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Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives Combination treatment with erlotinib plus bevacizumab has the potential to become a standard treatment regimen for patients with epidermal growth factor receptor mutation-positive (*EGFR*m$^+$) advanced non-small cell lung cancer (NSCLC). This study aimed to investigate the efficacy and safety of erlotinib plus bevacizumab in patients with *EGFR*m$^+$ advanced NSCLC.

Design Systematic review and meta-analysis.

Data sources The PubMed, Embase, Web of Science and Cochrane Library databases were searched, from inception to 15 January 2022.

Eligibility criteria We included randomised controlled trials (RCTs), reported in English, assessing the efficacy of erlotinib plus bevacizumab versus erlotinib monotherapy in patients with *EGFRm*$^+$ advanced NSCLC.

Data extraction and synthesis The main objective was to assess overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse events (AEs). Two independent reviewers extracted data and assessed the risk of bias. A random-effects model was used where there was evidence for homogeneous effects.

Results Four RCTs (reported across six publications) were included in the meta-analysis, with a total of 775 patients included in the pooled analyses of PFS, OS and ORR (387 in the erlotinib plus bevacizumab intervention group and 388 in the erlotinib group). Compared with the erlotinib alone group, the erlotinib plus bevacizumab group achieved a significantly prolonged PFS (HR: 0.59; 95% CI 0.49 to 0.72; p<0.00001; I^2=0%), but OS (HR: 0.95; 95% CI 0.78 to 1.15; p=0.59; I^2=0%) and ORR (OR: 1.25; 95% CI 0.89 to 1.74; p=0.19; I^2=0%) were not significantly prolonged. A total of 776 cases were used for a pooled analysis of AEs. Regarding AEs, combined treatment significantly increased the incidence of diarrhoea (51% vs 43%, 95% CI 1.03 to 1.38; p=0.006), haemorrhagic events (41% vs 20%, 95% CI 1.12 to 6.31; p=0.03), proteinuria (25% vs 3%, 95% CI 4.86 to 17.66; p<0.0001) and hypertension (40% vs 8%, 95% CI 3.66 to 7.88; p<0.0001).

Conclusions Erlotinib plus bevacizumab for the treatment of patients with *EGFR*m$^+$ advanced NSCLC was associated with significantly prolonged PFS compared with erlotinib alone, but the combination did not prolong OS.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present systematic review and meta-analysis pooled data from high-quality randomised controlled trials.
⇒ We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to inform our reporting and we evaluated the strength and quality of the evidence.
⇒ Limitations include publication biases and incomplete data in selected articles.
⇒ The literature searches only considered studies published in English.
⇒ There was no analysis of poststudy treatments that may have affected overall survival.

INTRODUCTION

Lung cancer leads in the incidence and mortality due to cancer in the world.[1] Approximately 80%–85% of lung cancer is characterised by the non-small cell lung cancer (NSCLC) subtype.[2] Despite the rapid development of new diagnostic and therapeutic strategies, approximately 62% of patients with lung cancer are diagnosed at an advanced stage and the prognosis remains poor.[3 4] The 5-year survival rate is less than 20%.[5] Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) have been established as the standard first-line treatment for patients with *EGFR* mutation-positive (*EGFR*m$^+$) lung cancer.[6] Although 60%–80% of patients with *EGFR*-mutant tumours achieve durable responses, the median progression-free survival (PFS) is approximately 1 year following treatment with first-generation *EGFR* TKIs (gefitinib

and erlotinib) as a result of acquired drug resistance and relapse.[7] Combination treatments with *EGFR* TKIs is one strategy to overcome acquired resistance and to improve outcomes for these patients.[8]

Bevacizumab is a recombinant antiangiogenic monoclonal antibody, which directly targets the vascular endothelial growth factor (VEGF) signalling pathway to inhibit tumour angiogenesis and suppress growth.[9] Studies have suggested that bevacizumab combined with first-line platinum-based chemotherapy has a significant survival benefit in several trials in NSCLC.[10–12] The combination of erlotinib and bevacizumab has the potential to prolong PFS in unselected populations of patients with NSCLC.[13 14] However, these studies were conducted in *EGFR*-mutant unselected cases. Furthermore, the clinical relevance of *EGFR*m$^+$ in NSCLC had not yet been clarified. The first study that provided some important information on the efficacy of combining bevacizumab and erlotinib in the population of the *EGFR*-mutant subgroup was Rosell *et al*[15] in a phase II trial evaluating erlotinib and bevacizumab. It showed the benefit of the combined use of erlotinib and bevacizumab in patients with *EGFR*-mutant NSCLC. However, the evidence in the single-arm trial was insufficient. The effects of erlotinib plus bevacizumab in advanced *EGFR*m$^+$ NSCLC remain controversial. The results of randomised controlled trials (RCTs) have shown that erlotinib plus bevacizumab can prolong the PFS and the objective response rate (ORR) in advanced *EGFR*m$^+$ NSCLC.[16–19] By contrast, some studies have reported comparable efficacy in patients treated with erlotinib plus bevacizumab and in those treated with erlotinib monotherapy.[20] Previous meta-analyses have investigated the effects of erlotinib plus bevacizumab in the treatment of NSCLC.[14 21] However, there has been no meta-analysis of erlotinib plus bevacizumab in the treatment of patients with advanced *EGFR*m$^+$ NSCLC. Thus, the aim of this systematic review and meta-analysis was to evaluate the effects and safety of erlotinib plus bevacizumab in patients with *EGFR*m$^+$ advanced NSCLC.

METHODS

We conducted the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[22]

Inclusion and exclusion criteria

Adult participants with histologically or cytologically diagnosed NSCLC harbouring an *EGFR* mutation with Eastern Cooperative Oncology Group performance status scores of 2 or lower were included. RCTs comparing erlotinib plus bevacizumab with erlotinib as a single agent for the treatment of *EGFR*m$^+$ NSCLC were included. There were no special restrictions on race, sex, nationality, histology or smoking history. Reviews without original data, as well as animal experimental studies and meta-analyses, were excluded.

Outcome assessment

The primary outcomes were overall survival (OS), PFS and ORR of NSCLC treatment. Secondary outcome was adverse events (AEs) of treatment.

Search strategy and selection

A systematic search of PubMed, Embase, Web of Science and Cochrane Library was performed for studies before 15 January 2022. The language was limited to English. The combined text and medical subject heading terms used were: 'Carcinoma, Non-Small-Cell Lung' and 'Erlotinib Hydrochloride' and 'Bevacizumab' (see online supplemental material 1 file for further details on the search strategy).

Data extraction

All steps were performed independently by two investigators; any discrepancies were resolved by discussion with a third investigator. The following information was extracted: the name of the first author, year of publication, region, characteristics (eg, age, sex, clinical stage, study design), the number of participants in each group, description and doses of therapeutic agents administered, outcome data, tumour histology, type of *EGFR* mutation and AEs. The outcomes analysed were: PFS, OS, ORR and safety.

Assessing risk of bias and grading the quality of evidence

The Cochrane risk of bias tool was used to assess the risk of bias of included trials.[23] Two investigators independently evaluated each trial based on random sequence generation, allocation concealment, blinding of participants, blinding of outcome, incomplete outcome date, selective reporting and other biases.[24] Discrepancies and divergence in quality assessment were resolved by group discussion.

Statistical analysis

The results of OS and PFS were estimated by HR with a 95% CI. Relative risk (RR) was used to estimate the results of AEs and ORR with 95% CI. We used the I^2 statistic to assess the level of heterogeneity. Values of I^2 <25%, 25%–50% and >50% were defined as low, mild and substantial heterogeneity, respectively.[25] If I^2 was <50% and p>0.05, a fixed-effects model was used in the meta-analysis; if I^2 ≥50% and p≤0.05, a random effects model was used to assess the resource of the heterogeneity. All statistical analyses were performed with RevMan V.5.4 provided by the Cochrane Collaboration and the value of p<0.05 was considered statistically significant.

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Results of the literature search

The study flow chart is presented in figure 1. A total of 783 publications were identified by our search strategy, of which 139 duplicates were excluded. The remaining 644 publications were read by title and abstract; 485

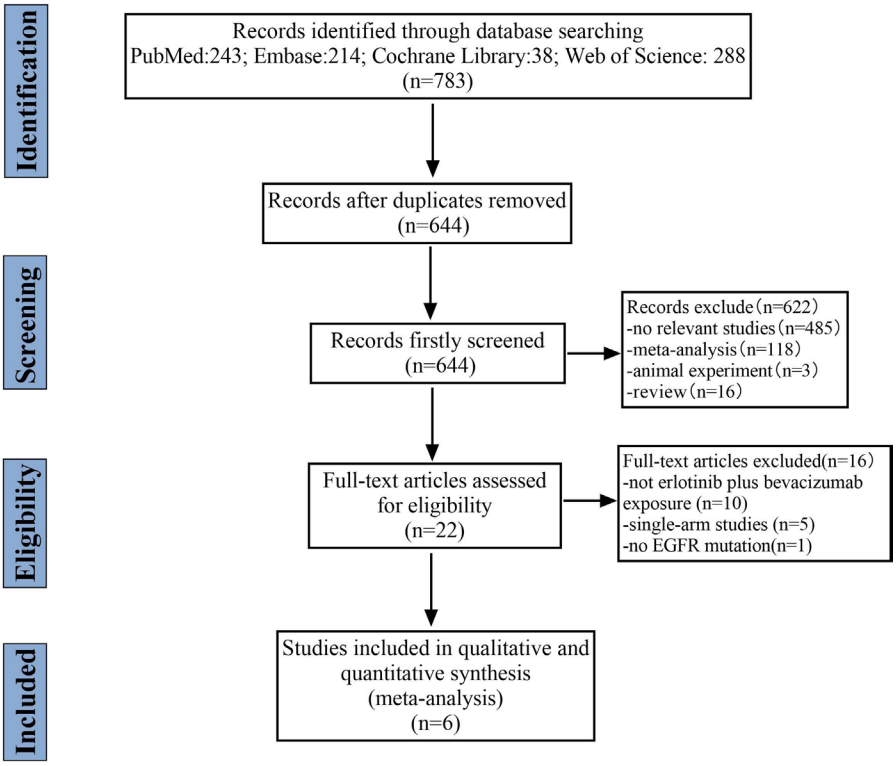

Figure 1 Flow chart of the literature screening. EGFR, epidermal growth factor receptor.

publications were not relevant studies, 118 publications were meta-analyses, 3 publications involved animal experiments and 16 publications were reviews. Overall, 622 studies were excluded. We carefully selected the remaining 22 articles; 6 studies met our eligibility criteria and were included in the present meta-analysis.

Characteristics of the included studies

Basic information included author names, date of publication, region of participants, age, tumour histology, clinical stage, genomic aberration of *EGFR* (table 1). Among the six publications[16–20 26] included in the meta-analysis, Saito *et al*[17] and Kawashima *et al*[26] were reports of the NEJ026 Study, and Seto *et al*[16] and Yamamoto *et al*[18] were reports of the JO25567 Study. In total, the erlotinib plus bevacizumab group included 387 cases and the erlotinib group included 388 cases across the four RCTs. Patients assigned to the erlotinib plus bevacizumab group received 150 mg of oral erlotinib once daily and 15 mg/kg of intravenous bevacizumab once every 21 days, beginning on day 1 of cycle 1. Patients in the erlotinib alone group received 150 mg of oral erlotinib once daily. A treatment cycle was defined as 21 days.

Table 1 Characteristics of included RCTs

Study	Region	Participant (erlotinib plus bevacizumab group/ erlotinib group)	Gender (male/female)	Age	Histology (adenocarcinoma/ large cell carcinoma/ squamous cell/ others)	Clinical stage	*EGFR* genomic aberration (19 deletion/ 21 Leu858Arg mutation)	Outcome	Study design
JO25567 (Seto *et al* 2014; Yamamoto *et al* 2021)[16 18]	Japan	152 (75/77)	56/96	67 (59–73)	150/1/0/1	IIIb–IV	80/72	PFS, OS, ORR, AEs	Phase II RCT
Stinchcombe *et al* 2019[20]	America	88 (43/45)	26/62	63 (31–84)	–	M1a,M1b	59/29	PFS, OS, ORR, AEs	Phase II RCT
NEJ026 (Saito *et al* 2019; Kawashima *et al* 2021)[17 26]	Japan	224 (112/112)	80/144	67 (61–73)	222/1/0/1	IIIb–IV	111/113	PFS, OS, ORR, AEs,	Phase III RCT
Zhou *et al*, 2021[19]	China	311 (157/154)	118/193	57(27–78)	311/0/0/0	IIIb–IV	161/150	PFS, OS, ORR, AEs	Phase III RCT

AE, adverse event; EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

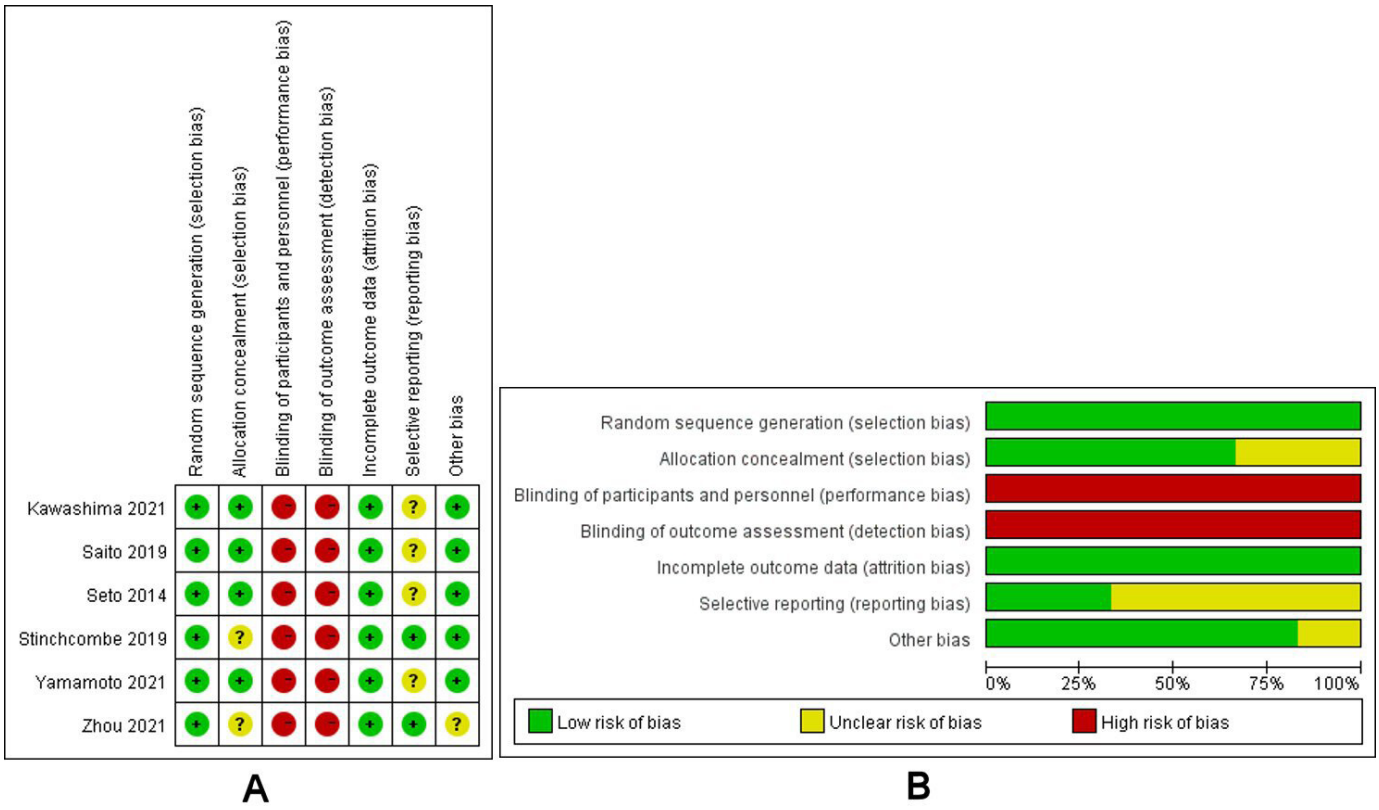

Figure 2 Summary (A) and graphical representation (B) of the risk of bias assessment.

Risk of bias and quality assessment

All publications presented adequate random sequence generation, and four publications indicated adequate allocation concealment.[16–18 26] There was not enough information to evaluate selective reporting in four publications.[16–18 26] Two publications[19 20] did not observe selective outcome reporting. All trials were open-label studies without blinding. All studies were free of incomplete outcome data. Five publications[16–18 20 26] guaranteed no other bias while another study[19] provided unclear information about bias. There was sufficient evidence to assess that all studies were moderate or high quality, and the results are shown in figure 2A,B.

Progression-free survival

Four publications[16 17 19 20] reported PFS across the four RCTs, with 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib group. Pooled analyses showed that erlotinib plus bevacizumab significantly reduced PFS compared with the erlotinib group (HR: 0.59; 95% CI 0.49 to 0.72; p<0.00001) (figure 3). No heterogeneity was observed (I^2=0%; p=0.55).

Overall survival

Four publications[17–19 26] reported OS across the four RCTs, with 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib group. Pooled analyses showed that erlotinib plus bevacizumab did not significantly reduce OS compared with the erlotinib group (HR: 0.95; 95% CI 0.78 to 1.15; p=0.59) (figure 4). No heterogeneity was observed (I^2=0%; p=0.58).

Objective response rate

Four publications[16 17 19 20] reported ORR across the four RCTs, with 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the

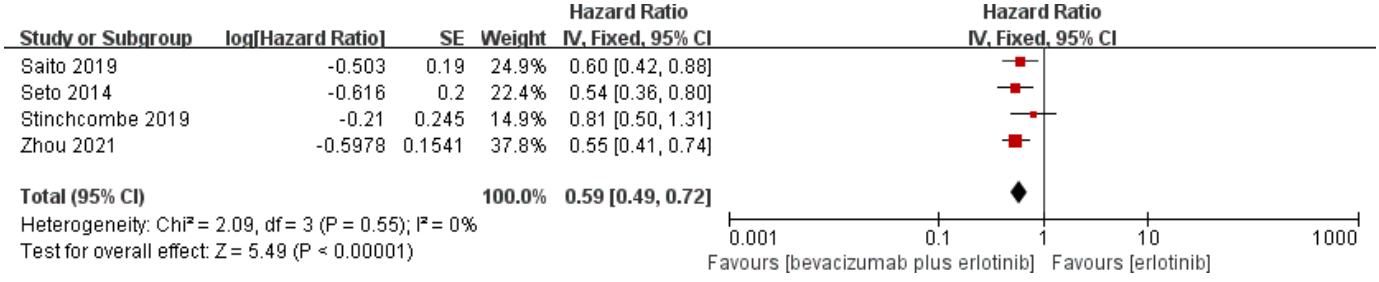

Figure 3 Forest plot of study results of progression-free survival (PFS).

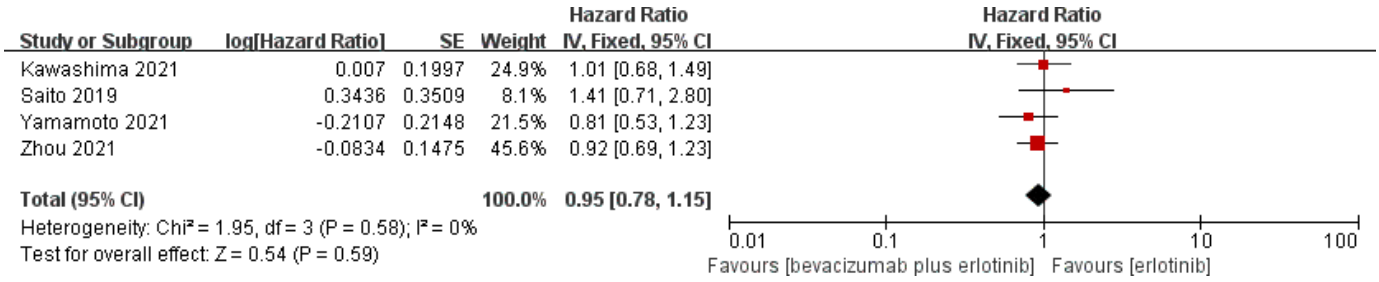

Figure 4 Forest plot of study results of overall survival (OS).

erlotinib group. The pooled analyses showed that erlotinib plus bevacizumab did not significantly reduce ORR compared with the erlotinib group (OR: 1.25; 95% CI 0.89 to 1.74; p=0.19) (figure 5). No heterogeneity was observed (I^2=0%; p=0.98).

Adverse effects

Eligible studies were specifically analysed to extract all grades of AEs and severe AEs (table 2). Four publications[16 17 19 20] reported AEs and severe AEs. A total of 776 cases were used for a pooled analysis of AEs, with 387 participants in the erlotinib plus bevacizumab intervention group and 389 participants in the erlotinib group. The numbers differed from the efficacy analyses because in the study by Zhou *et al*[19] one patient in the erlotinib alone group withdrew from the study before starting treatment, and in the study by Saito *et al*[17] two patients in the erlotinib monotherapy group were randomised in error. We defined grade 3–5 AEs as severe AEs. The results showed that incidence of diarrhoea (51% vs 43%, 95% CI 1.03 to 1.38; p=0.006) (online supplemental figure S1), haemorrhagic events (41% vs 20%, 95% CI 1.12 to 6.31; p=0.03) (online supplemental figure S2), proteinuria (25% vs 3%, 95% CI 4.86 to 17.66; p<0.0001) (online supplemental figure S3), hypertension (40% vs 8%, 95% CI 3.66 to 7.88; p<0.0001) (online supplemental figure S4), were higher when using erlotinib plus bevacizumab, in all grades of AE. No significant difference was found for rash (81% vs 85%, 95% CI 0.90 to 1.07; p=0.63) (online supplemental figure S5), paronychia (30% vs 28%, 95% CI 0.87 to 1.30; p=0.57) (online supplemental figure S6), stomatitis (28% vs 22%, 95% CI 0.89 to 1.96; p=0.17) (online supplemental figure S7). In the analysis of severe AEs, the combination treatment yielded significantly higher rates for proteinuria (8% vs 0.3%, 95% CI 3.54 to 45.97; p<0.001) (online supplemental figure S8) and hypertension (30% vs 5%, 95% CI 2.14 to 11.68; p<0.001) (online supplemental figure S9). There were no statistically significant differences for severe rash (14% vs 13%, 95% CI 0.78 to 1.56; p=0.59) (online supplemental figure S10), diarrhoea (4% vs 2%, 95% CI 0.76 to 3.68; p=0.20) (online supplemental figure S11), paronychia (1% vs 2%, 95% CI 0.17 to 1.66; p=0.28) (online supplemental figure S12), stomatitis (0.9% vs 1%, 95% CI 0.17 to 3.36; p=0.71) (online supplemental figure S13) or haemorrhagic event (2% vs 0.3%, 95% CI 0.74 to 16.87; p=0.11) (online supplemental figure S14). See the online supplemental material 2 file for the forest plot of the study results of AEs and severe AEs.

DISCUSSION

We performed a meta-analysis by combining patient data from four RCTs, with a total of 775 cases of lung cancer included in our efficacy analyses. We found that the concurrent use of erlotinib plus bevacizumab contributed to prolonging PFS compared with erlotinib as a single agent, but not to improving OS and ORR, in the treatment of *EGFRm*$^+$ advanced NSCLC. All grades of AEs and rash were more commonly found in the combination group and the single agent group. Furthermore, the incidence of diarrhoea, haemorrhagic events, proteinuria and hypertension was higher when erlotinib plus bevacizumab was used compared with erlotinib, in all grades of AEs. In the analysis of severe AE, combination treatment produced significantly higher rates for proteinuria and hypertension compared with erlotinib alone. Although a previous meta-analysis showed that the first-line angiogenesis inhibitor plus erlotinib prolonged PFS and did not improve OS in patients with *EGFRm*$^+$ advanced NSCLC compared with the erlotinib monotherapy group.[27] The

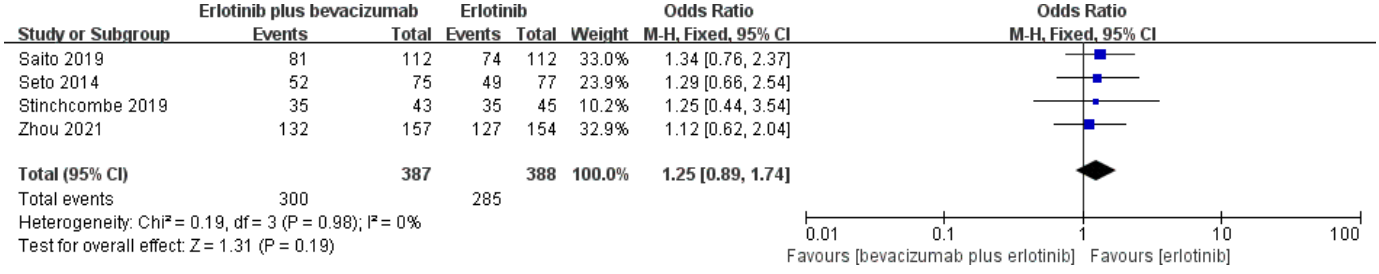

Figure 5 Forest plot of study results of objective response rate (ORR).

Table 2 All adverse effects and severe adverse effects of erlotinib plus bevacizumab

Adverse effects (all grades followed severe grades)	Erlotinib plus bevacizumab (event/total)	Erlotinib (event/total)	RR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
Rash	280/344	292/344	0.98 (0.90 to 1.07)	0.63	67	0.05
Diarrhoea	176/344	149/344	1.19 (1.03 to 1.38)	0.02	49	0.14
Paronychia	102/344	97/344	1.06 (0.87 to 1.30)	0.57	0	0.55
Stomatitis	95/344	75/344	1.32 (0.89 to 1.96)	0.17	52	0.12
Haemorrhagic event	141/344	70/344	2.66 (1.12 to 6.31)	0.03	89	<0.001
Proteinuria	86/344	9/344	9.26 (4.86 to 17.66)	<0.0001	0	0.41
Hypertension	138/344	26/344	5.37 (3.66 to 7.88)	<0.0001	0	0.89
Rash	54/387	50/389	1.10 (0.78 to 1.56)	0.59	0	0.69
Diarrhoea	15/387	9/389	1.67 (0.76 to 3.68)	0.20	25	0.26
Paronychia	4/344	8/344	0.54 (0.17 to 1.66)	0.28	0	0.75
Stomatitis	4/344	4/344	0.76 (0.17 to 3.36)	0.71	0	0.91
Haemorrhagic event	6/344	1/344	3.52 (0.74 to 16.87)	0.11	0	0.86
Proteinuria	30/387	1/389	12.75 (3.54 to 45.97)	<0.0001	0	0.95
Hypertension	117/387	18/389	5.00 (2.14 to 11.68)	0.0002	71	0.02

anti-VEGF plus erlotinib group in that meta-analysis included two different angiogenesis inhibitors (bevacizumab and ramucirumab), bevacizumab and ramucirumab showed different degrees of efficacy in cancer management, and thus with a potential for bias, which were overcome in the present analysis. In this study, we compared patient groups treated with erlotinib plus bevacizumab with those treated with erlotinib alone, to potentially increase the precision and decrease the bias of our study compared with the previous meta-analyses. Furthermore, we added three recent publications to our systematic review and meta-analysis. Therefore, we believe that our study provides comprehensive evidence-based recommendations for the relative efficacy and safety of erlotinib plus bevacizumab in *EGFR*m$^+$ advanced NSCLC.

Erlotinib plus bevacizumab significantly prolonged PFS compared with erlotinib alone in patients with *EGFR*m$^+$ advanced NSCLC. Furthermore, the addition of bevacizumab to chemotherapy treatment has been shown to be effective in patients with NSCLC with central nervous system metastases.[28–30] There are several possible reasons why the addition of bevacizumab to the erlotinib regimen improved efficacy in terms of PFS compared with erlotinib. One possible mechanism is that the combination of bevacizumab could improve drug delivery[31] because bevacizumab alters tumour blood vessel physiology, leading to increased intratumoural absorption of drugs.[32] A preclinical study[33] demonstrated that tumours treated with the lowest dose of an *EGFR* TKI (gefitinib) developed drug resistance earlier than those with higher doses. Therefore, a higher intratumoural concentration of erlotinib could prolong resistance to TKIs. Another possible mechanism is that bevacizumab may restore cell apoptosis by inhibiting the VEGF-mediated pathway.[34] Due to synergistic inhibition of cancer growth signalling, VEGF signal inhibition is still effective for cancers with *EGFR* TKI resistant mutations.[35] An animal study[36] suggested that erlotinib plus bevacizumab treatment restored resistance to the VEGF-mediated pathway. Therefore, in the clinic, the addition of bevacizumab to erlotinib is an optional strategy to delay the onset of TKI resistance in NSCLC.[21 37]

In our meta-analysis, neither ORR nor OS were prolonged by combination therapy. For ORR, this lack of improvement can be explained by the high sensitivity of these NSCLCs to *EGFR* TKIs. Due to the high ORR in the erlotinib alone group, a larger study population is required to demonstrate a significant effect of the combination regimen. The combination of bevacizumab and erlotinib failed to translate into OS benefit, which can be explained as outlined below. Although OS might have been influenced by patient therapy after disease progression, because there are many options for the treatment of NSCLC, any outcome of first-line treatment on OS can be influenced by subsequent treatment.[38] In a study by Zhou *et al*[19] more patients in the erlotinib group received subsequent anticancer treatment than in the erlotinib plus bevacizumab group (50.0% (77/154) vs 33.8% (53/157)), which could have influenced the OS result. Conversely, there may be different acquired resistance mechanisms between the two groups. Furthermore, the lack of OS benefit in the erlotinib plus bevacizumab group may be explained by the differences in the proportion of patients who receive subsequent lines of osimertinib therapy. In the Zhou *et al*[19] study, more patients received osimertinib in the erlotinib group as a subsequent treatment than in the erlotinib plus bevacizumab group (29.2% (27/157) vs 17.2% (45/154)).

Concerning safety, erlotinib plus bevacizumab is more toxic than erlotinib alone and there are known toxicities associated with bevacizumab treatment, especially for diarrhoea, haemorrhagic events, proteinuria and hypertension.[39 40] In most cases, toxicity of combination

therapy was considered to be tolerable and manageable;[41] patients will not choose to terminate drug treatment early due to an AE, so patients can achieve the benefits of treatment with erlotinib plus bevacizumab.

Our current meta-analysis has some strengths. We comprehensively researched the pooled data from the most up-to-date high-quality RCTs and provided best level of evidence that demonstrated the efficacy and safety of erlotinib plus bevacizumab in patients with advanced *EGFR*m$^+$ NSCLC. The recommended first-line treatment for advanced *EGFR*m$^+$ NSCLC is often osimertinib, a third-generation *EGFR* TKI. First-generation and second-generation *EGFR* TKIs, *EGFR* TKI plus bevacizumab or *EGFR* TKI plus ramucirumab are also available as treatment options.[42 43] However, most patients eventually develop disease progression due to acquired drug resistance.[44] Our meta-analysis provided evidence that the erlotinib plus bevacizumab combination prolongs PFS compared with erlotinib alone; therefore, in the clinic, when erlotinib monotherapy is ineffective, the addition of bevacizumab to erlotinib is an optional strategy for the treatment of *EGFR*m$^+$ advanced NSCLC.

Our meta-analysis had several potential limitations. First, only four trials were available to include in the analysis, and some of these studies had relatively small sample sizes. Although these results were of high quality and were derived from well-performing trials, our conclusions should be interpreted with caution because smaller trials are more likely to result in an overestimation of the treatment effects. Second, our study failed to consider the effects of previous treatment and smoking status in some of the enrolled participants, due to the lack of corresponding data and information. Third, a subgroup analysis of *EGFR* mutation status of NSCLC was not conducted due to insufficient information on these factors in the included trials. NSCLC is a molecularly heterogeneous disease,[45] the ex19del and ex21 L858R mutations are the two most commonly reported *EGFR* variants,[46] therefore, a subgroup analysis based on the *EGFR* mutation status of patients treated with erlotinib plus bevacizumab is warranted in the future. Finally, there may have been a bias in the selection of positive studies. It is understandable that journals do not like to present negative data, so this may also have led to an overestimation of the treatment effect.

CONCLUSIONS

Based on the present evidence, although the combined strategy of erlotinib plus bevacizumab prolonged PFS for the treatment of *EGFR*m$^+$ advanced NSCLC, this strategy failed to significantly improve OS, and exhibited common but acceptable AEs such as diarrhoea, haemorrhagic event, proteinuria and hypertension. This combination can be recommended as a therapeutic strategy for patients with advanced *EGFR*m$^+$ NSCLC.

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Contributors WD: study design, data collection and analysis, statistical analysis and manuscript drafting, manuscript revision. KW: study design, data collection and analysis, statistical analysis and manuscript drafting. YJ: data collection and analysis, manuscript revision. DL: data collection and analysis, statistical analysis. CB: data collection and analysis, manuscript revision. JL: study design, manuscript revision. LL: data collection. BH: statistical analysis. JK: study design, manuscript drafting and manuscript revision. JK is responsible for the overall content as the guarantor. All authors read and approved the manuscript.

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Disclaimer This study was a systematic review and meta-analysis. Ethics committee approval was not necessary because all data were carefully extracted from existing literature.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

1 Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71:7–33.
2 Suster DI, Mino-Kenudson M. Molecular pathology of primary non-small cell lung cancer. *Arch Med Res* 2020;51:784–98.
3 Jones GS, Baldwin DR. Recent advances in the management of lung cancer. *Clin Med* 2018;18:s41–6.
4 Harðardottir H, Jonsson S, Gunnarsson O, *et al*. [Advances in lung cancer diagnosis and treatment - a review]. *Laeknabladid* 2022;108:17–29.
5 The Lancet. Lung cancer: some progress, but still a lot more to do. *Lancet* 2019:1880.
6 Wu S-G, Shih J-Y. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. *Mol Cancer* 2018;17:38.

7 Wu Y-L, Zhou C, Hu C-P, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:213–22.
8 He J, Huang Z, Han L, *et al*. Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (review). *Int J Oncol* 2021;59.
9 Garcia J, Hurwitz HI, Sandler AB, *et al*. Bevacizumab (Avastin(R)) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev* 2020;86:102017.
10 Sandler A, Gray R, Perry MC, *et al*. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–50.
11 Bagley SJ, Talento S, Mitra N, *et al*. Comparative effectiveness of carboplatin/pemetrexed with versus without bevacizumab for advanced nonsquamous non-small cell lung cancer. *J Natl Compr Canc Netw* 2019;17:469–77.
12 Ding T, Li Z-T, Zhang X, *et al*. Comparison of carboplatin and paclitaxel with or without bevacizumab in chemotherapeutic regimens for unresectable stage III non-small cell lung cancer. *Eur Rev Med Pharmacol Sci* 2017;21:3723–9.
13 Wang Y, Wang H, Jiang Y, *et al*. A randomized phase III study of combining erlotinib with bevacizumab and panitumumab versus erlotinib alone as second-line therapy for Chinese patients with non-small-cell lung cancer. *Biomed Pharmacother* 2017;89:875–9.
14 Zhao B, Zhang W, Yu D, *et al*. Erlotinib in combination with bevacizumab has potential benefit in non-small cell lung cancer: a systematic review and meta-analysis of randomized clinical trials. *Lung Cancer* 2018;122:10–21.
15 Rosell R, Dafni U, Felip E, *et al*. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. *Lancet Respir Med* 2017;5:435–44.
16 Seto T, Kato T, Nishio M, *et al*. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014;15:1236–44.
17 Saito H, Fukuhara T, Furuya N, *et al*. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019;20:625–35.
18 Yamamoto N, Seto T, Nishio M, *et al*. Erlotinib plus bevacizumab vs erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: survival follow-up results of the randomized JO25567 study. *Lung Cancer* 2021;151:20–4.
19 Zhou Q, Xu C-R, Cheng Y, *et al*. Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study. *Cancer Cell* 2021;39:e1273:1279–91.
20 Stinchcombe TE, Jänne PA, Wang X, *et al*. Effect of erlotinib plus bevacizumab vs erlotinib alone on progression-free survival in patients with advanced *EGFR*-mutant non-small cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2019;5:1448–55.
21 Yang Y, Wang L, Li X, *et al*. Efficacy and safety of bevacizumab combined with EGFR-TKIs in advanced non-small cell lung cancer: a meta-analysis. *Thorac Cancer* 2022;13:31–7.
22 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W65–94.
23 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
24 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
25 Zhao Y, Liu J, Cai X, *et al*. Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis. *BMJ* 2019;367:l5460.
26 Kawashima Y, Fukuhara T, Saito H, *et al*. Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutant non-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Respir Med* 2022;10:72–82.
27 Landre T, Des Guetz G, Chouahnia K, *et al*. First-line angiogenesis inhibitor plus erlotinib versus erlotinib alone for advanced non-small-cell lung cancer harboring an EGFR mutation. *J Cancer Res Clin Oncol* 2020;146:3333–9.
28 Nie K, Zhang Z, You Y, *et al*. A randomized clinical study to compare intrapleural infusion with intravenous infusion of bevacizumab in the management of malignant pleural effusion in patients with non-small-cell lung cancer. *Thorac Cancer* 2020;11:8–14.
29 Lu Z-Q, Cai J, Wang X, *et al*. Osimertinib combined with bevacizumab for leptomeningeal metastasis from EGFR-mutation non-small cell lung cancer: a phase II single-arm prospective clinical trial. *Thorac Cancer* 2021;12:172–80.
30 Gubens MA, Chuang JC, Akerley W, *et al*. A pooled analysis of advanced nonsquamous non-small cell lung cancer patients with stable treated brain metastases in two phase II trials receiving bevacizumab and pemetrexed as second-line therapy. *J Thorac Dis* 2018;10:219–27.
31 Ilhan-Mutlu A, Osswald M, Liao Y, *et al*. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther* 2016;15:702–10.
32 Dickson PV, Hamner JB, Sims TL, *et al*. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res* 2007;13:3942–50.
33 Hayakawa H, Ichihara E, Ohashi K, *et al*. Lower gefitinib dose led to earlier resistance acquisition before emergence of T790M mutation in epidermal growth factor receptor-mutated lung cancer model. *Cancer Sci* 2013;104:1440–6.
34 Pan C-F, Zhang X, Wang J-W, *et al*. Weichang'an formula inhibits tumor growth in combination with bevacizumab in a murine model of colon cancer-making up for the deficiency of bevacizumab by inhibiting VEGFR-1. *Front Pharmacol* 2020;11:512598.
35 Ichihara E, Ohashi K, Takigawa N, *et al*. Effects of vandetanib on lung adenocarcinoma cells harboring epidermal growth factor receptor T790M mutation in vivo. *Cancer Res* 2009;69:5091–8.
36 Masuda C, Yanagisawa M, Yorozu K, *et al*. Bevacizumab counteracts VEGF-dependent resistance to erlotinib in an EGFR-mutated NSCLC xenograft model. *Int J Oncol* 2017;51:425–34.
37 Herbst RS, Sandler A. Bevacizumab and erlotinib: a promising new approach to the treatment of advanced NSCLC. *Oncologist* 2008;13:1166–76.
38 Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc* 2019;94:1623–40.
39 Zhang S, Mao X-D, Wang H-T, *et al*. Efficacy and safety of bevacizumab plus erlotinib versus bevacizumab or erlotinib alone in the treatment of non-small-cell lung cancer: a systematic review and meta-analysis. *BMJ Open* 2016;6:e011714.
40 Herbst RS, O'Neill VJ, Fehrenbacher L, *et al*. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. *J Clin Oncol* 2007;25:4743–50.
41 Kato T, Seto T, Nishio M, *et al*. Erlotinib plus bevacizumab phase LI study in patients with advanced non-small-cell lung cancer (JO25567): updated safety results. *Drug Saf* 2018;41:229–37.
42 Yoneda K, Imanishi N, Ichiki Y, *et al*. Treatment of non-small cell lung cancer with EGFR-mutations. *J Uoeh* 2019;41:153–63.
43 Johnson M, Garassino MC, Mok T, *et al*. Treatment strategies and outcomes for patients with EGFR-mutant non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors: focus on novel therapies. *Lung Cancer* 2022;170:41–51.
44 Tsubata Y, Tanino R, Isobe T. Current therapeutic strategies and prospects for EGFR Mutation-Positive lung cancer based on the mechanisms underlying drug resistance. *Cells* 2021;10:3192 doi:10.3390/cells10113192
45 Jamal-Hanjani M, Wilson GA, McGranahan N, *et al*. Tracking the evolution of non-small-cell lung cancer. *N Engl J Med* 2017;376:2109–21.
46 Ramalingam SS, Vansteenkiste J, Planchard D, *et al*. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med* 2020;382:41–50.