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REVIEW ARTICLE

Use of Monoclonal Antibodies and Tyrosine Kinase Inhibitors in the Treatment of Lung Cancer: A Systematic Review and Meta-analysis

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Abstract

Introduction: Advanced epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) responds to EGFR tyrosine kinase inhibitors (TKIs); however, resistance commonly emerges through secondary EGFR alterations, mesenchymal-epithelial transition amplification, bypass signaling, and microenvironmental adaptation, motivating combinations with monoclonal antibodies targeting angiogenesis or alternative receptors. **Objective:** The main aim of this study was to assess progression-free survival (PFS). The secondary aims included overall survival, response, severe toxicity, mechanistic differences, risk of bias, and application of a pooled class estimate to treatment decisions. **Materials and Methods:** This Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020–guided systematic review and meta-analysis searched PubMed/MEDLINE (January 2014–July 2026) for English-language phase II/III randomized trials in adults with unresectable locally advanced, recurrent, or metastatic EGFR-mutated NSCLC comparing an antibody plus EGFR TKI with a relevant TKI control. **Results:** Five trials (JO25567, NEJ026, ARTEMIS-CTONG1509, RELAY, and MARIPOSA; ~2,000 participants) were included: four evaluated antiangiogenic antibodies (bevacizumab or ramucirumab) with erlotinib, and MARIPOSA evaluated amivantamab plus lazertinib versus osimertinib. The log hazard ratios for PFS were pooled using inverse-variance random effects (DerSimonian–Laird). Combination therapy favored PFS in all trials (hazard ratio [HR] 0.54–0.70), with a pooled HR of 0.62 (95% confidence interval 0.55–0.70), no heterogeneity (I^2 = 0%; τ^2 = 0), a prediction interval of 0.53–0.72, and robust leave-one-out results. Anti-angiogenic combinations yielded HR 0.58 (0.51–0.67), while MARIPOSA reported HR 0.70 (0.58–0.85), reflecting differing comparators and mechanisms rather than proven superiority. **Conclusion:** Overall, adding a monoclonal antibody to an EGFR TKI provides consistent first-line PFS benefits in EGFR-mutated NSCLC; however, regimen selection should be individualized based on comparator potency, intracranial considerations, toxicity, vascular/thrombotic risk, patient preference, and health system capacity. Further evidence on OS and quality of life is needed.

Key words: Amivantamab, anti-angiogenic, monoclonal antibodies, non-small cell lung cancer, osimertinib, resistance mechanisms

INTRODUCTION

Lung cancer remains a leading cause of cancer-related deaths because many patients present with or develop an incurable disease. Non-small cell lung cancer (NSCLC) comprises most cases and includes diseases in addition to one therapeutic category. The identification of oncogenic drivers has shifted treatment from morphology-based

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selection to molecularly stratified therapy. Alterations in epidermal growth factor receptor (EGFR), especially exon 19 deletions and exon 21 L858R substitutions, drive kinase signaling through the RAS–RAF–MEK, PI3K–AKT–mTOR, and JAK–STAT pathways. These changes are common in adenocarcinoma, non-smokers, women, and East Asian populations, although testing should not be limited by demographic assumptions.[1-4]

Small-molecule EGFR tyrosine kinase inhibitors (TKIs) target this dependency in tumor cells. First-generation reversible inhibitors, such as erlotinib and gefitinib, second-generation irreversible inhibitors, such as afatinib and dacomitinib, and third-generation mutant-selective inhibitors, such as osimertinib, produce higher response rates and longer progression-free survival (PFS) than chemotherapy.[5-8] Osimertinib also improves central nervous system control and overall survival compared to first-generation TKIs, making it an accepted first-line treatment.[8,9] However, TKI therapy selects for resistant clones. Resistance mechanisms include secondary EGFR alterations, Mesenchymal–epithelial transition (MET) amplification, bypass signaling, phenotypic changes, altered apoptosis, or combinations of these processes.[10,11] A potent intracellular inhibitor may not suppress all the escape routes.

Monoclonal antibodies offer a unique approach. Bevacizumab targets vascular endothelial growth factor A, whereas ramucirumab targets vascular endothelial growth factor receptor 2. Both disrupt angiogenic support rather than inhibiting the mutant EGFR. EGFR signaling can increase angiogenic mediators, and abnormal vasculature causes hypoxia and drug-delivery variability. Dual EGFR– vascular endothelial growth factor (VEGF) inhibition may delay resistance.[12-15]Amivantamab offers a different treatment strategy. It is a bispecific antibody against EGFR and MET with receptor-blocking, receptor-degrading, and immune effector functions. When combined with lazertinib, a third-generation EGFR TKI that penetrates the central nervous system, it merges extracellular multi-receptor engagement with intracellular kinase inhibition.[16,17]

These treatment regimens cannot be classified as a drug class by mechanism. Anti-angiogenic combinations can cause hypertension, proteinuria, bleeding, wound-healing issues, and thrombotic events. Amivantamab-based therapy introduces infusion reactions, skin toxicity, paronychia, edema, venous thromboembolism, and intravenous administration and chair time. Comparator choice is crucial. Superiority over erlotinib does not establish superiority to osimertinib, and cross-trial PFS comparisons can mislead because of differences in populations, imaging schedules, subsequent therapies, and censoring. A synthesis must distinguish whether adding a monoclonal antibody to an EGFR TKI improves outcomes and which regimen is preferable for a patient. Previous evaluations focused on combining anti-angiogenic drugs with first-generation EGFR TKIs.

MARIPOSA introduced direct antibodies and a third-generation comparator, thereby changing the evidence-based framework.[17] Consequently, we performed a study-level systematic review and meta-analysis of randomized first-line trials comparing monoclonal antibodies plus EGFR-TKI with EGFR-TKI monotherapy in patients with advanced EGFR-mutated NSCLC. The main aim of this study was to assess PFS. The secondary aims included overall survival, response, severe toxicity, mechanistic differences, risk of bias (RoB), and application of a pooled class estimate to treatment decisions.

MATERIALS AND METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[18] The synthesis focused on randomized comparisons, linking multiple reports from a single trial to avoid duplication. Although the protocol preceded quantitative synthesis, it was not registered prospectively, which is a limitation. No patient-level data were gathered, and ethics approval was unnecessary because the analysis used aggregate published data.

Eligible studies were phase II or III randomized controlled trials in adults with unresectable locally advanced, recurrent, or metastatic NSCLC with an activating EGFR mutation. They had to assess first-line treatment, comparing a monoclonal antibody plus an EGFR TKI with the same or a relevant EGFR-TKI monotherapy control, and report a hazard ratio (HR) with a 95% confidence interval (CI) for PFS or sufficient data to derive it. Both anti-angiogenic and direct receptor-targeting antibodies were eligible. Trials permitting prior adjuvant treatment were included if the protocol specified a treatment-free interval.

Non-randomized studies, single-arm trials, retrospective cohorts, case series, conference abstracts lacking numerical outcome data, studies without molecularly confirmed EGFR-mutated populations, and trials in which chemotherapy or another systemic agent varied between randomized groups were excluded from the synthesis. Studies on acquired resistance after a prior EGFR TKI were excluded because of different prognosis and treatment contrast versus first-line therapy. Publications on exploratory biomarkers or later follow-up of an included trial were used for context or updated outcomes but did not contribute duplicate participants.

Searches covered PubMed/MEDLINE from January 01, 2014, to July 31, 2026, for English reports. The PubMed strategy used terms: (lung neoplasms OR lung cancer OR NSCLC) AND (EGFR OR epidermal growth factor receptor) AND (monoclonal antibody OR bevacizumab OR ramucirumab OR amivantamab) AND (tyrosine kinase inhibitor OR erlotinib OR gefitinib OR afatinib OR dacomitinib OR osimertinib OR lazertinib) AND (randomized controlled trial OR random*). References from trials and reviews were examined.

Records were evaluated using predetermined criteria. The following were extracted: trial name; country or geographical area; phase; blinding; sample size; EGFR alteration; baseline brain-metastasis policy; experimental and control regimens; PFS definition; analysis population; median follow-up; median PFS; PFS HR and CI; overall-survival results; response outcomes; grade 3 or higher adverse events; serious adverse events; discontinuations; and funding source. The most mature eligible PFS estimate from the primary randomized comparison was used. When both investigator- and independent-review estimates were reported, the protocol-defined primary estimate was prioritized. Numerical values were verified against the primary report and PubMed bibliographic record, and study-level calculations are presented for independent verification.

RoB was evaluated using the Cochrane RoB2 domains: randomization process, deviations from intended intervention, missing outcome data, outcome measurement, and selective reporting.[19] An open-label design was not automatically high risk for PFS, but was concerning when assessments were investigator-based without blinded central confirmation. Industry sponsorship was noted but not considered a bias judgment. Certainty was assessed using GRADE concepts RoB, inconsistency, indirectness, imprecision, and publication bias, without converting the assessment into a mechanistic numerical score.[20]

The primary outcome was PFS, expressed as the HR for progression or death; values below 1 favored antibody–TKI combination therapy. Secondary outcomes included overall survival, objective response rate, duration of response, intracranial outcomes, grade 3 or higher adverse events, serious adverse events, treatment discontinuation, and treatment-related mortality. PFS was selected because it was consistently reported and was the primary endpoint of included trials, although it remains a surrogate endpoint influenced by assessment schedules, censoring, and non-proportional hazards.

The natural logarithm of each PFS HR was analyzed, with standard error reconstructed as (ln[upper 95% CI]−ln[lower 95% CI])/(2×1.96). Estimates were pooled using inverse-variance weighting. A random-effects model was primary because of clinical differences in antibody targets and TKI generations; between-study variance was estimated using the DerSimonian-Laird moment method and compared with the fixed-effect result. Heterogeneity was measured with The Chi-square Test (Cochran's Q), Tau-Squared (τ^2, Between-Study Variance), and Inconsistency Percentage (I^2); leave-one-out analyses assessed the influence results.

RESULTS

Through structured searches, we identified 102 studies in PubMed. The initial screening process involved the application of predetermined eligibility criteria. After excluding 48 studies owing to the unavailability of full-text data, 54 studies were screened. Of these, 44 studies were excluded from the review. The remaining 10 studies underwent an eligibility assessment, resulting in the exclusion of five studies with inadequate data and conclusions. Ultimately, five papers satisfied the inclusion criteria and were included in this systematic review, leaving five trials for meta-analysis: JO25567, NEJ026, ARTEMIS-CTONG1509, RELAY, and MARIPOSA.[13-17] Figure 1 illustrates the selection process, and Table 1 lists the six papers included.

Trial and participant characteristics

Four studies assessed anti-angiogenic antibodies with erlotinib. In Japan, JO25567 and NEJ026 investigated bevacizumab, while ARTEMIS-CTONG1509 evaluated it in China.[13-15] RELAY examined ramucirumab plus erlotinib in a multinational, placebo-controlled setting.[16] MARIPOSA combined the EGFR-MET bispecific antibody amivantamab with lazertinib, using osimertinib as the control.[17] Although MARIPOSA adds relevance, it introduces variability not reflected by the statistical I^2 value.

Sensitizing mutations were EGFR exon 19 deletion and L858R. Brain metastases eligibility varied. RELAY excluded patients with untreated central nervous system metastases,[16] whereas MARIPOSA and some bevacizumab trials allowed stable or asymptomatic conditions. Participants had a performance status.[17] All trials received sponsorship or support from the manufacturers of the drugs. Randomization was deemed adequate in reports, and open-label designs were prevalent in bevacizumab studies, due to masking challenges related to infusion and toxicity profiles.

Primary meta-analysis of PFS

In every comparison, combination treatment was favored. The study-specific HRs ranged from 0.54 to 0.70. The pooled HR using a random-effects model was 0.62 (95% CI 0.55–0.70), indicating a 38% relative reduction in the risk of progression or death. No between-study heterogeneity was detected ($Q = 2.85$, $df = 4$, $P = 0.58$; $\tau^2 = 0$; $I^2 = 0\%$). The fixed-effect estimate matched the precision. The 95% prediction interval was 0.53–0.72, below the null value. These results suggest consistency in the relative effect on PFS despite differences in antibody mechanisms and control TKIs.[13-17]

The lack of heterogeneity should not be mistaken for interchangeability. With five trials, the statistical power to detect heterogeneity is limited, and the HR represents a relative effect averaged over the follow-up period.[13-17] MARIPOSA compared a dual EGFR–MET antibody with a third-generation TKI against a third-generation TKI alone, while the other trials evaluated whether anti-angiogenic blockade enhanced erlotinib.[17] Therefore, the pooled

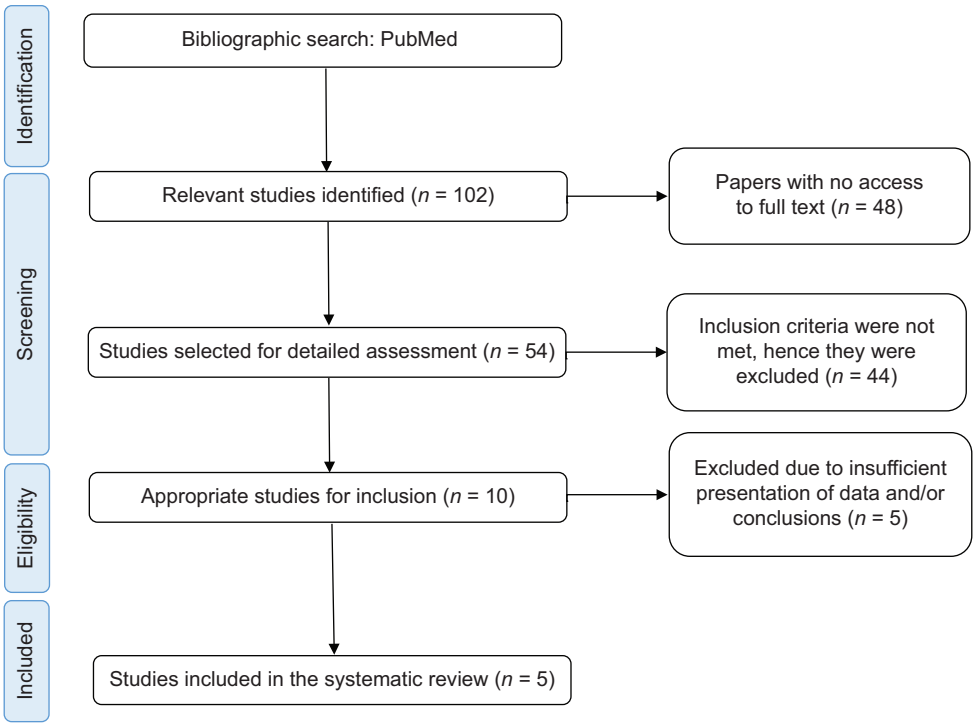


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart depicting the literature search and study selection process for the systematic review

Table 1: Characteristics of randomized trials included in the quantitative synthesis

Trial	Phase/setting	Participants	Experimental regimen	Control	Primary PFS result
JO25567[13]	II; Japan; untreated EGFR-mutated nonsquamous NSCLC	154	Bevacizumab +Erlotinib	Erlotinib	HR 0.54 (0.36–0.79)
NEJ026[14]	III; Japan; untreated EGFR-mutated nonsquamous NSCLC	228	Bevacizumab+ Erlotinib	Erlotinib	HR 0.605 (0.417–0.877)
ARTEMIS-CTONG1509[15]	III; China; untreated EGFR-mutated advanced NSCLC	311	Bevacizumab+ Erlotinib	Erlotinib	HR 0.55 (0.41–0.73)
RELAY[16]	III; multinational; untreated metastatic EGFR-mutated NSCLC	449	Ramucirumab+ Erlotinib	Placebo+ Erlotinib	HR 0.59 (0.46–0.76)
MARIPOSA[17]	III; multinational; untreated EGFR exon 19 deletion/L858R advanced NSCLC	858 relevant arms	Amivantamab+ lazertinib	Osimertinib	HR 0.70 (0.58–0.85)

CI: Confidence interval, EGFR: Epidermal growth factor receptor, HR: hazard ratio, MET: Mesenchymal-epithelial transition factor receptor, NSCLC: Non-small-cell lung cancer, PFS: Progression-free survival, TKI: Tyrosine kinase inhibitor, VEGF: Vascular endothelial growth factor, VEGFR2: Vascular endothelial growth factor receptor 2

HR addresses a class question but does not confirm that bevacizumab, ramucirumab, and amivantamab share the same benefit–risk profile.

Subgroup and sensitivity analyses

The anti-angiogenic subgroup, including JO25567, NEJ026, ARTEMIS-CTONG1509, and RELAY, yielded a combined HR of 0.58 (95% CI 0.51–0.67).[13-16] MARIPOSA showed the benefit of amivantamab plus lazertinib versus osimertinib (HR 0.70, 95% CI 0.58–0.85) [Figure 2].[17] This variation should not be considered proof that anti-angiogenic combinations are superior because it reflects a stronger control regimen, distinct antibody mechanisms, trial era, patient demographics, and follow-up duration. No direct randomized comparisons exist between these strategies.

Sequential omission of each study did not alter the pooled estimate; pooled HRs remained at approximately 0.60–0.64. Omitting the phase II JO25567 trial did not change this conclusion.[13] Excluding MARIPOSA, there was limited evidence for anti-angiogenic antibodies plus erlotinib, which enhanced the numerical effect, as anticipated from its lower

HRs. Conversely, MARIPOSA alone provides the most direct evidence for current osimertinib-based practices.[17] Thus, the combination signal was robust, but its clinical relevance depended on the question posed.

Overall survival and response outcomes

The PFS benefit did not consistently lead to an overall survival advantage in anti-angiogenic trials. Factors such as crossover, osimertinib availability, post-progression therapy, immature event counts, and dilution by later treatments can obscure survival differences. Survival follow-up from JO25567 and mature analyses of NEJ026 and RELAY did not show a consistent,[13,14,16] statistically significant overall survival advantage, despite PFS improvement.[21-23] The MARIPOSA publication confirmed a PFS advantage for amivantamab plus lazertinib over osimertinib; however, the survival data were not mature enough to draw a conclusion.[17] Because survival publications represented different data cuts and trial estimates were not equally mature, overall survival was not pooled.

Objective response rates were high in both experimental and control groups, indicating the sensitivity of EGFR-driven tumors to EGFR inhibition. The added benefit of antibody therapy was reflected more consistently in delayed progression and prolonged disease control than in increased initial response proportion. This is biologically plausible, as the antibody partner may limit bypass signaling, angiogenic adaptation, or clonal escape rather than determining early radiographic response.[13-17]

Safety

Increased clinically significant toxicity was observed with combination therapy across all programs, though the specific pattern varied by antibody target.[13-17] In the NEJ026 study, 88% of patients receiving the combination experienced grade 3 or more severe adverse events, compared to 46% on erlotinib alone, with much of the additional toxicity being protocol-defined laboratory or manageable.[14] The ARTEMIS-CTONG1509 trial found treatment-related adverse events of grade 3 or higher in 54.8% of participants, compared to 26.1%.[15] Regimens containing bevacizumab and ramucirumab are associated with increased hypertension and proteinuria, necessitating vigilance for bleeding, thrombosis, wound healing, and gastrointestinal perforation.[13-16] Therefore, careful patient selection is crucial for those with uncontrolled hypertension, significant hemoptysis, recent surgeries, substantial vascular disease, or high bleeding risk.[24,25]

The combination of amivantamab and lazertinib results in a unique toxicity profile. Infusion-related reactions occurred primarily during initial administration, while rash, paronychia, edema, hypoalbuminemia, and venous thromboembolism required proactive monitoring and management.[17] Thrombosis prevention and treatment should be tailored based on the bleeding risk, comorbidities, concurrent medications, current product information, and institutional guidelines.[24,25] This regimen also requires time and monitoring at infusion centers, unlike oral EGFR-TKI monotherapy.[17]

The pooled risk ratio for grade 3 or higher toxicity was intentionally omitted. The trials differed in terms of adverse event attribution rules, toxicity criteria versions, reporting periods, and denominators; MARIPOSA's mechanism-specific events are not directly comparable to anti-VEGF toxicity.[17]

RoB

The pivotal trials provided adequate descriptions of random sequence generation and allocation procedures, indicating a

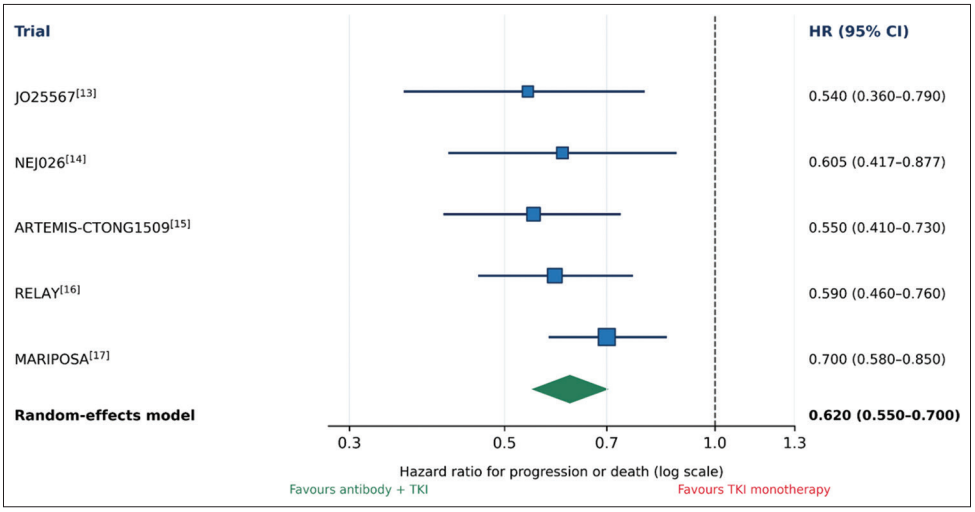


Figure 2: Progression-free survival for monoclonal antibody with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor versus EGFR tyrosine kinase inhibitor alone

low concern regarding the randomization process [Figure 3]. The RELAY trial's use of a placebo control reduced concerns about performance and ascertainment.[16] The bevacizumab trials and MARIPOSA were open-label; however, PFS based on blinded independent central review reduced but did not eliminate concerns.[17] Missing outcome data were minimal and balanced, and intention-to-treat populations were reported. Concerns about selective reporting were low to moderate, as outcomes were consistent with registered protocols, although multiple analyses, updated data cuts, and sponsor involvement necessitate careful use of prespecified endpoints. Overall, the RoB for PFS was considered low for RELAY and low with some concerns for open-label trials.[16]

DISCUSSION

This review demonstrates a consistent PFS advantage when a monoclonal antibody is added to an EGFR TKI for first-line treatment of advanced EGFR-mutated NSCLC. Across five randomized trials and 2,000 participants, the pooled HR was 0.62, with a confidence interval excluding a small or null relative effect and no detected statistical heterogeneity. The result remained stable when individual trials were removed. It therefore supports the central pharmacological proposition that simultaneous extracellular or microenvironmental targeting can deepen or prolong control achieved through intracellular kinase inhibition.

The most important interpretive point is that a coherent pooled effect does not create a single therapeutic class. Anti-VEGF/VEGFR antibodies paired with erlotinib and an EGFR-MET bispecific antibody paired with lazertinib differ in target biology, TKI backbone, toxicity, administration, and the strength of the comparator. The anti-angiogenic trials largely establish superiority over a first-generation TKI. MARIPOSA addresses a more contemporary benchmark by comparing against osimertinib.[17] In practice, the latter comparison may be more decision-relevant where osimertinib is accessible, whereas bevacizumab- or ramucirumab-based evidence may remain relevant in settings where erlotinib is used or where anti-angiogenic intensification is specifically considered.

The consistency of PFS benefit across different antibodies suggests that resistance delay may be achieved through more than one biological route. VEGF pathway blockade alters endothelial survival, vascular permeability, and angiogenic adaptation. It may transiently normalize tumor vasculature, improve drug delivery, reduce hypoxia-associated selection, and interrupt reciprocal signaling between EGFR-driven tumor cells and the microenvironment. These hypotheses are plausible but should not be overextended: clinical trials establish treatment effects, not the dominance of a single proposed mechanism.[10-16]

Amivantamab adds a more direct form of vertical and parallel pathway suppression. Its EGFR-binding arm can interfere with ligand–receptor interaction, its MET-binding arm addresses a major bypass route, receptor cross-linking promotes internalization and degradation, and the Fc region can recruit immune effector mechanisms. Lazertinib inhibits mutant EGFR within the cell and reaches the central nervous system. This complementary pharmacology may reduce the probability that one resistance mechanism restores sufficient signaling, but it also expands on-target epithelial toxicity and introduces antibody-specific systemic effects.[10,11,17]

Pharmacokinetics further distinguish the strategies. Oral TKI exposure is continuous but can be altered by adherence, drug–drug interactions, acid-suppressive therapy for some agents, hepatic function, and pharmacogenetic variability. Intravenous antibodies have long half-lives, target-mediated disposition, and intermittent administration. Their exposure cannot be rapidly reversed after toxicity. A combination may therefore preserve pathway suppression across compartments while simultaneously complicating dose modification: clinicians must identify which component most likely caused toxicity and decide whether to hold one or both agents.[24,25]

This review highlights the consistent PFS advantage of combining monoclonal antibodies with an EGFR TKI for the initial treatment of advanced EGFR-mutated NSCLC.

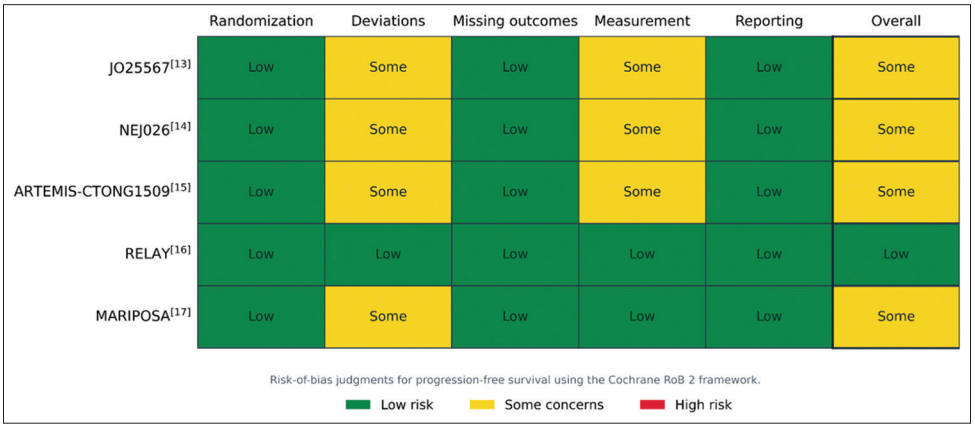


Figure 3: Cochrane Risk of Bias 2 of trials for progression-free survival

Analyzing five randomized studies involving 2,000 participants, the combined hazard ratio was 0.62, with a confidence interval ruling out a negligible relative effect and no statistical heterogeneity. The findings remained consistent even when individual studies were excluded, supporting the pharmacological theory that targeting extracellular or microenvironmental factors alongside intracellular kinase inhibition enhances or extends control.[13-17]

The primary interpretive insight is that a unified pooled effect does not equate to a single therapeutic category. Anti-VEGF/VEGFR antibodies with erlotinib and EGFR–MET bispecific antibodies with lazertinib differ in terms of target biology, TKI foundation, toxicity, administration, and comparator strength. Anti-angiogenic studies have mainly demonstrated the superiority of first-generation TKIs. MARIPOSA sets a modern standard by comparing it with osimertinib.[17] In practice, this comparison is more relevant where osimertinib is available, while evidence for bevacizumab or ramucirumab remains pertinent where erlotinib is used, or anti-angiogenic intensification is specifically considered.

The consistent PFS benefit across antibodies indicates that resistance may be delayed through multiple biological pathways. Blocking the VEGF pathway affects endothelial survival, vascular permeability, and angiogenic adaptation. It may temporarily normalize tumor vasculature, enhance drug delivery, reduce hypoxia-related selection, and disrupt reciprocal signaling between EGFR-driven tumor cells and the microenvironment. These hypotheses are plausible but should not be overstated, as clinical trials determine treatment effects, not the predominance of a single proposed mechanism.

Amivantamab offers a direct approach to vertical and parallel pathway suppression. Its EGFR-binding component disrupts ligand–receptor interaction, its MET-binding component addresses a significant bypass route, receptor cross-linking encourages internalization and degradation, and the Fc region engages immune effector mechanisms. Lazertinib inhibits mutant EGFR within the cell and penetrates the central nervous system. This complementary pharmacology lowers the likelihood that one resistance mechanism restores signaling, but increases on-target epithelial toxicity and introduces antibody-specific systemic effects.[10,11,17]

Pharmacokinetics further differentiate these strategies. Oral TKI exposure is continuous but influenced by adherence, drug–drug interactions, acid-suppressive therapy, liver function, and pharmacogenetic variability. Intravenous antibodies have prolonged half-lives, target-mediated disposition, and are administered intermittently; their exposure cannot be quickly reversed after toxicity. Thus, a combination may maintain pathway suppression across compartments while complicating dose adjustments: clinicians must determine which component caused toxicity and decide whether to pause one or both agents.[24,25]

PFS is significant when progression causes symptoms, neurological issues, imaging, hospital admissions, or treatment changes. It is less influenced by post-progression therapy than overall survival. However, an HR of 0.62 does not mean a 38% increase in median survival or that 38% of patients avoid progression. The HR reflects a relative event rate at a time under proportional-hazards assumptions and should be complemented by median estimates, landmark rates, restricted mean survival time when available, and patient-reported outcomes.[26,27] Inconsistent overall survival evidence in anti-angiogenic trials may reflect salvage therapies, crossover, limited power, or failure of early disease-control benefits to extend life. MARIPOSA survival data are promising versus osimertinib, but interpretation should remain tied to predefined analysis and follow-up. PFS cannot judge treatments that increase toxicity, clinic visits, or treatment-related mortality; benefit–risk assessment should remain regimen-specific.[17,21-23]

Preventing adverse events is integral to treatment. Unchecked toxicity can cause interruptions, dose reductions, discontinuation, hospitalization, and reduced drug exposure. For anti-angiogenic treatments, the baseline assessment included blood pressure, urine protein levels, renal function, bleeding history, recent surgeries, anticoagulant use, and other vascular events. Therefore, monitoring blood pressure and proteinuria is necessary in these patients. Elective surgeries require an antibody washout period according to the product label because of the risk of impaired wound healing.[13-16,24,25]

In amivantamab therapy, premedication and a structured first-infusion protocol help minimize infusion reactions. Treatment can be maintained through skin care, topical treatments, oral antibiotics when needed, nail care, and early dermatological involvement. The risk of venous thromboembolism should be assessed before and during treatment. Anticoagulant prophylaxis must follow regulatory labeling, trial guidance, platelet count, renal function, bleeding risk, drug interactions, and institutional policies; it is not universally applicable.[17,24,25]

These findings are pertinent to clinical pharmacology and pharmaceutical practices. Combination regimens require procurement, cold-chain management of antibodies, sterile preparation, infusion capacity, support for oral adherence, interaction screening, dose-hold protocols, and pharmacovigilance. Although biosimilar bevacizumab may reduce acquisition costs in some contexts, the total cost includes infusion delivery, monitoring, management of hypertension or proteinuria, and patient opportunity costs. Similarly, amivantamab-based care requires initial infusion resources and pathways for preventing toxicity. Economic evaluations should consider local prices and health system perspectives rather than list prices from different countries.[13-17,24,25]

Pharmacists can enhance safety by reconciling antihypertensive, anticoagulant, acid suppressants, CYP-modulating medications, herbal products, and adherence

barriers. They can detect rash, paronychia, diarrhea, edema, or blood pressure changes before they become dose-limiting factors. Standardized treatment plans should distinguish between immune-mediated, vascular, infusion-related, and TKI-class toxicities, as management varies.[24,25]

The strengths of this review include a well-defined randomized question, avoidance of duplicate trial populations, HR use, complete dataset presentation, and inclusion of MARIPOSA.[13-17]

Several limitations of this study should be highlighted. First, the literature search relied on PubMed and citation searching rather than a comprehensive multi-database export; an update using Embase, Scopus, Web of Science, and CENTRAL should be conducted before submission. Second, study-level data cannot determine individual patient effect modification or correlations among co-mutations, circulating tumor DNA clearance, treatment exposure, and outcomes. Third, only five trials were pooled, reducing the sensitivity of heterogeneity and small-study bias statistics. Fourth, open-label designs can affect treatment management and investigator-assessed progression, although independent review mitigated this concern in pivotal studies. Fifth, the proportional hazards assumption could not be verified from aggregate reports. Sixth, toxicity could not be summarized with a single pooled number because of differing definitions and mechanisms. Finally, overall survival maturity and subsequent treatment varied across trials.[13-17,27,28]

Future trials should use biological criteria rather than universally intensifying treatment. Prospective studies should test whether TP53, MET amplification, baseline and on-treatment circulating tumor DNA, angiogenic signatures, or spatial heterogeneity predict benefit. Standardized central nervous system endpoints, baseline imaging, and analyses accounting for competing risks are essential. Conventional hazard ratios should be complemented by patient-reported symptoms, time to deterioration, cumulative toxicity, treatment-free intervals, and restricted mean survival.

To distinguish antibody–TKI intensification from TKI–chemotherapy combinations or sequential strategies, trials or platform studies are needed. Pharmacoeconomic studies should detail acquisition, administration, toxicity, and productivity costs. In low- and middle-income countries, affordability and infusion capacity may determine whether a superior regimen improves population outcomes. Meta-analyses should incorporate individual-patient data and time-varying effects as survival curves mature.

CONCLUSION

Randomized trials have indicated that monoclonal antibodies plus EGFR-TKI are first-line treatments for advanced EGFR-mutated NSCLC. In studies with 2,000 participants, combination therapy reduced progression or death compared to EGFR-TKI monotherapy (pooled HR 0.62, 95% CI 0.55–0.70) without statistical heterogeneity. The benefit was clear for anti-angiogenic antibodies with erlotinib and amivantamab plus lazertinib versus osimertinib.

Regimen-level differences are important. The value is influenced by the comparator potency, intracranial activity, antibody mechanism, vascular or thromboembolic risk, infusion burden, patient preference, and health-system capacity. Evidence on overall survival, quality of life, predictive biomarkers, and context-specific cost-effectiveness analyses is required. Thus, combination therapy should not be universal; rational antibody–TKI co-targeting delays progression and requires individualized benefit–risk evaluation.

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