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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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4 **Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-**
5 **positive advanced non-small-cell lung cancer: A Systematic Review and Meta-**
6 **Analysis of Randomized Controlled Trials**
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24

25 **ABSTRACT**

26
27 **Objectives** Therapy erlotinib plus bevacizumab has the potential to become a
28 standard treatment for patients with epidermal growth factor receptor mutation-
29 positive (*EGFRm*⁺) advanced non-small cell lung cancer (NSCLC). This study aimed
30 to investigate the efficacy and safety of erlotinib plus bevacizumab in *EGFRm*⁺
31 advanced NSCLC patients.
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37 **Setting** A systematic review and meta-analysis.

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39 **Participants** Patients were diagnosed as *EGFRm*⁺ advanced NSCLC.

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41 **Interventions** Erlotinib plus bevacizumab.

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43 **Primary and secondary outcome measures** Progression-free survival (PFS), overall
44 survival (OS), and objective response rate (ORR) and adverse effects (AEs).
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47 **Results** Six RCTs with a total of 775 cases were included in the meta-analysis. Of
48 these, 387 cases were treated by erlotinib plus bevacizumab, and 388 cases were
49 treated by erlotinib alone. Compared with erlotinib alone group, erlotinib plus
50 bevacizumab group significantly prolonged the PFS (hazard ratio (HR): 0.59; 95%
51 confidence interval (CI): 0.49-0.72; $P < 0.00001$; $I^2 = 0\%$), but failed to significantly
52 prolonged the OS (HR: 0.95; 95% CI: 0.78-1.15; $P = 0.59$; $I^2 = 0\%$), and the ORR
53 (odds ratio (OR): 1.25; 95% CI: 0.89–1.74; $P = 0.19$; $I^2 = 0\%$). Incidence of
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4 proteinuria, hypertension or proteinuria was higher in erlotinib plus bevacizumab
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6 group than in erlotinib alone group.

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

13 Lung cancer is the leading incidence and mortality of cancer in the world.¹
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15 Approximately 80-85% lung cancer has non-small cell lung cancer (NSCLC)
16 subtypes.² Despite the rapid development of novel diagnosis and therapeutic
17 strategies, approximately 62% patients with lung cancer are diagnosed at advanced
18 stage and prognosis remains poor,^{3 4} 5-year survival rate is less than 20%.⁵ Epidermal
19 growth factor receptor (*EGFR*) tyrosine-kinase inhibitors (TKIs) have been
20 established as the standard first-line treatment for patients with epidermal growth
21 factor receptor mutation-positive (*EGFR*^{m+}) lung cancer.⁶ Although 60-80% of
22 patients with *EGFR*-mutant tumors had durable responses, median progression-free
23 survival (PFS) is around 1 year with first-generation *EGFR* TKIs (gefitinib and
24 erlotinib) as a result of acquired drug resistance and relapse.⁷ Combination treatments
25 with *EGFR* TKIs is one strategy to overcome acquired resistance and improve
26 outcomes for these patients.
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40 Bevacizumab is a recombinant anti-angiogenic monoclonal antibody, which
41 directly targets the vascular endothelial growth factor (VEGF) signaling pathway to
42 inhibit tumor angiogenesis and suppress growth.⁸ Studies have suggested that
43 bevacizumab combined with first-line platinum-based chemotherapy has a significant
44 survival benefit in several trials in NSCLC.⁹⁻¹¹ The combination of erlotinib and
45 bevacizumab has the potential to prolong PFS in unselected populations of patients
46 with NSCLC.^{12 13} However, these studies were conducted in *EGFR*-unselected cases.
47
48 Moreover, the clinical relevance of *EGFR*^{m+} in NSCLC had not yet been clarified.
49 The first study that provided some important information respecting the efficacy of
50 combining bevacizumab and erlotinib in *EGFR*-mutant subgroup population was
51 Rosell:¹⁴ a phase 2 trial of erlotinib and bevacizumab. It showed that the benefit for
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3 the combined use of erlotinib and bevacizumab in patients with *EGFR*-mutant
4 NSCLC. However, this study evidence is insufficient as a result of single-arm trial.
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6 The effects of erlotinib plus bevacizumab in *EGFR*^{m+} advanced NSCLC remain
7 controversial. The results of some randomized controlled trials (RCTs) have shown
8 that erlotinib plus bevacizumab can prolong the PFS, objective response rate (ORR)
9 in *EGFR*^{m+} advanced NSCLC.¹⁵⁻¹⁸ In contrast, some studies reported comparable
10 efficacy in erlotinib plus bevacizumab group and erlotinib alone group.¹⁹ Thus, the
11 aim of this systematic review and meta-analysis was to evaluate the effects of
12 erlotinib plus bevacizumab in *EGFR*^{m+} advanced NSCLC patients.
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22 **METHODS**

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24 We conducted the systematic review based on the Preferred Reporting Items for
25 Systematic Reviews and Meta-analyses guidelines.²⁰
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28 **Inclusion and exclusion criteria**

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30 Adult participants with histologically or cytologically diagnosed NSCLC harboring
31 *EGFR*-mutant with Eastern Cooperative Oncology Group performance status scores
32 of 2 or lower. RCTs comparing erlotinib plus bevacizumab with erlotinib as a single
33 agent for the treatment of *EGFR*^{m+} NSCLC, were included. There were no special
34 restrictions on race, sex, nationality, histology, smoking history. Reviews without
35 original data as well as animal experimental studies and meta-analyses were excluded.
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42 **Outcome assessment**

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44 The primary outcomes were overall survival (OS), PFS, ORR of treatment for
45 NSCLC. Secondary outcome was adverse events (AEs) of the treatment.
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48 **Search strategy and selection**

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50 A systematic search of PubMed, Embase, Web of Science, and Cochrane Library was
51 performed for studies before 15 January 2022. Language was limited to English. The
52 combined text and medical subject heading (MeSH) terms used were: “Carcinoma,
53 Non-Small-Cell Lung” and “Erlotinib Hydrochloride” and “Bevacizumab” (see online
54 supplemental material 1 file for further details on search strategy).
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60 **Data extraction**

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4 All steps were performed independently by two investigators, any discrepancies were
5 resolved by discussion with a third investigator. The following information were
6 extracted: the first author's name, year of publication, region, participants'
7 characteristics [e.g., age, sex, ethnic origin, brain], the number of participants in each
8 group, description and doses of therapeutic agents administered, tumor histology, and
9 type of *EGFR* mutation and AEs. The efficacy criteria analyzed were: PFS, OS, ORR
10 and safety.
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17 **Assessing risk of bias and grading the quality of evidence**

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19 The Cochrane risk of bias tool was used to assess risk of bias of included trials²¹. Two
20 investigators evaluated each trial independently based on random sequence
21 generation, allocation concealment, blinding of participants, blinding of outcome,
22 incomplete outcome data, selective reporting, and other biases²². Discrepancies and
23 divergence in the quality assessment were resolved by group discussion.
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29 **Statistical analysis**

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31 The outcomes of OS and PFS were estimated by Hazard ratio (HR) with 95%
32 confidence interval (CI). Relative risk (RR) was used to estimate the outcomes of AEs
33 and ORR with 95% CI. We used I^2 statistic to assess the level of heterogeneity. The I^2
34 < 25%, 25-50%, and > 50% were defined as low, mild, and substantial
35 heterogeneity²³. If $I^2 < 50%$, p value > 0.05, a fixed-effects model was used in the
36 meta-analysis; In contrast, If $I^2 \geq 50%$, p value ≤ 0.05 , a random effect model was
37 used to assess the resource of the heterogeneity. All statistical analyses were
38 performed using RevMan version 5.4 provided by the Cochrane Collaboration, and P
39 value < 0.05 was considered statistically significant.
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48 **Patient and public involvement statement**

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50 Neither patients nor the public were involved in the design and planning of our
51 research.
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54 **RESULTS**

55 **Results of the literature search**

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57 The study flowchart is presented in Figure 1. A total of 783 publications were
58 identified by our search strategy, of which 139 duplicates were excluded. The
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4 remaining 644 publications were read by title and abstract, and 485 publications were
5 no relevant studies, 118 publications were meta-analysis, 3 publications were animal
6 experiment, and 16 publications were review. 622 of which were excluded. We
7 screened the remaining 22 articles carefully, and 6 studies met our eligibility criteria
8 and were included in the present meta-analysis.
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13 **Basic characteristics of studies included**

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15 The basic information included the authors, date of publication, participants region,
16 age, tumor histology, clinical stage, *EGFR* genomic aberration (Table 1). In the 6
17 studies^{15-19 24} included in the meta-analysis, Saito et al.¹⁶ and Kawashima et al.²⁴ are
18 NEJ026 study, and Seto et al.¹⁵ and Yamamoto et al.¹⁷ are JO25567 study. The
19 erlotinib plus bevacizumab group contained 387 cases and the erlotinib group
20 contained 388 cases. Patients assigned to the erlotinib plus bevacizumab group
21 received 150 mg of oral erlotinib form once daily and 15 mg/kg of intravenous
22 bevacizumab once every 21 days, starting from day 1 of cycle 1. Patients in the
23 erlotinib alone group received 150 mg of oral erlotinib once daily. One treatment
24 cycle was defined as 21 days.
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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 gene mutation 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 study¹⁸ 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

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

8 **Adverse effects**

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10 Eligible studies were specifically analyzed to extract all grades of AEs and severe
11 AEs (Table 2). We defined grade 3-5 AEs as severe AEs. The results showed that
12 incidence of diarrhea (51 vs. 43%, 95% CI: 1.03-1.38; P = 0.006; Figure S1),
13 haemorrhagic event (41 vs. 20%, 95% CI: 1.12-6.31; P = 0.03; Figure S2), proteinuria
14 (25 vs. 3%, 95% CI: 4.86-17.66; P < 0.0001; Figure S3), hypertension (40 vs. 8%,
15 95% CI: 3.66-7.88; P < 0.0001; Figure S4), were higher when using erlotinib plus
16 bevacizumab, in all grades of AE. No significant difference was found for rash (81 vs.
17 85%, 95% CI: 0.90-1.07; P = 0.63; Figure S5), paronychia (30 vs. 28%, 95% CI:
18 0.87-1.30; P = 0.57; Figure S6), stomatitis (28 vs. 22%, 95% CI: 0.89-1.96; P = 0.17;
19 Figure S7). In the analysis of severe AEs, the combination treatment yielded
20 significantly higher rates for proteinuria (8 vs. 0.3%, 95% CI: 3.54-45.97; P < 0.001;
21 Figure S8) and hypertension (30 vs. 5%, 95% CI: 2.14-11.68; P < 0.001; Figure S9).
22 No significant difference existed for severe rash (14 vs. 13%, 95% CI: 0.78-1.56; P =
23 0.59; Figure S10), diarrhea (4 vs. 2%, 95% CI: 0.76-3.68; P = 0.20; Figure S11),
24 paronychia (1 vs. 2%, 95% CI: 0.17-1.66; P = 0.28; Figure S12), stomatitis (0.9 vs.
25 1%, 95% CI: 0.17-3.36; P = 0.71; Figure S13), or haemorrhagic event (2 vs. 0.3%,
26 95% CI: 0.74-16.87; P = 0.11; Figure S14). (see online supplemental material 2 file
27 for forest plot of study results of AEs and severe AEs).

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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

DISCUSSION

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

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

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8 Erlotinib plus bevacizumab significantly prolonged PFS compared with erlotinib
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10 alone in *EGFR*m+ advanced NSCLC patients. Moreover, the addition of bevacizumab
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12 to chemotherapy treatment is proved to be effective in NSCLC patients with central
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14 nervous system metastases.²⁵⁻²⁷ There are several possible reasons why the addition of
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16 bevacizumab to erlotinib improved efficacy in terms of PFS compared with erlotinib.
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18 One possible mechanism is that bevacizumab combination could be improved drug
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20 delivery.²⁸ Since bevacizumab alter tumour blood vessel physiology, which will lead
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22 to increase intratumoral absorb of drugs.²⁹ A preclinical study³⁰ demonstrated that
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24 tumors treated with the lower dose of *EGFR* TKIs(gefitinib) developed earlier drug
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26 resistance than those with higher doses. Hence, a higher doses intratumoral
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28 concentration of erlotinib could extend TKIs resistant. Another possible mechanism is
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30 that bevacizumab may improve the restoration of cell apoptosis via VEGF-mediated
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32 pathway inhibition.³¹ Due to synergistic inhibition of cancer growth signalling, VEGF
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34 signal inhibition is still effective for cancers with *EGFR* TKIs resistance mutations.³²
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36 An animal study³³ suggested that erlotinib plus bevacizumab treatment restored
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38 resistance to the VEGF-mediated pathway. Therefore, in the clinic, the addition of
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40 bevacizumab to the erlotinib treatment is option strategy to delay the time of TKIs
41
42 resistant in the treatment of NSCLC.^{34 35}

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44 In contrast, in our meta-analysis, neither the ORR nor OS be prolonged by the
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46 combination therapy. For ORR, this lack of improvement can be explained by the
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48 high sensitivity of these NSCLC to *EGFR* TKIs. Owing to a high ORR for in erlotinib
49
50 alone group, thereby it is required a larger study population to prove significant effect
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52 of the combination regimen. For OS, the combination of bevacizumab and erlotinib
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54 failed to be translated into OS benefit, which can be explained by the following
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56 possible reasons. On one hand, OS might have been influenced by the patient therapy
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58 after disease progression. As there are many options for the treatment of NSCLC, any
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60 impact of first-line treatment on OS may be affected by subsequent treatment.³⁶ In
zhou¹⁸ study, more patients from erlotinib group received subsequent anticancer

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4 treatment than in the erlotinib plus bevacizumab group (50.0% [77/154] versus 33.8%
5 [53/157]), could have affected the OS result. On the other hand, there may be
6 different acquired resistance mechanisms between the two groups. The lack of OS
7 benefit in the erlotinib plus bevacizumab group may be explained by the difference in
8 the proportion of patients who subsequent-line osimertinib therapy. In Zhou¹⁸ study,
9 more patients received osimertinib in the erlotinib group as subsequent treatment than
10 in the erlotinib plus bevacizumab group (29.2% [27/157] versus 17.2% [45/154]).

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

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

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54 Our meta-analysis had several potential limitations. First, only six studies were
55 available to include in the analysis, and some of these studies had relatively small
56 sample sizes. Although these studies were high quality and well-performed trials, our
57 conclusions should be cautiously interpreted, because smaller trials are more likely to
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4 result in overestimation of the treatment effect. Second, our study failed to consider
5 the effect of previous treatment, and smoking status on partially enrolled participants,
6 due to lack of corresponding data and information. Third, subgroup analyses of *EGFR*
7 mutation state of NSCLC were not conducted due to insufficient information on these
8 factors in the included trials. NSCLC is a molecularly heterogeneous disease,⁴¹ the
9 ex19del and ex21 L858R were the two most common mutations in *EGFR*,⁴² hence the
10 subgroup analysis of *EGFR* mutation state of patients treated with erlotinib plus
11 bevacizumab is need further study. Finally, the OS data from the included trials were
12 not mature enough, so the data might change in the future and, hence, updating the
13 meta-analysis with final OS data will be essential.
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23 CONCLUSIONS

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25 The results of this meta-analysis confirmed the PFS prolongation achieved with
26 erlotinib plus bevacizumab compared to erlotinib alone to treat *EGFR*^{m+} advanced
27 NSCLC, without being able to prolong OS.
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31 **Contributors** WSD: study design, data collection and analysis, statistical analysis and
32 manuscript drafting, manuscript revision. KW: study design, data collection
33 and analysis, statistical analysis and manuscript drafting. DBL: data collection and
34 analysis, statistical analysis. CXB: data collection and analysis, manuscript revision.
35 JL: study design, manuscript revision. LYL: data collection. BH: statistical analysis.
36 JLK: study design, manuscript drafting, and manuscript revision. All authors read and
37 approved the manuscript.
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44
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46 China (No.81760743、 82160783 and 82104499).
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50 **Disclaimer** This study was a systematic review and meta-analysis. Ethics committee
51 approval was not necessary because all data were carefully extracted from existing
52 literature.
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55 **Competing interests** None declared.

56
57 **Ethics approval** This study does not involve human participants.

58
59 **Patient consent for publication** Not applicable.
60

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.

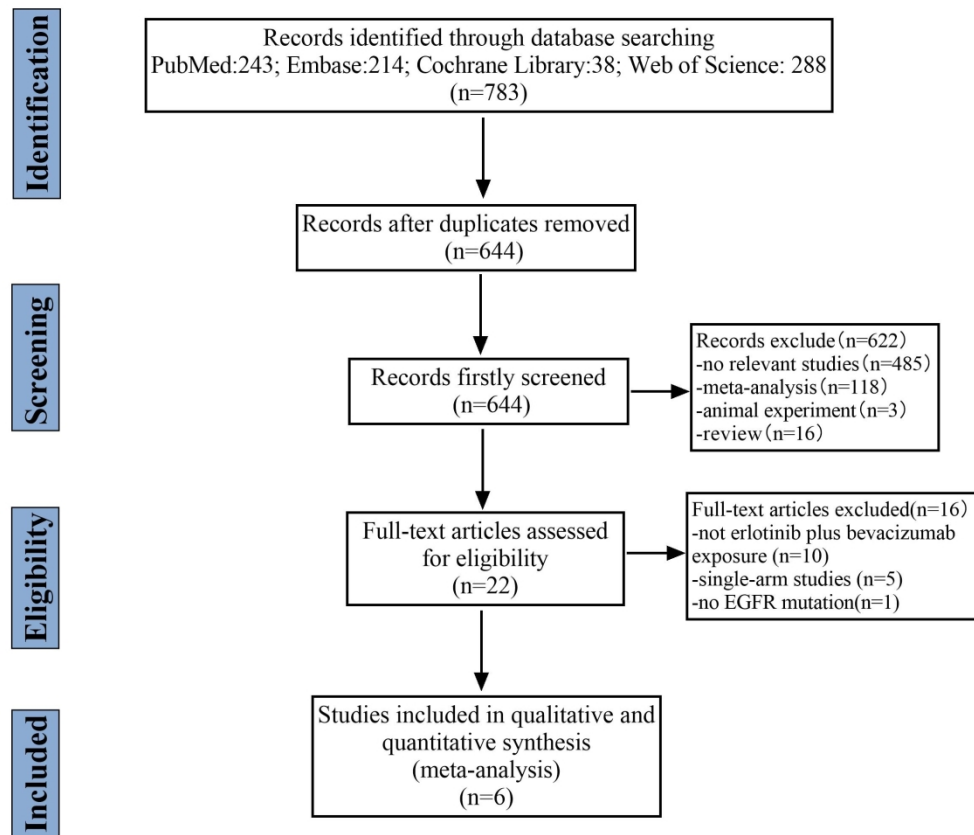


Figure 1 Flowchart of the literature screening.

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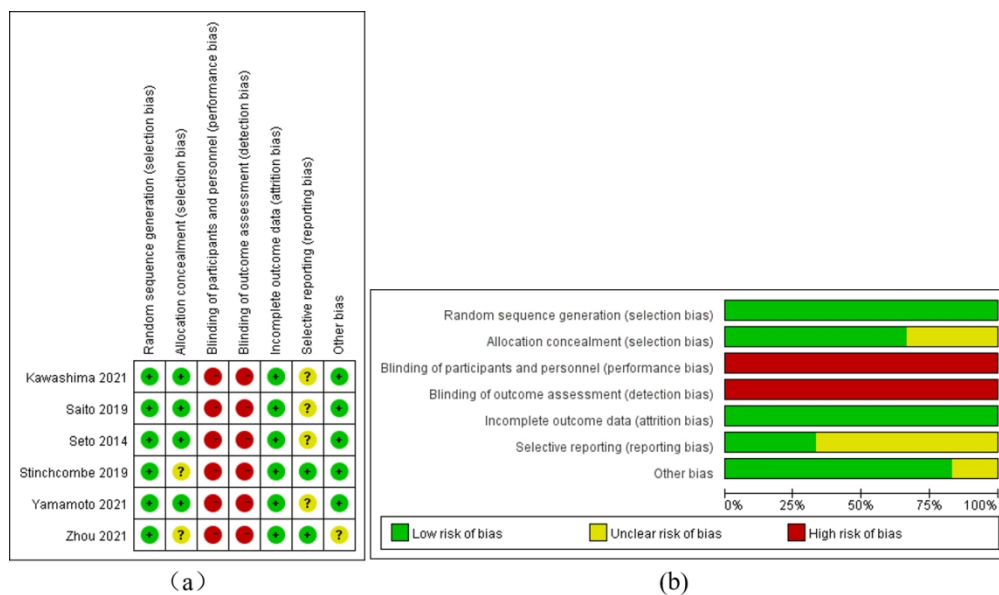


Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

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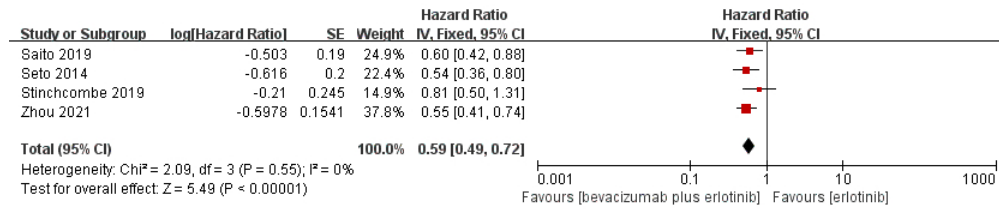


Figure 3 Forest plot of study results of PFS.

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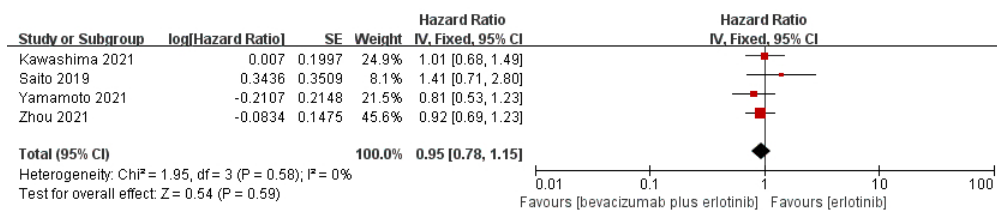


Figure 4 Forest plot of study results of OS.

293x62mm (72 x 72 DPI)

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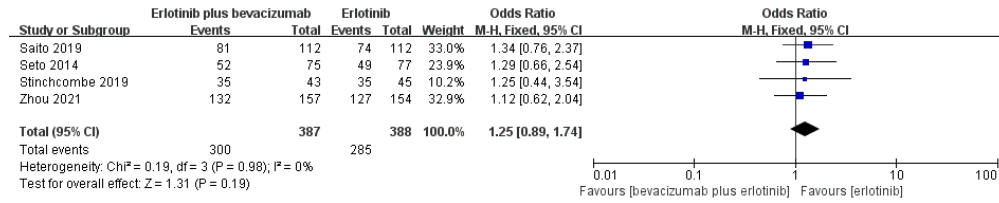


Figure 5 Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

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4 Pubmed Search Strategy:

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7 Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract]))
8 OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-
9 Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract]))
10 OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung
11 Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract]))
12 OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung
13 Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cance[Title/Abstract]))) AND
14 ("Erlotinib Hydrochloride"[Mesh])) OR (((((((((((((((Hydrochloride,
15 Erlotinib[Title/Abstract]) OR (Erlotinib HCl[Title/Abstract])) OR (HCl,
16 Erlotinib[Title/Abstract])) OR (OSI-774[Title/Abstract])) OR (OSI
17 774[Title/Abstract])) OR (OSI774[Title/Abstract])) OR (CP 358774[Title/Abstract]))
18 OR (358774, CP[Title/Abstract])) OR (CP 358,774[Title/Abstract])) OR (358,774,
19 CP[Title/Abstract])) OR (CP-358,774[Title/Abstract])) OR
20 (CP358,774[Title/Abstract])) OR (CP-358774[Title/Abstract])) OR
21 (CP358774[Title/Abstract])) OR (11C-erlotinib[Title/Abstract])) OR (11C
22 erlotinib[Title/Abstract])) OR (Erlotinib[Title/Abstract])) OR (N-(3-ethynylphenyl)-
23 6,7-bis(2-methoxyethoxy)quinazolin-4-amine[Title/Abstract])) OR
24 (Tarceva[Title/Abstract])) AND ("Bevacizumab"[Mesh])) OR
25 (((Mvasi[Title/Abstract]) OR (Bevacizumab-awwb[Title/Abstract])) OR
26 (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) AND
27 ((randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR
28 placebo[Title/Abstract])).

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40 Embase Search Strategy:

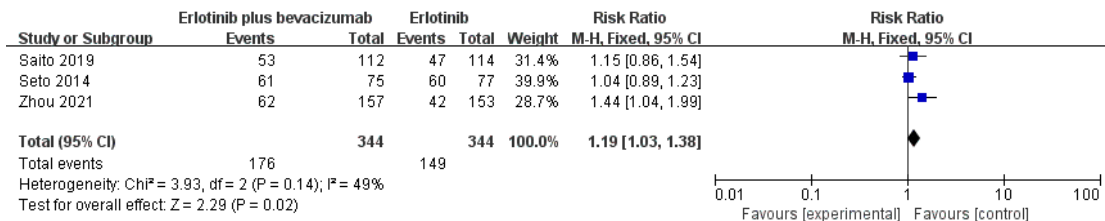
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43 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR
44 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR
45 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti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

web of science Search Strategy :

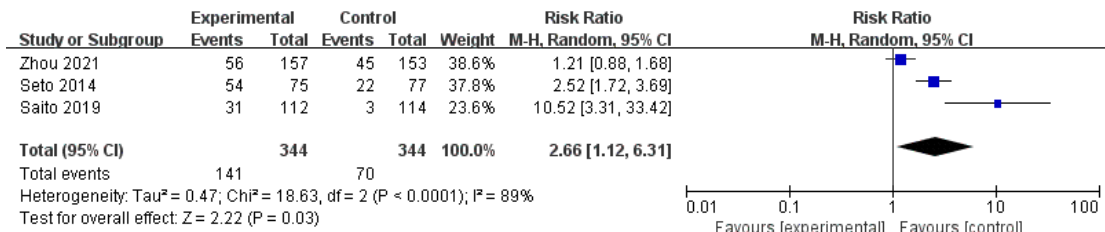
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Cochrane Library Search Strategy :

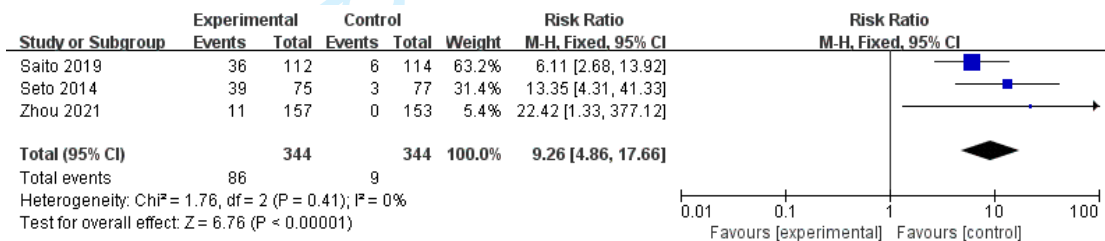
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw 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).



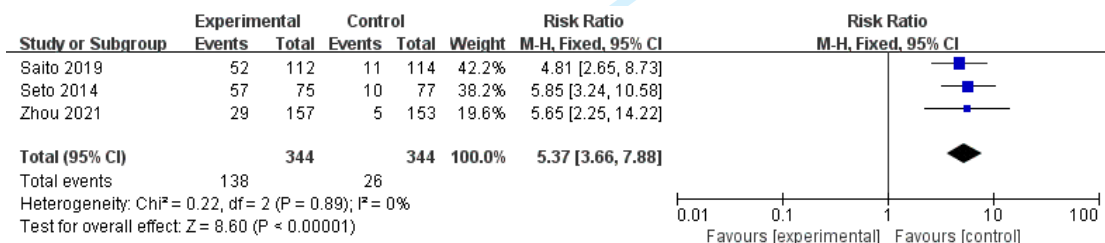
FigureS1 Forest plot of AEs of diarrhea



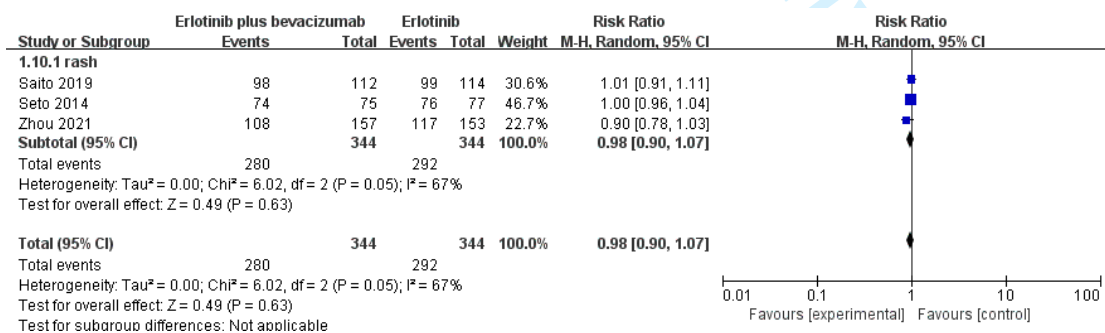
FigureS2 Forest plot of AEs of haemorrhagic event



FigureS3 Forest plot of AEs of proteinuria



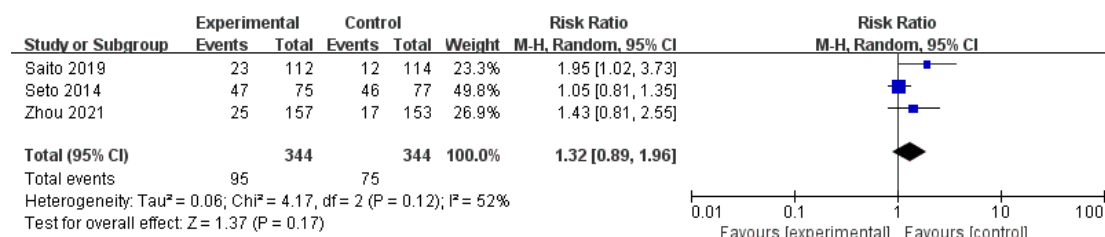
FigureS4 Forest plot of AEs of hypertension



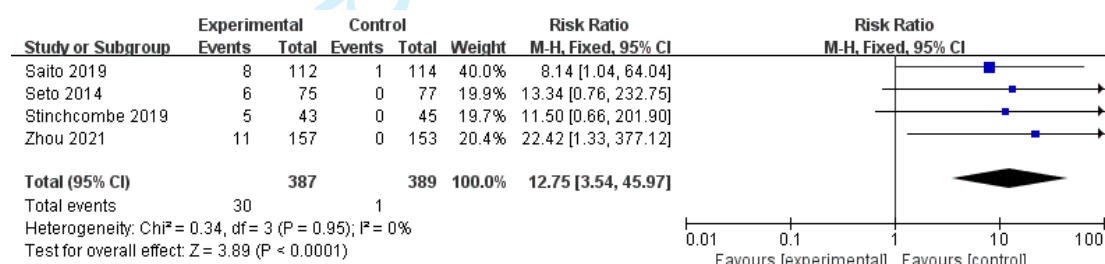
FigureS5 Forest plot of AEs of rash



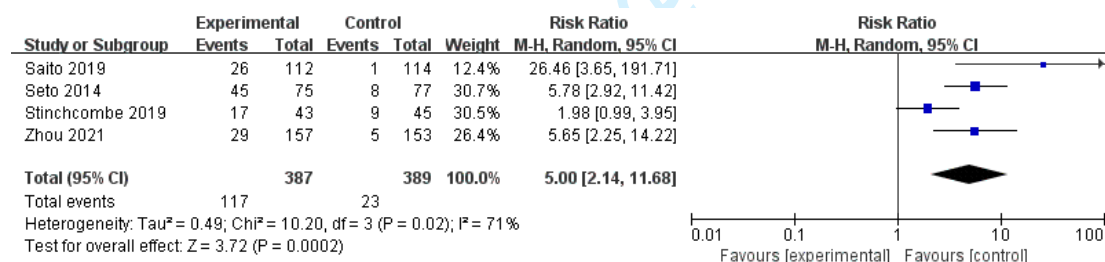
FigureS6 Forest plot of AEs of paronychia



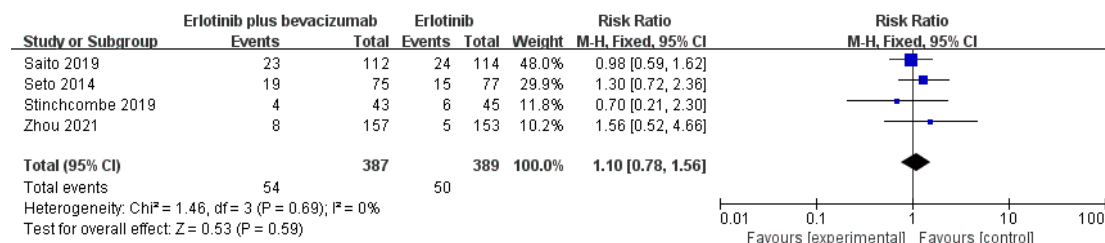
FigureS7 Forest plot of AEs of stomatitis



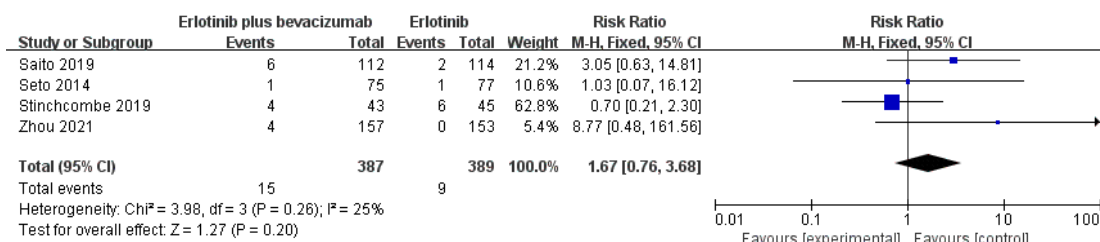
FigureS8 Forest plot of severe AEs of proteinuria



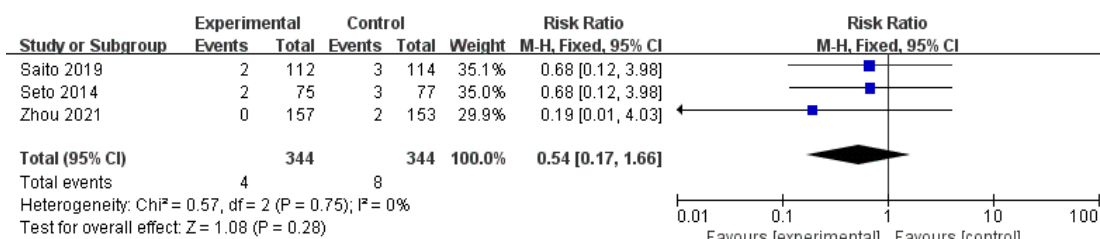
FigureS9 Forest plot of severe AEs of hypertension



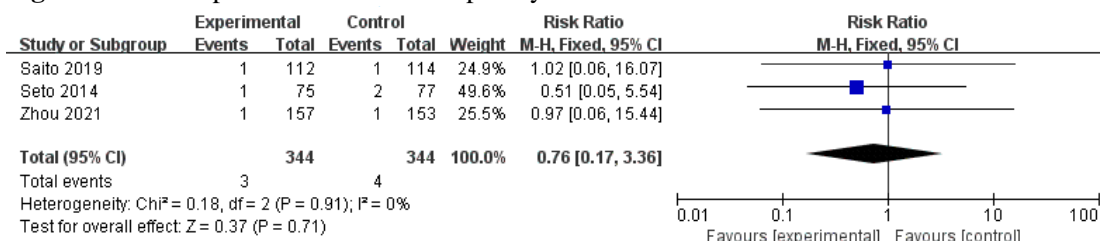
FigureS10 Forest plot of severe AEs of rash



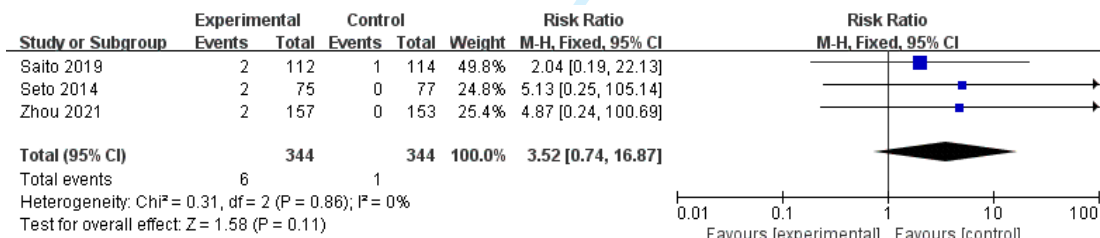
FigureS11 Forest plot of severe AEs of diarrhea



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



PRISMA 2020 Checklist

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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 randomized controlled trials

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4 1 **Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-**
5 **positive advanced non-small-cell lung cancer: a systematic review and meta-**
6 **analysis of randomized controlled trials**
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11 5 Wusheng Deng¹, Ke Wang¹, Dingbin Li², Chongxi Bao¹, Jing Luo¹, Liuyuan Liu¹, Bing Huang¹,
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36
37 18 **ABSTRACT**

38
39 19 **Objectives** Combination treatment with erlotinib plus bevacizumab has the potential
40 20 to become a standard treatment regimen for patients with epidermal growth factor
41 21 receptor mutation-positive (*EGFRm*⁺) advanced non-small cell lung cancer (NSCLC).
42 22 This study aimed to investigate the efficacy and safety of erlotinib plus bevacizumab
43 23 in patients with *EGFRm*⁺ advanced NSCLC.
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47 24

48 24 **Design** Systematic review and meta-analysis.

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50 25 **Data sources** The PubMed, Embase, Web of Science, and Cochrane Library
51 26 databases were searched, from inception to 15 January 2022.

52
53 27 **Eligibility criteria** We included randomized controlled trials (RCTs), reported in
54 28 English, assessing the efficacy of erlotinib plus bevacizumab versus erlotinib
55 29 monotherapy in patients with *EGFRm*⁺ advanced NSCLC.
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60 30 **Data extraction and synthesis** The main objective was to assess overall survival

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4 31 (OS), progression-free survival (PFS), objective response rate (ORR), and adverse
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6 32 events (AEs) in the treatment for NSCLC. Two independent reviewers extracted data
7
8 33 and assessed the risk of bias. A random-effect model was used where there was
9
10 34 evidence for homogeneous effects. The Higgins I^2 test was used to assess the
11
12 35 heterogeneity across the studies.

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14 36 **Results** Six RCTs (involving 775 cases) were included in the meta-analysis. 387
15
16 37 patients were treated with erlotinib plus bevacizumab and 388 patients were treated
17
18 38 with erlotinib alone. Compared with the erlotinib alone group, the erlotinib plus
19
20 39 bevacizumab group achieved a significantly prolonged PFS (HR: 0.59; 95%CI: 0.49–
21
22 40 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
23
24 41 ORR (OR: 1.25; 95%CI: 0.89–1.74; $P=0.19$; $I^2=0\%$) were not significantly prolonged.
25
26 42 Regarding AEs, combined treatment significantly increased the incidence of diarrhea
27
28 43 (51 vs. 43%, 95%CI: 1.03–1.38; $P=0.006$), haemorrhagic events (41 vs. 20%, 95%CI:
29
30 44 1.12–6.31; $P=0.03$), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; $P<0.0001$), and
31
32 45 hypertension (40 vs. 8%, 95%CI: 3.66–7.88; $P<0.0001$).

33
34 46 **Conclusions** Erlotinib plus bevacizumab for the treatment of patients with $EGFR^{m+}$
35
36 47 advanced NSCLC was associated with significantly prolonged PFS compared with
37
38 48 erlotinib alone, but use of the combination did not prolong OS.

49 50 **Strengths and limitations of this study**

51 * The present systematic review and meta-analysis was based on a comprehensive
52 search and the pooling of data from high-quality randomized controlled trials.

53 * We used the Preferred Reporting Items for Systematic reviews and Meta-analyses
54 guidelines to evaluate the strength and quality of the evidence.

55 * Limitations include publication biases and incomplete data for selected
56 articles.

57 * The literature searches only considered studies published in English.

58 * There was no analysis of post-study treatments that may have affected overall
59 survival.

60

61 INTRODUCTION

62 Lung cancer is the leading incidence and mortality of cancer in the world.¹
63 Approximately 80–85% of lung cancer is characterised by the non-small cell lung
64 cancer (NSCLC) subtype.² Despite the rapid development of new diagnostic and
65 therapeutic strategies, approximately 62% of patients with lung cancer are diagnosed
66 at an advanced stage and the prognosis remains poor.^{3 4} The 5-year survival rate is less
67 than 20%.⁵ Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors
68 (TKIs) have been established as the standard first-line treatment for patients with
69 *EGFR* mutation-positive (*EGFRm*⁺) lung cancer.⁶ Although 60–80% of patients with
70 *EGFR*-mutant tumours achieve durable responses, the median progression-free
71 survival (PFS) is approximately 1 year following treatment with first-generation
72 *EGFR* TKIs (gefitinib and erlotinib) as a result of acquired drug resistance and
73 relapse.⁷ Combination treatments with *EGFR* TKIs is one strategy to overcome
74 acquired resistance and to improve outcomes for these patients.⁸

75 Bevacizumab is a recombinant anti-angiogenic monoclonal antibody, which
76 directly targets the vascular endothelial growth factor (VEGF) signalling pathway to
77 inhibit tumour angiogenesis and suppress growth.⁹ Studies have suggested that
78 bevacizumab combined with first-line platinum-based chemotherapy has a significant
79 survival benefit in several trials in NSCLC.¹⁰⁻¹² The combination of erlotinib and
80 bevacizumab has the potential to prolong PFS in unselected populations of patients
81 with NSCLC.^{13 14} However, these studies were conducted in *EGFR*-mutant unselected
82 cases. Furthermore, the clinical relevance of *EGFRm*⁺ in NSCLC had not yet been
83 clarified. The first study that provided some important information on the efficacy of
84 combining bevacizumab and erlotinib in the population of the *EGFR*-mutant subgroup
85 population was Rosell et al.¹⁵ a phase 2 trial evaluating erlotinib and bevacizumab. It
86 showed the benefit of the combined use of erlotinib and bevacizumab in patients with
87 *EGFR*-mutant NSCLC. However, the evidence in single-arm trial was insufficient.
88 The effects of erlotinib plus bevacizumab in advanced *EGFRm*⁺ NSCLC remain
89 controversial. The results of randomized controlled trials (RCTs) have shown that
90 erlotinib plus bevacizumab can prolong the PFS and the objective response rate

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4 91 (ORR) in advanced *EGFR*m⁺ NSCLC.¹⁶⁻¹⁹ By contrast, some studies have reported
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6 92 comparable efficacy in patients treated with erlotinib plus bevacizumab and in those
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8 93 treated with the erlotinib monotherapy.²⁰ Previous meta-analyses have investigated
9
10 94 the effects of erlotinib plus bevacizumab in the treatment of NSCLC.^{14 21} However,
11
12 95 there has been no meta-analysis of erlotinib plus bevacizumab in the treatment of
13
14 96 advanced *EGFR*m⁺ NSCLC patients. Thus, the aim of this systematic review and
15
16 97 meta-analysis was to evaluate the effects and safety of erlotinib plus bevacizumab in
17
18 98 patients with *EGFR*m⁺ advanced NSCLC.

19 99

20 21 100 **METHODS**

22
23 101 We conducted the systematic review in accordance with the Preferred Reporting Items
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25 102 for Systematic Reviews and Meta-analyses guidelines.²²

26 27 103 **Inclusion and exclusion criteria**

28
29 104 Adult participants with histologically or cytologically diagnosed NSCLC harbouring
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31 105 an *EGFR*-mutation with Eastern Cooperative Oncology Group performance status
32
33 106 scores of 2 or lower were included. RCTs comparing erlotinib plus bevacizumab with
34
35 107 erlotinib as a single agent for the treatment of *EGFR*m⁺ NSCLC, were included. There
36
37 108 were no special restrictions on race, sex, nationality, histology, or smoking history.
38
39 109 Reviews without original data, as well as animal experimental studies and meta-
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41 110 analyses were excluded.

42 43 111 **Outcome assessment**

44
45 112 The primary outcomes were overall survival (OS), PFS, and ORR of NSCLC
46
47 113 treatment. Secondary outcome was adverse events (AEs) of treatment.

48 49 114 **Search strategy and selection**

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51 115 A systematic search of PubMed, Embase, Web of Science, and Cochrane Library was
52
53 116 performed for studies before 15 January 2022. The language was limited to English.
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55 117 The combined text and medical subject heading (MeSH) terms used were:
56
57 118 “Carcinoma, Non-Small-Cell Lung” and “Erlotinib Hydrochloride” and
58
59 119 “Bevacizumab” (see online Supplemental material 1 file for further details on the
60
120 search strategy).

121 **Data extraction**

122 All steps were performed independently by two investigators, any discrepancies were
123 resolved by discussion with a third investigator. The following information was
124 extracted: the name of the first author, year of publication, region, characteristics
125 (e.g., age, sex, ethnic origin, brain), the number of participants in each group,
126 description and doses of therapeutic agents administered, tumour histology and type
127 of *EGFR* mutation and AE. The efficacy criteria analysed were: PFS, OS, ORR and
128 safety.

129 **Assessing risk of bias and grading the quality of evidence**

130 The Cochrane risk of bias tool was used to assess the risk of bias of included trials²³.
131 Two investigators independently evaluated each trial based on random sequence
132 generation, allocation concealment, blinding of participants, blinding of outcome,
133 incomplete outcome data, selective reporting, and other biases²⁴. Discrepancies and
134 divergence in the quality assessment were resolved by group discussion.

135 **Statistical analysis**

136 The results of OS and PFS were estimated by Hazard ratio (HR) with a 95%
137 confidence interval (CI). Relative risk (RR) was used to estimate the results of AEs
138 and ORR with 95%CI. We used the I^2 statistic to assess the level of heterogeneity. An
139 $I^2 < 25\%$, $25-50\%$, and $> 50\%$ were defined as low, mild, and substantial
140 heterogeneity²⁵. If I^2 was $<50\%$ and the P value > 0.05 , a fixed-effects model was
141 used in the meta-analysis; In contrast, If $I^2 \geq 50\%$ and the P value ≤ 0.05 , a random
142 effects model was used to assess the resource of the heterogeneity. All statistical
143 analyses were performed with RevMan version 5.4 provided by the Cochrane
144 Collaboration and the P value < 0.05 was considered statistically significant.

145 **Patient and public involvement statement**

146 None.

148 **RESULTS**

149 **Results of the literature search**

150 The study flowchart is presented in Figure 1. A total of 783 publications were

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4 151 identified by our search strategy, of which 139 duplicates were excluded. The
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6 152 remaining 644 publications were read by title and abstract, and 485 publications were
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8 153 not relevant studies, 118 publications were meta-analyses, 3 publications involved
9
10 154 animal experiments, and 16 publications were reviews. Overall, 622 studies were
11
12 155 excluded. We carefully selected the remaining 22 articles, and 6 studies met our
13
14 156 eligibility criteria and were included in the present meta-analysis.

157 **Characteristics of the included studies**

158 Basic information included the author names, date of publication, region of
159 participants, age, tumour histology, clinical stage, genomic aberration of *EGFR*
160 (Table 1). The six studies^{16-20 26} included in the meta-analysis, Saito et al.¹⁷ and
161 Kawashima et al.²⁶ are NEJ026 study, and Seto et al.¹⁶ and Yamamoto et al.¹⁸ are
162 JO25567 study. The erlotinib plus bevacizumab group included 387 patients and the
163 erlotinib group included 388 patients. Patients assigned to the erlotinib plus
164 bevacizumab group received 150 mg of oral erlotinib form once daily and 15 mg/kg
165 of intravenous bevacizumab once every 21 days, beginning on day 1 of cycle 1.
166 Patients in the erlotinib alone group received 150 mg of oral erlotinib once daily. A
167 treatment cycle was defined as 21 days.

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171 **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 gene amplification/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, AEs, ORR,	Phase 2 RCT
Stinchcombe et al., ¹⁹ 2019	America (multicentre)	88(26/62)	63(31–84)	-	M1a,M1b	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

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176 **Risk of bias and quality assessment**

177 All studies presented adequate random sequence generation, and four studies
178 performed adequate allocation concealment.^{16-18 26} There was not enough information
179 to evaluate selective reporting in four studies,^{16-18 26} Two RCTs^{19 20} did not observe
180 selective outcome reporting. All RCT studies were open-label studies without
181 blinding. All studies were free of incomplete outcome data. Five studies^{16-18 20 26}
182 guaranteed no other bias while another study¹⁹ provided unclear information about
183 bias. There was sufficient evidence to assess that all studies of RCTs were moderate
184 or high quality, and the results are shown in Figure 2(a) and Figure 2(b).

185 **Progression-free survival**

186 Four studies^{16 17 19 20} reported PFS in the erlotinib plus bevacizumab group and the
187 erlotinib group. There were 387 participants in the erlotinib plus bevacizumab
188 intervention group and 388 participants in the erlotinib group. Pooled analyses
189 showed that erlotinib plus bevacizumab significantly reduced PFS compared to the
190 erlotinib group (HR: 0.59; 95%CI: 0.49–0.72; P<0.00001; Figure 3). No
191 heterogeneity was observed ($I^2=0\%$; P=0.55).

192 **Overall survival**

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

199 **Objective response rate**

200 Four studies^{16 17 19 20} reported ORR in the erlotinib plus bevacizumab group and the
201 erlotinib group. There were 387 participants in the erlotinib plus bevacizumab
202 intervention group and 388 participants in the erlotinib group. The pooled analyses
203 showed that erlotinib plus bevacizumab did not significantly reduce ORR compared to
204 the erlotinib group (OR: 1.25; 95%CI: 0.89–1.74; P=0.19); (Figure 5). No
205 heterogeneity was observed ($I^2=0\%$; P=0.98).

206 Adverse effects

207 Eligible studies were specifically analysed to extract all grades of AEs and severe AEs
 208 (Table 2). We defined grade 3–5 AEs as severe AEs. The results showed that
 209 incidence of diarrhea (51 vs. 43%, 95%CI: 1.03–1.38; P=0.006) (Figure S1),
 210 haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03) (Figure S2),
 211 proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001) (Figure S3), hypertension (40
 212 vs. 8%, 95%CI: 3.66–7.88; P<0.0001) (Figure S4), were higher when using erlotinib
 213 plus bevacizumab, in all grades of AE. No significant difference was found for rash
 214 (81 vs. 85%, 95%CI: 0.90–1.07; P=0.63) (Figure S5), paronychia (30 vs. 28%,
 215 95%CI: 0.87–1.30; P=0.57) (Figure S6), stomatitis (28 vs. 22%, 95%CI: 0.89–1.96;
 216 P=0.17) (Figure S7). In the analysis of severe AEs, the combination treatment yielded
 217 significantly higher rates for proteinuria (8 vs. 0.3%, 95%CI: 3.54–45.97; P<0.001)
 218 (Figure S8) and hypertension (30 vs. 5%, 95%CI: 2.14–11.68; P<0.001) (Figure S9).
 219 There were no significant differences for severe rash (14 vs. 13%, 95%CI: 0.78–1.56;
 220 P=0.59) (Figure S10), diarrhea (4 vs. 2%, 95%CI: 0.76–3.68; P=0.20) (Figure S11),
 221 paronychia (1 vs. 2%, 95%CI: 0.17–1.66; P=0.28) (Figure S12), stomatitis (0.9 vs.
 222 1%, 95%CI: 0.17–3.36; P=0.71) (Figure S13), or haemorrhagic event (2 vs. 0.3%,
 223 95%CI: 0.74–16.87; P=0.11) (Figure S14). (See the online supplemental material 2
 224 file for the forest plot of the study results of AEs and severe AEs).

225 **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

226

227 DISCUSSION

228 We performed the meta-analysis by combining patient data from six RCTs, a total of
 229 775 cases of lung cancer were included in our analyses. We found that the concurrent
 230 use of erlotinib plus bevacizumab contributed to prolonging PFS compared to
 231 erlotinib as a single agent, but not to improving OS and ORR, in the treatment of
 232 advanced *EGFR*^{m+} NSCLC. All grades of AEs and rash were more commonly found
 233 in the combination group and the single agent group. Furthermore, the incidence of
 234 diarrhea, haemorrhagic events, proteinuria, and hypertension was higher when
 235 erlotinib plus bevacizumab was used compared to erlotinib, in all grades of AEs. In
 236 the analysis of severe AE, combination treatment produced significantly higher rates
 237 for proteinuria and hypertension compared to erlotinib alone. Although a previous
 238 meta-analysis showed that the first-line angiogenesis inhibitor plus erlotinib
 239 prolonged PFS and did not improve OS in patients with *EGFR*^{m+} advanced NSCLC
 240 compared to the erlotinib monotherapy group,²⁷ the anti-VEGF plus erlotinib group in
 241 that meta-analysis included two different angiogenesis inhibitors (bevacizumab and
 242 ramucirumab), and bevacizumab and ramucirumab showed different degrees of

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4 243 efficacy in cancer management although with and a potential for bias was estimated,
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6 244 which were overcome in the present analysis. In this study, we compared patient
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8 245 groups treated with erlotinib plus bevacizumab with those treated with erlotinib alone,
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10 246 to potentially increase the precision and decrease the bias of our study compared to
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12 247 the previous meta-analysis. Furthermore, we added three recent RCT studies to our
13
14 248 systematic review and meta-analysis. Therefore, we believe that our study provides
15
16 249 comprehensive evidence-based recommendations for the relative efficacy and safety
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18 250 of erlotinib plus bevacizumab in *EGFR*^{m+} advanced NSCLC.

19 251 Erlotinib plus bevacizumab significantly prolonged PFS compared to erlotinib
20
21 252 alone in *EGFR*^{m+} advanced NSCLC patients. Furthermore, the addition of
22
23 253 bevacizumab to chemotherapy treatment has been shown to be effective in patients
24
25 254 with NSCLC with central nervous system metastases.²⁸⁻³⁰ There are several possible
26
27 255 reasons why the addition of bevacizumab to the erlotinib regimen improved efficacy
28
29 256 in terms of PFS compared to erlotinib. One possible mechanism is that the
30
31 257 combination of bevacizumab could improve drug delivery.³¹ Because bevacizumab
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33 258 alters tumour blood vessel physiology, leading to increased intertumoural absorption
34
35 259 of drugs.³² A preclinical study³³ demonstrated that tumours treated with the lowest
36
37 260 dose of a *EGFR* TKI (gefitinib) developed drug resistance earlier than those with
38
39 261 higher doses. Therefore, a higher intratumoural concentration of erlotinib could
40
41 262 prolong resistance to TKIs. Another possible mechanism is that bevacizumab may
42
43 263 restore of cell apoptosis by inhibiting the VEGF-mediated pathway.³⁴ Due to
44
45 264 synergistic inhibition of cancer growth signalling, VEGF signal inhibition is still
46
47 265 effective for cancers with *EGFR* TKI resistant mutations.³⁵ An animal study³⁶
48
49 266 suggested that erlotinib plus bevacizumab treatment restored resistance to the VEGF-
50
51 267 mediated pathway. Therefore, in the clinic, the addition of bevacizumab to erlotinib
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53 268 treatment is optional strategy to delay the onset of TKI resistance in NSCLC.^{21 37}

54 269 In our meta-analysis, neither ORR nor OS were prolonged by combination therapy.
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56 270 For ORR, this lack of improvement can be explained by the high sensitivity of these
57
58 271 NSCLC to *EGFR* TKIs. Due to the high ORR in the erlotinib alone group, a larger
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60 272 study population is required to demonstrate a significant effect of the combination

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4 273 regimen. For OS, the combination of bevacizumab and erlotinib failed to translate into
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6 274 OS benefit, which can be explained as outlined below. Although OS might have been
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8 275 influenced by patient therapy after disease progression , because there are many
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10 276 options for the treatment of NSCLC, any outcome of first-line treatment on OS can be
11
12 277 influenced by subsequent treatment.³⁸ In a study by Zhou et al.,¹⁹ more patients in the
13
14 278 erlotinib group received subsequent anticancer treatment than in the erlotinib plus
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16 279 bevacizumab group (50.0% [77/154] versus 33.8% [53/157]), which could have
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18 280 influenced the OS result. Conversely, there may be different acquired resistance
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20 281 mechanisms between the two groups. Furthermore, the lack of OS benefit in the
21
22 282 erlotinib plus bevacizumab group may be explained by the differences in the
23
24 283 proportion of patients who receive subsequent lines of osimertinib therapy. In the
25
26 284 Zhou¹⁹ et al. study, more patients received osimertinib in the erlotinib group as a
27
28 285 subsequent treatment than in the erlotinib plus bevacizumab group (29.2% [27/157]
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30 286 vs.17.2% [45/154]).

31 287 Concerning safety, erlotinib plus bevacizumab is more toxic than erlotinib alone
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33 288 group and are known toxicities associated with bevacizumab treatment, especially for
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35 289 diarrhea, haemorrhagic events, proteinuria, and hypertension.^{39 40} In most cases,
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37 290 toxicity of combination therapy was considered to be tolerable and manageable,⁴¹
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39 291 patients will not choose to terminate drug treatment early due to AE, so patients can
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41 292 achieve the benefits of treatment with erlotinib plus bevacizumab.

42 293 Our current meta-analysis has some strengths. We comprehensively researched the
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44 294 pooled data from the most up-to-date high-quality RCTs and provided best level of
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46 295 evidence that demonstrated the efficacy and safety of erlotinib plus bevacizumab in
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48 296 patients with advanced *EGFR*^{m+} NSCLC. The recommended first-line treatment for
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50 297 advanced *EGFR*^{m+} NSCLC is often osimertinib, a third-generation EGFR TKI. The
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52 298 first generation, second generation *EGFR* TKI, *EGFR* TKI plus bevacizumab or
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54 299 *EGFR* TKI plus ramucirumab are also available as treatment options.^{42 43} However,
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56 300 most patients eventually develop disease progression due to acquired drug
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58 301 resistance.⁴⁴ Our meta-analysis provided evidence that the erlotinib plus bevacizumab
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60 302 combination prolongs PFS compared to the erlotinib alone; therefore, in the clinic,

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4 303 when erlotinib monotherapy is ineffective, the addition of bevacizumab to the
5
6 304 erlotinib is an optional strategy for the treatment of *EGFR*^{m+} advanced NSCLC.

7 305 Our meta-analysis had several potential limitations. First, only six studies were
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9 306 available to include in the analysis, and some of these studies had relatively small
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11 307 sample sizes. Although these results were of high-quality and derived from well-
12
13 308 performing trials, our conclusions should be interpreted with caution because smaller
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15 309 trials are more likely to result in an overestimation of the treatment effects. Second,
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17 310 our study failed to consider the effects of previous treatment and smoking status in
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19 311 some of the enrolled participants, due to the lack of corresponding data and
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21 312 information. Third, a subgroup analysis of *EGFR* mutation status of NSCLC was not
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23 313 conducted due to insufficient information on these factors in the included trials.
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25 314 NSCLC is a molecularly heterogeneous disease,⁴⁵ the ex19del and ex21 L858R
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27 315 mutations are the two most common reported *EGFR* variants,⁴⁶ therefore, a subgroup
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29 316 analysis based on the *EGFR* mutation status of patients treated with erlotinib plus
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31 317 bevacizumab is warranted in the future. Finally, there may have been a bias in the
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33 318 selection of positive studies. It is understandable that journals do not like to present
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35 319 negative data, so this may also have led to an overestimation of a treatment effect.

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38 321 **CONCLUSIONS**

39
40 322 Based on the present evidence, although the combined strategy of erlotinib plus
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42 323 bevacizumab prolonged PFS for the treatment of *EGFR*^{m+} advanced NSCLC, this
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44 324 strategy failed to significantly improve OS, and exhibited common but acceptable
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46 325 AEs such as diarrhea, haemorrhagic event, proteinuria and hypertension. This
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48 326 combination can be recommended as a therapeutic strategy for patients with advanced
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50 327 *EGFR*^{m+} NSCLC.

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56 330 **Contributors** WSD: study design, data collection and analysis, statistical analysis and manuscript drafting,

57
58 331 manuscript revision. KW: study design, data collection and analysis, statistical analysis and manuscript drafting.

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60 332 DBL: data collection and analysis, statistical analysis. CXB: data collection and analysis, manuscript revision. JL:

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

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341 and the Advanced Innovation Teams and Xinghu Scholars Program of Guangxi Medical University.

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

344 **Competing interests** None declared.

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

346 **Patient consent for publication** Not applicable.

347 **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

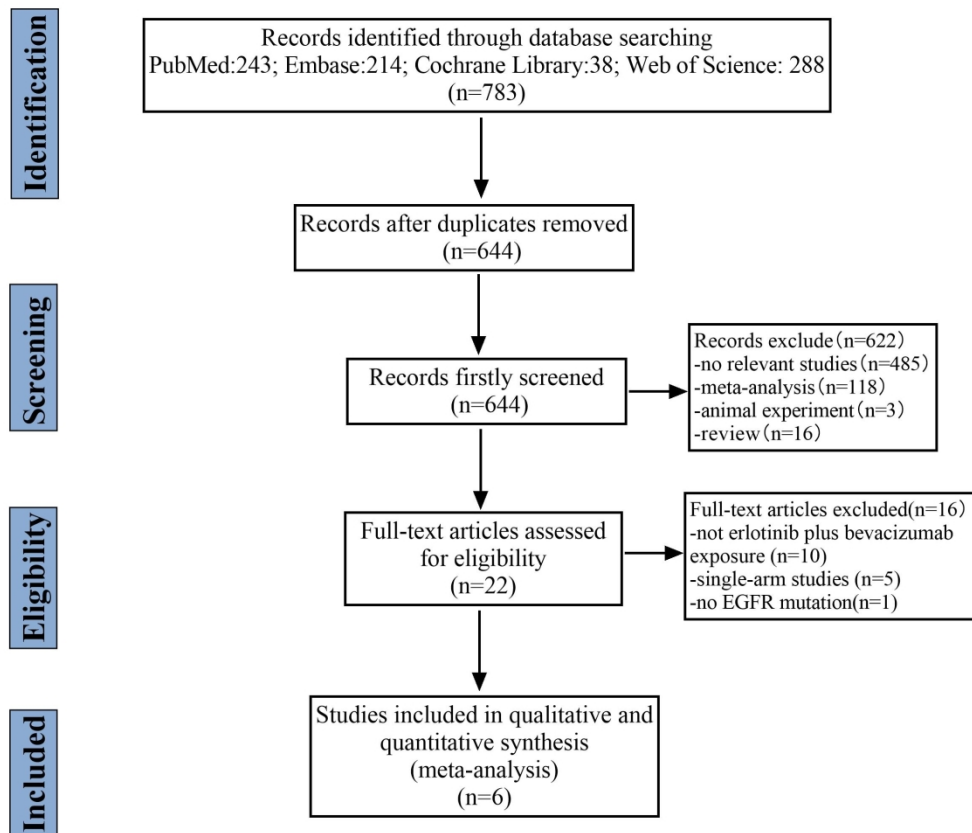


Figure 1 Flowchart of the literature screening.

200x171mm (300 x 300 DPI)

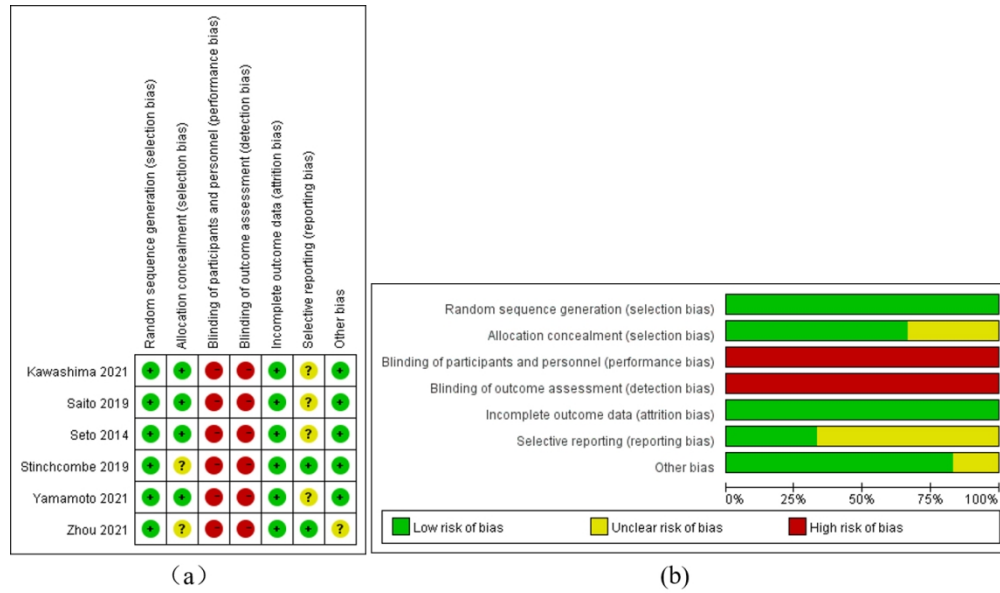


Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

250x150mm (150 x 150 DPI)

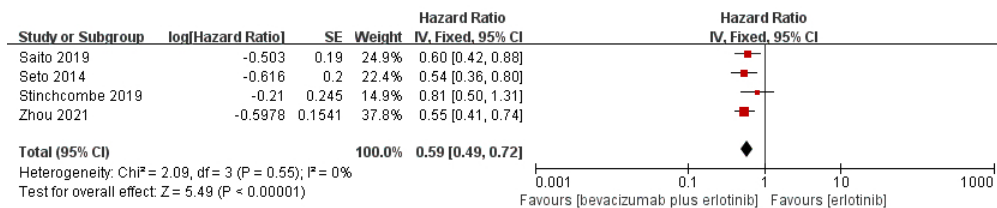


Figure 3. Forest plot of study results of PFS.

293x62mm (72 x 72 DPI)

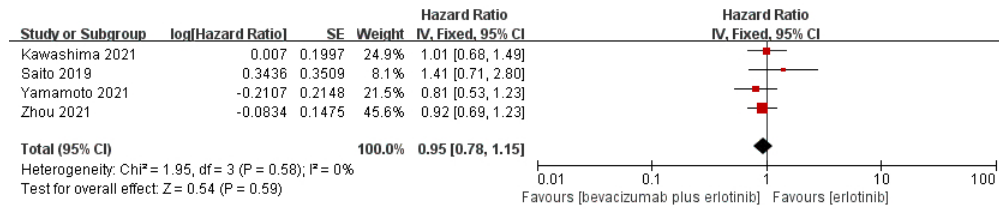


Figure 4. Forest plot of study results of OS.

293x62mm (72 x 72 DPI)

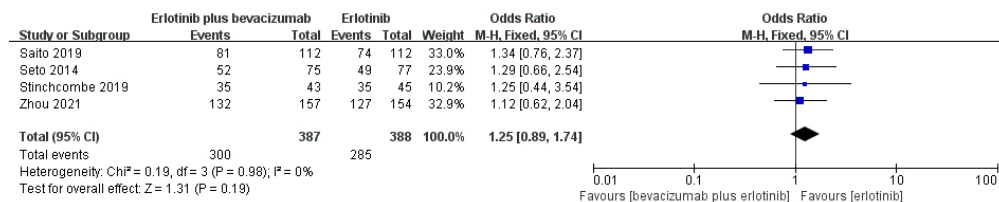


Figure 5. Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

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4 Pubmed Search Strategy:

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6 (((((((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR (((((((((((Carcinoma, Non Small
7 Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract]))
8 OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-
9 Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract]))
10 OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung
11 Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract]))
12 OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung
13 Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cance[Title/Abstract])) AND
14 ("Erlotinib Hydrochloride"[Mesh])) OR (((((((((((((((Hydrochloride,
15 Erlotinib[Title/Abstract]) OR (Erlotinib HCl[Title/Abstract])) OR (HCl,
16 Erlotinib[Title/Abstract])) OR (OSI-774[Title/Abstract])) OR (OSI
17 774[Title/Abstract])) OR (OSI774[Title/Abstract])) OR (CP 358774[Title/Abstract]))
18 OR (358774, CP[Title/Abstract])) OR (CP 358,774[Title/Abstract])) OR (358,774,
19 CP[Title/Abstract])) OR (CP-358,774[Title/Abstract])) OR
20 (CP358,774[Title/Abstract])) OR (CP-358774[Title/Abstract])) OR
21 (CP358774[Title/Abstract])) OR (11C-erlotinib[Title/Abstract])) OR (11C
22 erlotinib[Title/Abstract])) OR (Erlotinib[Title/Abstract])) OR (N-(3-ethynylphenyl)-
23 6,7-bis(2-methoxyethoxy)quinazolin-4-amine[Title/Abstract])) OR
24 (Tarceva[Title/Abstract])) AND ("Bevacizumab"[Mesh])) OR
25 (((Mvasi[Title/Abstract]) OR (Bevacizumab-awwb[Title/Abstract])) OR
26 (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) AND
27 ((randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR
28 placebo[Title/Abstract])).

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40 Embase Search Strategy:

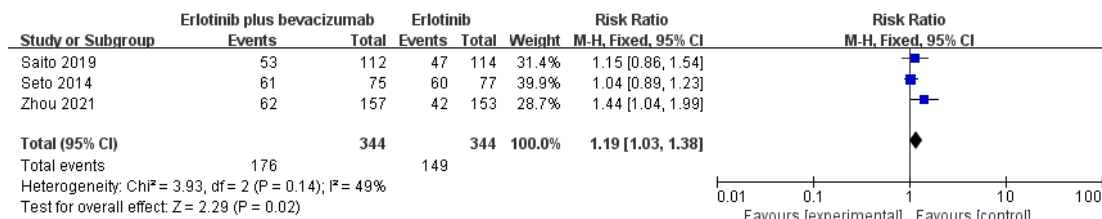
41
42 'carcinoma, non small cell lung':ab,ti OR ('carcinomas, non-small-cell lung':ab,ti OR
43 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR
44 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR
45 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR
46 'non-small cell lung carcinoma':ab,ti OR 'non-small cell lung cancer':ab,ti)
47 AND(erlotinib AND hydrochloride OR 'hydrochloride, erlotinib':ab,ti OR 'erlotinib
48 hcl':ab,ti OR 'hcl, erlotinib':ab,ti OR 'osi-774':ab,ti OR 'osi 774':ab,ti OR 'osi774':ab,ti
49 OR 'cp 358774':ab,ti OR '358774, cp':ab,ti OR 'cp 358,774':ab,ti OR '358,774,
50 cp':ab,ti OR 'cp-358,774':ab,ti OR 'cp358,774':ab,ti OR 'cp-358774':ab,ti OR
51 'cp358774':ab,ti OR '11c-erlotinib':ab,ti OR '11c erlotinib':ab,ti OR 'erlotinib':ab,ti OR
52 'n-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine':ab,ti OR
53 'tarceva':ab,ti) AND (bevacizumab OR 'mvasi':ab,ti OR 'bevacizumab-awwb':ab,ti OR
54 'bevacizumab awwb':ab,ti OR 'avastin':ab,ti) AND ('randomized controlled trial':ab,ti
55 OR 'randomized':ab,ti OR 'placebo':ab,ti OR 'rct':ab,ti).

web of science Search Strategy :

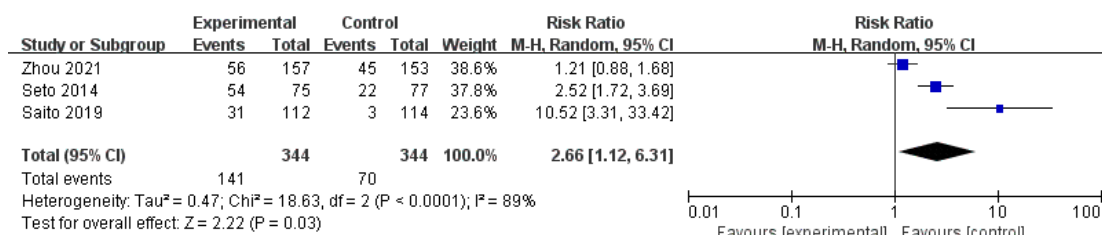
(TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell 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 :

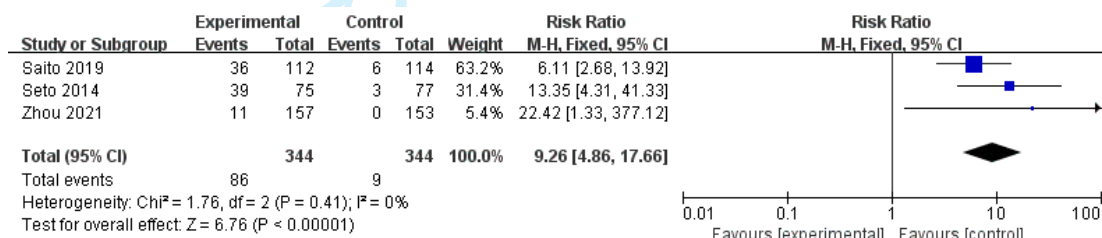
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw 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).



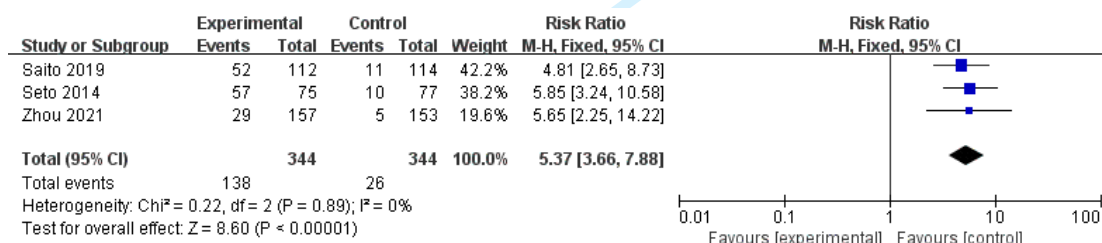
FigureS1 Forest plot of AEs of diarrhea



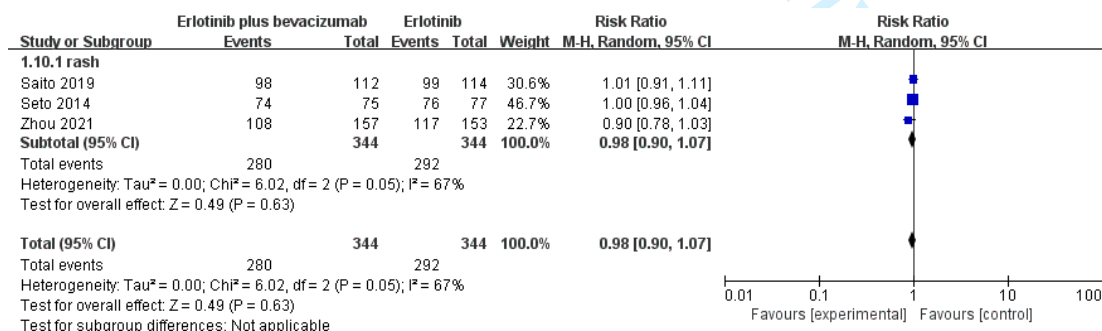
FigureS2 Forest plot of AEs of haemorrhagic event



FigureS3 Forest plot of AEs of proteinuria



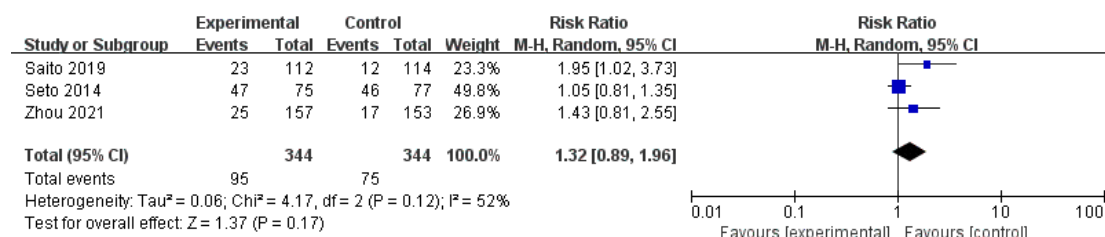
FigureS4 Forest plot of AEs of hypertension



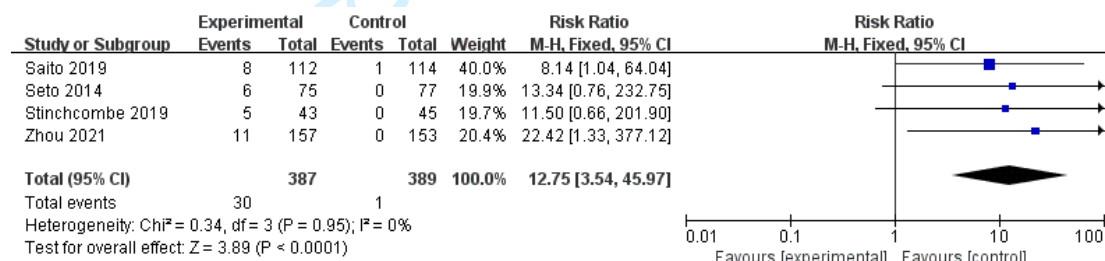
FigureS5 Forest plot of AEs of rash



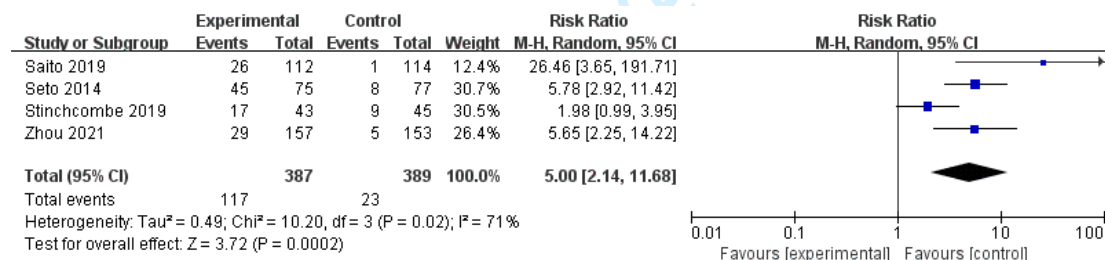
FigureS6 Forest plot of AEs of paronychia



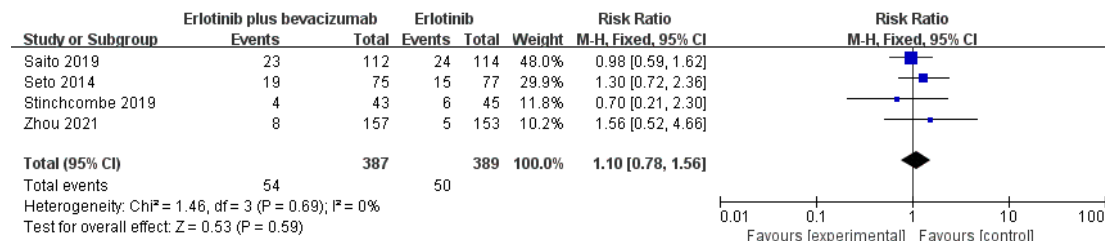
FigureS7 Forest plot of AEs of stomatitis



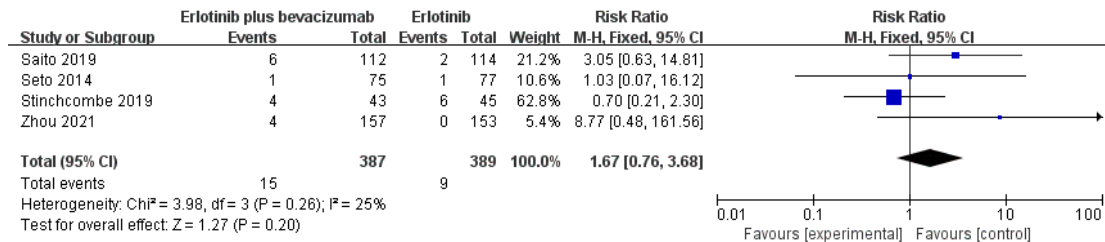
FigureS8 Forest plot of severe AEs of proteinuria



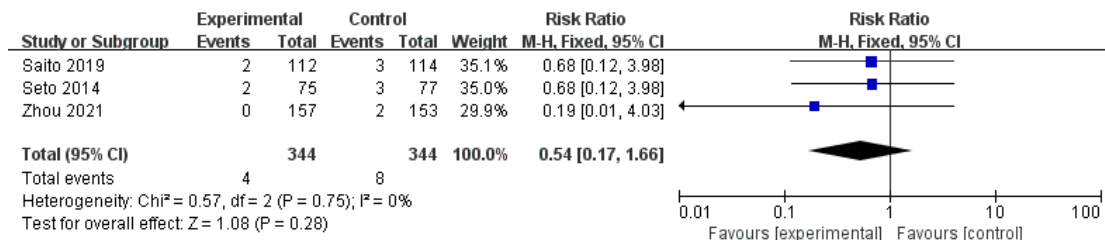
FigureS9 Forest plot of severe AEs of hypertension



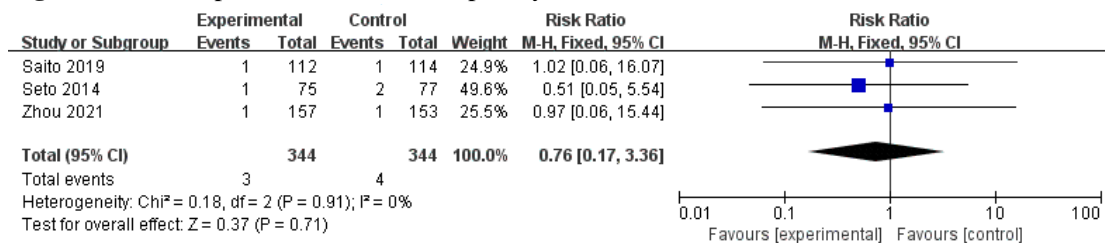
FigureS10 Forest plot of severe AEs of rash



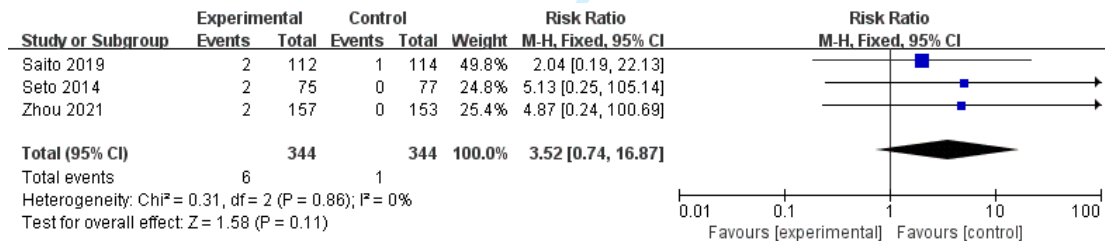
FigureS11 Forest plot of severe AEs of diarrhea



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

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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

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PRISMA 2020 Checklist

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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



PRISMA 2020 Checklist

10.1136/bmj.n71

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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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062036.R2
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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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4 1 **Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-**
5 **positive advanced non-small-cell lung cancer: a systematic review and meta-**
6 **analysis of randomised controlled trials**
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11 5 Wusheng Deng¹, Ke Wang¹, Yun Jiang², Dingbin Li³, Chongxi Bao¹, Jing Luo¹, Liuyuan Liu¹,
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39 19 **ABSTRACT**

40 20 **Objectives** Combination treatment with erlotinib plus bevacizumab has the potential
41 21 to become a standard treatment regimen for patients with epidermal growth factor
42 22 receptor mutation-positive (*EGFRm*⁺) advanced non-small cell lung cancer (NSCLC).
43 23 This study aimed to investigate the efficacy and safety of erlotinib plus bevacizumab
44 24 in patients with *EGFRm*⁺ advanced NSCLC.
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50 25 **Design** Systematic review and meta-analysis.

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52 26 **Data sources** The PubMed, Embase, Web of Science, and Cochrane Library
53 27 databases were searched, from inception to 15 January 2022.

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56 28 **Eligibility criteria** We included randomised controlled trials (RCTs), reported in
57 29 English, assessing the efficacy of erlotinib plus bevacizumab versus erlotinib
58 30 monotherapy in patients with *EGFRm*⁺ advanced NSCLC.
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4 31 **Data extraction and synthesis** The main objective was to assess overall survival
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6 32 (OS), progression-free survival (PFS), objective response rate (ORR), and adverse
7
8 33 events (AEs). Two independent reviewers extracted data and assessed the risk of bias.
9
10 34 A random-effect model was used where there was evidence for homogeneous effects.

11 35 **Results** Four RCTs (reported across six publications) were included in the meta-
12
13 36 analysis, with a total of 775 patients included in the pooled analyses of PFS, OS and
14
15 37 ORR (387 in the erlotinib plus bevacizumab intervention group and 388 in the
16
17 38 erlotinib group). Compared with the erlotinib alone group, the erlotinib plus
18
19 39 bevacizumab group achieved a significantly prolonged PFS (HR: 0.59; 95%CI: 0.49–
20
21 40 0.72; $P < 0.00001$; $I^2 = 0\%$), but OS (HR: 0.95; 95%CI: 0.78–1.15; $P = 0.59$; $I^2 = 0\%$)
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23 41 and ORR (OR: 1.25; 95%CI: 0.89–1.74; $P = 0.19$; $I^2 = 0\%$) were not significantly
24
25 42 prolonged. A total of 776 cases were used to pooled analysis of AEs. Regarding AEs,
26
27 43 combined treatment significantly increased the incidence of diarrhoea (51 vs. 43%,
28
29 44 95%CI: 1.03–1.38; $P = 0.006$), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31;
30
31 45 $P = 0.03$), proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; $P < 0.0001$), and hypertension
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33 46 (40 vs. 8%, 95%CI: 3.66–7.88; $P < 0.0001$).

34
35 47 **Conclusions** Erlotinib plus bevacizumab for the treatment of patients with *EGFR*^{m+}
36
37 48 advanced NSCLC was associated with significantly prolonged PFS compared with
38
39 49 erlotinib alone, but the combination did not prolong OS.

50 51 **Strengths and limitations of this study**

52 * The present systematic review and meta-analysis pooled data from high-quality
53 randomised controlled trials.

54 * We used the Preferred Reporting Items for Systematic reviews and Meta-analyses
55 guidelines to inform our reporting and we evaluated the strength and quality of the
56 evidence.

57 * Limitations include publication biases and incomplete data in selected articles.

58 * The literature searches only considered studies published in English.

59 * There was no analysis of post-study treatments that may have affected overall
60 survival.

61

62 **INTRODUCTION**63 Lung cancer is the leading incidence and mortality of cancer in the world.¹

64 Approximately 80–85% of lung cancer is characterised by the non-small cell lung

65 cancer (NSCLC) subtype.² Despite the rapid development of new diagnostic and

66 therapeutic strategies, approximately 62% of patients with lung cancer are diagnosed

67 at an advanced stage and the prognosis remains poor.^{3 4} The 5-year survival rate is less68 than 20%.⁵ Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors

69 (TKIs) have been established as the standard first-line treatment for patients with

70 *EGFR* mutation-positive (*EGFR*^{m+}) lung cancer.⁶ Although 60–80% of patients with71 *EGFR*-mutant tumours achieve durable responses, the median progression-free

72 survival (PFS) is approximately 1 year following treatment with first-generation

73 *EGFR* TKIs (gefitinib and erlotinib) as a result of acquired drug resistance and74 relapse.⁷ Combination treatments with *EGFR* TKIs is one strategy to overcome75 acquired resistance and to improve outcomes for these patients.⁸

76 Bevacizumab is a recombinant anti-angiogenic monoclonal antibody, which

77 directly targets the vascular endothelial growth factor (VEGF) signalling pathway to

78 inhibit tumour angiogenesis and suppress growth.⁹ Studies have suggested that

79 bevacizumab combined with first-line platinum-based chemotherapy has a significant

80 survival benefit in several trials in NSCLC.¹⁰⁻¹² The combination of erlotinib and

81 bevacizumab has the potential to prolong PFS in unselected populations of patients

82 with NSCLC.^{13 14} However, these studies were conducted in *EGFR*-mutant unselected83 cases. Furthermore, the clinical relevance of *EGFR*^{m+} in NSCLC had not yet been

84 clarified. The first study that provided some important information on the efficacy of

85 combining bevacizumab and erlotinib in the population of the *EGFR*-mutant subgroup86 population was Rosell et al.¹⁵ a phase 2 trial evaluating erlotinib and bevacizumab. It

87 showed the benefit of the combined use of erlotinib and bevacizumab in patients with

88 *EGFR*-mutant NSCLC. However, the evidence in single-arm trial was insufficient.89 The effects of erlotinib plus bevacizumab in advanced *EGFR*^{m+} NSCLC remain

90 controversial. The results of randomized controlled trials (RCTs) have shown that

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4 91 erlotinib plus bevacizumab can prolong the PFS and the objective response rate
5 92 (ORR) in advanced *EGFR*^{m+} NSCLC.¹⁶⁻¹⁹ By contrast, some studies have reported
6 93 comparable efficacy in patients treated with erlotinib plus bevacizumab and in those
7 94 treated with the erlotinib monotherapy.²⁰ Previous meta-analyses have investigated
8 95 the effects of erlotinib plus bevacizumab in the treatment of NSCLC.^{14 21} However,
9 96 there has been no meta-analysis of erlotinib plus bevacizumab in the treatment of
10 97 advanced *EGFR*^{m+} NSCLC patients. Thus, the aim of this systematic review and
11 98 meta-analysis was to evaluate the effects and safety of erlotinib plus bevacizumab in
12 99 patients with *EGFR*^{m+} advanced NSCLC.

100 **METHODS**

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

103 **Inclusion and exclusion criteria**

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

111 **Outcome assessment**

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

114 **Search strategy and selection**

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

121 **Data extraction**

122 All steps were performed independently by two investigators, any discrepancies were
123 resolved by discussion with a third investigator. The following information was
124 extracted: the name of the first author, year of publication, region, characteristics
125 (e.g., age, sex, ethnic origin, brain), the number of participants in each group,
126 description and doses of therapeutic agents administered, tumour histology and type
127 of *EGFR* mutation and AEs. The outcomes analysed were: PFS, OS, ORR and safety.

128 **Assessing risk of bias and grading the quality of evidence**

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

134 **Statistical analysis**

135 The results of OS and PFS were estimated by hazard ratio (HR) with a 95%
136 confidence interval (CI). Relative risk (RR) was used to estimate the results of AEs
137 and ORR with 95%CI. We used the I^2 statistic to assess the level of heterogeneity. An
138 $I^2 < 25\%$, $25-50\%$, and $> 50\%$ were defined as low, mild, and substantial
139 heterogeneity.²⁵ If I^2 was $< 50\%$ and the P value > 0.05 , a fixed-effects model was
140 used in the meta-analysis; if $I^2 \geq 50\%$ and the P value ≤ 0.05 , a random effects model
141 was used to assess the resource of the heterogeneity. All statistical analyses were
142 performed with RevMan version 5.4 provided by the Cochrane Collaboration and the
143 P value < 0.05 was considered statistically significant.

144 **Patient and public involvement statement**

145 None.

147 **RESULTS**

148 **Results of the literature search**

149 The study flowchart is presented in Figure 1. A total of 783 publications were
150 identified by our search strategy, of which 139 duplicates were excluded. The

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4 151 remaining 644 publications were read by title and abstract, and 485 publications were
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6 152 not relevant studies, 118 publications were meta-analyses, 3 publications involved
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8 153 animal experiments, and 16 publications were reviews. Overall, 622 studies were
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10 154 excluded. We carefully selected the remaining 22 articles, and 6 studies met our
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12 155 eligibility criteria and were included in the present meta-analysis.

13 156 **Characteristics of the included studies**

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15 157 Basic information included the author names, date of publication, region of
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17 158 participants, age, tumour histology, clinical stage, genomic aberration of *EGFR*
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19 159 (Table 1). Among the six publications^{16-20 26} included in the meta-analysis, Saito et
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21 160 al.¹⁷ and Kawashima et al.²⁶ were reports of the NEJ026 study, and Seto et al.¹⁶ and
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23 161 Yamamoto et al.¹⁸ were reports of the JO25567 study. In total, the erlotinib plus
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25 162 bevacizumab group included 387 cases and the erlotinib group included 388 cases
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27 163 across the four RCTs. Patients assigned to the erlotinib plus bevacizumab group
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29 164 received 150 mg of oral erlotinib form once daily and 15 mg/kg of intravenous
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31 165 bevacizumab once every 21 days, beginning on day 1 of cycle 1. Patients in the
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33 166 erlotinib alone group received 150 mg of oral erlotinib once daily. A treatment cycle
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35 167 was defined as 21 days.

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171 **Table 1. Characteristics of included randomised controlled trials**

Study	Region	Participant (Erlotinib plus bevacizumab group/Erlotin ib group)	Gender (male/ female)	Age	Histology (adenocar cinoma/la rge cell carcinoma /squamous cell/ others)	Clinical stage	<i>EGFR</i> 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	111/111	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

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175 **Risk of bias and quality assessment**

176 All publications presented adequate random sequence generation, and four
177 publications indicated adequate allocation concealment.^{16-18 26} There was not enough
178 information to evaluate selective reporting in four publications.^{16-18 26} Two
179 publications^{19 20} did not observe selective outcome reporting. All trials were open-
180 label studies without blinding. All studies were free of incomplete outcome data. Five
181 publications^{16-18 20 26} guaranteed no other bias while another study¹⁹ provided unclear
182 information about bias. There was sufficient evidence to assess that all studies were
183 moderate or high quality, and the results are shown in Figure 2(a) and Figure 2(b).

184 **Progression-free survival**

185 Four publications^{16 17 19 20} reported PFS across the four RCTs, with 387 participants in
186 the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib
187 group. Pooled analyses showed that erlotinib plus bevacizumab significantly reduced
188 PFS compared to the erlotinib group (HR: 0.59; 95%CI: 0.49–0.72; P<0.00001;
189 Figure 3). No heterogeneity was observed ($I^2=0\%$; P=0.55).

190 **Overall survival**

191 Four publications^{17-19 26} reported OS across the four RCTs, with 387 participants in
192 the erlotinib plus bevacizumab intervention group and 388 participants in the erlotinib
193 group. Pooled analyses showed that erlotinib plus bevacizumab did not significantly
194 reduce OS compared to the erlotinib group (HR: 0.95; 95%CI: 0.78–1.15; P=0.59)
195 (Figure 4). No heterogeneity was observed ($I^2=0\%$; P=0.58).

196 **Objective response rate**

197 Four publications^{16 17 19 20} reported ORR across the four RCTs, with 387 participants
198 in the erlotinib plus bevacizumab intervention group and 388 participants in the
199 erlotinib group. The pooled analyses showed that erlotinib plus bevacizumab did not
200 significantly reduce ORR compared to the erlotinib group (OR: 1.25; 95%CI: 0.89–
201 1.74; P=0.19); (Figure 5). No heterogeneity was observed ($I^2=0\%$; P=0.98).

202 **Adverse effects**

203 Eligible studies were specifically analysed to extract all grades of AEs and severe AEs
204 (Table 2). Four publications^{16 17 19 27} reported AEs and severe AEs across the four

205 RCTs. A total of 776 cases were used to pooled analysis of AEs, with 387 participants
 206 in the erlotinib plus bevacizumab intervention group and 389 participants in the
 207 erlotinib group. The numbers differed from the efficacy analyses because in Zhou et
 208 al.¹⁹, one patient in the erlotinib alone group withdrew from the study before starting
 209 treatment, and in Saito et al.¹⁷, two patients in the erlotinib monotherapy group
 210 were randomised in error. We defined grade 3–5 AEs as severe AEs. The results
 211 showed that incidence of diarrhoea (51 vs. 43%, 95%CI: 1.03–1.38; P=0.006) (Figure
 212 S1), haemorrhagic events (41 vs. 20%, 95%CI: 1.12–6.31; P=0.03) (Figure S2),
 213 proteinuria (25 vs. 3%, 95%CI: 4.86–17.66; P<0.0001) (Figure S3), hypertension (40
 214 vs. 8%, 95%CI: 3.66–7.88; P<0.0001) (Figure S4), were higher when using erlotinib
 215 plus bevacizumab, in all grades of AE. No significant difference was found for rash
 216 (81 vs. 85%, 95%CI: 0.90–1.07; P=0.63) (Figure S5), paronychia (30 vs. 28%,
 217 95%CI: 0.87–1.30; P=0.57) (Figure S6), stomatitis (28 vs. 22%, 95%CI: 0.89–1.96;
 218 P=0.17) (Figure S7). In the analysis of severe AEs, the combination treatment yielded
 219 significantly higher rates for proteinuria (8 vs. 0.3%, 95%CI: 3.54–45.97; P<0.001)
 220 (Figure S8) and hypertension (30 vs. 5%, 95%CI: 2.14–11.68; P<0.001) (Figure S9).
 221 There were no significant differences for severe rash (14 vs. 13%, 95%CI: 0.78–1.56;
 222 P=0.59) (Figure S10), diarrhoea (4 vs. 2%, 95%CI: 0.76–3.68; P=0.20) (Figure S11),
 223 paronychia (1 vs. 2%, 95%CI: 0.17–1.66; P=0.28) (Figure S12), stomatitis (0.9 vs.
 224 1%, 95%CI: 0.17–3.36; P=0.71) (Figure S13), or haemorrhagic event (2 vs. 0.3%,
 225 95%CI: 0.74–16.87; P=0.11) (Figure S14). (See the online supplemental material 2
 226 file for the forest plot of the study results of AEs and severe AEs).
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Table 2. All and severe adverse effects of erlotinib plus bevacizumab

Adverse effects (all grades followed severe grades)	Erlotinib plus Erlotinib (event/total)	plus Erlotinib (event/to tal)	RR (95% CI)	P value	Heterogeneity
	bevacizumab (event/total)				

					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

230

231 **DISCUSSION**

232 We performed the meta-analysis by combining patient data from four RCTs, with a
 233 total of 775 cases of lung cancer were included in our efficacy analyses. We found
 234 that the concurrent use of erlotinib plus bevacizumab contributed to prolonging PFS
 235 compared to erlotinib as a single agent, but not to improving OS and ORR, in the
 236 treatment of advanced NSCLC with *EGFRm+*. All grades of AEs and rash were more
 237 commonly found in the combination group and the single agent group. Furthermore,
 238 the incidence of diarrhoea, haemorrhagic events, proteinuria, and hypertension was
 239 higher when erlotinib plus bevacizumab was used compared to erlotinib, in all grades
 240 of AEs. In the analysis of severe AE, combination treatment produced significantly

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4 241 higher rates for proteinuria and hypertension compared to erlotinib alone. Although a
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6 242 previous meta-analysis showed that the first-line angiogenesis inhibitor plus erlotinib
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8 243 prolonged PFS and did not improve OS in patients with *EGFRm⁺* advanced NSCLC
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10 244 compared to the erlotinib monotherapy group,²⁸ the anti-VEGF plus erlotinib group in
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12 245 that meta-analysis included two different angiogenesis inhibitors (bevacizumab and
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14 246 ramucirumab), and bevacizumab and ramucirumab showed different degrees of
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16 247 efficacy in cancer management although with and a potential for bias was estimated,
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18 248 which were overcome in the present analysis. In this study, we compared patient
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20 249 groups treated with erlotinib plus bevacizumab with those treated with erlotinib alone,
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22 250 to potentially increase the precision and decrease the bias of our study compared to
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24 251 the previous meta-analysis. Furthermore, we added three recent RCT studies to our
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26 252 systematic review and meta-analysis. Therefore, we believe that our study provides
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28 253 comprehensive evidence-based recommendations for the relative efficacy and safety
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30 254 of erlotinib plus bevacizumab in *EGFRm⁺* advanced NSCLC.

31 255 Erlotinib plus bevacizumab significantly prolonged PFS compared to erlotinib
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33 256 alone in *EGFRm⁺* advanced NSCLC patients. Furthermore, the addition of
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35 257 bevacizumab to chemotherapy treatment has been shown to be effective in patients
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37 258 with NSCLC with central nervous system metastases.²⁹⁻³¹ There are several possible
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39 259 reasons why the addition of bevacizumab to the erlotinib regimen improved efficacy
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41 260 in terms of PFS compared to erlotinib. One possible mechanism is that the
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43 261 combination of bevacizumab could improve drug delivery.³² Because bevacizumab
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45 262 alters tumour blood vessel physiology, leading to increased intratumoural absorption
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47 263 of drugs.³³ A preclinical study³⁴ demonstrated that tumours treated with the lowest
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49 264 dose of a *EGFR* TKI (gefitinib) developed drug resistance earlier than those with
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51 265 higher doses. Therefore, a higher intratumoural concentration of erlotinib could
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53 266 prolong resistance to TKIs. Another possible mechanism is that bevacizumab may
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55 267 restore of cell apoptosis by inhibiting the VEGF-mediated pathway.³⁵ Due to
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57 268 synergistic inhibition of cancer growth signalling, VEGF signal inhibition is still
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59 269 effective for cancers with *EGFR* TKI resistant mutations.³⁶ An animal study³⁷
60 270 suggested that erlotinib plus bevacizumab treatment restored resistance to the VEGF-

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4 271 mediated pathway. Therefore, in the clinic, the addition of bevacizumab to erlotinib
5 272 treatment is optional strategy to delay the onset of TKI resistance in NSCLC.^{21 38}

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7 273 In our meta-analysis, neither ORR nor OS were prolonged by combination therapy.
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9 274 For ORR, this lack of improvement can be explained by the high sensitivity of these
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11 275 NSCLC to *EGFR* TKIs. Due to the high ORR in the erlotinib alone group, a larger
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13 276 study population is required to demonstrate a significant effect of the combination
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15 277 regimen. For OS, the combination of bevacizumab and erlotinib failed to translate into
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17 278 OS benefit, which can be explained as outlined below. Although OS might have been
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19 279 influenced by patient therapy after disease progression , because there are many
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21 280 options for the treatment of NSCLC, any outcome of first-line treatment on OS can be
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23 281 influenced by subsequent treatment.³⁹ In a study by Zhou et al.¹⁹, more patients in the
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25 282 erlotinib group received subsequent anticancer treatment than in the erlotinib plus
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27 283 bevacizumab group (50.0% [77/154] versus 33.8% [53/157]), which could have
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29 284 influenced the OS result. Conversely, there may be different acquired resistance
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31 285 mechanisms between the two groups. Furthermore, the lack of OS benefit in the
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33 286 erlotinib plus bevacizumab group may be explained by the differences in the
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35 287 proportion of patients who receive subsequent-lines of osimertinib therapy. In the
36
37 288 Zhou et al.¹⁹ study, more patients received osimertinib in the erlotinib group as a
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39 289 subsequent treatment than in the erlotinib plus bevacizumab group (29.2% [27/157]
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41 290 vs.17.2% [45/154]).

42 291 Concerning safety, erlotinib plus bevacizumab is more toxic than erlotinib alone
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44 292 group and are known toxicities associated with bevacizumab treatment, especially for
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46 293 diarrhoea, haemorrhagic events, proteinuria, and hypertension.^{40 41} In most cases,
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48 294 toxicity of combination therapy was considered to be tolerable and manageable,⁴²
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50 295 patients will not choose to terminate drug treatment early due to AE, so patients can
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52 296 achieve the benefits of treatment with erlotinib plus bevacizumab.

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54 297 Our current meta-analysis has some strengths. We comprehensively researched the
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56 298 pooled data from the most up-to-date high-quality RCTs and provided best level of
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58 299 evidence that demonstrated the efficacy and safety of erlotinib plus bevacizumab in
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60 300 patients with advanced *EGFR*m⁺ NSCLC. The recommended first-line treatment for

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4 301 advanced *EGFR*^{m+} NSCLC is often osimertinib, a third-generation *EGFR* TKI. The
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6 302 first generation, second generation *EGFR* TKI, *EGFR* TKI plus bevacizumab or
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8 303 *EGFR* TKI plus ramucirumab are also available as treatment options.^{43 44} However,
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10 304 most patients eventually develop disease progression due to acquired drug
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12 305 resistance.⁴⁵ Our meta-analysis provided evidence that the erlotinib plus bevacizumab
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14 306 combination prolongs PFS compared to the erlotinib alone; therefore, in the clinic,
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16 307 when erlotinib monotherapy is ineffective, the addition of bevacizumab to the
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18 308 erlotinib is an optional strategy for the treatment of *EGFR*^{m+} advanced NSCLC.

19 309 Our meta-analysis had several potential limitations. First, only four trials were
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21 310 available to include in the analysis, and some of these studies had relatively small
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23 311 sample sizes. Although these results were of high-quality and derived from well-
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25 312 performing trials, our conclusions should be interpreted with caution because smaller
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27 313 trials are more likely to result in an overestimation of the treatment effects. Second,
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29 314 our study failed to consider the effects of previous treatment and smoking status in
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31 315 some of the enrolled participants, due to the lack of corresponding data and
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33 316 information. Third, a subgroup analysis of *EGFR* mutation status of NSCLC was not
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35 317 conducted due to insufficient information on these factors in the included trials.
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37 318 NSCLC is a molecularly heterogeneous disease,⁴⁶ the ex19del and ex21 L858R
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39 319 mutations are the two most common reported *EGFR* variants,⁴⁷ therefore, a subgroup
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41 320 analysis based on the *EGFR* mutation status of patients treated with erlotinib plus
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43 321 bevacizumab is warranted in the future. Finally, there may have been a bias in the
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45 322 selection of positive studies. It is understandable that journals do not like to present
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47 323 negative data, so this may also have led to an overestimation of a treatment effect.

48 324 **CONCLUSIONS**

49
50 325 Based on the present evidence, although the combined strategy of erlotinib plus
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52 326 bevacizumab prolonged PFS for the treatment of *EGFR*^{m+} advanced NSCLC, this
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54 327 strategy failed to significantly improve OS, and exhibited common but acceptable
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56 328 AEs such as diarrhoea, haemorrhagic event, proteinuria and hypertension. This
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58 329 combination can be recommended as a therapeutic strategy for patients with advanced
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60 330 *EGFR*^{m+} NSCLC.

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4 331 **Contributors** WSD: study design, data collection and analysis, statistical analysis and manuscript drafting,
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6 332 manuscript revision. KW: study design, data collection and analysis, statistical analysis and manuscript drafting.
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8 333 YJ: data collection and analysis, manuscript revision. DBL: data collection and analysis, statistical analysis. CXB:
9
10 334 data collection and analysis, manuscript revision. JL: study design, manuscript revision. LYL: data collection. BH:
11
12 335 statistical analysis. JLK: study design, manuscript drafting, and manuscript revision. All authors read and approved
13
14 336 the manuscript.

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26
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29 344 **Disclaimer** This study was a systematic review and meta-analysis. Ethics committee approval was not necessary
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31 345 because all data were carefully extracted from existing literature.

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33 346 **Competing interests** None declared.

34
35 347 **Ethics approval** This study did not require ethics approval as is based on existing, publicly available data.

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37 348 **Patient consent for publication** Not applicable.

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39 349 **Data availability statement** No additional data available.

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Figure titles

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4 491 **Figure 1. Flowchart of the literature screening**
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6 492 **Figure 2. Summary (a) and graphical representation (b) of the risk of bias assessment**
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8 493 **Figure 3. Forest plot of study results of PFS**
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10 494 **Figure 4. Forest plot of study results of OS**
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12 495 **Figure 5. Forest plot of study results of ORR**
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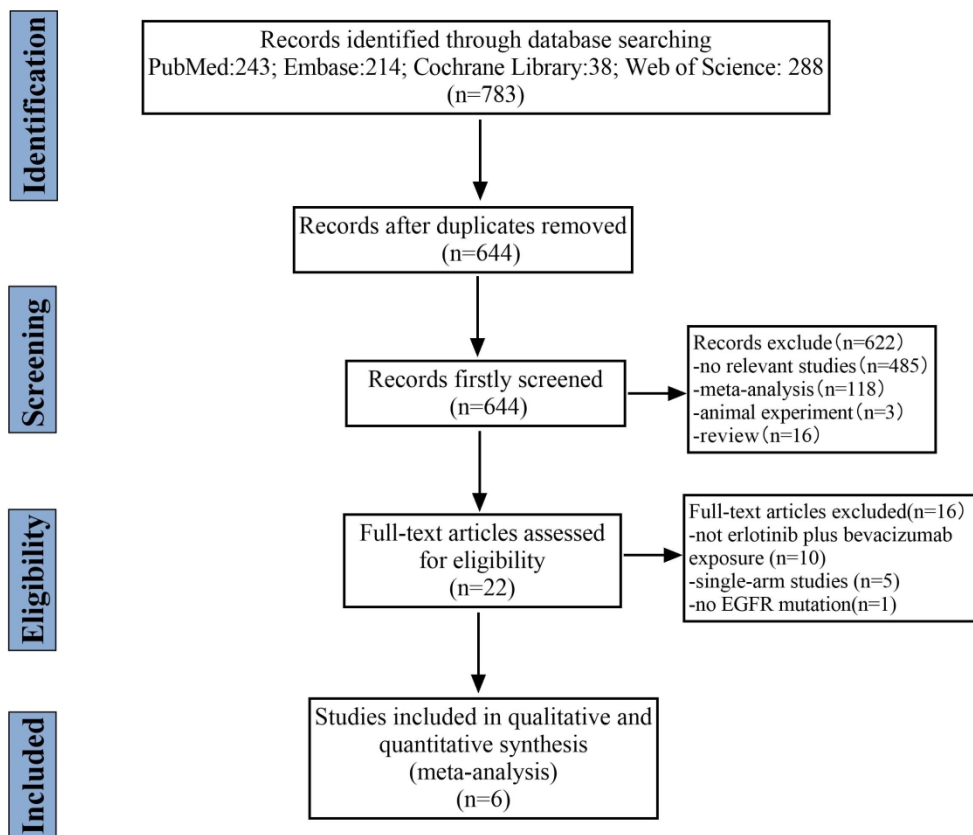


Figure 1 Flowchart of the literature screening.

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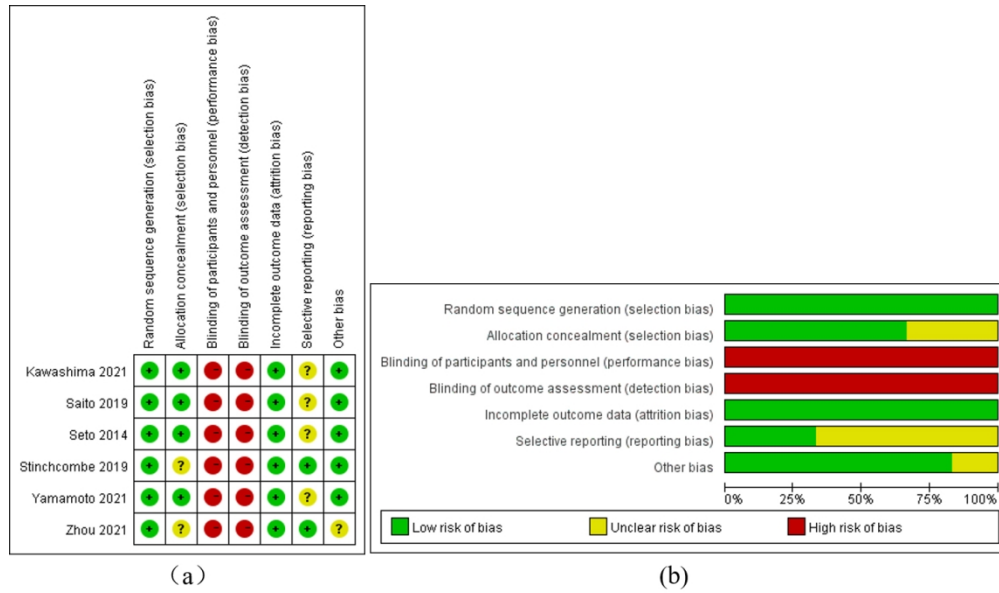


Figure 2 Risk of bias assessment for the included studies: (a) a summary for the risk of bias; (b) a graphic view for the risk of bias.

250x150mm (150 x 150 DPI)

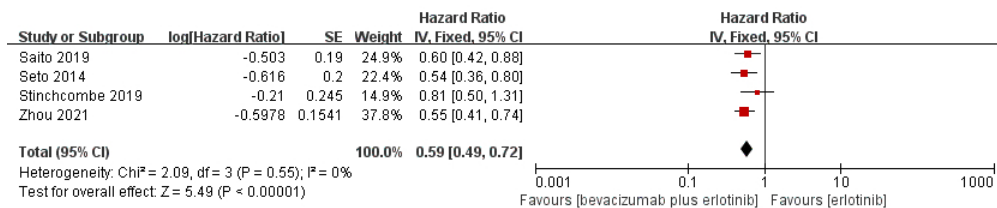


Figure 3. Forest plot of study results of PFS.

293x62mm (72 x 72 DPI)

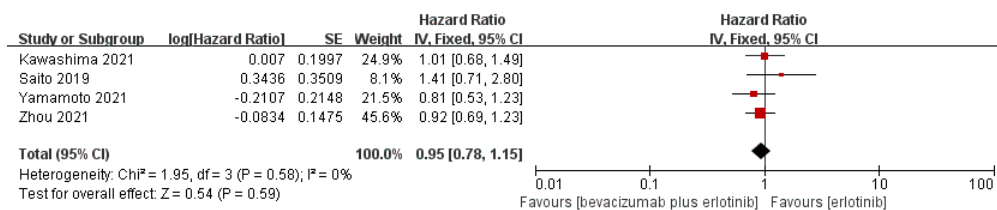


Figure 4. Forest plot of study results of OS.

293x62mm (72 x 72 DPI)

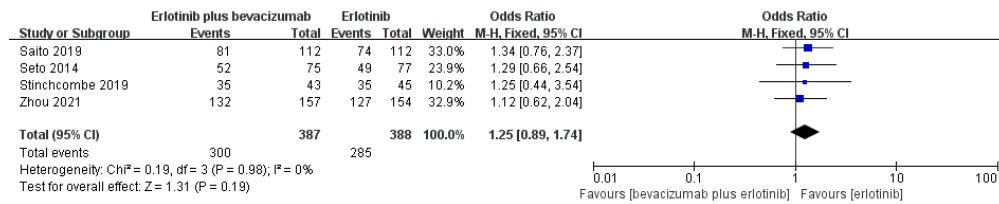


Figure 5. Forest plot of study results of ORR.

333x67mm (72 x 72 DPI)

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4 PubMed Search Strategy:

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6 (((((((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR (((((((((((Carcinoma, Non Small
7 Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract]))
8 OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-
9 Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract]))
10 OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung
11 Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract]))
12 OR (Non-Small Cell Lung Carcinoma[Title/Abstract])) OR (Non-Small Cell Lung
13 Cancer[Title/Abstract])) OR (Nonsmall Cell Lung Cance[Title/Abstract])) AND
14 ("Erlotinib Hydrochloride"[Mesh])) OR (((((((((((((((Hydrochloride,
15 Erlotinib[Title/Abstract]) OR (Erlotinib HCl[Title/Abstract])) OR (HCl,
16 Erlotinib[Title/Abstract])) OR (OSI-774[Title/Abstract])) OR (OSI
17 774[Title/Abstract])) OR (OSI774[Title/Abstract])) OR (CP 358774[Title/Abstract]))
18 OR (358774, CP[Title/Abstract])) OR (CP 358,774[Title/Abstract])) OR (358,774,
19 CP[Title/Abstract])) OR (CP-358,774[Title/Abstract])) OR
20 (CP358,774[Title/Abstract])) OR (CP-358774[Title/Abstract])) OR
21 (CP358774[Title/Abstract])) OR (11C-erlotinib[Title/Abstract])) OR (11C
22 erlotinib[Title/Abstract])) OR (Erlotinib[Title/Abstract])) OR (N-(3-ethynylphenyl)-
23 6,7-bis(2-methoxyethoxy)quinazolin-4-amine[Title/Abstract])) OR
24 (Tarceva[Title/Abstract])) AND ("Bevacizumab"[Mesh])) OR
25 (((Mvasi[Title/Abstract]) OR (Bevacizumab-awwb[Title/Abstract])) OR
26 (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) AND
27 ((randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR
28 placebo[Title/Abstract])).

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40 Embase Search Strategy:

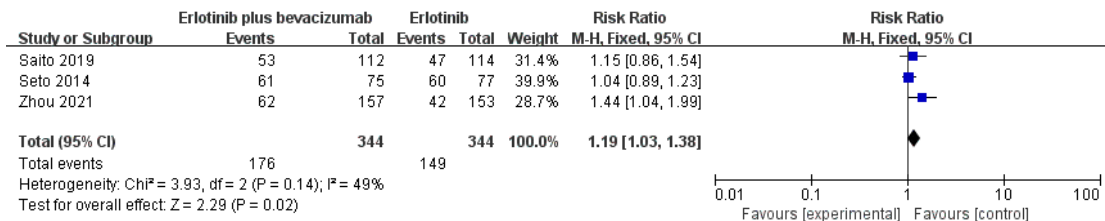
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43 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR
44 'non-small-cell lung carcinomas':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR
45 'non small cell lung carcinoma':ab,ti OR 'carcinoma, non-small cell lung':ab,ti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

web of science Search Strategy :

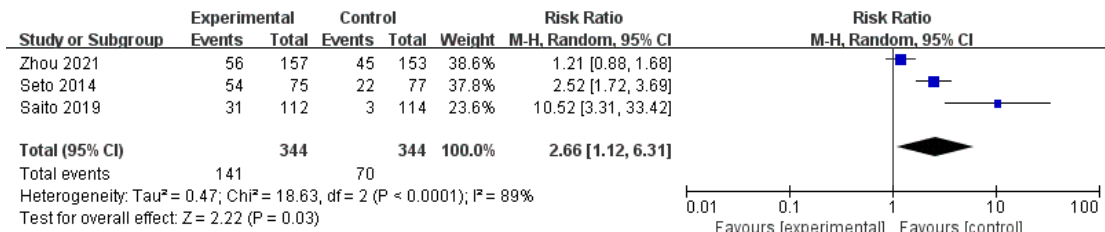
(TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell 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 :

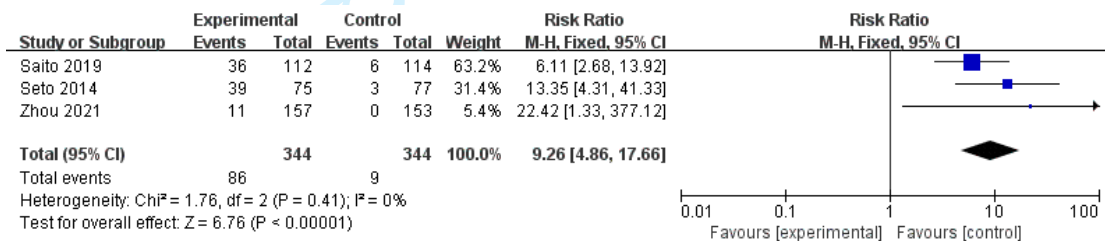
((Carcinoma, Non-Small-Cell Lung) OR (Carcinoma, Non Small Cell Lung):ab,ti,kw OR (Carcinomas, Non-Small-Cell Lung):ab,ti,kw OR (Lung Carcinoma, Non-Small-Cell):ab,ti,kw OR (Lung Carcinomas, Non-Small-Cell):ab,ti,kw OR (Non-Small-Cell Lung Carcinomas):ab,ti,kw OR (Non-Small-Cell Lung Carcinoma):ab,ti,kw 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).



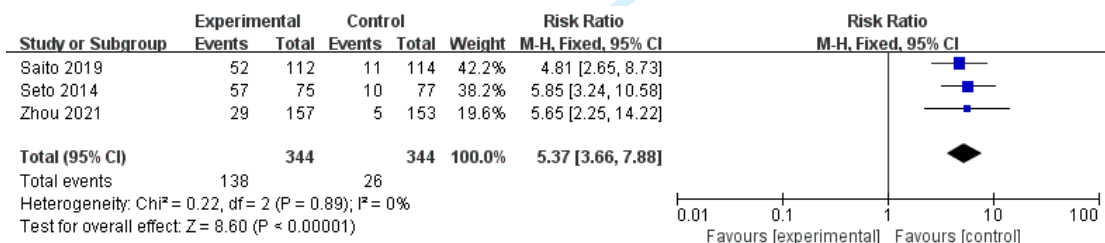
FigureS1 Forest plot of AEs of diarrhea



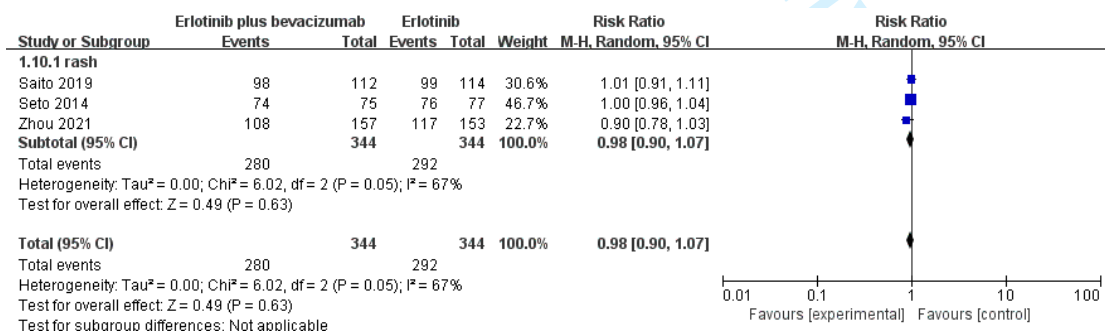
FigureS2 Forest plot of AEs of haemorrhagic event



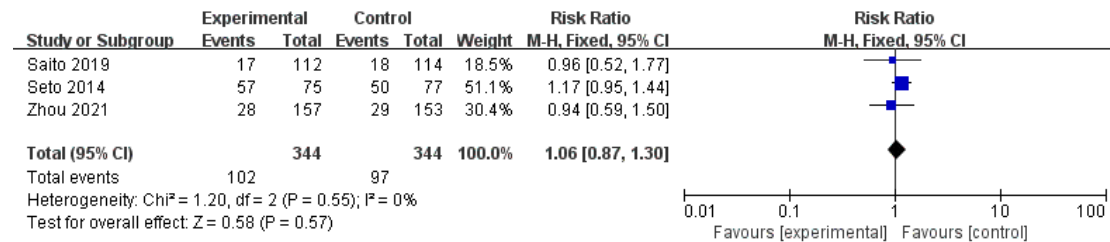
FigureS3 Forest plot of AEs of proteinuria



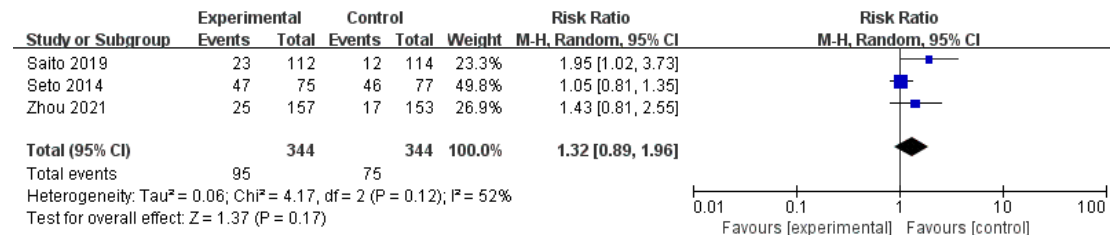
FigureS4 Forest plot of AEs of hypertension



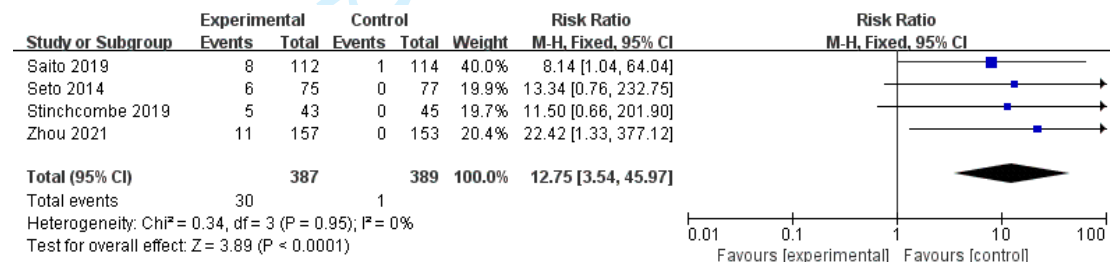
FigureS5 Forest plot of AEs of rash



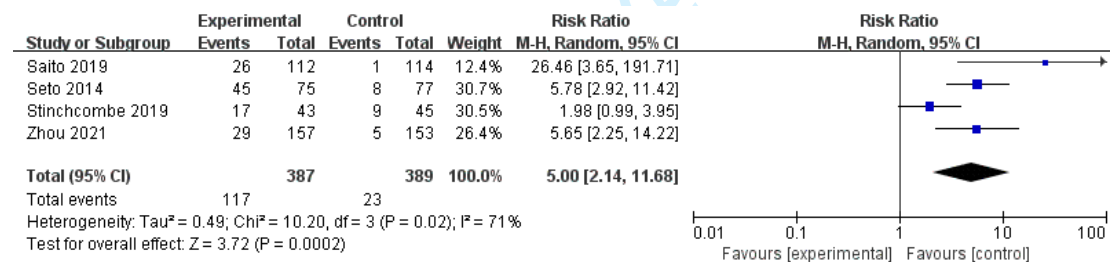
FigureS6 Forest plot of AEs of paronychia



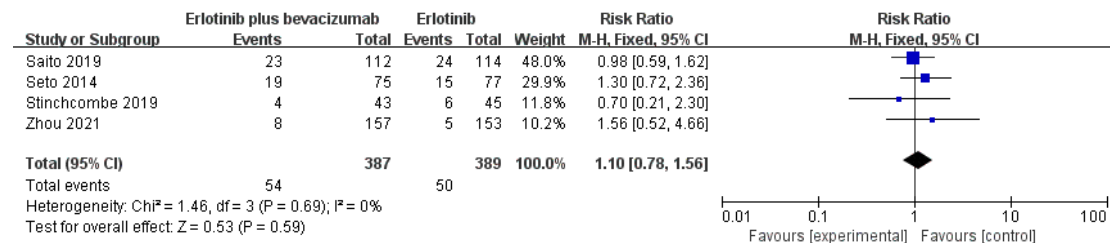
FigureS7 Forest plot of AEs of stomatitis



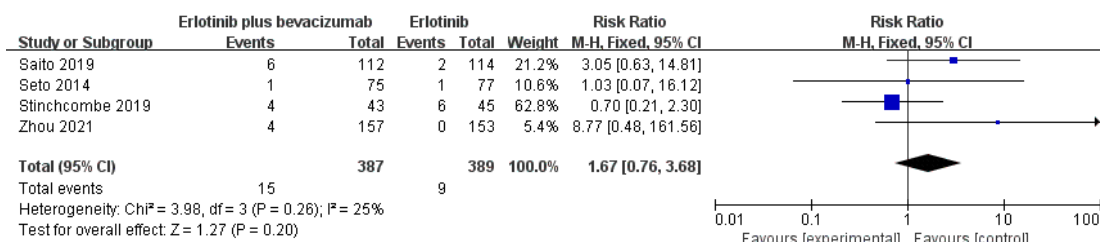
FigureS8 Forest plot of severe AEs of proteinuria



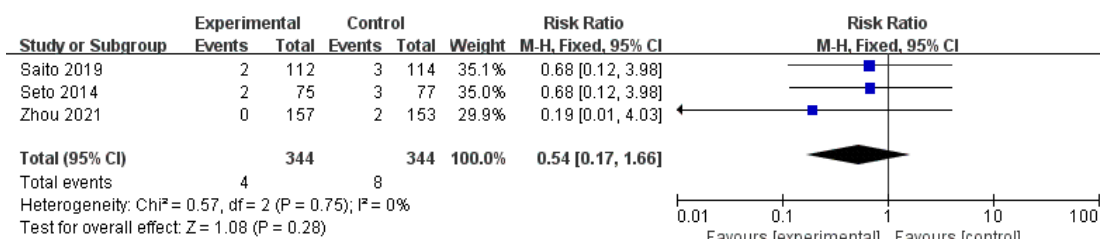
FigureS9 Forest plot of severe AEs of hypertension



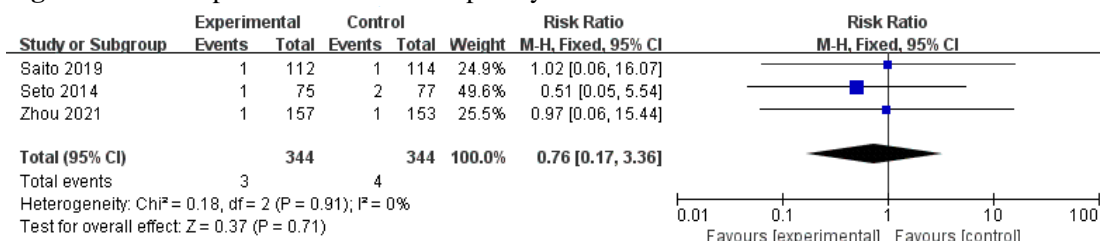
FigureS10 Forest plot of severe AEs of rash



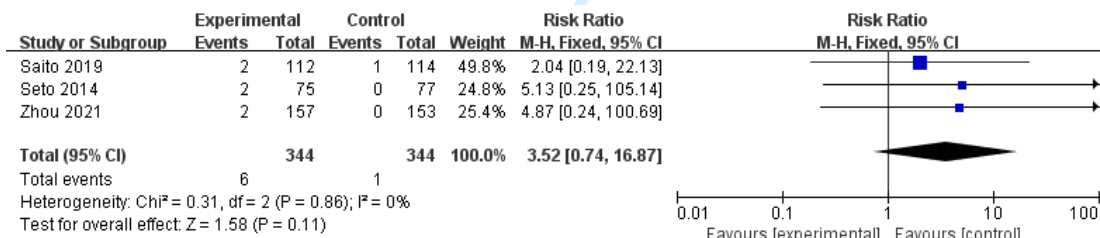
FigureS11 Forest plot of severe AEs of diarrhea



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



PRISMA 2020 Checklist

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10.1136/bmj.n71

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

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