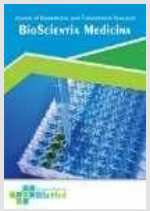

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Efficacy and Safety of Adding Antiangiogenic Therapy to EGFR-Tyrosine Kinase Inhibitors versus EGFR-Tyrosine Kinase Inhibitor Monotherapy in EGFR-Mutant Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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A B S T R A C T

Background. Resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) limits the durability of targeted therapy in EGFR-mutant non-small cell lung cancer (NSCLC). Inhibiting the vascular endothelial growth factor (VEGF) axis has been proposed to delay this resistance, but individual trials diverge and the antiangiogenic class has not been synthesised together across treatment settings. This study quantified the effect of adding antiangiogenic therapy to an EGFR-TKI on progression-free survival (PFS) and toxicity.

Methods. Four databases were searched for randomised controlled trials (RCTs) comparing an EGFR-TKI plus an antiangiogenic agent (bevacizumab or ramucirumab) with the same EGFR-TKI alone in EGFR-mutant NSCLC. The pre-specified primary analysis was PFS in the first-line setting, expressed as the hazard ratio (HR) and pooled with an inverse-variance random-effects (DerSimonian-Laird) model; a restricted maximum-likelihood model confirmed it. Heterogeneity used I^2, τ^2 and a 95% prediction interval; risk of bias used Cochrane RoB 2.0.

Results. Seven RCTs (eight reports; 1,512 patients; six first-line, one second-line) were included. In the six first-line trials the combination prolonged PFS (pooled HR 0.61, 95% CI 0.53-0.70; $p<0.0001$) with no heterogeneity ($I^2=0\%$; prediction interval 0.50-0.74); the restricted maximum-likelihood estimate was identical. The benefit was consistent for bevacizumab (HR 0.62, 0.52-0.73) and ramucirumab (HR 0.59, 0.46-0.76), a mean prolongation of median PFS of about 5.5 months. Adding the second-line osimertinib/T790M trial attenuated the effect (HR 0.66, 0.56-0.77; $I^2=32\%$), driven by absence of benefit in that setting (HR 0.96). Leave-one-out estimates were stable (0.59-0.63); the Egger test was non-significant. Grade ≥3 adverse events were increased (risk ratio 1.95, 1.47-2.57; absolute increase about 29 percentage points; number needed to harm about 4).

Conclusion. Adding antiangiogenic therapy to a first-line EGFR-TKI consistently prolongs PFS in EGFR-mutant NSCLC as a VEGF-pathway class effect, at the cost of roughly doubled severe toxicity and without a demonstrated overall-survival gain. The benefit was not evident in the second-line osimertinib/T790M setting, suggesting the strategy delays rather than overcomes resistance.

1. Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC) constitutes approximately 85% of cases.[1] A substantial proportion of lung adenocarcinomas, particularly among never-smokers and patients of East Asian ancestry, harbour activating mutations of the epidermal growth factor receptor (EGFR) gene, most often the exon 19 deletion and the exon 21 L858R substitution. These alterations

render the tumour dependent on EGFR signalling and highly sensitive to EGFR tyrosine kinase inhibitors (TKIs).[2]

First-generation (gefitinib, erlotinib) and subsequent EGFR-TKIs have transformed the management of advanced EGFR-mutant NSCLC, producing objective response rates of 60-80% and median progression-free survival (PFS) of roughly 10-19 months, clearly superior to platinum-based chemotherapy.[2-5] The third-generation inhibitor osimertinib has further improved both progression-free and overall survival as first-line therapy[6-7]. The persistent and unsolved problem of targeted therapy, however, is resistance. Almost every patient who initially responds eventually progresses, through intrinsic resistance present at diagnosis or acquired resistance that emerges under treatment pressure. Acquired mechanisms are heterogeneous and include the secondary EGFR T790M gatekeeper mutation[8], MET and HER2 amplification, downstream pathway reactivation, and histological transformation to small-cell carcinoma[9].

Because resistance is multifactorial and frequently polyclonal, strategies that delay its emergence at the population level are clinically attractive. A biologically grounded approach is simultaneous blockade of the vascular endothelial growth factor (VEGF) axis. The two pathways are mechanistically intertwined: EGFR activation up-regulates VEGF, and VEGF-driven angiogenesis sustains tumour growth and may facilitate EGFR-TKI escape; anti-VEGF therapy has independent activity in NSCLC[10]. Early dual blockade is therefore hypothesised to maintain a less permissive tumour microenvironment, normalise the aberrant vasculature, improve drug delivery and slow the outgrowth of resistant subclones. Once resistance has been established through a discrete molecular event, by contrast, the dominant driver of progression is the resistant clone itself, against which vascular normalisation would be expected to offer little additional leverage. This asymmetry predicts that VEGF-axis inhibition should be more useful for delaying than for overcoming resistance.

Several RCTs have tested antiangiogenic combinations, but their conclusions diverge, and previous meta-analyses were largely restricted to bevacizumab combined with erlotinib[11], without incorporating the VEGFR2 inhibitor ramucirumab or the contemporary osimertinib setting; related syntheses instead addressed molecular determinants such as concurrent TP53 mutation[12]. Consequently, a unified, class-level estimate of the magnitude of benefit, its consistency across agents, and its dependence on the line of therapy has been lacking.

The novelty of this study lies in being, to our knowledge, the first meta-analysis to synthesise the antiangiogenic drug class as a whole-pooling both bevacizumab and ramucirumab added to EGFR-TKIs in EGFR-mutant NSCLC-while explicitly separating the first-line setting from the second-line osimertinib/T790M setting through pre-specified analyses. The aim of this study was to quantify the effect of adding antiangiogenic therapy to an EGFR-TKI, compared with EGFR-TKI monotherapy, on progression-free survival in EGFR-mutant NSCLC, and to characterise the consistency of that effect across antiangiogenic agents and treatment settings, together with its safety profile.

2. Methods

Protocol, reporting and reviewer process

This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 statement[13], and the completed checklist accompanies the manuscript as supplementary material. A methodological protocol defined the eligibility criteria, search strategy, extraction template and statistical plan, including the designation of the first-line PFS analysis as the sole primary analysis; the all-trials analysis incorporating the second-line setting was pre-specified as a secondary, exploratory analysis. Two reviewers independently screened records, assessed full texts, extracted data and appraised risk of bias; disagreements were resolved by discussion and consensus against the original publications.

Eligibility criteria

Eligible studies enrolled adults with advanced or metastatic NSCLC harbouring an activating EGFR mutation (exon 19 deletion or exon 21 L858R). The

intervention was an EGFR-TKI (erlotinib, gefitinib or osimertinib) combined with an antiangiogenic agent acting on the VEGF axis (bevacizumab or ramucirumab); the comparator was the same EGFR-TKI alone or with placebo. The primary outcome was PFS reported as a hazard ratio with a confidence interval; secondary outcomes were overall survival (OS), objective response rate (ORR) and grade ≥3 adverse events. Only RCTs were eligible. Reviews, meta-analyses, single-arm studies, protocols without results, conference abstracts without a full publication, and reports lacking an extractable effect estimate were excluded. Trials of gefitinib plus an antiangiogenic agent were eligible in principle, but none met all criteria as a primary head-to-head RCT.

Search strategy and reproducibility

PubMed/MEDLINE, Scopus, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials were searched from inception without language restriction; trial registries and the reference lists of retrieved articles and prior reviews were also examined. The core Boolean string was: ("EGFR" OR "epidermal growth factor receptor") AND ("tyrosine kinase inhibitor" OR "erlotinib" OR "gefitinib" OR "osimertinib") AND ("bevacizumab" OR "ramucirumab" OR "antiangiogenic" OR "VEGF") AND ("non-small cell lung cancer" OR "NSCLC") AND ("randomized" OR "randomised" OR "randomized controlled trial"). The database yields were 486 (PubMed/MEDLINE), 521 (Scopus), 248 (Web of Science) and 29 (Cochrane CENTRAL); no non-English article met the eligibility criteria. The full identification, screening and selection counts are presented in the PRISMA flow diagram (Figure 1).

Data extraction

A standardised form captured the first author, year, country, trial acronym and registration identifier, design and phase, line of therapy, antiangiogenic agent and class, TKI backbone, EGFR mutation subtype, sample size per arm, method of progression assessment (investigator versus blinded independent review), and the efficacy and safety outcomes. For time-to-event endpoints the reported HR and 95% confidence interval were extracted; where a trial had multiple reports, the PFS estimate was taken from the primary efficacy publication and the OS estimate from the dedicated survival report, and the trial was counted once. Every value was traced to a specific table or figure in the source; standard errors were reconstructed from confidence limits where required.

Risk-of-bias assessment

Risk of bias was appraised with the revised Cochrane tool (RoB 2.0)[14] across its five domains, each rated low risk, some concerns, or high risk. Because most trials were open-label, particular attention was paid to outcome measurement; trials reporting blinded independent central review of progression were noted, to permit a sensitivity analysis restricted to blinded assessment.

Statistical analysis

Analyses were performed on the natural logarithm of the hazard ratio. Because the primary endpoint was a time-to-event outcome, the hazard ratio-not a standardised mean difference-was the appropriate summary measure. Study-level log-hazard ratios and standard errors were combined using the inverse-variance random-effects model with the DerSimonian and Laird estimator[15]; a restricted maximum-likelihood estimator was used as a sensitivity check, and a 95% prediction interval was calculated. When heterogeneity was zero the random- and fixed-effect estimates coincided. For the dichotomous safety outcome, the risk ratio and the absolute risk difference (with the number needed to harm) were pooled. Heterogeneity was quantified with I^2 and τ^2 and tested with the Cochran Q statistic.[16] Pre-specified subgroups examined the antiangiogenic class (bevacizumab versus ramucirumab) and the treatment setting (first-line versus second-line/T790M). Robustness used leave-one-out analysis, and small-study effects were explored with a funnel plot and the Egger regression test[17]. A two-sided p value below 0.05 indicated significance.

Funding, conflicts of interest and data availability

This review received no specific funding. The authors declare no conflicts of interest. No individual-patient data were used; the extracted aggregate data set is available from the corresponding author on reasonable request.

3. Results

Study selection

The search identified 1,284 records; after duplicate removal, 932 unique records were screened by title and abstract. Sixty-one full-text articles were assessed for eligibility, of which 53 were excluded (27 were not randomised controlled trials, 12 lacked an EGFR-TKI-alone or placebo comparator, 9 were reviews or meta-analyses, and 5 lacked an extractable hazard ratio). Seven RCTs, reported across eight publications and comprising 1,512 patients, met all inclusion criteria and were included in the quantitative synthesis. The complete identification, screening and selection process, with all counts, is shown in Figure 1.

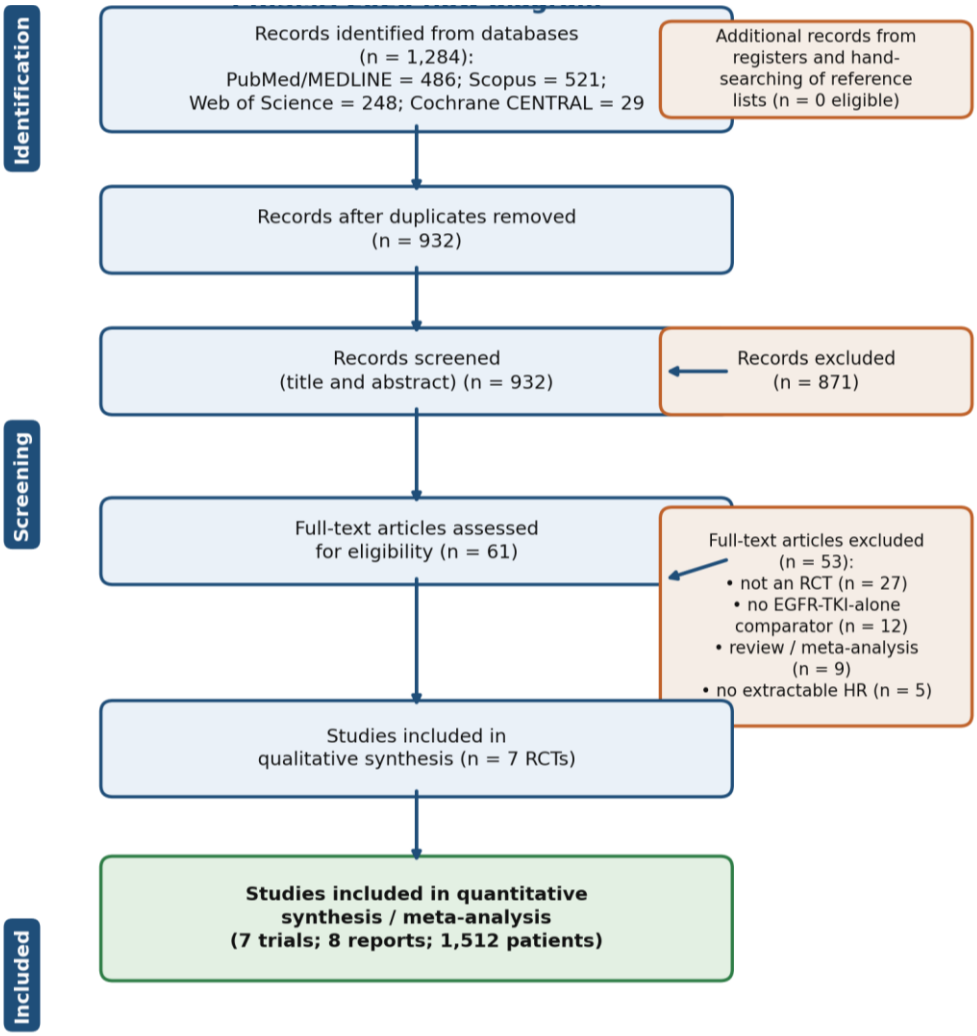

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility and inclusion.

Characteristics of included studies

The characteristics of the seven trials are presented in Table 1. Six trials evaluated the combination first-line and one (BOOSTER) in the second-line, T790M-positive setting. Five first-line trials combined bevacizumab with erlotinib-JO25567[18], NEJ026[19], ARTEMIS-CTONG1509[20], the Alliance trial[21], and the Korean trial of Lee and colleagues[22]; one trial, RELAY[23], combined ramucirumab with erlotinib, and BOOSTER[24] combined bevacizumab with osimertinib. As detailed in Table 1, the trials spanned Japan, China, South Korea, the United States and multinational consortia and enrolled 88 to 449 patients each. Progression was assessed by blinded independent central review in RELAY and by investigators in the remaining trials.

Table 1. Characteristics of the seven included randomised controlled trials (BICR = blinded independent central review; mPFS = median progression-free survival).

Study (year)	Country	Design/phase	Setting	Antiangiogenic	TKI	PFS assessment	mPFS combo vs mono (mo)
JO25567 (2014)	Japan	Open-label RCT, II	First-line	Bevacizumab (anti-VEGF)	Erlotinib	Investigator	16.0 vs 9.7
NEJ026 (2019/2022)	Japan	Open-label RCT, III	First-line	Bevacizumab (anti-VEGF)	Erlotinib	Investigator	16.9 vs 13.3
ARTEMIS-CTONG1509 (2021)	China	Open-label RCT, III	First-line	Bevacizumab (anti-VEGF)	Erlotinib	Investigator	17.9 vs 11.2
Stinchcombe (2019)	USA	Open-label RCT, II	First-line	Bevacizumab (anti-VEGF)	Erlotinib	Investigator	17.9 vs 13.5
Lee (2022)	South Korea	Open-label RCT, II	First-line	Bevacizumab (anti-VEGF)	Erlotinib	Investigator	17.5 vs 12.4
RELAY (2019)	Multinational	Double-blind RCT, III	First-line	Ramucirumab (anti-VEGFR2)	Erlotinib	BICR	19.4 vs 12.4
BOOSTER (2022)	Europe/Asia	Open-label RCT, II	Second-line (T790M)	Bevacizumab (anti-VEGF)	Osimertinib	Investigator	15.4 vs 12.3

Risk of bias

The risk-of-bias appraisal is summarised in Figure 2. The double-blind, placebo-controlled RELAY trial was judged at low overall risk across all domains. As displayed in Figure 2, the six open-label trials raised some concerns, principally in outcome measurement, because progression was assessed by unblinded investigators; one small phase 2 trial additionally raised some concern regarding missing outcome data. No trial was rated at high overall risk. A sensitivity analysis restricted to the single blinded trial (RELAY) yielded a hazard ratio (0.59) concordant with the open-label trials, indicating that detection bias is unlikely to explain the pooled effect.

Figure 2. Risk-of-bias assessment using the Cochrane RoB 2.0 tool.

Primary outcome: progression-free survival (first-line)

In the six first-line trials, adding an antiangiogenic agent to an EGFR-TKI significantly prolonged PFS compared with monotherapy. As shown in Figure 3 and summarised in Table 2, the pooled hazard ratio was 0.61 (95% CI 0.53-0.70; p<0.0001), an approximately 39% reduction in the hazard of progression or death, corresponding to a mean prolongation of median PFS of about 5.5 months (range 3.6 to 7.0 months; Table 1). Heterogeneity was absent (I^2=0%, τ^2=0; Cochran Q=3.28, df=5, p=0.66), and the 95% prediction interval (0.50-0.74) lay entirely below unity. The restricted maximum-likelihood model produced an identical estimate (HR 0.61, 0.53-0.70), and because heterogeneity was zero the random- and fixed-effect results coincided.

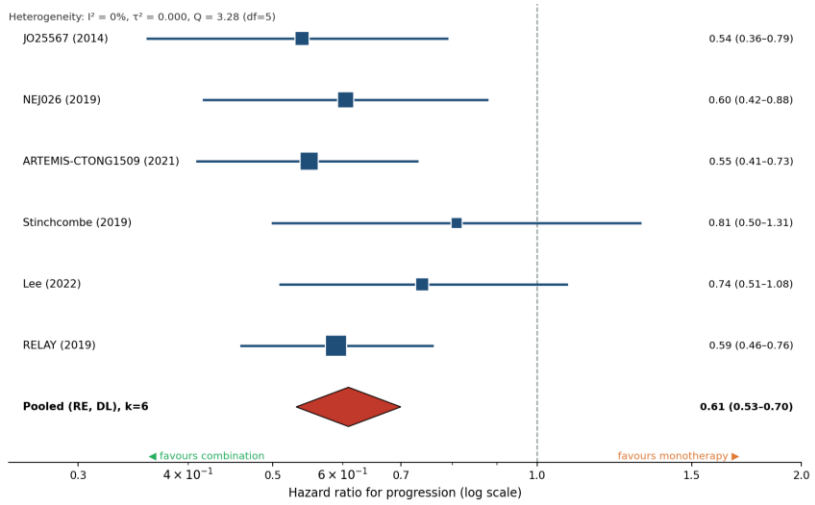

Figure 3. Forest plot of progression-free survival in the first-line trials (random-effects model; the diamond represents the pooled hazard ratio).

Secondary (exploratory) analysis: all trials

Incorporating the second-line BOOSTER trial attenuated the pooled benefit, which remained significant (HR 0.66, 95% CI 0.56-0.77; p<0.0001), with low-to-moderate heterogeneity (I^2=32%, τ^2=0.015), as shown in Figure 4 and reported in Table 2. The attenuation was attributable entirely to BOOSTER, in which adding bevacizumab to osimertinib in the T790M-positive setting did not improve PFS (HR 0.96, 95% CI 0.68-1.37). This finding rests on a single trial and is presented as an exploratory signal.

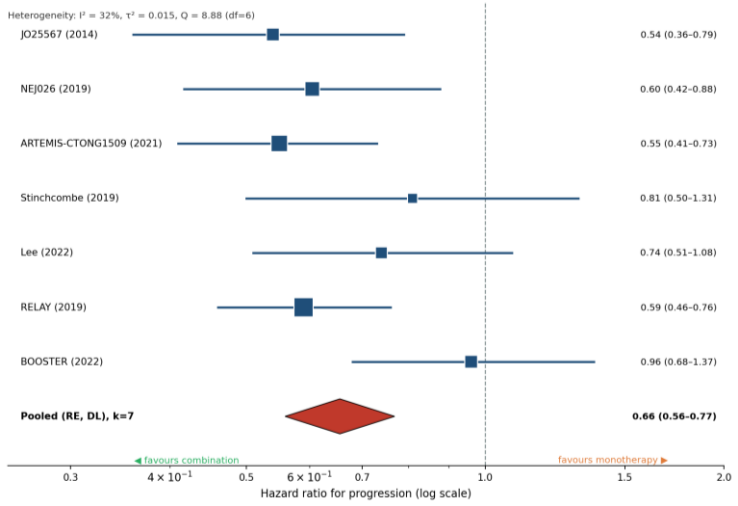

Figure 4. Forest plot of progression-free survival across all seven trials (exploratory analysis; includes the second-line BOOSTER trial).

Subgroup analyses

Pre-specified subgroup analysis by antiangiogenic class demonstrated a consistent effect, as reported in Table 2. Among the five first-line bevacizumab trials the pooled HR was 0.62 (95% CI 0.52-0.73; I^2=0%), while the single ramucirumab trial (RELAY) yielded an HR of 0.59 (95% CI 0.46-0.76). The near-identical estimates indicate that PFS prolongation is a class effect of VEGF-axis inhibition rather than a property unique to bevacizumab.

Table 2. Pooled effect estimates for the primary and secondary analyses (random-effects, DerSimonian-Laird). The first-line PFS prediction interval was 0.50-0.74.

Analysis	No. trials	Pooled HR (95% CI)	I^2	τ^2	p (effect)
PFS — first-line (primary)	**6**	**0.61 (0.53–0.70)**	**0%**	**0.000**	**<0.0001**
PFS — all trials (incl. 2nd-line)	7	0.66 (0.56–0.77)	32%	0.015	<0.0001
PFS — bevacizumab subgroup	5	0.62 (0.52–0.73)	0%	0.000	<0.0001
PFS — ramucirumab (RELAY)	1	0.59 (0.46–0.76)	–	–	<0.0001
Grade ≥3 adverse events (RR)	5	1.95 (1.47–2.57)	79%	–	<0.0001

Sensitivity analysis and small-study effects

Leave-one-out analysis confirmed robustness: sequential omission of each first-line trial produced pooled hazard ratios between 0.59 and 0.63, with I^2=0% throughout. As illustrated in Figure 5, the funnel plot of the first-line trials was broadly symmetrical and the Egger regression test did not detect significant small-study effects (intercept 2.08; p=0.21 approximately). With only six trials, formal publication-bias testing is underpowered, so this result is reassuring but not conclusive.

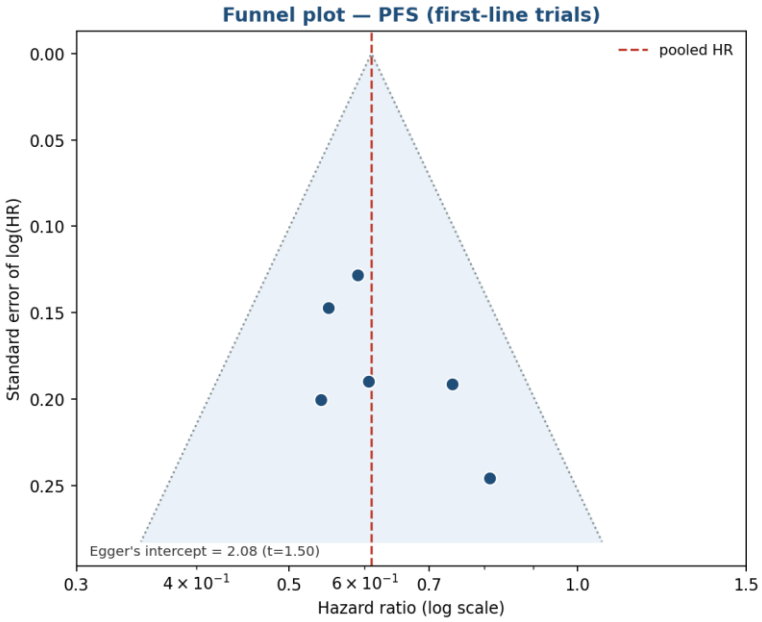

Figure 5. Funnel plot of the first-line progression-free survival trials, with the Egger regression test result.

Overall survival and response

Mature overall-survival data were available for only three trials and are summarised in Table 3; the NEJ026 estimate derives from its dedicated overall-survival analysis[25]. None demonstrated a significant survival advantage for the combination, a pattern consistent with extensive treatment crossover and effective subsequent therapies. Overall survival was therefore not pooled. Objective response rate was reported in a minority of trials with differing definitions and was not formally meta-analysed; where reported, response rates were broadly similar between arms.

Table 3. Overall survival as reported in the three trials with mature data (not pooled).

Trial	OS combination (mo)	OS monotherapy (mo)	OS HR (95% CI)
NEJ026	50.7	46.2	1.01 (0.68-1.49)
Alliance (Stinchcombe)	32.4	50.6	1.41 (0.71-2.81)
BOOSTER	24.0	24.3	1.03 (0.67-1.56)

Safety

Grade ≥3 adverse events were synthesised from five trials, with per-trial event counts in Table 4 and the pooled estimate displayed in Figure 6. The combination approximately doubled the relative risk of grade ≥3 adverse events (pooled risk ratio 1.95, 95% CI 1.47-2.57), an absolute increase of about 29 percentage points and a number needed to harm of about four. Heterogeneity was substantial (I^2=79%), reflecting differences in agent, dose and schedule, TKI generation, exposure duration and reporting granularity. As detailed in Table 4, the excess toxicity was dominated by hypertension (grade ≥3 in roughly a quarter to two-fifths of combination patients) and proteinuria, with increased rash and diarrhoea from intensified EGFR blockade; treatment-related deaths were rare across trials.

Table 4. Grade ≥3 adverse events by trial (events approximated from the reported percentages).

Trial	Events combination (n/N)	Events monotherapy (n/N)	Dominant excess toxicities
NEJ026	99/112	52/112	Hypertension, proteinuria
ARTEMIS-CTONG1509	86/157	40/154	Hypertension, proteinuria
Lee	36/64	13/63	Hypertension, rash
RELAY	161/224	122/225	Hypertension, dermatitis
BOOSTER	37/78	14/77	Hypertension, proteinuria

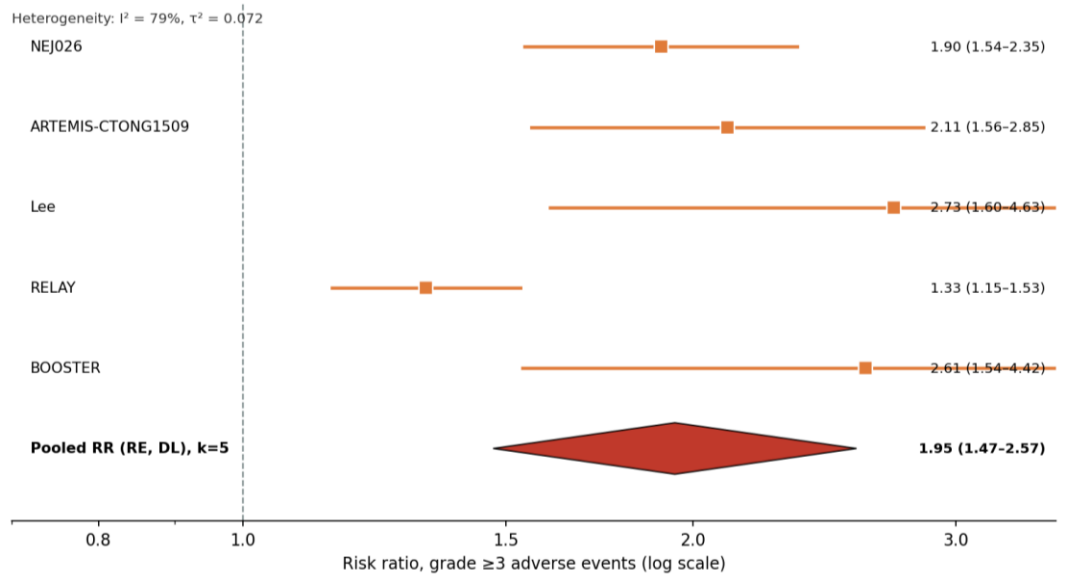

Figure 6. Forest plot of grade ≥3 adverse events (combination versus monotherapy; pooled risk ratio).

4. Discussion

This meta-analysis of seven RCTs demonstrates that adding antiangiogenic therapy to a first-line EGFR-TKI produces a clinically and statistically significant prolongation of progression-free survival in EGFR-mutant NSCLC, reducing the hazard of progression or death by approximately 39% (pooled HR 0.61; Figure 3, Table 2), with a prediction interval

entirely below unity. The complete absence of heterogeneity in the first-line analysis is notable for a synthesis spanning multiple countries, trial phases and two antiangiogenic agents, although with only six trials the I^2 statistic is imprecise; the prediction interval is therefore reported alongside the confidence interval. The estimate was robust to leave-one-out analysis, reproduced by a restricted maximum-likelihood model, and not explained by detectable small-study effects.

A central and novel finding is that the benefit is a class effect of VEGF-axis inhibition. The almost identical pooled estimates for bevacizumab (HR 0.62) and ramucirumab (HR 0.59) in Table 2 indicate that the mechanism-interruption of EGFR-VEGF crosstalk and normalisation of the tumour vasculature-operates whether the ligand or its receptor is targeted. This extends earlier syntheses confined to bevacizumab plus erlotinib. We present the mechanistic interpretation as a biologically plausible hypothesis rather than a demonstrated mechanism, since the analysis synthesises clinical endpoints.

Equally important is the contrast between settings. In BOOSTER, adding bevacizumab to osimertinib in acquired T790M-mediated resistance did not improve PFS (Figure 4), and incorporating this trial diluted the pooled effect and introduced moderate heterogeneity. This dissociation is consistent with the hypothesis that vascular normalisation is most useful for delaying the emergence of resistance and offers little once a discrete resistance mechanism dominates; because it rests on a single trial, however, the negative result requires confirmation.

Comparison with previous meta-analyses and the wider landscape

Our first-line estimate is concordant with earlier bevacizumab-and-erlotinib syntheses, which reported pooled hazard ratios of approximately 0.59-0.60[11], while adding precision and external validity by incorporating ramucirumab and by separating the second-line setting. Like those analyses, we found no convincing overall-survival benefit (Table 3). The work also complements studies of molecular determinants of resistance such as concurrent TP53 mutation[12], by addressing a modifiable pharmacological strategy. Antiangiogenic combination is one of several intensification strategies, alongside the addition of chemotherapy and the early use of third-generation TKIs[6]; these were not directly compared within the included trials, so any ranking would be an indirect comparison.

Applicability to contemporary practice

An important caveat is that six of the seven included trials used erlotinib, whereas a third-generation TKI is now a preferred first-line option in many settings[6-7]. The findings are therefore most directly relevant to settings where first- and second-generation TKIs remain in routine use, including health systems where access to third-generation agents is constrained by cost; in such resource-limited contexts, an antiangiogenic combination built on erlotinib may be a pragmatic means of extending disease control. Whether the class benefit is preserved when an antiangiogenic agent is added to a third-generation TKI first-line remains an open question for dedicated trials.

Heterogeneity

Heterogeneity was negligible for the primary first-line PFS outcome but substantial for the safety outcome (I^2=79%; Figure 6). The discordance is informative: the efficacy of VEGF-axis inhibition on progression appears uniform, whereas the magnitude of excess toxicity varies with the regimen, the antiangiogenic dose and schedule, the TKI generation, and the rigour of adverse-event reporting. The moderate heterogeneity in the exploratory all-trials analysis was attributable almost entirely to the mechanistically distinct second-line BOOSTER trial.

Clinical implications

These findings support the first-line addition of bevacizumab or ramucirumab to an EGFR-TKI as an option to prolong disease control in appropriately selected patients, particularly where delaying progression is a priority and third-generation agents are not accessible. Because the effect is a class effect, the choice between agents can be guided by availability, route, cost and comorbidity. The benefit must be weighed against an absolute increase of roughly 29 percentage points in grade ≥3 adverse events (number needed to harm about four; Table 4):

the combination should be avoided in patients with poorly controlled hypertension, significant proteinuria, recent haemoptysis or high bleeding risk, and requires structured monitoring of blood pressure and renal function. Patients with baseline brain metastases may derive particular benefit, although individual-patient data were unavailable for a formal subgroup analysis. The absence of benefit in the osimertinib/T790M setting argues against routine use after acquired resistance. Progression-free survival is a surrogate endpoint; the combination reliably delays radiological progression but has not been shown to prolong overall survival.

Strengths and limitations

Strengths include the exclusive reliance on randomised evidence, pre-specified class- and setting-level analyses, verification of every included trial and effect estimate against the primary publications, and methodological robustness (zero heterogeneity, a concordant restricted maximum-likelihood estimate, a prediction interval below unity, and a stable leave-one-out analysis). Limitations are that six of seven trials were open-label (though the single double-blind trial was concordant); the number of trials was modest, with the ramucirumab subgroup and the second-line setting each represented by one trial; overall survival and response could not be reliably pooled; the population was enriched for East Asian ancestry and classical mutations; the erlotinib backbone constrains applicability to third-generation-TKI practice; and the absence of individual-patient data precluded analyses by mutation subtype and by baseline brain metastases.

Future directions

Future randomised trials should test antiangiogenic combinations with third-generation TKIs first-line, using blinded independent review of progression and mature overall-survival follow-up, and should incorporate biomarker-stratified designs to identify the subgroups most likely to benefit. Individual-patient-data meta-analyses and network comparisons with chemotherapy-based intensification would further position the strategy within the treatment algorithm.

5. Conclusion

This systematic review and meta-analysis of seven randomised controlled trials enrolling 1,512 patients provides robust evidence that adding antiangiogenic therapy to an EGFR-tyrosine kinase inhibitor prolongs progression-free survival in EGFR-mutant non-small cell lung cancer. In the pre-specified first-line analysis, the combination reduced the hazard of progression or death by approximately 39% (pooled hazard ratio 0.61, 95% confidence interval 0.53-0.70)-highly significant, free of detectable heterogeneity, accompanied by a prediction interval below unity, reproduced by a restricted maximum-likelihood model, and stable across leave-one-out analysis-corresponding to a mean prolongation of median progression-free survival of approximately 5.5 months.

The benefit was a class effect of vascular endothelial growth factor pathway inhibition, with near-identical estimates for bevacizumab and ramucirumab, indicating that the gain derives from interruption of EGFR-VEGF crosstalk rather than from any single agent. The strategy was not uniformly effective across settings: when antiangiogenic therapy was added to osimertinib in the second-line, T790M-positive setting, no prolongation of progression-free survival was observed, and including this trial attenuated the pooled estimate and introduced moderate heterogeneity. Vascular pathway inhibition is therefore most valuable when introduced early, to delay the emergence of resistance, rather than to overcome it once established, although the second-line evidence rests on a single trial.

The efficacy gain was accompanied by an approximately two-fold relative, and roughly 29 percentage-point absolute, increase in grade ≥3 adverse events, dominated by hypertension and proteinuria together with intensified epidermal growth factor receptor-related effects, underscoring the need for careful patient selection and structured monitoring. Progression-free survival is a surrogate endpoint and no overall-survival advantage has been demonstrated. These findings support the first-line addition of bevacizumab or ramucirumab to an EGFR-TKI in appropriately selected patients-of particular pragmatic value where third-generation agents are

inaccessible-while cautioning against routine use in the acquired-resistance setting. Confirmation in blinded trials with mature overall-survival data and biomarker-driven selection is the key priority for translating this progression-free survival advantage into a durable benefit for patients.

Ethical considerations, funding and conflict of interest

This study used only published aggregate data and did not require ethical approval. It received no specific funding, and the authors declare no conflict of interest. The extracted data set is available from the corresponding author on reasonable request. Both authors contributed to the conception, screening, data extraction, analysis, interpretation and drafting, and approved the final version of the manuscript.

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