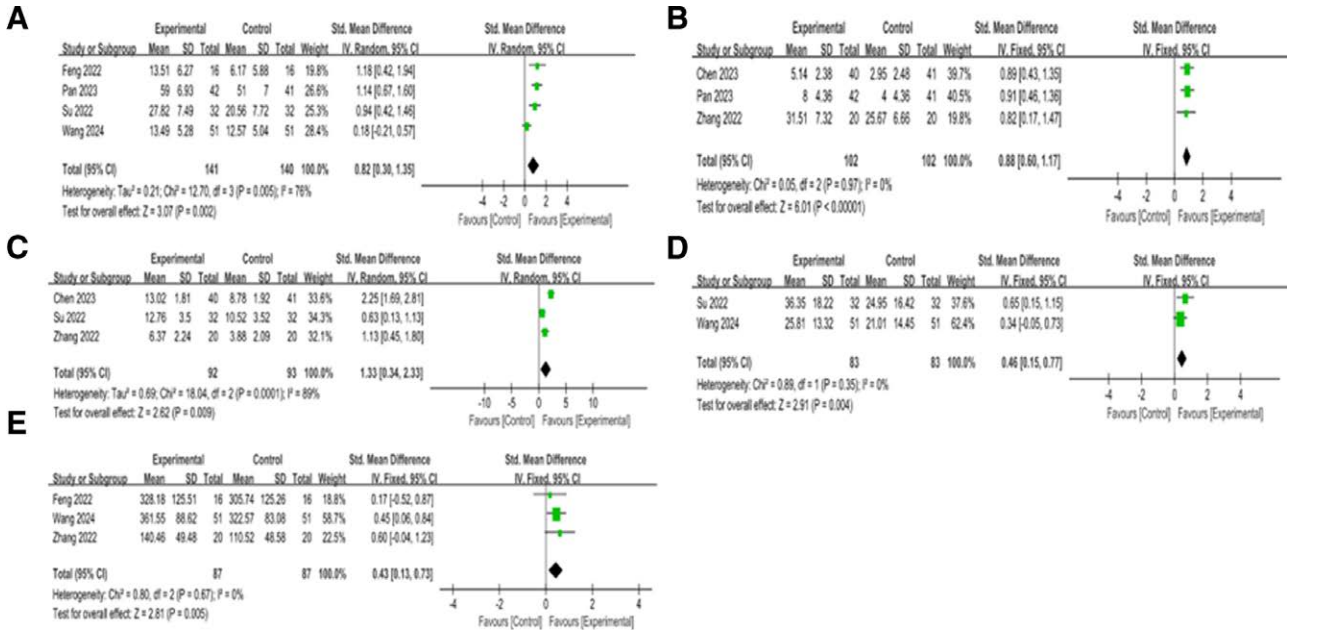

Figure 6. Tumor markers forest plot of osimertinib plus bevacizumab versus osimertinib alone. (A) CEA, (B) NSE, (C) Cyfra21-1, (D) CA125, (E) VEGF. CA125 = carbohydrate antigen 125, CEA = carcinoembryonic antigen, CI = confidence interval, Cyfra21-1 = cytokeratin 19 fragments, NSE = neuron-specific enolase, VEGF = vascular endothelial growth factor.

Table 3

Comparison of adverse events between the experimental group and the control group.

Adverse events	Number of studies	Heterogeneity	RR (95% CI)	*P*
Proteinuria	6	$P = .0005$, $I^2 = 77\%$	4.22 (1.41–12.66)	.01
Thrombocytopenia	8	$P = .66$, $I^2 = 0\%$	1.15 (0.94–1.41)	.16
Hypertension	5	$P = .001$, $I^2 = 78\%$	4.47 (1.36–14.67)	.01
Neutropenia	3	$P = .13$, $I^2 = 51\%$	1.10 (0.63–1.92)	.73
Diarrhea	8	$P = .94$, $I^2 = 0\%$	0.98 (0.84–1.15)	.82
Liver function damage	7	$P = .84$, $I^2 = 0\%$	1.21 (0.93–1.56)	.15
Leukopenia	6	$P = .43$, $I^2 = 0\%$	0.97 (0.79–1.20)	.77
Creatinine elevated	2	$P = .49$, $I^2 = 0\%$	1.01 (0.62–1.66)	.96
Rash	9	$P = .90$, $I^2 = 0\%$	1.05 (0.88–1.26)	.59
Anemia	6	$P = .09$, $I^2 = 47\%$	0.95 (0.70–1.29)	.75
Decreased appetite	4	$P = .18$, $I^2 = 38\%$	1.38 (0.97–1.97)	.07
Oral mucositis	3	$P = .37$, $I^2 = 0\%$	1.61 (1.17–2.23)	.004
Fatigue	4	$P = .64$, $I^2 = 0\%$	1.29 (0.88–1.89)	.19
Paronychia	3	$P = .07$, $I^2 = 62\%$	1.09 (0.62–1.92)	.76
Bleeding	3	$P = .23$, $I^2 = 31\%$	2.73 (1.43–5.20)	.002
Interstitial pneumonia	2	$P = .11$, $I^2 = 60\%$	0.40 (0.09–1.83)	.24
Dry skin	3	$P = .81$, $I^2 = 0\%$	1.31 (0.90–1.90)	.16
Nausea and vomiting	7	$P = .23$, $I^2 = 27\%$	1.21 (1.02–1.44)	.03
Pruritus	2	$P = .13$, $I^2 = 56\%$	0.77 (0.29–2.04)	.60

CI = confidence interval, RR = relative risk.

Compared with the control group, there was no significant advantage in the high-dose and low-dose experimental groups. This suggests that an oral standard dose (80 mg qd) of osimertinib plus a medium dose (7.5 mg/kg q3w) of bevacizumab may be the most appropriate combination treatment mode for patients with advanced EGFR-mutant NSCLC. However, among the 6 RCTs evaluating PFS and OS, only 2 and 1 RCT, respectively, specifically provided 1-year PFS and OS data of medium-dose (7.5 mg/kg q3w) bevacizumab, and the strength of evidence was quite limited.

Angiogenesis can create a favorable vascular microenvironment for tumor proliferation and metastasis.[33] VEGF is an important vascular growth factor, that can stimulate tumor angiogenesis, and its expression level is closely related to tumor invasion and metastasis. CEA, NSE, CA125, and CYFRA21-1 are common tumor markers of NSCLC, and their expression levels are of great significance for efficacy evaluation and prognosis. The results of our meta-analysis showed that the experimental group could significantly reduce the expression levels of CEA, NSE, CA125, Cyfra21-1, and VEGF in the serum of patients. The efficacy of the combined regimen was verified at the molecular level. In terms of adverse drug events, the use of bevacizumab in the experimental group significantly increased the incidence of proteinuria, hypertension, oral mucositis, bleeding, nausea and vomiting, and some patients discontinued the drug because of this, so the exposure time of bevacizumab is short, which will have a certain impact on the survival time of patients. However, the incidence of proteinuria, hypertension, nausea, and vomiting in the experimental group was not significantly different from that in the control group when

Table 4

Subgroup analyses of ORR, DCR, 1-year PFS, and 1-year OS between the experimental and control group.

Parameter	Factors at study	Number of studies	Heterogeneity	RR 95% CI	*P*
ORR	Country				
	China	7	$P = .37$, $I^2 = 7\%$	1.47 (1.21–1.79)	<.0001
	Japan	2	$P = .18$, $I^2 = 43\%$	1.03 (0.88–1.20)	.72
	Global multicenter	1	-	1.01 (0.76–1.34)	.94
	Age (yr)				
	≥65	4	$P = .09$, $I^2 = 54\%$	1.09 (0.87–1.34)	.46
	<65	4	$P = .61$, $I^2 = 0\%$	1.53 (1.17–1.99)	.002
	Treatment scheme				
	AZD (80 mg qd) + BEV (15 mg/kg q3w) vs AZD (80 mg qd)	4	$P = .33$, $I^2 = 12\%$	1.06 (0.92–1.22)	.44
	AZD (80 mg qd) + BEV (7.5 mg/kg q3w) vs AZD (80 mg qd)	5	$P = .16$, $I^2 = 39\%$	1.54 (1.23–1.94)	.0002
	AZD (80 mg qd) + BEV (5 mg/kg q3w) vs AZD (80 mg qd)	1	-	1.24 (0.81–1.90)	.32
	Treatment line				
	First-line treatment	4	$P = .01$, $I^2 = 72\%$	1.31 (0.83–2.06)	.24
	Second-line treatment	2	$P = .44$, $I^2 = 0\%$	1.08 (0.86–1.34)	.50
DCR	Country				
	China	7	$P = .04$, $I^2 = 56\%$	1.26 (1.07–1.48)	.007
	Japan	2	$P = .47$, $I^2 = 0\%$	0.99 (0.95–1.03)	.60
	Global multicenter	1	-	1.10 (0.96–1.25)	.16
	Age (yr)				
	≥65	4	$P < .00001$, $I^2 = 94\%$	1.12 (0.91–1.38)	.28
	<65	4	$P = .33$, $I^2 = 12\%$	1.23 (1.06–1.42)	.005
	Treatment scheme				
	AZD (80 mg qd) + BEV (15 mg/kg q3w) vs AZD (80 mg qd)	4	$P < .00001$, $I^2 = 91\%$	1.07 (0.90–1.27)	.42
	AZD (80 mg qd) + BEV (7.5 mg/kg q3w) vs AZD (80 mg qd)	5	$P = .03$, $I^2 = 64\%$	1.27 (1.03–1.56)	.03
	AZD (80 mg qd) + BEV (5 mg/kg q3w) vs AZD (80 mg qd)	1	-	1.10 (0.85–1.42)	.49
	Treatment line				
	First-line treatment	4	$P < .00001$, $I^2 = 96\%$	1.21 (0.76–1.93)	.41
	Second-line treatment	2	$P = .07$, $I^2 = 70\%$	1.03 (0.89–1.18)	.72
1-yr PFS	Country				
	China	2	$P = .43$, $I^2 = 0\%$	1.37 (1.07–1.75)	.01
	Japan	2	$P = .06$, $I^2 = 71\%$	0.94 (0.57–1.55)	.80
	Global multicenter	1	-	1.19 (0.89–1.58)	.23
	Age (yr)				
	≥65	3	$P = .15$, $I^2 = 47\%$	1.07 (0.90–1.27)	.46
	<65	1	-	1.44 (1.07–1.95)	.02
	Treatment scheme				
	AZD (80 mg qd) + BEV (15 mg/kg q3w) vs AZD (80 mg qd)	3	$P = .15$, $I^2 = 47\%$	1.07 (0.90–1.27)	.46
	AZD (80 mg qd) + BEV (7.5 mg/kg q3w) vs AZD (80 mg qd)	2	$P = .43$, $I^2 = 0\%$	1.37 (1.07–1.75)	.01
	Treatment line				
	First-line treatment	3	$P = .50$, $I^2 = 0\%$	1.26 (1.06–1.50)	.008
	Second-line treatment	2	$P = .06$, $I^2 = 71\%$	0.95 (0.56–1.59)	.84
1-yr OS	Country				
	China	2	$P = .40$, $I^2 = 0\%$	1.40 (1.15–1.71)	.0007
	Japan	2	$P = .24$, $I^2 = 26\%$	0.96 (0.87–1.05)	.32
	Global multicenter	1	-	1.06 (0.88–1.27)	.55
	Age (yr)				
	≥65	3	$P = .16$, $I^2 = 46\%$	0.99 (0.91–1.09)	.89
	<65	2	$P = .40$, $I^2 = 0\%$	1.40 (1.15–1.71)	.0007
	Treatment scheme				
	AZD (80 mg qd) + BEV (15 mg/kg q3w) vs AZD (80 mg qd)	4	$P = .003$, $I^2 = 78\%$	1.06 (0.87–1.29)	.57
	AZD (80 mg qd) + BEV (7.5 mg/kg q3w) vs AZD (80 mg qd)	1	-	1.31 (1.07–1.62)	.009
	Treatment line				
	First-line treatment	3	$P < .00001$, $I^2 = 93\%$	1.21 (0.78–1.89)	.40
	Second-line treatment	2	$P = .81$, $I^2 = 0\%$	1.05 (0.91–1.20)	.52

AZD = osimertinib, BEV = bevacizumab, CI = confidence interval, DCR = disease control rate, ORR = objective response rate, OS = overall survival, PFS = q3w = every 3 weeks, qd = once daily, RR = relative risk.

the experimental group was given a medium dose of bevacizumab (7.5 mg/kg q3w). Perhaps adjusting the dose of bevacizumab in the experimental group can improve the efficacy without increasing the incidence of drug-related adverse events. However, the strength of the evidence is limited because only 2 to 4 RCTs independently provided data on the aforementioned adverse events.

Although our meta-analysis failed to show a clear advantage of the combination regimen, some relevant studies have found that this combination regimen may improve survival in selected populations. Kenmotsu et al[16] found that the subgroup of patients with EGFR exon 19 deletion in the experimental group showed a trend toward longer PFS. In addition, Kenmotsu et al[16] and Soo et al[19] found that the experimental group could prolong the PFS of smokers compared with the control group. Similarly, Dafni et al[34] also showed that in advanced EGFR-mutant NSCLC patients, the addition of angiogenesis inhibitors to EGFR-TKI treatment prolonged PFS and OS in smokers, but did not significantly improve PFS and OS in nonsmokers. Tobacco exposure may cause TP53 mutations in tumors, which may increase the expression of VEGF in tumors and thus favor the effect of angiogenesis inhibitors.[35,36] Case reports have also

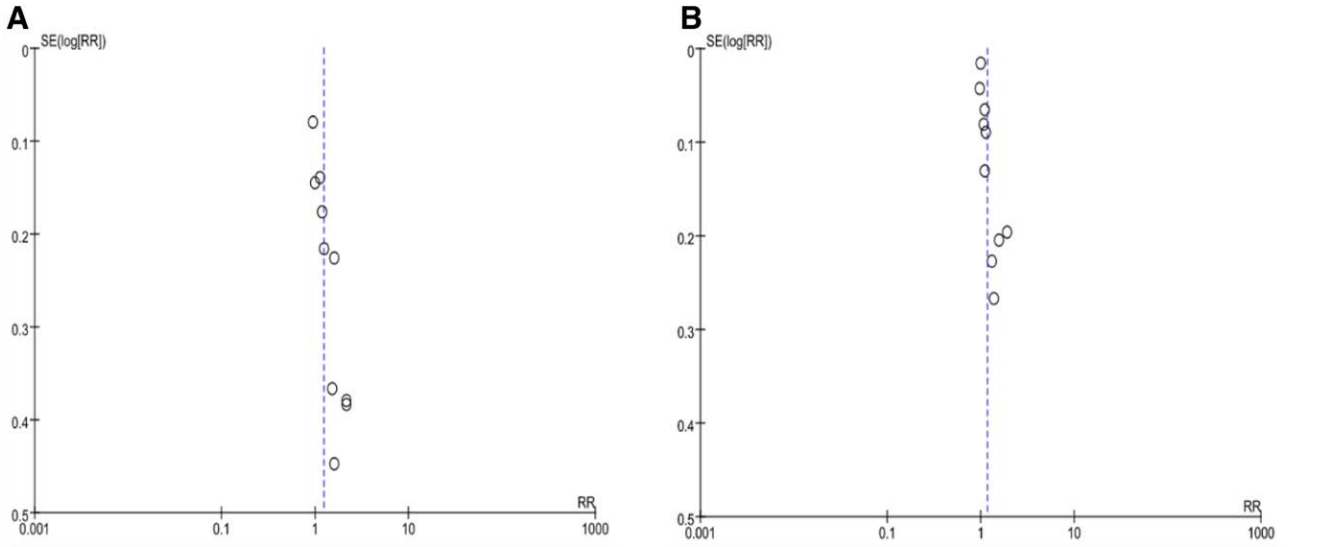

Figure 7. Funnel plot of ORR (A), DCR (B). DCR = disease control rate, ORR = objective response rate.

suggested that osimertinib plus bevacizumab may be an effective option for NSCLC patients with EGFR exon 20 insertion mutation and brain metastases.[37] Although this combination may not benefit all patients with advanced EGFR-mutant NSCLC, it may benefit selected populations. Certain predictors of efficacy would help identify subgroups of patients most likely to benefit from combination therapy.[38] For example, programmed cell death-ligand 1 expression on tumor cells can be used as a predictor of the efficacy of immune checkpoint inhibitors in NSCLC.[39–42] Due to the limited number of cases included in our study, and most of them were Chinese population, there is a lack of large sample and global multicenter studies, and it is difficult to draw firm conclusions based on the current data. In addition, the limitations of our study include: Due to the inconsistency or missing of the relevant original data provided by the included studies, subgroup analysis could not be performed according to tumor stage, EGFR mutation type, smoking status, brain metastasis, etc. Some studies had insufficient follow-up time and lacked long-term survival data. The number of eligible RCTs is limited, resulting in insufficient data for pooled analysis of some outcome indicators, and the statistical power may not be sufficient to prove the effect of the combined regimen. Therefore, these results need to be interpreted with caution.

In summary, osimertinib plus bevacizumab failed to provide additional DCR, PFS, and OS benefits with higher toxicity compared with osimertinib alone in patients with advanced EGFR-mutant NSCLC, although it improved ORR and reduced serum tumor markers and VEGF expression. This suggests that widespread clinical adoption of this combination regimen remains to be considered. However, the efficacy of this combination regimen in the Chinese population and relatively young patients should not be ignored. In the future, more well-designed, multicenter RCTs are needed to identify the subgroups of patients who are most likely to benefit and to verify the optimal dose of this combination regimen.

Author contributions

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