BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062036
Article Type:	Original research
Date Submitted by the Author:	17-Feb-2022
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Keywords:	Adult oncology < ONCOLOGY, Gene therapy < ONCOLOGY, Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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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 Randomized Controlled Trials

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ABSTRACT

Objectives Therapy erlotinib plus bevacizumab has the potential to become a standard treatment 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 *EGFR*m$^+$ advanced NSCLC patients.

Setting A systematic review and meta-analysis.

Participants Patients were diagnosed as *EGFR*m$^+$ advanced NSCLC.

Interventions Erlotinib plus bevacizumab.

Primary and secondary outcome measures Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) and adverse effects (AEs).

Results Six RCTs with a total of 775 cases were included in the meta-analysis. Of these, 387 cases were treated by erlotinib plus bevacizumab, and 388 cases were treated by erlotinib alone. Compared with erlotinib alone group, erlotinib plus bevacizumab group significantly prolonged the PFS (hazard ratio (HR): 0.59; 95% confidence interval (CI): 0.49-0.72; $P < 0.00001$; $I^2 = 0\%$), but failed to significantly prolonged the OS (HR: 0.95; 95% CI: 0.78-1.15; $P = 0.59$; $I^2 = 0\%$), and the ORR (odds ratio (OR): 1.25; 95% CI: 0.89–1.74; $P = 0.19$; $I^2 = 0\%$). Incidence of

proteinuria, hypertension or proteinuria was higher in erlotinib plus bevacizumab group than in erlotinib alone group.

Conclusions For treatment of patients with *EGFR*m$^+$ advanced NSCLC, the erlotinib plus bevacizumab, compared to erlotinib alone, was associated with significantly prolonged PFS, but there is no substantial difference in OS and ORR.

INTRODUCTION

Lung cancer is the leading incidence and mortality of cancer in the world.[1] Approximately 80-85% lung cancer has non-small cell lung cancer (NSCLC) subtypes.[2] Despite the rapid development of novel diagnosis and therapeutic strategies, approximately 62% patients with lung cancer are diagnosed at advanced stage and prognosis remains poor,[3 4] 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 epidermal growth factor receptor mutation-positive (*EGFR*m$^+$) lung cancer.[6] Although 60-80% of patients with *EGFR*-mutant tumors had durable responses, median progression-free survival (PFS) is around 1 year 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 improve outcomes for these patients.

Bevacizumab is a recombinant anti-angiogenic monoclonal antibody, which directly targets the vascular endothelial growth factor (VEGF) signaling pathway to inhibit tumor angiogenesis and suppress growth.[8] Studies have suggested that bevacizumab combined with first-line platinum-based chemotherapy has a significant survival benefit in several trials in NSCLC.[9-11] The combination of erlotinib and bevacizumab has the potential to prolong PFS in unselected populations of patients with NSCLC.[12 13] However, these studies were conducted in *EGFR*-unselected cases. Moreover, the clinical relevance of *EGFR*m$^+$ in NSCLC had not yet been clarified. The first study that provided some important information respecting the efficacy of combining bevacizumab and erlotinib in *EGFR*-mutant subgroup population was Rosell:[14] a phase 2 trial of erlotinib and bevacizumab. It showed that the benefit for

the combined use of erlotinib and bevacizumab in patients with *EGFR*-mutant NSCLC. However, this study evidence is insufficient as a result of single-arm trail. The effects of erlotinib plus bevacizumab in *EGFR*m$^+$ advanced NSCLC remain controversial. The results of some randomized controlled trials (RCTs) have shown that erlotinib plus bevacizumab can prolong the PFS、objective response rate (ORR) in *EGFR*m$^+$ advanced NSCLC.[15-18] In contrast, some studies reported comparable efficacy in erlotinib plus bevacizumab group and erlotinib alone group.[19] Thus, the aim of this systematic review and meta-analysis was to evaluate the effects of erlotinib plus bevacizumab in *EGFR*m$^+$ advanced NSCLC patients.

METHODS

We conducted the systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[20]

Inclusion and exclusion criteria

Adult participants with histologically or cytologically diagnosed NSCLC harboring *EGFR*-mutant with Eastern Cooperative Oncology Group performance status scores of 2 or lower. 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, 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, ORR of treatment for NSCLC. Secondary outcome was adverse events (AEs) of the 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. Language was limited to English. The combined text and medical subject heading (MeSH) terms used were: “Carcinoma, Non-Small-Cell Lung” and “Erlotinib Hydrochloride” and “Bevacizumab” (see online supplemental material 1 file for further details on 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 were extracted: the first author's name, year of publication, region, participants' characteristics [e.g., age, sex, ethnic origin, brain], the number of participants in each group, description and doses of therapeutic agents administered, tumor histology, and type of *EGFR* mutation and AEs. The efficacy criteria analyzed 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 risk of bias of included trials[21]. Two investigators evaluated each trial independently based on random sequence generation, allocation concealment, blinding of participants, blinding of outcome, incomplete outcome date, selective reporting, and other biases[22]. Discrepancies and divergence in the quality assessment were resolved by group discussion.

Statistical analysis

The outcomes of OS and PFS were estimated by Hazard ratio (HR) with 95% confidence interval (CI). Relative risk (RR) was used to estimate the outcomes of AEs and ORR with 95% CI. We used I^2 statistic to assess the level of heterogeneity. The I^2 < 25%, 25-50%, and > 50% were defined as low, mild, and substantial heterogeneity[23]. If $I^2 < 50\%$, p value > 0.05, a fixed-effects model was used in the meta-analysis; In contrast, If $I^2 \geq 50\%$, p value ≤ 0.05, a random effect model was used to assess the resource of the heterogeneity. All statistical analyses were performed using RevMan version 5.4 provided by the Cochrane Collaboration, and P value < 0.05 was considered statistically significant.

Patient and public involvement statement

Neither patients nor the public were involved in the design and planning of our research.

RESULTS

Results of the literature search

The study flowchart 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, and 485 publications were no relevant studies, 118 publications were meta-analysis, 3 publications were animal experiment, and 16 publications were review. 622 of which were excluded. We screened the remaining 22 articles carefully, and 6 studies met our eligibility criteria and were included in the present meta-analysis.

Basic characteristics of studies included

The basic information included the authors, date of publication, participants region, age, tumor histology, clinical stage, *EGFR* genomic aberration (Table 1). In the 6 studies[15-19 24] included in the meta-analysis, Saito et al.[16] and Kawashima et al.[24] are NEJ026 study, and Seto et al.[15] and Yamamoto et al.[17] are JO25567 study. The erlotinib plus bevacizumab group contained 387 cases and the erlotinib group contained 388 cases. Patients assigned to the erlotinib plus bevacizumab group received 150 mg of oral erlotinib form once daily and 15 mg/kg of intravenous bevacizumab once every 21 days, starting from day 1 of cycle 1. Patients in the erlotinib alone group received 150 mg of oral erlotinib once daily. One treatment cycle was defined as 21 days.

Table 1 Characteristics of included randomized controlled trials

Study	Region	Participant (male/female)	Age	Histology(adenocarcinoma/large cell carcinoma/squamous cell/ others)	Clinical stage	EGFR genomic aberration(19 deletion/21 Leu858Arg mutation)	Outcome	Study design
Seto et al.,[15] 2014	Japan (multicenter)	152(56/96)	67(59-73)	150/1/0/1	IIIb-IV	80/72	PFS 、 ORR 、 AEs	phase 2 RCT
Stinchcombe et al.,[19] 2019	America (multicenter)	88(26/62)	63(31-84)	-	M1a 、 M1b	59/29	PFS 、 ORR 、 OS、AEs	Phase 2 RCT
Saito et al.,[16] 2019	Japan (multicenter)	224(80/144)	67(61-73)	222/1/0/1	IIIb-IV	111/113	PFS、AEs、	phase 3 RCT
Kawashima et al.,[24] 2021	Japan (multicenter)	224(80/144)	67(61-73)	222/1/0/1	IIIb-IV	111/113	OS	phase 3 RCT
Yamamoto et al.,[17] 2021	Japan (multicenter)	152(56/96)	67(59-73)	150/1/0/1	IIIb-IV	80/72	OS	phase 2 RCT
Zhou et al.,[18] 2021	Chinese (multicenter)	311(118/193)	57 (27-78)	311/0/0/0	IIIb-IV	161/150	PFS 、 OS 、 ORR	phase 3 RCT

Risk of bias and quality assessment

All studies performed adequate random sequence generation, and four studies performed adequate allocation concealment.[15-17 24] There was not enough information to assess the selective reporting in four studies,[15-17 24] Two RCTs[18 19] performed no selective outcome reporting was observed. All RCTs studies were open-label studies without blinding. All the studies were free of incomplete outcome data. Five studies[15-17 19 24] guaranteed no other bias while the other one study[18] provided unclear information about bias. There was sufficient evidence to assess that all the RCTs studies were moderate or high quality, and the results are shown in Figure 2(a) and Figure 2(b).

Progression-free survival

Four studies[15 16 18 19] reported PFS in the erlotinib plus bevacizumab group and erlotinib group. There were 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 erlotinib group (HR: 0.59; 95% CI: 0.49-0.72; P < 0.00001; Figure 3). No heterogeneity was observed (I^2 = 0%; P = 0.55).

Overall survival

Four studies[16-18 24] reported OS in the erlotinib plus bevacizumab group and erlotinib group. There were 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib group. Pooled analyses showed that erlotinib plus bevacizumab not significantly reduced the os compared with erlotinib group (HR: 0.95; 95% CI: 0.78–1.15; P = 0.59; Figure 4). No heterogeneity was observed (I^2 = 0%; P = 0.58).

Objective response rate

Four studies[15 16 18 19] reported ORR in the erlotinib plus bevacizumab group and erlotinib group. There were 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib group. Pooled analyses showed that erlotinib plus bevacizumab not significantly reduced the ORR compared

with erlotinib group (Odds ratio: 1.25; 95% CI: 0.89–1.74; P = 0.19; Figure 5). No heterogeneity was observed (I^2 = 0%; P = 0.98).

Adverse effects

Eligible studies were specifically analyzed to extract all grades of AEs and severe AEs (Table 2). We defined grade 3-5 AEs as severe AEs. The results showed that incidence of diarrhea (51 vs. 43%, 95% CI: 1.03-1.38; P = 0.006; Figure S1), haemorrhagic event (41 vs. 20%, 95% CI: 1.12-6.31; P = 0.03; Figure S2), proteinuria (25 vs. 3%, 95% CI: 4.86-17.66; P < 0.0001; Figure S3), hypertension (40 vs. 8%, 95% CI: 3.66-7.88; P < 0.0001; 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: 0.90-1.07; P = 0.63; Figure S5), paronychia (30 vs. 28%, 95% CI: 0.87-1.30; P = 0.57; Figure S6), stomatitis (28 vs. 22%, 95% CI: 0.89-1.96; P = 0.17; Figure S7). In the analysis of severe AEs, the combination treatment yielded significantly higher rates for proteinuria (8 vs. 0.3%, 95% CI: 3.54-45.97; P < 0.001; Figure S8) and hypertension (30 vs. 5%, 95% CI: 2.14-11.68; P < 0.001; Figure S9). No significant difference existed for severe rash (14 vs. 13%, 95% CI: 0.78-1.56; P = 0.59; Figure S10), diarrhea (4 vs. 2%, 95% CI: 0.76-3.68; P = 0.20; Figure S11), paronychia (1 vs. 2%, 95% CI: 0.17-1.66; P = 0.28; Figure S12), stomatitis (0.9 vs. 1%, 95% CI: 0.17-3.36; P = 0.71; Figure S13), or haemorrhagic event (2 vs. 0.3%, 95% CI: 0.74-16.87; P = 0.11; Figure S14). (see online supplemental material 2 file for forest plot of study results of AEs and severe AEs).

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

DISCUSION

We conducted the meta-analysis by combining six RCTs studies, a total of 775 lung cancer cases were included in our analyses. We found that concurrent use of erlotinib plus bevacizumab contributed to prolong PFS compared with erlotinib as a single agent, but not to improve OS and ORR, in the treatment of *EGFR*m$^+$ advanced NSCLC patients. All grades of AEs, rash were more commonly found in the combination group and single agent group. In addition, incidence of diarrhea, haemorrhagic event, proteinuria and hypertension were higher when using erlotinib plus bevacizumab compared with erlotinib, in all grades of AEs. In the analysis of

severe AEs, the combination treatment yielded significantly higher rates for proteinuria and hypertension compared with erlotinib alone.

Erlotinib plus bevacizumab significantly prolonged PFS compared with erlotinib alone in *EGFR*m+ advanced NSCLC patients. Moreover, the addition of bevacizumab to chemotherapy treatment is proved to be effective in NSCLC patients with central nervous system metastases.[25-27] There are several possible reasons why the addition of bevacizumab to erlotinib improved efficacy in terms of PFS compared with erlotinib. One possible mechanism is that bevacizumab combination could be improved drug delivery.[28] Since bevacizumab alter tumour blood vessel physiology, which will lead to increase intratumoral absorb of drugs.[29] A preclinical study[30] demonstrated that tumors treated with the lower dose of *EGFR* TKIs(gefitinib) developed earlier drug resistance than those with higher doses. Hence, a higher doses intratumoral concentration of erlotinib could extend TKIs resistant. Another possible mechanism is that bevacizumab may improve the restoration of cell apoptosis via VEGF-mediated pathway inhibition.[31] Due to synergistic inhibition of cancer growth signalling, VEGF signal inhibition is still effective for cancers with *EGFR* TKIs resistance mutations.[32] An animal study[33] suggested that erlotinib plus bevacizumab treatment restored resistance to the VEGF-mediated pathway. Therefore, in the clinic, the addition of bevacizumab to the erlotinib treatment is option strategy to delay the time of TKIs resistant in the treatment of NSCLC.[34 35]

In contrast, in our meta-analysis, neither the ORR nor OS be prolonged by the combination therapy. For ORR, this lack of improvement can be explained by the high sensitivity of these NSCLC to *EGFR* TKIs. Owing to a high ORR for in erlotinib alone group, thereby it is required a larger study population to prove significant effect of the combination regimen. For OS, the combination of bevacizumab and erlotinib failed to be translated into OS benefit, which can be explained by the following possible reasons. On one hand, OS might have been influenced by the patient therapy after disease progression. As there are many options for the treatment of NSCLC, any impact of first-line treatment on OS may be affected by subsequent treatment.[36] In zhou[18] study, more patients from erlotinib group received subsequent anticancer

treatment than in the erlotinib plus bevacizumab group (50.0% [77/154] versus 33.8% [53/157]), could have affected the OS result. On the anther hand, there may be different acquired resistance mechanisms between the two groups. The lack of OS benefit in the erlotinib plus bevacizumab group may be explained by the difference in the proportion of patients who subsequent-line osimertinib therapy. In zhou[18] study, more patients received osimertinib in the erlotinib group as subsequent treatment than in the erlotinib plus bevacizumab group (29.2% [27/157] versus 17.2% [45/154]).

Concerning safety, the erlotinib plus bevacizumab is more toxic than erlotinib alone group and are known toxicities associated with bevacizumab treatment, especially for diarrhea, haemorrhagic event, proteinuria, and hypertension.[37 38] In most cases, the toxicity of combination therapy was deemed to be tolerable and manageable,[39] patients will not choose to terminate drug treatment early because of these AEs, so patients can obtain the benefit from erlotinib plus bevacizumab group treatment.

Our current meta-analysis has some strengths. We comprehensively researched pooled data of the most up-to-date high-quality RCTs and provided best level of evidence demonstrating the efficacy and safety of erlotinib plus bevacizumab in *EGFR*m$^+$ advanced NSCLC patients. As we all known, the recommended first-line treatment for advanced *EGFR*m$^+$ NSCLC is first generation, second generation, third generation *EGFR* TKI, *EGFR* TKI plus bevacizumab or *EGFR* TKI plus ramucirumab.[40] Our meta-analysis provided evidence that erlotinib plus bevacizumab group prolong PFS compared with erlotinib alone group, therefore, in the clinic, when erlotinib monotherapy is not effective, the addition of bevacizumab to the erlotinib is option strategy in the treatment of *EGFR*m$^+$ advanced NSCLC. However, our meta-analysis demonstrated that erlotinib plus bevacizumab group failed to improve OS compared with erlotinib alone group, so additional high-quality RCTs with large samples are still required.

Our meta-analysis had several potential limitations. First, only six studies were available to include in the analysis, and some of these studies had relatively small sample sizes. Although these studies were high quality and well-performed trials, our conclusions should be cautiously interpreted, because smaller trials are more likely to

result in overestimation of the treatment effect. Second, our study failed to consider the effect of previous treatment, and smoking status on partially enrolled participants, due to lack of corresponding data and information. Third, subgroup analyses of *EGFR* mutation state of NSCLC were not conducted due to insufficient information on these factors in the included trials. NSCLC is a molecularly heterogeneous disease,[41] the ex19del and ex21 L858R were the two most common mutations in *EGFR*,[42] hence the subgroup analysis of *EGFR* mutation state of patients treated with erlotinib plus bevacizumab is need further study. Finally, the OS data from the included trials were not mature enough, so the data might change in the future and, hence, updating the meta-analysis with final OS data will be essential.

CONCLUSIONS

The results of this meta-analysis confirmed the PFS prolongation achieved with erlotinib plus bevacizumab compared to erlotinib alone to treat *EGFR*m$^+$ advanced NSCLC, without being able to prolong OS.

Contributors WSD: 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. DBL: data collection and analysis, statistical analysis. CXB: data collection and analysis, manuscript revision. JL: study design, manuscript revision. LYL: data collection. BH: statistical analysis. JLK: study design, manuscript drafting, and manuscript revision. All authors read and approved the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No.81760743、82160783 and 82104499).

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.

Ethics approval This study does not involve human participants.

Patient consent for publication Not applicable.

Data sharing statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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figure legend

Figure 1 Flowchart of the literature screening.

Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

Figure 3 Forest plot of study results of PFS.

Figure 4 Forest plot of study results of OS.

Figure 5 Forest plot of study results of ORR.

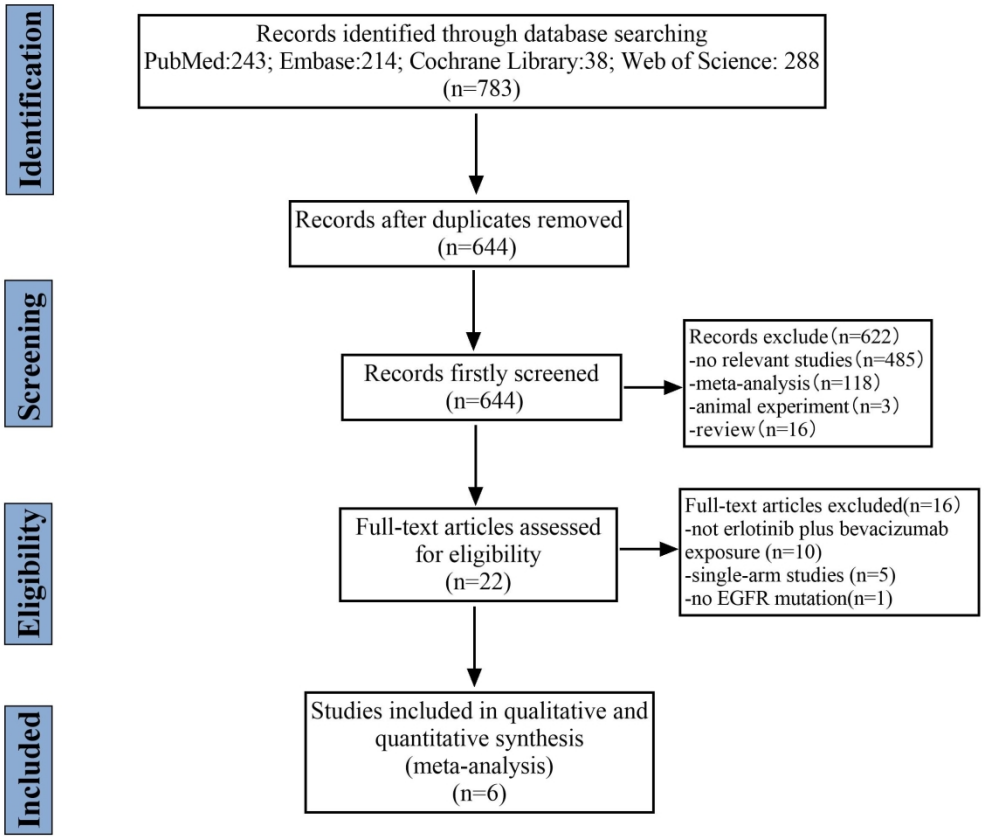

Figure 1 Flowchart of the literature screening.

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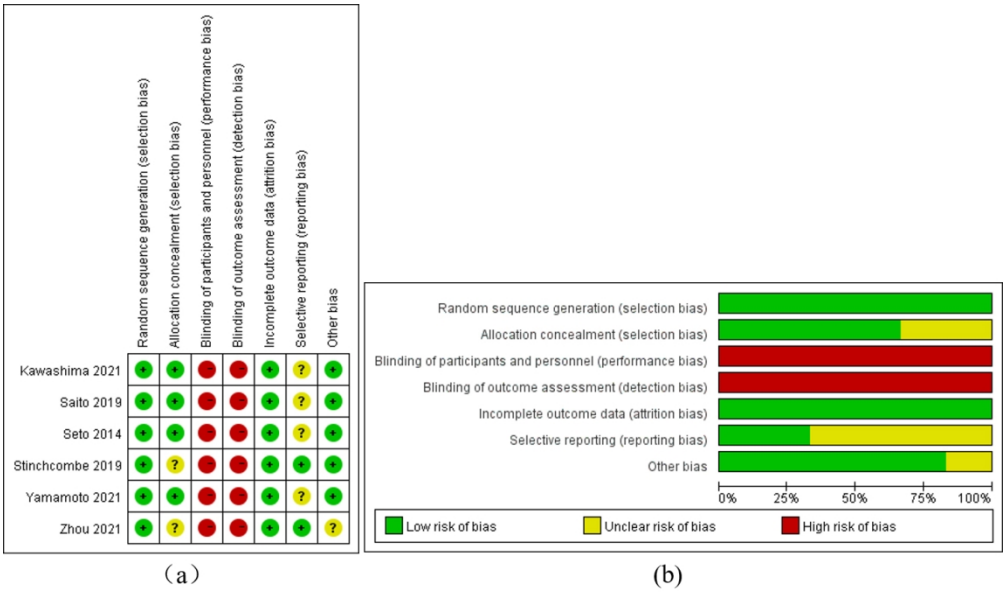

Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

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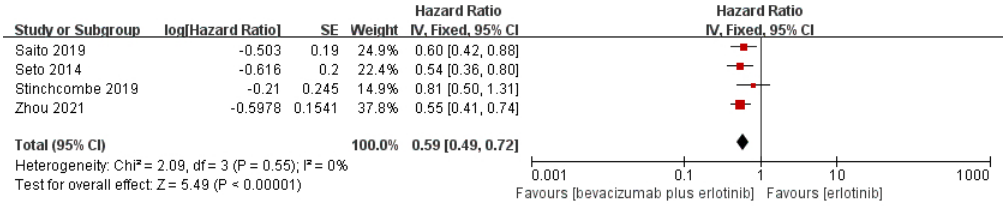

Figure 3 Forest plot of study results of PFS.

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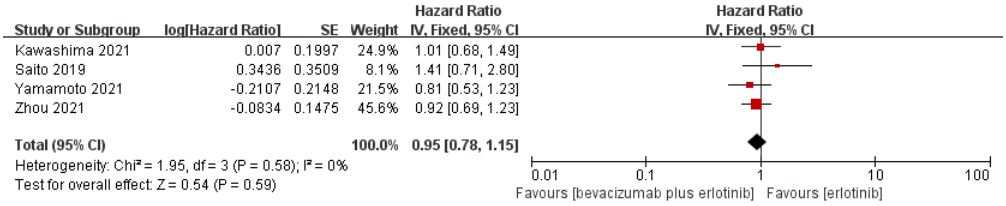


Figure 4 Forest plot of study results of OS.

293x62mm (72 x 72 DPI)

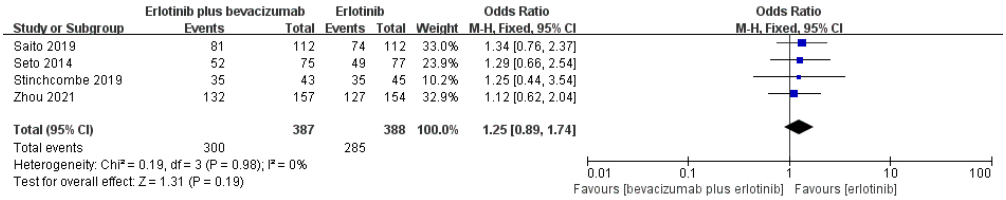


Figure 5 Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

Pubmed Search Strategy:

((((((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR ((((((((((Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cance[Title/Abstract]))) AND ("Erlotinib Hydrochloride"[Mesh])) OR ((((((((((((((((((Hydrochloride, Erlotinib[Title/Abstract]) OR (Erlotinib HCl[Title/Abstract])) OR (HCl, Erlotinib[Title/Abstract])) OR (OSI-774[Title/Abstract])) OR (OSI 774[Title/Abstract])) OR (OSI774[Title/Abstract])) OR (CP 358774[Title/Abstract])) OR (358774, CP[Title/Abstract])) OR (CP 358,774[Title/Abstract])) OR (358,774, CP[Title/Abstract])) OR (CP-358,774[Title/Abstract])) OR (CP358,774[Title/Abstract])) OR (CP-358774[Title/Abstract])) OR (CP358774[Title/Abstract])) OR (11C-erlotinib[Title/Abstract])) OR (11C erlotinib[Title/Abstract])) OR (Erlotinib[Title/Abstract])) OR (N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine[Title/Abstract])) OR (Tarceva[Title/Abstract]))) AND ("Bevacizumab"[Mesh])) OR ((((Mvasi[Title/Abstract]) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract]))) AND

(（randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR

placebo[Title/Abstract]）).

Embase Search Strategy:

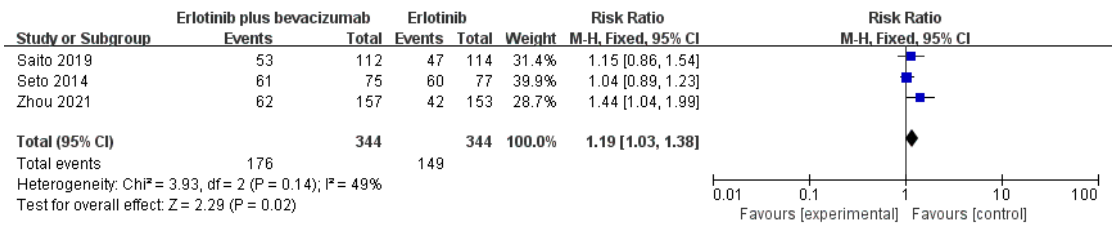
'carcinoma, non small cell lung':ab,ti OR ('carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung carcinoma':ab,ti OR 'non-small cell lung cancer':ab,ti) AND(erlotinib AND hydrochloride OR 'hydrochloride, erlotinib':ab,ti OR 'erlotinib hcl':ab,ti OR 'hcl, erlotinib':ab,ti OR 'osi-774':ab,ti OR 'osi 774':ab,ti OR 'osi774':ab,ti OR 'cp 358774':ab,ti OR '358774, cp':ab,ti OR 'cp 358,774':ab,ti OR '358,774, cp':ab,ti OR 'cp-358,774':ab,ti OR 'cp358,774':ab,ti OR 'cp-358774':ab,ti OR 'cp358774':ab,ti OR '11c-erlotinib':ab,ti OR '11c erlotinib':ab,ti OR 'erlotinib':ab,ti OR 'n-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine':ab,ti OR 'tarceva':ab,ti) AND (bevacizumab OR 'mvasi':ab,ti OR 'bevacizumab-awwb':ab,ti OR 'bevacizumab awwb':ab,ti OR 'avastin':ab,ti) AND ('randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'rct':ab,ti).

web of science Search Strategy:

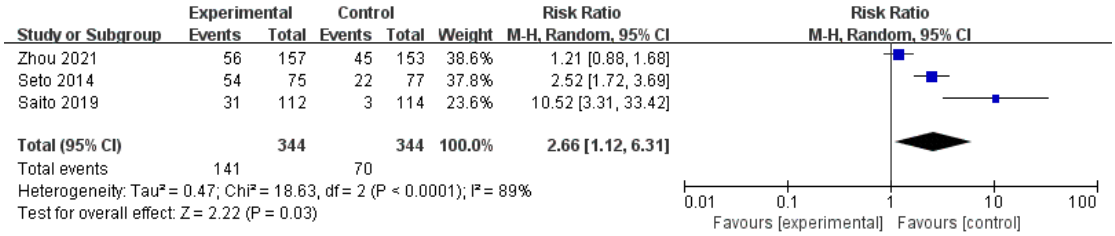
(TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Cancer OR Nonsmall Cell Lung Cance))AND(TS=(Erlotinib Hydrochloride OR Hydrochloride, Erlotinib OR Erlotinib HCl OR HCl, Erlotinib OR OSI-774 OR OSI 774 OR OSI774 OR CP 358774 OR 358774, CP OR CP 358,774 OR 358,774, CP OR CP-358,774 OR CP358,774 OR CP-358774 OR CP358774 OR 11C-erlotinib OR 11C erlotinib OR Erlotinib OR N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine OR Tarceva))AND(TS=(Bevacizumab OR Mvasi OR Bevacizumab-awwb OR Bevacizumab awwb OR Avastin))AND(TS=(randomized controlled trial OR randomized OR placebo OR RCT)).

Cochrane Library Search Strategy:

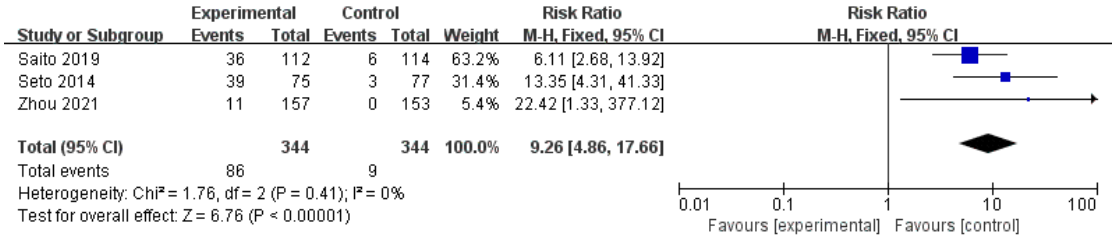
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw OR (Non Small Cell Lung Carcinoma):ab,ti,kw OR (Carcinoma, Non-Small Cell Lung):ab,ti,kw OR (Non-Small Cell Lung Carcinoma):ab,ti,kw) AND ((Erlotinib Hydrochloride) OR (Hydrochloride, Erlotinib):ab,ti,kw OR (Erlotinib HCl):ab,ti,kw OR (HCl, Erlotinib):ab,ti,kw OR (OSI-774):ab,ti,kw OR (OSI 774):ab,ti,kw OR (OSI774):ab,ti,kw OR (CP 358774):ab,ti,kw OR (358774, CP):ab,ti,kw OR (CP 358,774):ab,ti,kw OR (358,774, CP):ab,ti,kw OR (CP-358,774):ab,ti,kw OR (CP358,774):ab,ti,kw OR (CP-358774):ab,ti,kw OR (CP358774):ab,ti,kw OR (11C-erlotinib):ab,ti,kw OR (11C erlotinib):ab,ti,kw) AND ((Bevacizumab) OR (Mvasi):ab,ti,kw OR (Bevacizumab-awwb):ab,ti,kw OR (Bevacizumab awwb):ab,ti,kw OR (Avastin):ab,ti,kw) AND ((randomized controlled trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw OR (RCT):ab,ti,kw).



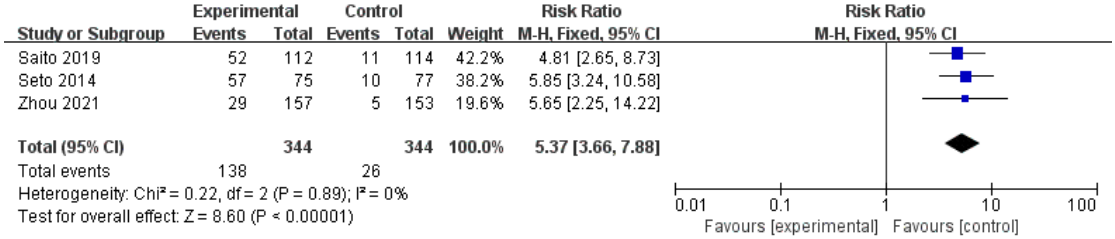
FigureS1 Forest plot of AEs of diarrhea



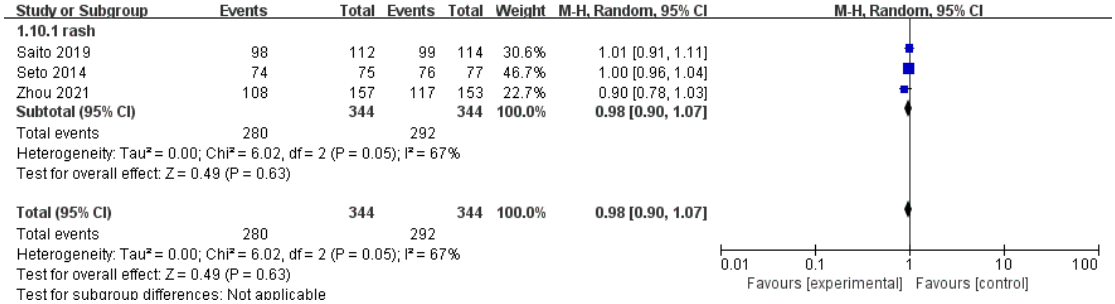
FigureS2 Forest plot of AEs of haemorrhagic event



FigureS3 Forest plot of AEs of proteinuria

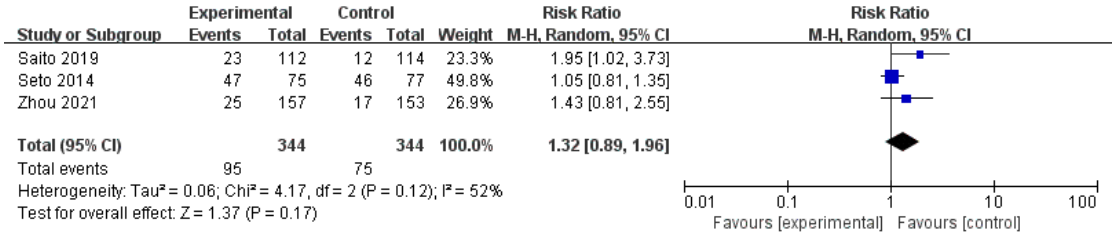


FigureS4 Forest plot of AEs of hypertension

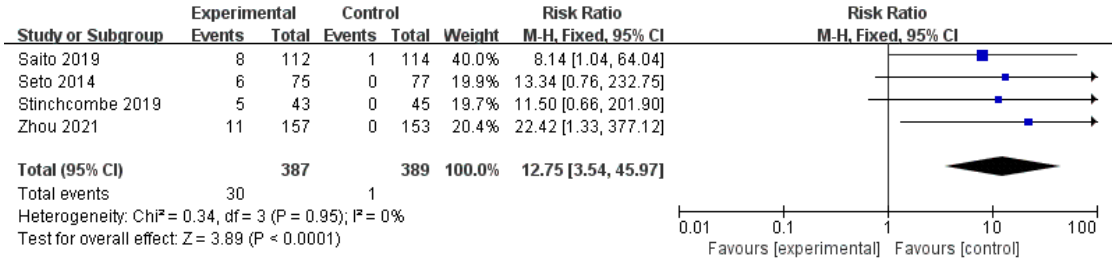


FigureS5 Forest plot of AEs of rash

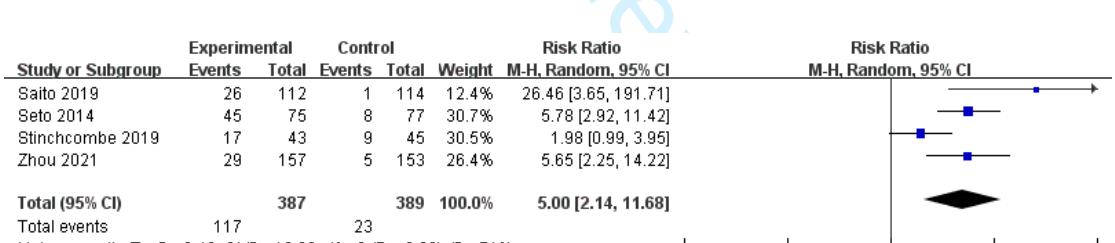
FigureS6 Forest plot of AEs of paronychia



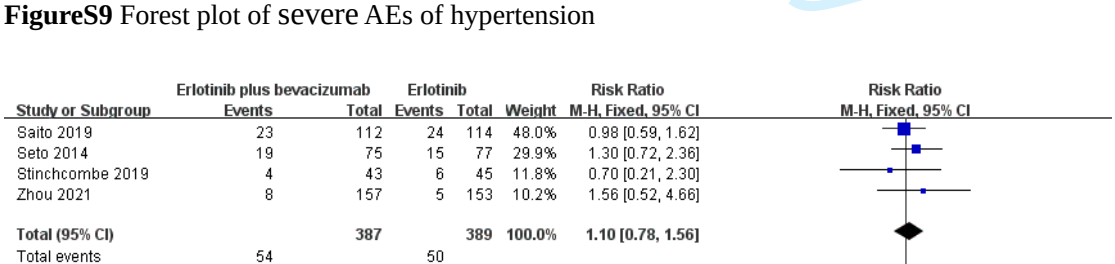
FigureS7 Forest plot of AEs of stomatitis



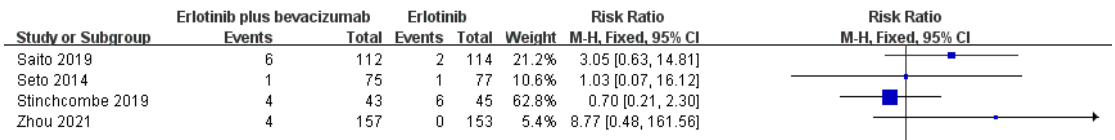
FigureS8 Forest plot of severe AEs of proteinuria



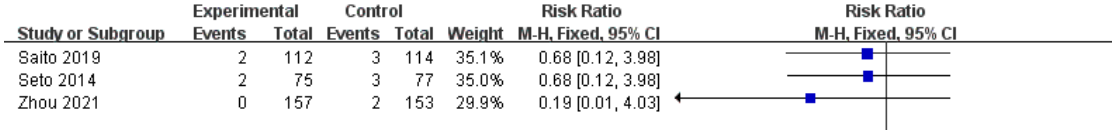
FigureS9 Forest plot of severe AEs of hypertension



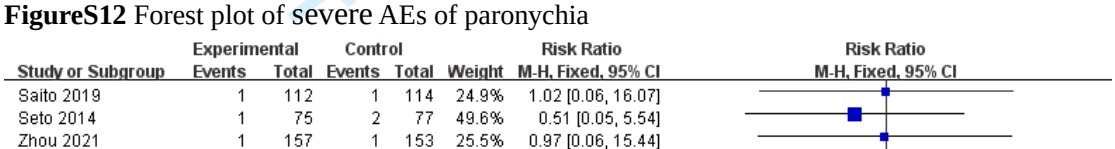
FigureS10 Forest plot of severe AEs of rash



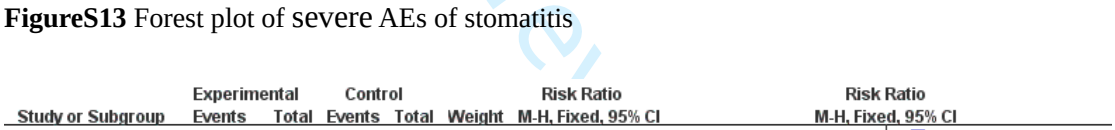
FigureS11 Forest plot of severe AEs of diarrhea



FigureS12 Forest plot of severe AEs of paronychia



FigureS13 Forest plot of severe AEs of stomatitis



FigureS14 Forest plot of severe AEs of haemorrhagic event

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			line/page
Title	1	Identify the report as a systematic review.	1-3/1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	13-30/1;1-5/2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-19/2.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20-30/2;1-10/3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	15-19/3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	27-28/3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	29-30/3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5/4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5/4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	12-16/4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	18-20/4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20-26/4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	20-26/4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	20-26/4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	20-26/4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	20-26/4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	20-26/4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12-16/4
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	20-26/4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	2-8/5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-30/8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-30/8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-30/8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-30/8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11-30/8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	4-20/9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-30/9
	23b	Discuss any limitations of the evidence included in the review.	1-13/12
	23c	Discuss any limitations of the review processes used.	1-13/12
	23d	Discuss implications of the results for practice, policy, and future research.	17-29/11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	26-27/12
Competing interests	26	Declare any competing interests of review authors.	1/13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	3-4/13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062036.R1
Article Type:	Original research
Date Submitted by the Author:	20-Jul-2022
Complete List of Authors:	Deng, Wusheng; The First Affiliated Hospital of Guangxi Medical University, Wang, Ke; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Li, Dingbin; The First Affiliated Hospital of Guangxi Medical University, Department of Orthopedic Trauma and Hand Surgery Bao, Chongxi; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Luo, Jing; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Liu, Liuyuan; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Huang, Bing; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Kong, Jinliang; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Evidence based practice
Keywords:	Adult oncology < ONCOLOGY, Gene therapy < ONCOLOGY, Clinical governance < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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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 randomized 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 randomized 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) in the treatment for NSCLC. Two independent reviewers extracted data and assessed the risk of bias. A random-effect model was used where there was evidence for homogeneous effects. The Higgins I^2 test was used to assess the heterogeneity across the studies.

Results Six RCTs (involving 775 cases) were included in the meta-analysis. 387 patients were treated with erlotinib plus bevacizumab and 388 patients were treated with erlotinib alone. Compared with the erlotinib alone group, the erlotinib plus bevacizumab group achieved a significantly prolonged PFS (HR: 0.59; 95%CI: 0.49–0.72; P<0.00001; I^2=0%), but OS (HR: 0.95; 95%CI: 0.78–1.15; P=0.59; I^2=0%) and ORR (OR: 1.25; 95%CI: 0.89–1.74; P=0.19; I^2=0%) were not significantly prolonged. Regarding AEs, combined treatment significantly increased the incidence of diarrhea (51 vs. 43%, 95%CI: 1.03–1.38; P=0.006), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001), and hypertension (40 vs. 8%, 95%CI: 3.66–7.88; 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 use of the combination did not prolong OS.

Strengths and limitations of this study

* The present systematic review and meta-analysis was based on a comprehensive search and the pooling of data from high-quality randomized controlled trials.
* We used the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines to evaluate the strength and quality of the evidence.
* Limitations include publication biases and incomplete data for selected articles.
* The literature searches only considered studies published in English.
* There was no analysis of post-study treatments that may have affected overall survival.

INTRODUCTION

Lung cancer is the leading incidence and mortality of 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 anti-angiogenic 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 population was Rosell et al.[15] a phase 2 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 single-arm trail was insufficient. The effects of erlotinib plus bevacizumab in advanced *EGFR*m$^+$ NSCLC remain controversial. The results of randomized 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 the 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 advanced *EGFR*m+ NSCLC patients. 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 (MeSH) 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 (e.g., age, sex, ethnic origin, brain), the number of participants in each group, description and doses of therapeutic agents administered, tumour histology and type of *EGFR* mutation and AE. The efficacy criteria 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 the quality assessment were resolved by group discussion.

Statistical analysis

The results of OS and PFS were estimated by Hazard ratio (HR) with a 95% confidence interval (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. An I^2 < 25%, 25–50%, and > 50% were defined as low, mild, and substantial heterogeneity[25]. If I^2 was <50% and the P value > 0.05, a fixed-effects model was used in the meta-analysis; In contrast, If $I^2 \geq 50\%$ and the P value ≤ 0.05, a random effects model was used to assess the resource of the heterogeneity. All statistical analyses were performed with RevMan version 5.4 provided by the Cochrane Collaboration and the P value < 0.05 was considered statistically significant.

Patient and public involvement statement

None.

RESULTS

Results of the literature search

The study flowchart 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, and 485 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, and 6 studies met our eligibility criteria and were included in the present meta-analysis.

Characteristics of the included studies

Basic information included the author names, date of publication, region of participants, age, tumour histology, clinical stage, genomic aberration of *EGFR* (Table 1). The six studies[16-20 26] included in the meta-analysis, Saito et al.[17] and Kawashima et al.[26] are NEJ026 study, and Seto et al.[16] and Yamamoto et al.[18] are JO25567 study. The erlotinib plus bevacizumab group included 387 patients and the erlotinib group included 388 patients. Patients assigned to the erlotinib plus bevacizumab group received 150 mg of oral erlotinib form 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 randomized controlled trials

Study	Region	Participant (male/female)	Age	Histology(adenocarcinoma/large cell carcinoma/squamous cell/ others)	Clinical stage	EGFR genomic aberration(19 deletion/21 Leu858Arg mutation)	Outcome	Study design
Seto et al.,[15] 2014	Japan (multicentre)	152(56/96)	67(59–73)	150/1/0/1	IIIb–IV	80/72	PFS, ORR, AEs	Phase 2 RCT
Stinchcombe et al.,[19] 2019	America (multicentre)	88(26/62)	63(31–84)	-	M1a,M 1b	59/29	PFS, ORR, OS, AEs	Phase 2 RCT
Saito et al.,[16] 2019	Japan (multicentre)	224(80/144)	67(61–73)	222/1/0/1	IIIb–IV	111/113	PFS, AEs	Phase 3 RCT
Kawashima et al.,[24] 2021	Japan (multicentre)	224(80/144)	67(61–73)	222/1/0/1	IIIb–IV	111/113	OS	Phase 3 RCT
Yamamoto et al.,[17] 2021	Japan (multicentre)	152(56/96)	67(59–73)	150/1/0/1	IIIb–IV	80/72	OS	Phase 2 RCT
Zhou et al.,[18] 2021	Chinese (multicentre)	311(118/193)	57 (27–78)	311/0/0/0	IIIb–IV	161/150	PFS, OS, ORR	Phase 3 RCT

Risk of bias and quality assessment

All studies presented adequate random sequence generation, and four studies performed adequate allocation concealment.[16-18 26] There was not enough information to evaluate selective reporting in four studies,[16-18 26] Two RCTs[19 20] did not observe selective outcome reporting. All RCT studies were open-label studies without blinding. All studies were free of incomplete outcome data. Five studies[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 of RCTs were moderate or high quality, and the results are shown in Figure 2(a) and Figure 2(b).

Progression-free survival

Four studies[16 17 19 20] reported PFS in the erlotinib plus bevacizumab group and the erlotinib group. There were 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 to the erlotinib group (HR: 0.59; 95%CI: 0.49–0.72; P<0.00001; Figure 3). No heterogeneity was observed (I^2=0%; P=0.55).

Overall survival

Four studies[17-19 26] reported OS in the patients treated with erlotinib plus bevacizumab group and erlotinib group. There were 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib monotherapy group. Pooled analyses showed that erlotinib plus bevacizumab did not significantly reduce OS compared to the erlotinib group (HR: 0.95; 95%CI: 0.78–1.15; P=0.59) (Figure 4). No heterogeneity was observed (I^2 =0%; P=0.58).

Objective response rate

Four studies[16 17 19 20] reported ORR in the erlotinib plus bevacizumab group and the erlotinib group. There were 387 participants in the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib group. The pooled analyses showed that erlotinib plus bevacizumab did not significantly reduce ORR compared to the erlotinib group (OR: 1.25; 95%CI: 0.89–1.74; 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). We defined grade 3–5 AEs as severe AEs. The results showed that incidence of diarrhea (51 vs. 43%, 95%CI: 1.03–1.38; P=0.006) (Figure S1), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03) (Figure S2), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001) (Figure S3), hypertension (40 vs. 8%, 95%CI: 3.66–7.88; P<0.0001) (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: 0.90–1.07; P=0.63) (Figure S5), paronychia (30 vs. 28%, 95%CI: 0.87–1.30; P=0.57) (Figure S6), stomatitis (28 vs. 22%, 95%CI: 0.89–1.96; P=0.17) (Figure S7). In the analysis of severe AEs, the combination treatment yielded significantly higher rates for proteinuria (8 vs. 0.3%, 95%CI: 3.54–45.97; P<0.001) (Figure S8) and hypertension (30 vs. 5%, 95%CI: 2.14–11.68; P<0.001) (Figure S9). There were no significant differences for severe rash (14 vs. 13%, 95%CI: 0.78–1.56; P=0.59) (Figure S10), diarrhea (4 vs. 2%,95%CI: 0.76–3.68; P=0.20) (Figure S11), paronychia (1 vs. 2%, 95%CI: 0.17–1.66; P=0.28) (Figure S12), stomatitis (0.9 vs. 1%, 95%CI: 0.17–3.36; P=0.71) (Figure S13), or haemorrhagic event (2 vs. 0.3%, 95%CI: 0.74–16.87; P=0.11) (Figure S14). (See the online supplemental material 2 file for the forest plot of the study results of AEs and severe AEs).

Table 2, All 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 (0.90–1.07)	0.63	67	0.05
Diarrhea	176/344	149/344	1.19 (1.03–1.38)	0.02	49	0.14
Paronychia	102/344	97/344	1.06 (0.87–1.30)	0.57	0	0.55
Stomatitis	95/344	75/344	1.32 (0.89–1.96)	0.17	52	0.12

Haemorrhagic event	141/344	70/344	2.66 (1.12–6.31)	0.03	89	< 0.001
Proteinuria	86/344	9/344	9.26 (4.86–17.66)	< 0.0001	0	0.41
Hypertension	138/344	26/344	5.37 (3.66–7.88)	< 0.0001	0	0.89
Rash	54/387	50/389	1.10 (0.78–1.56)	0.59	0	0.69
Diarrhea	15/387	9/389	1.67 (0.76–3.68)	0.20	25	0.26
Paronychia	4/344	8/344	0.54 (0.17–1.66)	0.28	0	0.75
Stomatitis	4/344	4/344	0.76 (0.17–3.36)	0.71	0	0.91
Haemorrhagic event	6/344	1/344	3.52 (0.74–16.87)	0.11	0	0.86
Proteinuria	30/387	1/389	12.75 (3.54–45.97)	< 0.0001	0	0.95
Hypertension	117/387	18/389	5.00 (2.14–11.68)	0.0002	71	0.02

DISCUSSION

We performed the meta-analysis by combining patient data from six RCTs, a total of 775 cases of lung cancer were included in our analyses. We found that the concurrent use of erlotinib plus bevacizumab contributed to prolonging PFS compared to erlotinib as a single agent, but not to improving OS and ORR, in the treatment of advanced *EGFRm*$^+$ NSCLC. All grades of AEs and rash were more commonly found in the combination group and the single agent group. Furthermore, the incidence of diarrhea, haemorrhagic events, proteinuria, and hypertension was higher when erlotinib plus bevacizumab was used compared to erlotinib, in all grades of AEs. In the analysis of severe AE, combination treatment produced significantly higher rates for proteinuria and hypertension compared to 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 to the erlotinib monotherapy group,[27] the anti-VEGF plus erlotinib group in that meta-analysis included two different angiogenesis inhibitors (bevacizumab and ramucirumab), and bevacizumab and ramucirumab showed different degrees of

efficacy in cancer management although with and a potential for bias was estimated, 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 to the previous meta-analysis. Furthermore, we added three recent RCT studies 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 to erlotinib alone in *EGFR*m$^+$ advanced NSCLC patients. 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 regiment improved efficacy in terms of PFS compared to 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 intertumoural absorption of drugs.[32] A preclinical study[33] demonstrated that tumours treated with the lowest dose of a *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 of 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 treatment is 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 NSCLC 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. For OS, 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] versus 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[19] et al. 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 group and are known toxicities associated with bevacizumab treatment, especially for diarrhea, 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 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. The first generation, second generation *EGFR* TKI, *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 to the erlotinib alone; therefore, in the clinic,

when erlotinib monotherapy is ineffective, the addition of bevacizumab to the erlotinib is an optional strategy for the treatment of *EGFR*m$^+$ advanced NSCLC.

Our meta-analysis had several potential limitations. First, only six studies 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 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 common 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 a 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 diarrhea, haemorrhagic event, proteinuria and hypertension. This combination can be recommended as a therapeutic strategy for patients with advanced *EGFR*m$^+$ NSCLC.

Contributors WSD: 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. DBL: data collection and analysis, statistical analysis. CXB: data collection and analysis, manuscript revision. JL:

study design, manuscript revision. LYL: data collection. BH: statistical analysis. JLK: study design, manuscript drafting, and manuscript revision. All authors read and approved the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No.82160783, 82104499 and 81760743), Guangxi Zhuang Autonomous Region Health and Wellness Committee Science and Technology Project (S2019090), the Key Research Program of Guangxi Science and Technology Department (No.AB21196010), the First Affiliated Hospital of Guangxi Medical University Clinical Research Climbing Program Youth Science and Technology Morning Star Program(No.201903032 and YYZS2020016), the Health and Family Planning Commission of Guangxi Zhuang Autonomous Region, self-funded projects (No.Z20200825), and the Advanced Innovation Teams and Xinghu Scholars Program of Guangxi Medical University.

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.

Ethics approval This study does not require ethics approval as is based on existing data.

Patient consent for publication Not applicable.

Data availability statement No additional data available.

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Figure titles

Figure 1. Flowchart of the literature screening

Figure 2. Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias

Figure 3. Forest plot of study results of PFS

Figure 4. Forest plot of study results of OS

Figure 5. Forest plot of study results of ORR

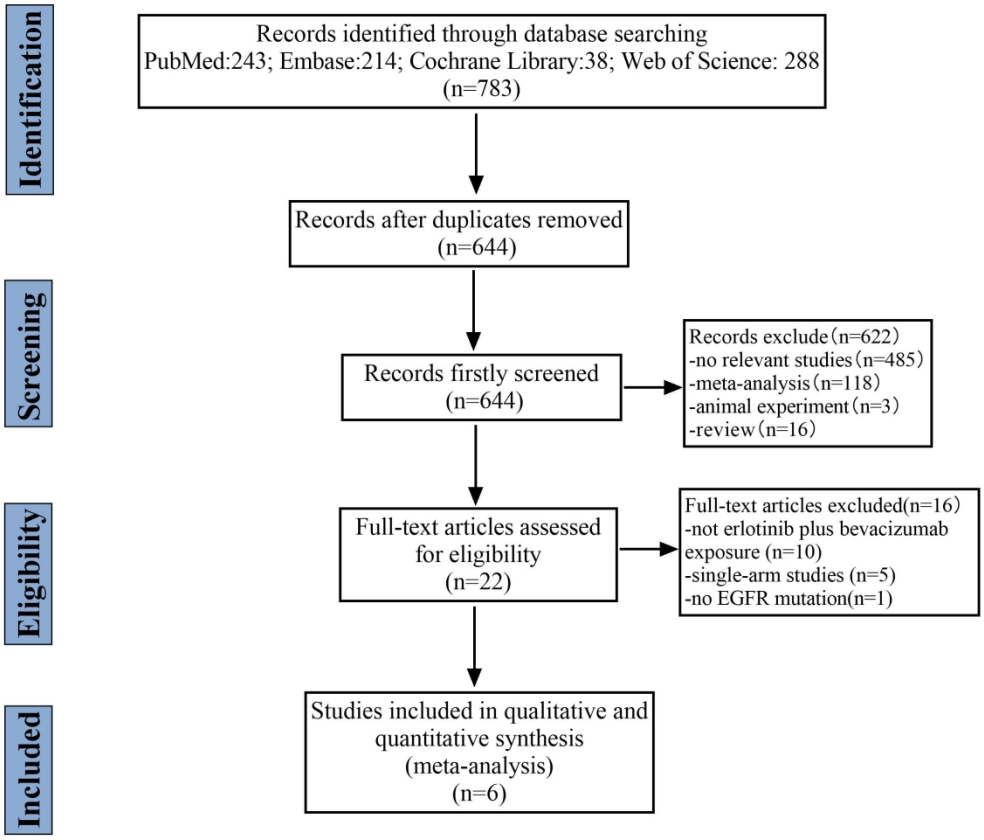

Figure 1 Flowchart of the literature screening.

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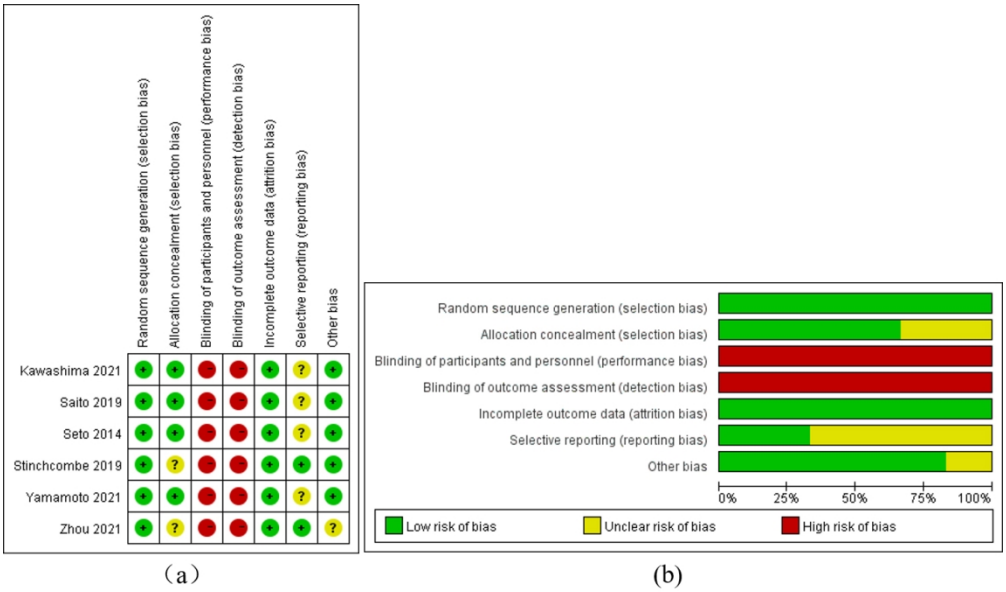

Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

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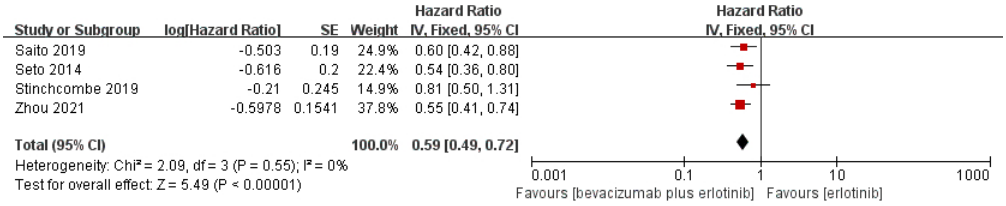

Figure 3. Forest plot of study results of PFS.

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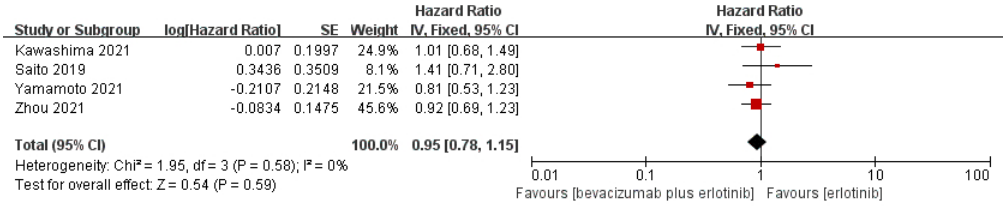

Figure 4. Forest plot of study results of OS.

293x62mm (72 x 72 DPI)

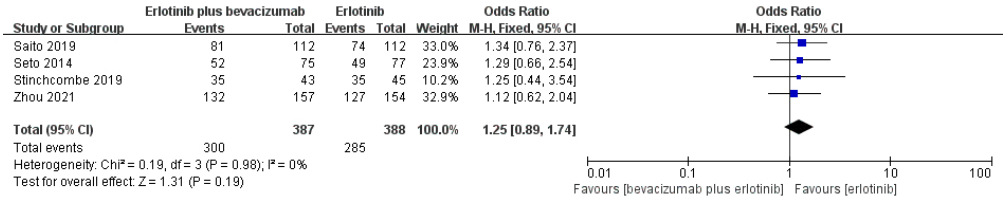

Figure 5. Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

Pubmed Search Strategy:

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(（randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR

placebo[Title/Abstract]）).

Embase Search Strategy:

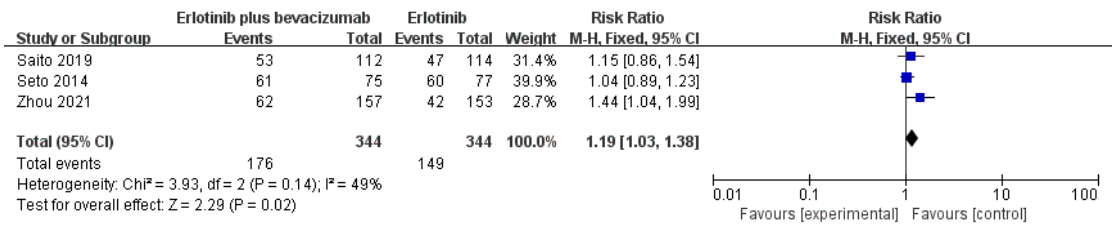
'carcinoma, non small cell lung':ab,ti OR ('carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung carcinoma':ab,ti OR 'non-small cell lung cancer':ab,ti) AND(erlotinib AND hydrochloride OR 'hydrochloride, erlotinib':ab,ti OR 'erlotinib hcl':ab,ti OR 'hcl, erlotinib':ab,ti OR 'osi-774':ab,ti OR 'osi 774':ab,ti OR 'osi774':ab,ti OR 'cp 358774':ab,ti OR '358774, cp':ab,ti OR 'cp 358,774':ab,ti OR '358,774, cp':ab,ti OR 'cp-358,774':ab,ti OR 'cp358,774':ab,ti OR 'cp-358774':ab,ti OR 'cp358774':ab,ti OR '11c-erlotinib':ab,ti OR '11c erlotinib':ab,ti OR 'erlotinib':ab,ti OR 'n-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine':ab,ti OR 'tarceva':ab,ti) AND (bevacizumab OR 'mvasi':ab,ti OR 'bevacizumab-awwb':ab,ti OR 'bevacizumab awwb':ab,ti OR 'avastin':ab,ti) AND ('randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'rct':ab,ti).

web of science Search Strategy:

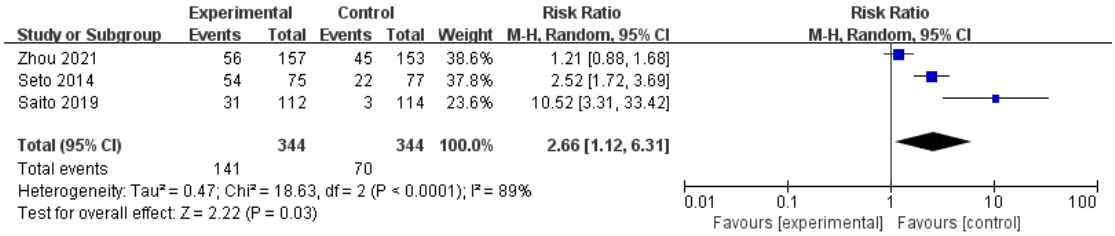
(TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Cancer OR Nonsmall Cell Lung Cance))AND(TS=(Erlotinib Hydrochloride OR Hydrochloride, Erlotinib OR Erlotinib HCl OR HCl, Erlotinib OR OSI-774 OR OSI 774 OR OSI774 OR CP 358774 OR 358774, CP OR CP 358,774 OR 358,774, CP OR CP-358,774 OR CP358,774 OR CP-358774 OR CP358774 OR 11C-erlotinib OR 11C erlotinib OR Erlotinib OR N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine OR Tarceva))AND(TS=(Bevacizumab OR Mvasi OR Bevacizumab-awwb OR Bevacizumab awwb OR Avastin))AND(TS=(randomized controlled trial OR randomized OR placebo OR RCT)).

Cochrane Library Search Strategy:

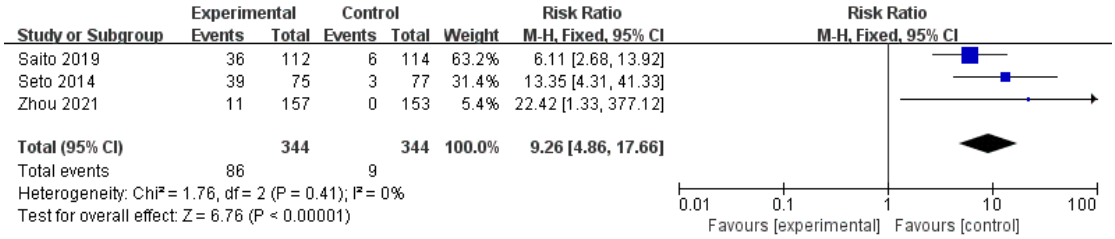
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw OR (Non Small Cell Lung Carcinoma):ab,ti,kw OR (Carcinoma, Non-Small Cell Lung):ab,ti,kw OR (Non-Small Cell Lung Carcinoma):ab,ti,kw) AND ((Erlotinib Hydrochloride) OR (Hydrochloride, Erlotinib):ab,ti,kw OR (Erlotinib HCl):ab,ti,kw OR (HCl, Erlotinib):ab,ti,kw OR (OSI-774):ab,ti,kw OR (OSI 774):ab,ti,kw OR (OSI774):ab,ti,kw OR (CP 358774):ab,ti,kw OR (358774, CP):ab,ti,kw OR (CP 358,774):ab,ti,kw OR (358,774, CP):ab,ti,kw OR (CP-358,774):ab,ti,kw OR (CP358,774):ab,ti,kw OR (CP-358774):ab,ti,kw OR (CP358774):ab,ti,kw OR (11C-erlotinib):ab,ti,kw OR (11C erlotinib):ab,ti,kw) AND ((Bevacizumab) OR (Mvasi):ab,ti,kw OR (Bevacizumab-awwb):ab,ti,kw OR (Bevacizumab awwb):ab,ti,kw OR (Avastin):ab,ti,kw) AND ((randomized controlled trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw OR (RCT):ab,ti,kw).



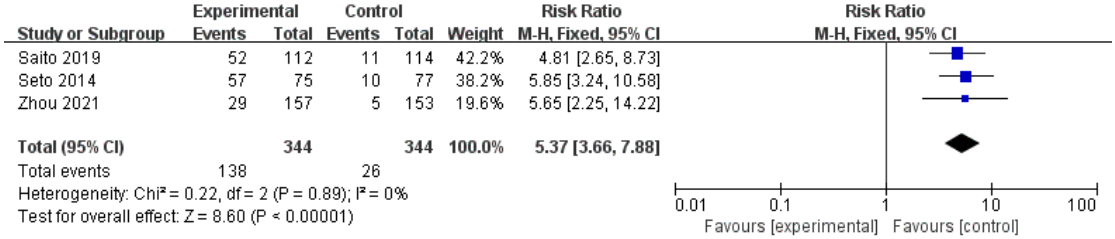
FigureS1 Forest plot of AEs of diarrhea



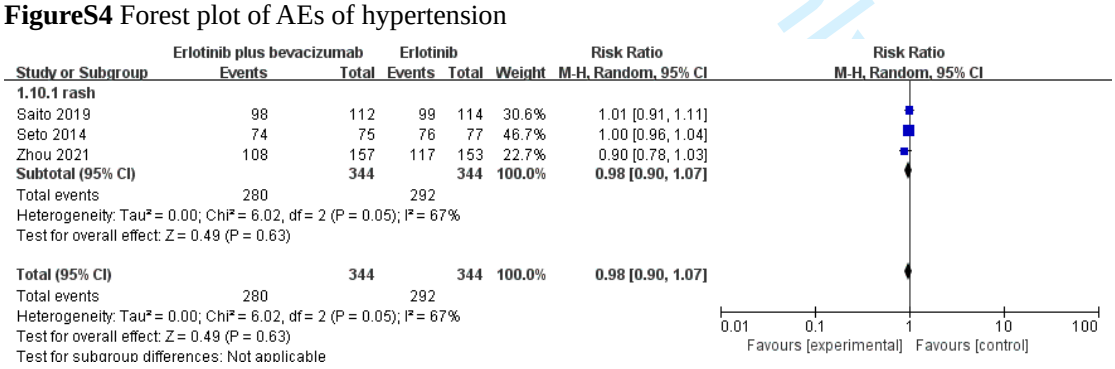
FigureS2 Forest plot of AEs of haemorrhagic event



FigureS3 Forest plot of AEs of proteinuria

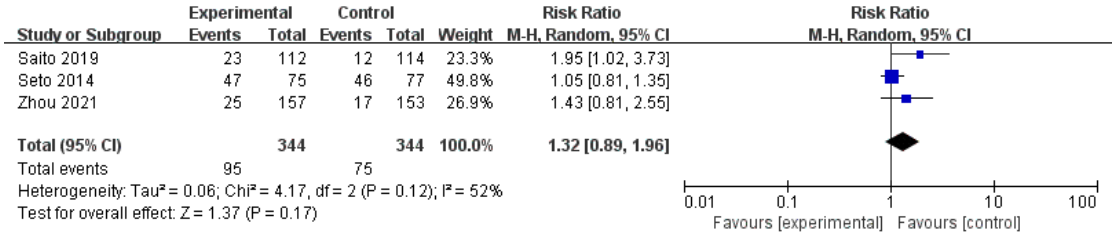


FigureS4 Forest plot of AEs of hypertension

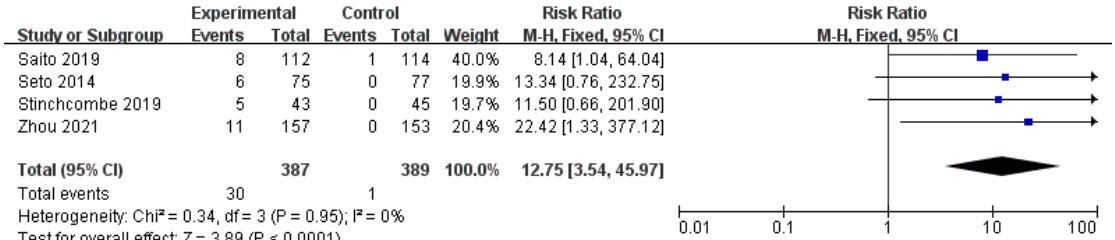


FigureS5 Forest plot of AEs of rash

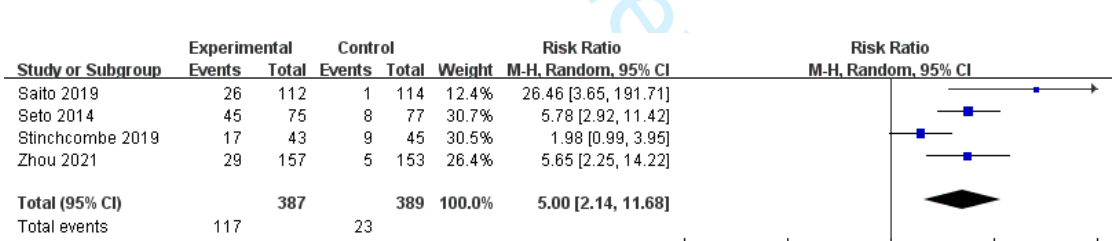
FigureS6 Forest plot of AEs of paronychia



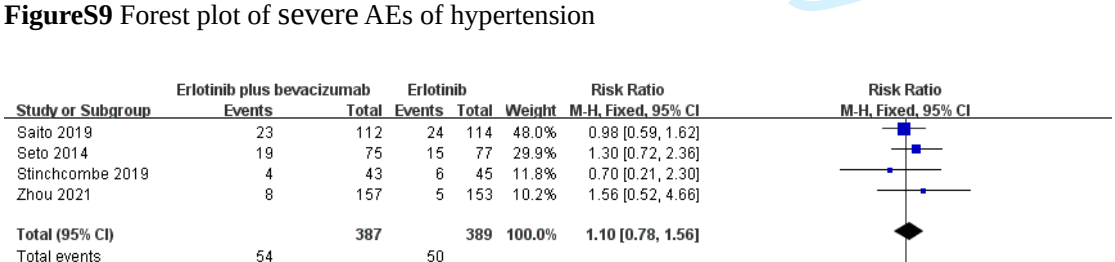
FigureS7 Forest plot of AEs of stomatitis



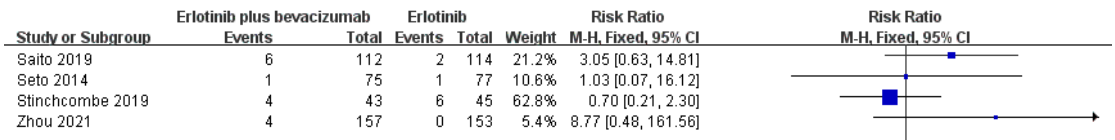
FigureS8 Forest plot of severe AEs of proteinuria



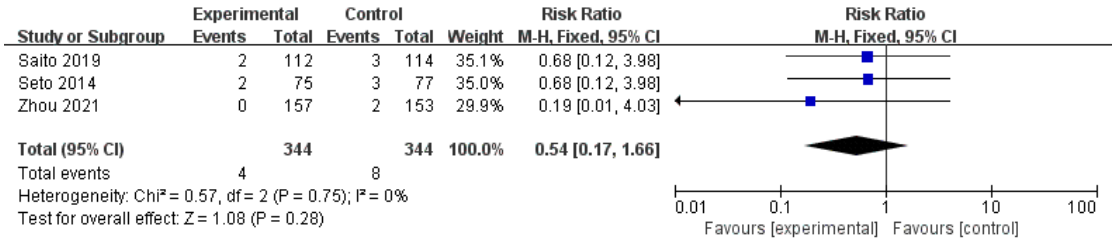
FigureS9 Forest plot of severe AEs of hypertension



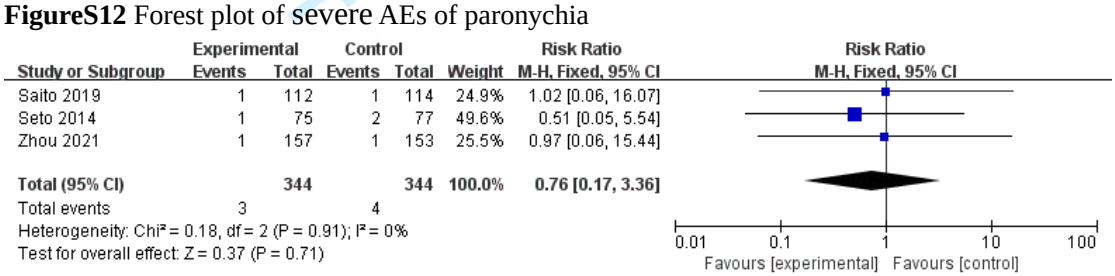
FigureS10 Forest plot of severe AEs of rash



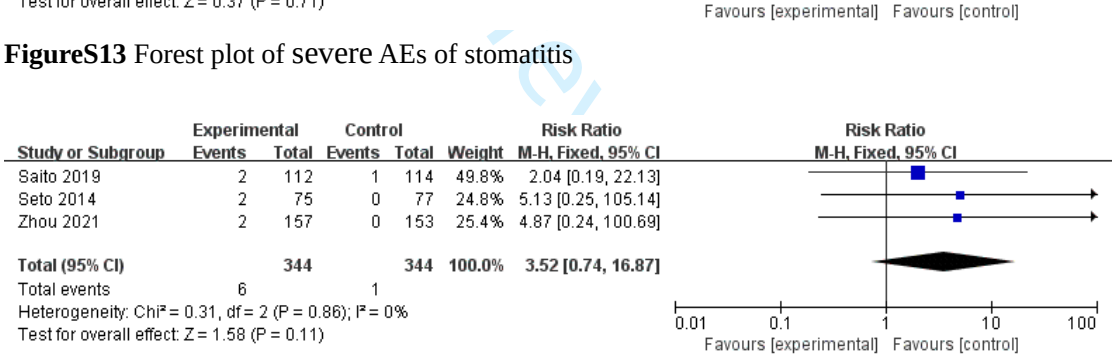
FigureS11 Forest plot of severe AEs of diarrhea



FigureS12 Forest plot of severe AEs of paronychia



FigureS13 Forest plot of severe AEs of stomatitis



FigureS14 Forest plot of severe AEs of haemorrhagic event

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			line/page
Title	1	Identify the report as a systematic review.	1-3/1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	13-30/1;1-5/2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-19/2.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20-30/2;1-10/3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	15-19/3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	27-28/3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	29-30/3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5/4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5/4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	12-16/4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	18-20/4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20-26/4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	20-26/4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	20-26/4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	20-26/4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	20-26/4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	20-26/4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12-16/4
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	20-26/4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	2-8/5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-30/8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-30/8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-30/8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-30/8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11-30/8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	4-20/9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-30/9
	23b	Discuss any limitations of the evidence included in the review.	1-13/12
	23c	Discuss any limitations of the review processes used.	1-13/12
	23d	Discuss implications of the results for practice, policy, and future research.	17-29/11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	26-27/12
Competing interests	26	Declare any competing interests of review authors.	1/13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	3-4/13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062036.R2
Article Type:	Original research
Date Submitted by the Author:	02-Aug-2022
Complete List of Authors:	Deng, Wusheng; The First Affiliated Hospital of Guangxi Medical University, Wang, Ke; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Jiang, Yun; The First Affiliated Hospital of Shaoyang University, Department of Respiratory and Critical Care Medicine Li, Dingbin; The First Affiliated Hospital of Guangxi Medical University, Department of Orthopedic Trauma and Hand Surgery Bao, Chongxi; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Luo, Jing; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Liu, Liuyuan; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Huang, Bing; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine Kong, Jinliang; The First Affiliated Hospital of Guangxi Medical University, Department of Respiratory and Critical Care Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Evidence based practice
Keywords:	Adult oncology < ONCOLOGY, Gene therapy < ONCOLOGY, Respiratory tract tumours < THORACIC MEDICINE

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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-effect 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: 0.49–0.72; P<0.00001; I^2=0%), but OS (HR: 0.95; 95%CI: 0.78–1.15; P=0.59; I^2=0% %) and ORR (OR: 1.25; 95%CI: 0.89–1.74; P=0.19; I^2=0%) were not significantly prolonged. A total of 776 cases were used to pooled analysis of AEs. Regarding AEs, combined treatment significantly increased the incidence of diarrhoea (51 vs. 43%, 95%CI: 1.03–1.38; P=0.006), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001), and hypertension (40 vs. 8%, 95%CI: 3.66–7.88; 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 post-study treatments that may have affected overall survival.

INTRODUCTION

Lung cancer is the leading incidence and mortality of 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 anti-angiogenic 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 population was Rosell et al.[15] a phase 2 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 single-arm trail was insufficient. The effects of erlotinib plus bevacizumab in advanced *EGFR*m$^+$ NSCLC remain controversial. The results of randomized 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 the 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 advanced *EGFR*m+ NSCLC patients. 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 (MeSH) 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 (e.g., age, sex, ethnic origin, brain), the number of participants in each group, description and doses of therapeutic agents administered, tumour histology and 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 the quality assessment were resolved by group discussion.

Statistical analysis

The results of OS and PFS were estimated by hazard ratio (HR) with a 95% confidence interval (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. An I^2 < 25%, 25–50%, and > 50% were defined as low, mild, and substantial heterogeneity.[25] If I^2 was < 50% and the P value > 0.05, a fixed-effects model was used in the meta-analysis; if $I^2 \geq 50\%$ and the P value ≤ 0.05, a random effects model was used to assess the resource of the heterogeneity. All statistical analyses were performed with RevMan version 5.4 provided by the Cochrane Collaboration and the P value < 0.05 was considered statistically significant.

Patient and public involvement statement

None.

RESULTS

Results of the literature search

The study flowchart 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, and 485 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, and 6 studies met our eligibility criteria and were included in the present meta-analysis.

Characteristics of the included studies

Basic information included the 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 form 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 randomised controlled trials

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.,[16] 2014; Yamamoto et al.,[18] 2021)	Japan	152(75/77)	56/96	67(59–73)	150/1/0/1	IIIb–IV	80/72	PFS, OS, ORR, AEs	phase 2 RCT
Stinchcombe et al.,[20] 2019	America	88(43/45)	26/62	63(31–84)	-	M1a,M1b	59/29	PFS, OS, ORR, AEs	phase 2 RCT
NEJ026 (Saito et al.,[17] 2019; Kawashima et al.,[26] 2021)	Japan	224(112/112)	80/144	67(61–73)	222/1/0/1	IIIb–IV	111/113	PFS, OS, ORR, AEs,	phase 3 RCT
Zhou et al.,[19] 2021	China	311(157/154)	118/193	57(27–78)	311/0/0/0	IIIb–IV	161/150	PFS, OS, ORR, AEs	phase 3 RCT

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 2(a) and Figure 2(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 to the erlotinib group (HR: 0.59; 95%CI: 0.49–0.72; 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 to the erlotinib group (HR: 0.95; 95%CI: 0.78–1.15; 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 erlotinib group. The pooled analyses showed that erlotinib plus bevacizumab did not significantly reduce ORR compared to the erlotinib group (OR: 1.25; 95%CI: 0.89–1.74; 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 27] reported AEs and severe AEs across the four

RCTs. A total of 776 cases were used to 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 Zhou et al.[19], one patient in the erlotinib alone group withdrew from the study before starting treatment, and in 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: 1.03–1.38; P=0.006) (Figure S1), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03) (Figure S2), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001) (Figure S3), hypertension (40 vs. 8%, 95%CI: 3.66–7.88; P<0.0001) (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: 0.90–1.07; P=0.63) (Figure S5), paronychia (30 vs. 28%, 95%CI: 0.87–1.30; P=0.57) (Figure S6), stomatitis (28 vs. 22%, 95%CI: 0.89–1.96; P=0.17) (Figure S7). In the analysis of severe AEs, the combination treatment yielded significantly higher rates for proteinuria (8 vs. 0.3%, 95%CI: 3.54–45.97; P<0.001) (Figure S8) and hypertension (30 vs. 5%, 95%CI: 2.14–11.68; P<0.001) (Figure S9). There were no significant differences for severe rash (14 vs. 13%, 95%CI: 0.78–1.56; P=0.59) (Figure S10), diarrhoea (4 vs. 2%,95%CI: 0.76–3.68; P=0.20) (Figure S11), paronychia (1 vs. 2%, 95%CI: 0.17–1.66; P=0.28) (Figure S12), stomatitis (0.9 vs. 1%, 95%CI: 0.17–3.36; P=0.71) (Figure S13), or haemorrhagic event (2 vs. 0.3%, 95%CI: 0.74–16.87; P=0.11) (Figure S14). (See the online supplemental material 2 file for the forest plot of the study results of AEs and severe AEs).

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

DISCUSSION

We performed the meta-analysis by combining patient data from four RCTs, with a total of 775 cases of lung cancer were included in our efficacy analyses. We found that the concurrent use of erlotinib plus bevacizumab contributed to prolonging PFS compared to erlotinib as a single agent, but not to improving OS and ORR, in the treatment of advanced NSCLC with *EGFRm+*. 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 to erlotinib, in all grades of AEs. In the analysis of severe AE, combination treatment produced significantly

higher rates for proteinuria and hypertension compared to 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 to the erlotinib monotherapy group,[28] the anti-VEGF plus erlotinib group in that meta-analysis included two different angiogenesis inhibitors (bevacizumab and ramucirumab), and bevacizumab and ramucirumab showed different degrees of efficacy in cancer management although with and a potential for bias was estimated, 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 to the previous meta-analysis. Furthermore, we added three recent RCT studies 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 to erlotinib alone in *EGFR*m+ advanced NSCLC patients. Furthermore, the addition of bevacizumab to chemotherapy treatment has been shown to be effective in patients with NSCLC with central nervous system metastases.[29-31] There are several possible reasons why the addition of bevacizumab to the erlotinib regiment improved efficacy in terms of PFS compared to erlotinib. One possible mechanism is that the combination of bevacizumab could improve drug delivery.[32] Because bevacizumab alters tumour blood vessel physiology, leading to increased intratumoural absorption of drugs.[33] A preclinical study[34] demonstrated that tumours treated with the lowest dose of a *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 of cell apoptosis by inhibiting the VEGF-mediated pathway.[35] Due to synergistic inhibition of cancer growth signalling, VEGF signal inhibition is still effective for cancers with *EGFR* TKI resistant mutations.[36] An animal study[37] suggested that erlotinib plus bevacizumab treatment restored resistance to the VEGF-

mediated pathway. Therefore, in the clinic, the addition of bevacizumab to erlotinib treatment is optional strategy to delay the onset of TKI resistance in NSCLC.[21 38]

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 NSCLC 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. For OS, 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.[39] 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] versus 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 group and are known toxicities associated with bevacizumab treatment, especially for diarrhoea, haemorrhagic events, proteinuria, and hypertension.[40 41] In most cases, toxicity of combination therapy was considered to be tolerable and manageable,[42] patients will not choose to terminate drug treatment early due to 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. The first generation, second generation *EGFR* TKI, *EGFR* TKI plus bevacizumab or *EGFR* TKI plus ramucirumab are also available as treatment options.[43 44] However, most patients eventually develop disease progression due to acquired drug resistance.[45] Our meta-analysis provided evidence that the erlotinib plus bevacizumab combination prolongs PFS compared to the erlotinib alone; therefore, in the clinic, when erlotinib monotherapy is ineffective, the addition of bevacizumab to the 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 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,[46] the ex19del and ex21 L858R mutations are the two most common reported *EGFR* variants,[47] 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 a 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.

Contributors WSD: 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. DBL: data collection and analysis, statistical analysis. CXB: data collection and analysis, manuscript revision. JL: study design, manuscript revision. LYL: data collection. BH: statistical analysis. JLK: study design, manuscript drafting, and manuscript revision. All authors read and approved the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No.82160783, 82104499 and 81760743), Guangxi Zhuang Autonomous Region Health and Wellness Committee Science and Technology Project (S2019090), the Key Research Program of Guangxi Science and Technology Department (No.AB21196010), the First Affiliated Hospital of Guangxi Medical University Clinical Research Climbing Program Youth Science and Technology Morning Star Program(No.201903032 and YYZS2020016), the Health and Family Planning Commission of Guangxi Zhuang Autonomous Region, self-funded projects (No.Z20200825), and the Advanced Innovation Teams and Xinghu Scholars Program of Guangxi Medical University.

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.

Ethics approval This study did not require ethics approval as is based on existing, publicly available data.

Patient consent for publication Not applicable.

Data availability statement No additional data available.

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Figure titles

Figure 1. Flowchart of the literature screening

Figure 2. Summary (a) and graphical representation (b) of the risk of bias assessment

Figure 3. Forest plot of study results of PFS

Figure 4. Forest plot of study results of OS

Figure 5. Forest plot of study results of ORR

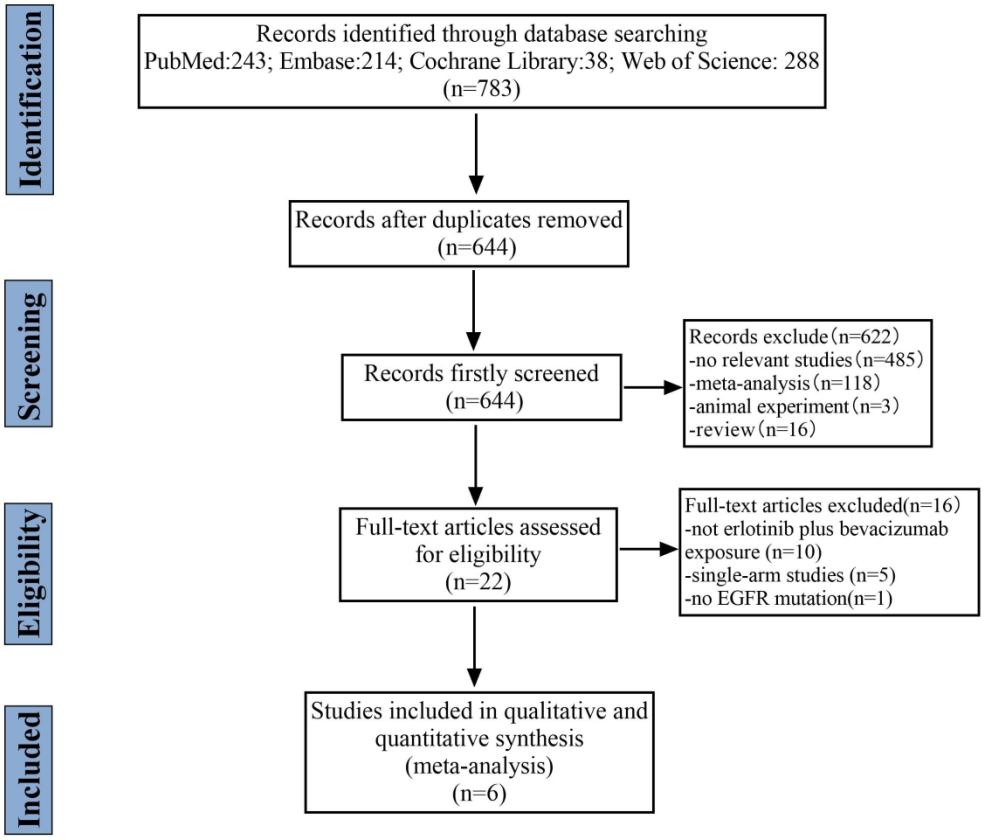

Figure 1 Flowchart of the literature screening.

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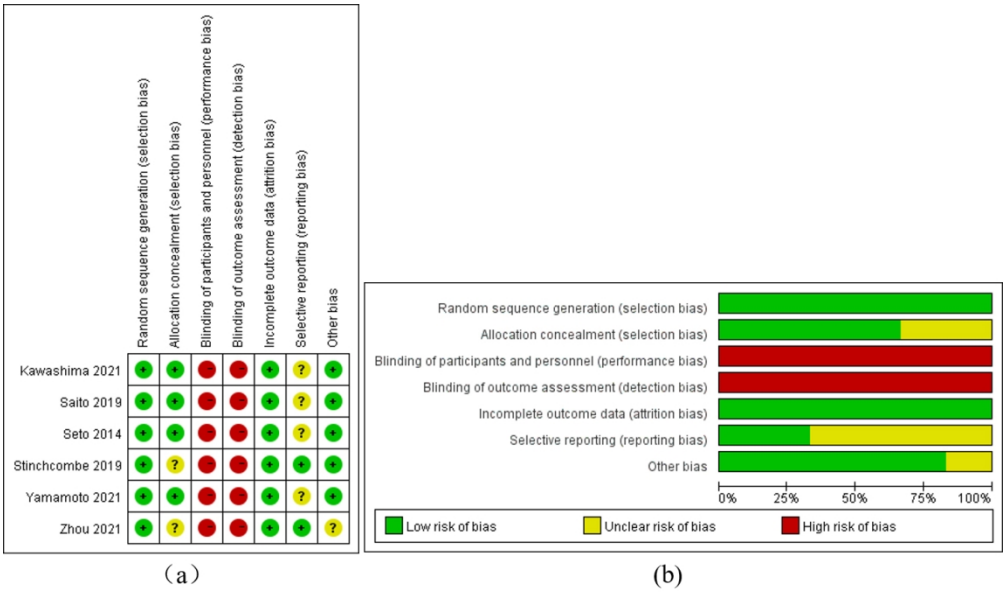

Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

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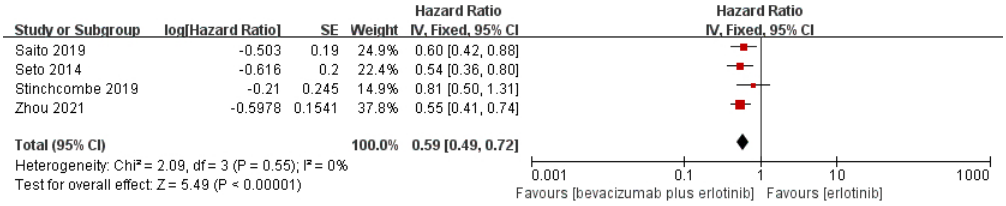

Figure 3. Forest plot of study results of PFS.

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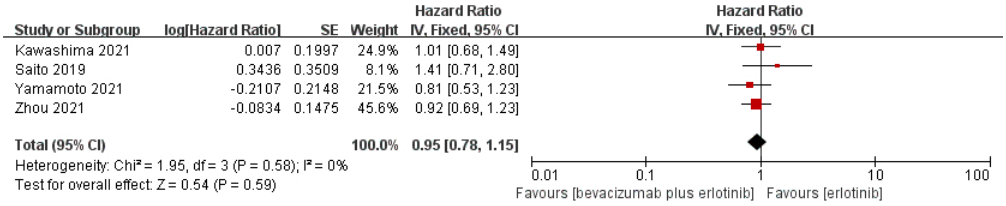

Figure 4. Forest plot of study results of OS.

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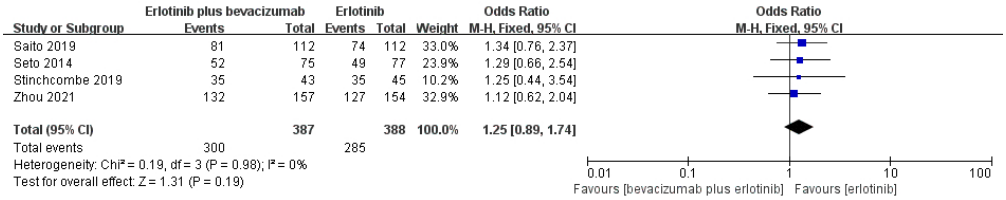


Figure 5. Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

Pubmed Search Strategy:

((((((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR ((((((((((Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cance[Title/Abstract]))) AND ("Erlotinib Hydrochloride"[Mesh])) OR ((((((((((((((((((Hydrochloride, Erlotinib[Title/Abstract]) OR (Erlotinib HCl[Title/Abstract])) OR (HCl, Erlotinib[Title/Abstract])) OR (OSI-774[Title/Abstract])) OR (OSI 774[Title/Abstract])) OR (OSI774[Title/Abstract])) OR (CP 358774[Title/Abstract])) OR (358774, CP[Title/Abstract])) OR (CP 358,774[Title/Abstract])) OR (358,774, CP[Title/Abstract])) OR (CP-358,774[Title/Abstract])) OR (CP358,774[Title/Abstract])) OR (CP-358774[Title/Abstract])) OR (CP358774[Title/Abstract])) OR (11C-erlotinib[Title/Abstract])) OR (11C erlotinib[Title/Abstract])) OR (Erlotinib[Title/Abstract])) OR (N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine[Title/Abstract])) OR (Tarceva[Title/Abstract]))) AND ("Bevacizumab"[Mesh])) OR ((((Mvasi[Title/Abstract]) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract]))) AND

(（randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR

placebo[Title/Abstract]）).

Embase Search Strategy:

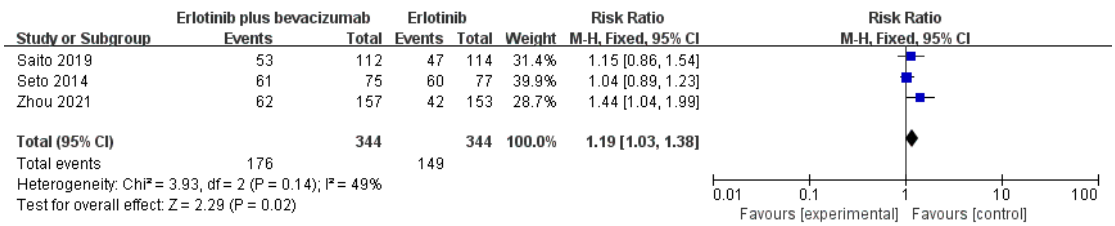
'carcinoma, non small cell lung':ab,ti OR ('carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung carcinoma':ab,ti OR 'non-small cell lung cancer':ab,ti) AND(erlotinib AND hydrochloride OR 'hydrochloride, erlotinib':ab,ti OR 'erlotinib hcl':ab,ti OR 'hcl, erlotinib':ab,ti OR 'osi-774':ab,ti OR 'osi 774':ab,ti OR 'osi774':ab,ti OR 'cp 358774':ab,ti OR '358774, cp':ab,ti OR 'cp 358,774':ab,ti OR '358,774, cp':ab,ti OR 'cp-358,774':ab,ti OR 'cp358,774':ab,ti OR 'cp-358774':ab,ti OR 'cp358774':ab,ti OR '11c-erlotinib':ab,ti OR '11c erlotinib':ab,ti OR 'erlotinib':ab,ti OR 'n-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine':ab,ti OR 'tarceva':ab,ti) AND (bevacizumab OR 'mvasi':ab,ti OR 'bevacizumab-awwb':ab,ti OR 'bevacizumab awwb':ab,ti OR 'avastin':ab,ti) AND ('randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'rct':ab,ti).

web of science Search Strategy:

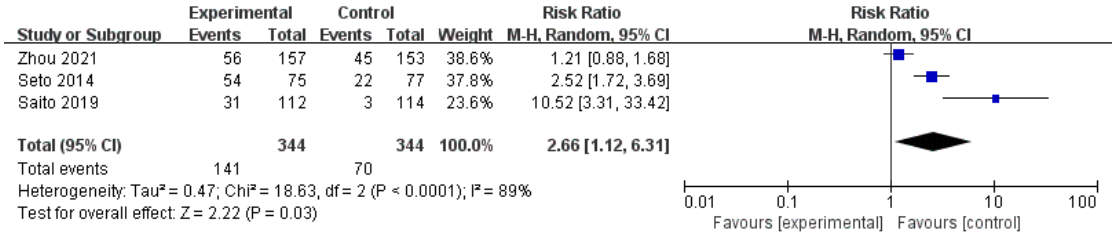
(TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung Cancer OR Nonsmall Cell Lung Cance))AND(TS=(Erlotinib Hydrochloride OR Hydrochloride, Erlotinib OR Erlotinib HCl OR HCl, Erlotinib OR OSI-774 OR OSI 774 OR OSI774 OR CP 358774 OR 358774, CP OR CP 358,774 OR 358,774, CP OR CP-358,774 OR CP358,774 OR CP-358774 OR CP358774 OR 11C-erlotinib OR 11C erlotinib OR Erlotinib OR N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine OR Tarceva))AND(TS=(Bevacizumab OR Mvasi OR Bevacizumab-awwb OR Bevacizumab awwb OR Avastin))AND(TS=(randomized controlled trial OR randomized OR placebo OR RCT)).

Cochrane Library Search Strategy:

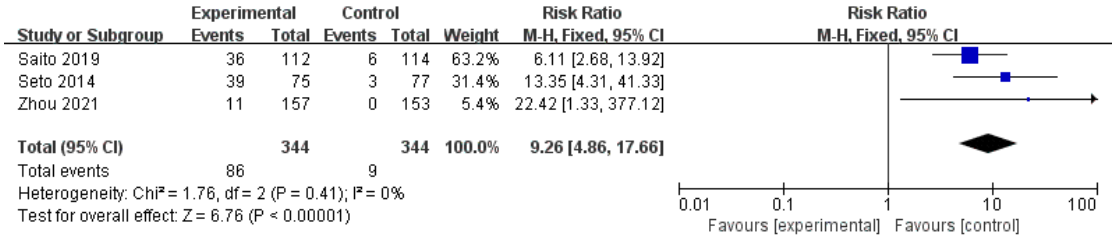
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw OR (Non Small Cell Lung Carcinoma):ab,ti,kw OR (Carcinoma, Non-Small Cell Lung):ab,ti,kw OR (Non-Small Cell Lung Carcinoma):ab,ti,kw) AND ((Erlotinib Hydrochloride) OR (Hydrochloride, Erlotinib):ab,ti,kw OR (Erlotinib HCl):ab,ti,kw OR (HCl, Erlotinib):ab,ti,kw OR (OSI-774):ab,ti,kw OR (OSI 774):ab,ti,kw OR (OSI774):ab,ti,kw OR (CP 358774):ab,ti,kw OR (358774, CP):ab,ti,kw OR (CP 358,774):ab,ti,kw OR (358,774, CP):ab,ti,kw OR (CP-358,774):ab,ti,kw OR (CP358,774):ab,ti,kw OR (CP-358774):ab,ti,kw OR (CP358774):ab,ti,kw OR (11C-erlotinib):ab,ti,kw OR (11C erlotinib):ab,ti,kw) AND ((Bevacizumab) OR (Mvasi):ab,ti,kw OR (Bevacizumab-awwb):ab,ti,kw OR (Bevacizumab awwb):ab,ti,kw OR (Avastin):ab,ti,kw) AND ((randomized controlled trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw OR (RCT):ab,ti,kw).



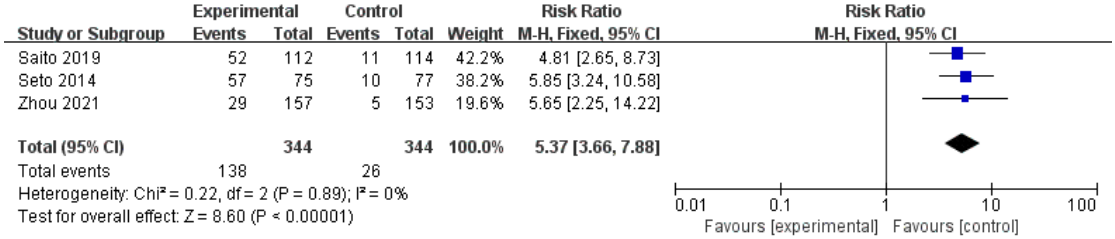
FigureS1 Forest plot of AEs of diarrhea



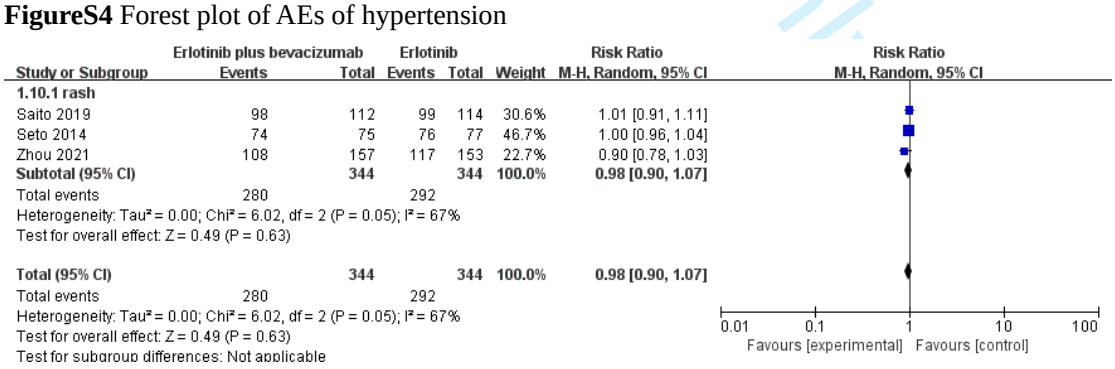
FigureS2 Forest plot of AEs of haemorrhagic event



FigureS3 Forest plot of AEs of proteinuria

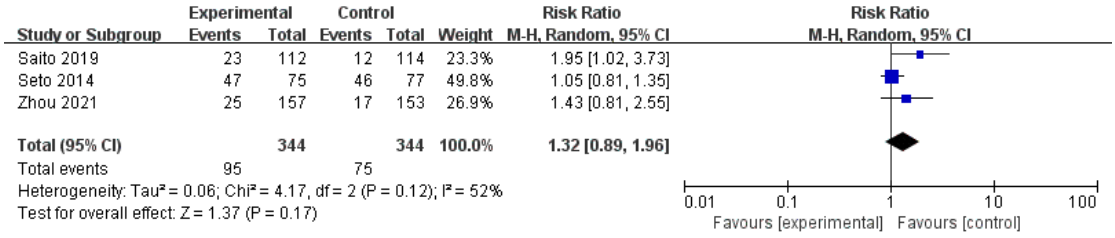


FigureS4 Forest plot of AEs of hypertension

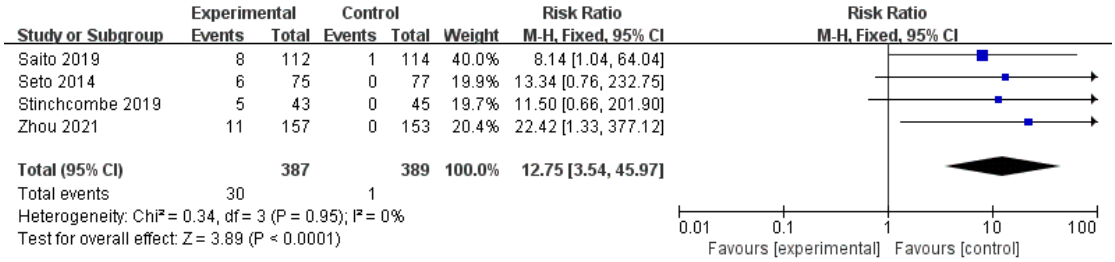


FigureS5 Forest plot of AEs of rash

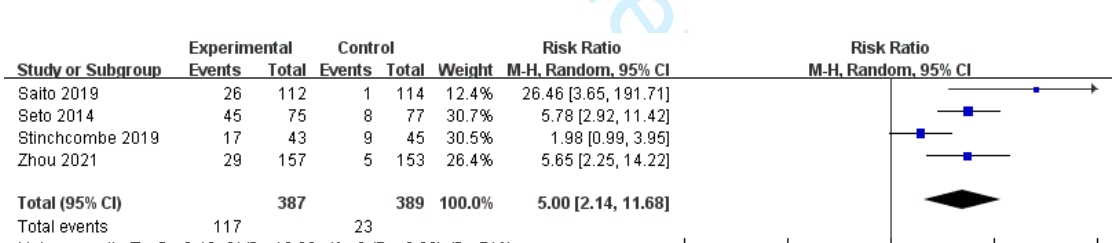
FigureS6 Forest plot of AEs of paronychia



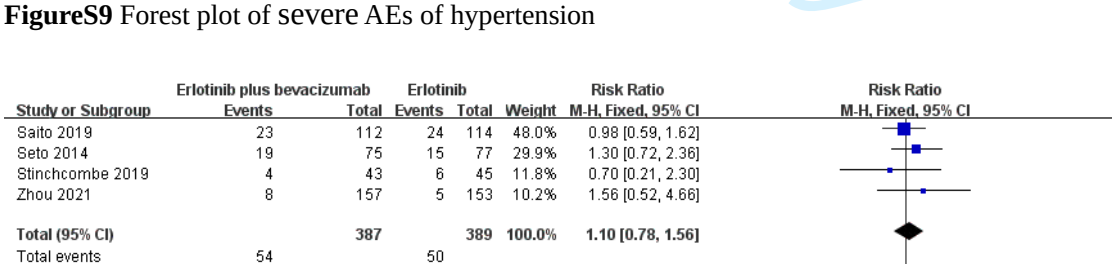
FigureS7 Forest plot of AEs of stomatitis



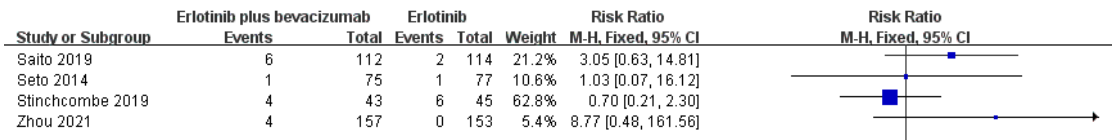
FigureS8 Forest plot of severe AEs of proteinuria



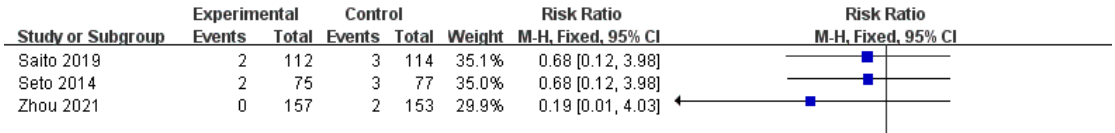
FigureS9 Forest plot of severe AEs of hypertension



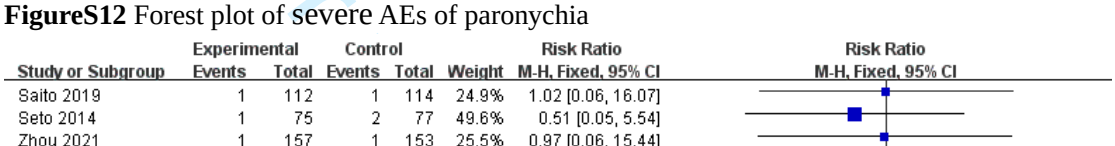
FigureS10 Forest plot of severe AEs of rash



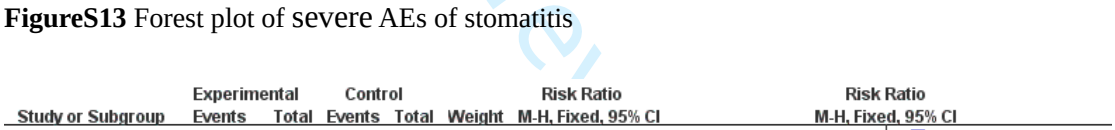
FigureS11 Forest plot of severe AEs of diarrhea



FigureS12 Forest plot of severe AEs of paronychia



FigureS13 Forest plot of severe AEs of stomatitis



FigureS14 Forest plot of severe AEs of haemorrhagic event

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			line/page
Title	1	Identify the report as a systematic review.	1-3/1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	13-30/1;1-5/2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7-19/2.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	20-30/2;1-10/3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	15-19/3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	27-28/3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	29-30/3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5/4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5/4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	12-16/4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	18-20/4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	20-26/4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	20-26/4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	20-26/4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	20-26/4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	20-26/4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	20-26/4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12-16/4
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	20-26/4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	2-8/5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-30/8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-30/8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-30/8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-30/8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11-30/8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	4-20/9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-30/9
	23b	Discuss any limitations of the evidence included in the review.	1-13/12
	23c	Discuss any limitations of the review processes used.	1-13/12
	23d	Discuss implications of the results for practice, policy, and future research.	17-29/11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	26-27/12
Competing interests	26	Declare any competing interests of review authors.	1/13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	3-4/13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

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10.1136/bmj.n71

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