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Effectiveness and Safety of the Bevacizumab and Erlotinib Combination *vs*. Erlotinib Alone in EGFR Mutant Metastatic Non-Small-Cell Lung Cancer: Systematic Review and Meta-Analysis

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Abstract

Background: The EGFR gene encodes a protein that stimulates molecular pathways that allow the growth and development of the tumor microenvironment. The current preferred TKI for first-line treatment of EGFRm metastatic NSCLC is Osimertinib. However, the combination of angiogenesis inhibitors and TKI has produced discordant results. We aimed to assess the effects of the Bevacizumab and Erlotinib combination in EGFRm metastatic NSCLC.

Methods: Using eligibility criteria focused on patients with EGFRm metastatic NSCLC treated with Bevacizumab and Erlotinib, we searched databases including clinical trial randomized studies, and reviews published until April 15th, 2023, in Medline (PubMed), Scopus, and Embase. Eight clinical trials (1052 patients) were selected from 1,343 articles for quantitative and qualitative assessment. The risk of bias was assessed using the Cochrane Risk of Bias tool. Data were synthesized through random-effects meta-analysis.

Results: The Bevacizumab and Erlotinib combination significantly improved PFS (Log (HR)=0.63; 95% CI: 0.54-0.73, p<0.001) and ORR (RR=0.79, 95% CI; 0.64-0.97, p=0.03). However, it did not improve OS (Log (HR) = 0.93; 95% CI; 0.78-1.10, p=0.38) and was associated with higher SAEs (OR=3.48, 95% CI; 1.76-6.88, p=0.005). Subgroup analysis suggested similar benefits in different mutation subtypes and brain metastasis condition. The evidence is limited by a moderate risk of bias across studies and heterogeneity in the reporting of SAEs.

Conclusion: The Bevacizumab and Erlotinib combination significantly improved PFS and ORR in EGFRm metastatic NSCLC but were also associated with higher grade ≥ 3 adverse events. These results suggest that while the combination therapy may enhance progression-free survival and overall response, it does not improve overall survival and is associated with higher toxicity. Thus, the treatment should be personalized based on individual patient comorbidities. Further prospective trials are needed to validate these results.

Keywords: Non-small cell lung cancer; EGFR gene; VEGFR; Tyrosine kinase inhibitor PP1; Erlotinib

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Introduction

Worldwide, according to GLOBOCAN, lung cancer has the second highest incidence, representing 11.4% of cases diagnosed with cancer. Lung cancer is also the leading cause of cancer death, with an estimated 1.8 million deaths in 2020 [1]. Tobacco smoking remains the predominant risk factor for lung cancer development [2]. The Epidermal Growth Factor Receptor (EGFR) pathway is a well-studied oncogenic pathway in metastatic Non-Small Cell Lung Cancer (NSCLC) [3]. The activation of the tyrosine kinase domain of the EGFR is a key reason for lung

cancer progression [4]. The subsequent activation of the JAK-STAT, the PI3-K-Akt-mTOR and the RAS-RAF-MEK-ERK pathways leads the cell proliferation, inhibition of apoptosis, and tumor microenvironment development [3,5]. The prevalence of *EGFR mutation* is higher in younger, non or light-smokers and those with wood smoke exposure [6]. The frequency of *EGFR mutation* varies widely worldwide and occurs more commonly (40% to 60%) in the South-East of Asia [7]. It appears that Japan (64.8%), Thailand (57.8%), and Taiwan (54.3%) harbor the highest frequency of *EGFR mutations* in the Asian continent [8]. Meanwhile, the *EGFR mutation* rate in Western patients with adenocarcinoma is around 14% to 19% [9]. In Latin America, it has been reported that Peru (51.1%), Mexico (34.3%), Costa Rica (31.4%) and Panama (27.3%) might harbor the highest rates [10]. *EGFR mutant* (*EGFRm*) metastatic Non-Small Cell Lung Cancer (NSCLC) is generally sensitive to Tyrosine Kinase Inhibitors (TKIs), considered the standard first-line of treatment [11,12]. TKIs have revolutionized the *EGFRm* metastatic NSCLC treatment landscape since the introduction of the first-generation TKIs in first line [6]. Second-generation and third-generation TKIs improved survival in comparison with the first-generation [13-17]. Osimertinib, third generation TKI, is the preferred agent for first line of therapy because of its significant Central Nervous System (CNS) activity and a favorable safety profile [11,12,18]. Different targets and regimens of treatment have been evaluated in *EGFRm* metastatic NSCLC. The Vascular Endothelial Growth Factor (VEGF) has been identified as a molecular pathway involved in the lung cancer tumoral microenvironment [3]. In the last decade, preclinical trials demonstrated that the combination of angiogenesis inhibitors and TKIs improves survival in *EGFRm* advanced NSCLC [19,20]. However, discordant results limit its use in clinical practice [21-24]. The objective of this meta-analysis is to evaluate the safety and efficacy of the bevacizumab-erlotinib combination in *EGFRm* metastatic NSCLC.

Materials and Methods

Study setting and eligibility criteria of studies

This systematic review was performed following the recommendations of the Cochrane Handbook for Systematic Reviews [25], Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26], and AMSTAR 2 guidelines [27]. We previously registered the protocol in Prospective Register of Systematic Review (PROSPERO) (CDR 42022364692, registered on October 14th, 2022).

Database and search strategy

We searched for clinical trial randomized studies and reviews published until April 15th, 2023; in Medline (PubMed), Scopus, and Embase. We combined different keywords, controlled vocabulary terms (e.g., MeSH and Emtree terms), and free terms, according to the PICO strategy (Population: "carcinoma, non-small-cell lung"; exposure: "erlotinib hydrochloride" AND "bevacizumab"; comparator: "erlotinib hydrochloride") (Supplementary material). Searches were not limited by date or language. We included articles in full text and excluded observational studies, review articles, abstracts, case reports, letters, editorials, studies not available in full text, and duplicated publications. Inclusion criteria included: Histologically or cytologically confirmed NSCLC, assessment of erlotinib combined with bevacizumab or erlotinib alone. Exclusion criteria included: Animal or cadaver studies, studies without extractable or valid data, studies with patients aged <18 years, patients with other types of cancer, and patients who have received previous treatment.

Study selection and data extraction

We exported all retrieved references from databases to Rayyan QCRI (Rayyan Systems Inc®, MA, USA). After removing duplicates, two authors (VEFR and ATM) performed independently the screening of title and abstracts. These authors independently reviewed the remaining references in the full text. Discrepancies were resolved by a third researcher. References from retrieved papers were screened for additional articles. The articles found were analyzed using the terms of the PICO strategy and the inclusion and exclusion criteria. Relevant data from each article were extracted by two authors (VEFR and MJVG) independently and recorded in a spreadsheet of Microsoft Excel©: Name of authors, year and country of publication, number of patients, number of events, measure of association, with their 95% Confidence Intervals). Any conflict regarding the extracted information was resolved through consensus.

Quality assessment

Two sets of investigators (VEFR and ATM) independently evaluated the risk of bias in each eligible RCT. Any discrepancies were resolved by consensus or discussion with another investigator (MJVG). The Cochrane Collaboration tool for assessing the risk of bias in RCTs was used [28]. The following items were evaluated: Generation of the allocation sequence (selection bias); concealment of the allocation sequence (selection bias); blinding (detection and performance bias); blinding of participants and personnel to outcome assessment; incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other biases. For each RCT, each item was described as having either a low risk of bias, a high risk of bias, or an unclear risk of bias.

Outcome measures

Primary outcome variables were Progression-Free Survival (PFS) defined as the time from randomization to tumor progression or death. Secondary outcomes were Overall Survival (OS) defined as the time from randomization to death, considered as the best therapeutic endpoint in cancer clinical trials; Overall Response Ratio (ORR) defined as proportion of patients whose symptoms were relieved to a predetermined value within the minimum time limit; and Serious Adverse Event (SAE) defined adverse event grade 3 or more.

Statistical analyses

In the meta-analysis, we pooled Hazard Ratios (HR) with 95% Confidence Intervals (95% CI) using fixed effects models and followed the inverse variance method (Due to the large number of events in each arm, more than 10%). The Paule-Mandel estimator was used for the assessment of the between-study variance [29]. Outcomes data available in ≥ 3 studies were meta-analyzed. Time-event variables, including OS and PFS, were assessed according to the HR. Dichotomous variables, including ORR and incidence of adverse events, were assessed as Risk Ratios (RR) with 95% Confidence Interval (CI) estimates. For studies reporting OR, or RR stratified into different subgroups, we considered each subgroup analysis as a separate study. The quantitative synthesis was represented by forest plots. Heterogeneity among studies was assessed with Cochran's Q test and Higgins I^2 statistics. Heterogeneity was significant ($p<0.05$, I^2 statistics >40%), then we used a random effects model. Publication bias was assessed with funnel plots and formally tested with Egger's test.

Results

Study eligibility results

We collected a total of 1,343 in the primary search. After eliminating duplicates, 1,201 publications remained which were evaluated in titles and abstracts. Subsequently, 11 articles remained that were analyzed in full text, of which eight clinical trials were selected for qualitative and quantitative assessment. The PRISMA checklist is provided in Figure 1. We only included full-text papers that reported adjusted association measures HR and a control group. The lack of a proper control group was the main cause for the exclusion of most studies (Supplementary material).

Study characteristics

This study included 1,052 patients with an age average range of 57 to 69 years and more frequently in females. The included population was from China, Japan, Italy, South Korea, and the USA. Brain metastases were reported in 26% to 47.6% of patients (Table 1).

Meta-analysis of the effect of Bevacizumab plus Erlotinib on EGFR analysis of primary outcome (PFS)

Six trials were included in analyzing of the combination Bevacizumab and Erlotinib in *EGFRm* metastatic NSCLC. A low heterogeneity among the six studies was found (I^2=0%, p=0.65). The result of the Meta-analysis and forest plot analysis showed that the bevacizumab and erlotinib combination improves progression-free survival in *EGFRm* advanced NSCLC, (Log (HR)=0.63; 95% CI: 0.54-0.73, p<0.001) (Figure 2).

Analysis of secondary outcome (OS, ORR, and SAE) Overall Survival (OS)

Six trials reported the median and confidence interval of overall survival as shown in the figure, the forest plot showed no significant enhancement in overall survival [Log (HR) =0.93; 95% CI; 0.78-1.10, p=0.38]. There is no heterogeneity between the clinical trials (I^2=0%; p=0.51) (Figure 3).

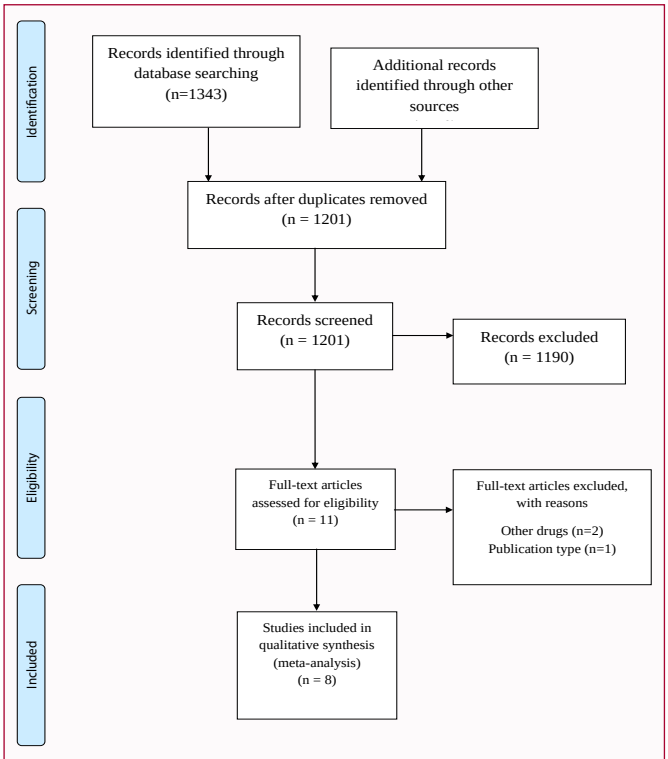

Figure 1: Flow diagram of selection of reviews for analysis.

Overall Respond Rate (ORR)

The Overall Response Rate (ORR) was reported in five trials, the meta-analysis shows that a significantly improvement in the overall response rate was found (RR=0.79, 95% Confidence Interval; 0.64-0.97, p=0.03). Insignificant heterogeneity was detected among the studies (I^2=0%, p =0.79) (Figure 4).

Adverse Events (AEs)

Serious Adverse Events (SAEs) were reported in six trials, the sub-group meta-analysis shows that SAEs are significant higher with the combination (OR=3.48, 95% Confidence Interval; 1.76-6.88, p<0.001), random effect. High significant heterogeneity was found among the studies (I^2=82%, p<0.0001) (Figure 5).

Analysis by subgroups

Subgroup analysis was performed to assess whether the SLP varied by mutation, ECOG and status. As shown in Supplementary Figure 1, the HR of mutational group was similar in *Exon 19 deletion* (HR=0.62; 95% CI: 0.50-0.77) and *Exon* 21 L858R (HR=0.60; 0.47-0.77). Similarly observed in the ECOG 0 (HR=0.61; 95% CI: 0.48-0.77) and ECOG 1 (HR=0.62; 0.50-0.76). The report of three clinical trials (namely, ARTEMIS, Lee, and NEJ026) revealed that the combination bevacizumab+erlotinib resulted in a positive outcome for patients both with and without brain metastases, displaying a Hazard Ratio (HR) of 0.58 (95% CI: 0.41-0.81) and 0.63 (95% CI: 0.49-0.81), respectively. This is certainly an intriguing finding, Supplementary Figure 3. Only the Beverly trial reported subgroup analysis of OS, so it was not possible to perform a subgroup meta-analysis for this outcome.

Grade ≥ 3 adverse events reported were diarrhea, hypertension, rash, and proteinuria. The risk of grade ≥ 3 diarrhea in the bevacizumab+erlotinib group was 53% higher than the risk of ≥ 3 diarrhea concerning erlotinib monotherapy (HR: 1.53; 95% CI: 0.82-2.86; p=0.18). The risk of skin rash grade ≥ 3 was higher in the experimental group (HR: 1.49; 95% CI: 1.13 to 1.97; I^2=0%). The risk of grade ≥ 3 hypertension in the erlotinib-bevacizumab group was found to be 5.1 times higher than that to the erlotinib group (HR=5.10; 95% CI: 2.66-9.77; I^2=56%). Finally, the combination also had a higher association of presenting grade ≥ 3 proteinuria than the erlotinib monotherapy group (HR=12.33; 95% CI: 4.49-33.88; I^2=0%). All forest plots can be found in Supplementary Figure 4.

Risk of bias

The eight randomized clinical trials were analyzed, and a methodological review of Cochrane's bias assessment was carried out, presenting the biases individually and as a group. Of the eight studies found, the BEVERLY trial showed a low risk of bias in all seven domains, followed by the Lee et al. and Stinchcombe et al. studies, which had a low risk of bias in the domains, except for the blinding of participants and personnel. The ARTEMIS trial presented biases in the blinding of participants and personnel, as well as biases in the outcome assessors (as no information is mentioned in the protocol). In addition, the NEJ026 and the JO25567 trials presented other biases (due to pharmaceutical funding) or had unclear randomized methods (Table 2).

In general, the highest risk of bias was in the blinding of participants and personnel (open trials), followed by blinding of data assessors. All studies handled missing data well (intention-to-treat),

Table 1: General characteristics of the studies included.

Study	Design, Country	Patients	Age (mean or median)	Male (n, %)	Brain metastasis (n, %)	mPFS (IC 95%)	mOS (IC 95%)	ORR	Adverse events ≥ 3	Follow-up survival	Sponsor	NCT
Artemis-Ctong 1509 (2021)	Phase III	Erlotinib+ Bevacizumab: 157	57	58 (37.7%)	47 (30.5%)	17.9 (15.2 to 19.9)	36.2 (32.5 to 42.4)	86.80%	54.80%	48 months	Guangdong Association of Clinical Trials	NCT02759614
	China	Erlotinib: 154	59	60 (38.2%)	44 (28.0%)	11.2 (9.7 to 13.8)	31.6 (27.2 to 40.0)	84.70%	26.10%			
NEJ026 Saito (2019)	Phase III Japan	Erlotinib+ Bevacizumab: 112	67	41 (37%)	36 (32%)	16.9 (14.2 to 21.0)	50.7 (37.3 to NE)	72%	88%	39.2 months	Chugai Pharmaceutical	UMIN000017069
Kawashima (2021)*		Erlotinib: 112	68	39(35%)	36 (32%)	13.3 (11.1 to 15.3)	46.2 (38.2 to NE)	66%	46%			
Stinchcombe et al. (2019)	Phase II	Erlotinib+ Bevacizumab: 43	65	12 (28%)	11 (26%)	17.9 (13.3 to 24.1)	32.4 (26.9 to 54.4)	81%	40%	33 months	Academic and Community Cancer Research United	NCT01532089
	USA	Erlotinib: 45	63	14 (31%)	14 (31%)	13.5 (8.8 to 21.6)	50.6 (49.4 to NE)	83%	27%			
Beverly (2022)	Phase III	Erlotinib+ Bevacizumab: 80	65.9	28 (35%)	NA	14.7 (12.0 to 18.3)	33.3 (24.3 to 45.1)	NA	NA	36.3 months	National Cancer Institute, Naples	NCT02633189
	Italy	Erlotinib: 80	67.7	30 (37.5%)	NA	9.6 (7.1 to 10.6)	22.8 (18.3 to 33.0)	NA	NA			
JO25567 Seto (2014)	Phase II Japan	Erlotinib+ Bevacizumab: 75	67	30 (40%)	NA	16.0 (13.9 to 18.1)	47	69%	91%	60 months	Chugai Pharmaceutical Co Ltd	JapicCTI-111390 (Japan)
Yamamoto (2021)*		Erlotinib: 77	69	26 (34%)	NA	9.7 (5.7 to 11.1)	47.4	64%	53%			
Lee et al. (2023)	Phase II South Korea	Erlotinib+ Bevacizumab: 64	NA	20 (31.2%)	29 (45.3%)	17.5 (12.5 to 22.5)	NA	85.90%	56.60%	38.9 months	National Cancer Center Research Grant	NCT03126799
		Erlotinib: 63	NA	23 (36.5%)	30 (47.6%)	12.4 (9.1 to 15.7)	NA	83.90%	20.60%			

*Used to evaluate overall survival. mPFS: median Progression-Free Survival; mOS: median Overall Survival; ORR: Objective Response Rate; NCT: Number Clinical Trial

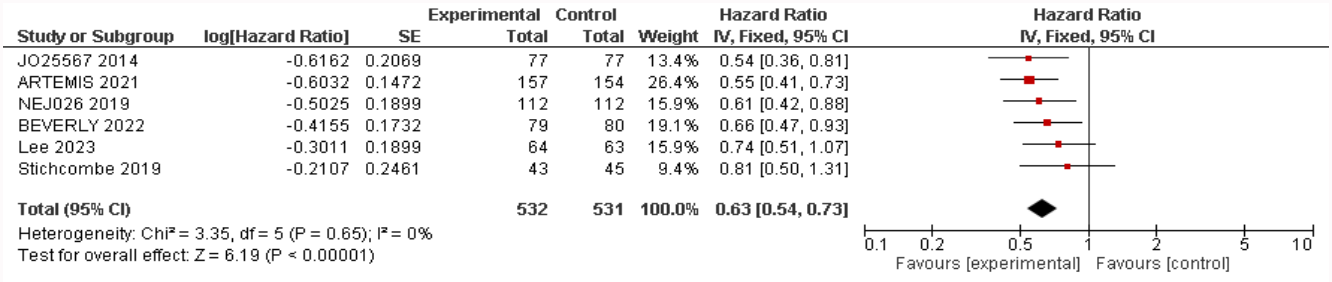

Figure 2: A forest plot of the effect of Bevacizumab Plus Erlotinib in PFS.

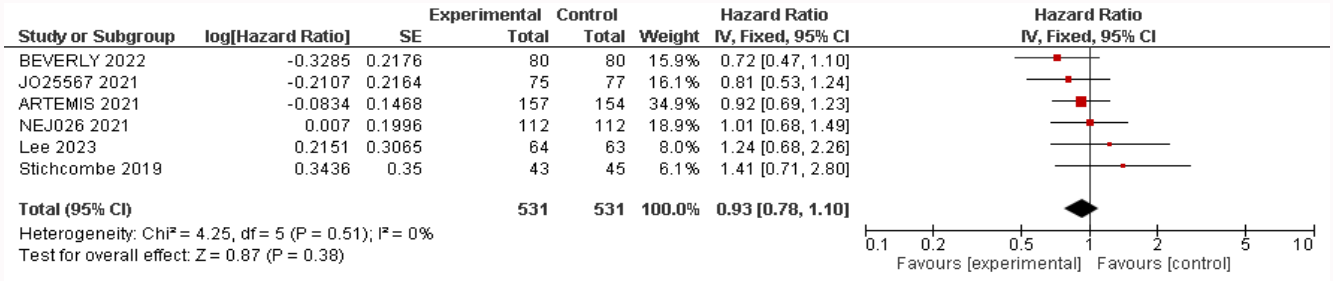

Figure 3: A forest plot of the effect of Bevacizumab plus Erlotinib in overall survival.

as can be seen in Table 3. Despite the limitations presented, we are confident that the results obtained in each clinical trial are useful in terms of efficacy and safety.

Analysis of publication bias

The funnel plots of the studies included in the primary and secondary outcome was shown in Figure 6, a symmetric funnel plot was observed with no evidence of publication bias among the studies. There was no evidence of apparent publication bias based on the assessment using a funnel plot and Egger's test (p>0.05).

Discussion

This study provides new insights that could help resolve the controversies surrounding the combined use of erlotinib and bevacizumab in the treatment of EGFR-mutated NSCLC.

The *EGFR* gene encodes the protein located on the cell surface whose activation stimulates the molecular pathways that allow the growth and development of the tumor microenvironment [3,5]. As previously described, Osimertinib is the preferred TKI for first-line of treatment of *EGFRm* metastatic NSCLC [11,12]. Several trials

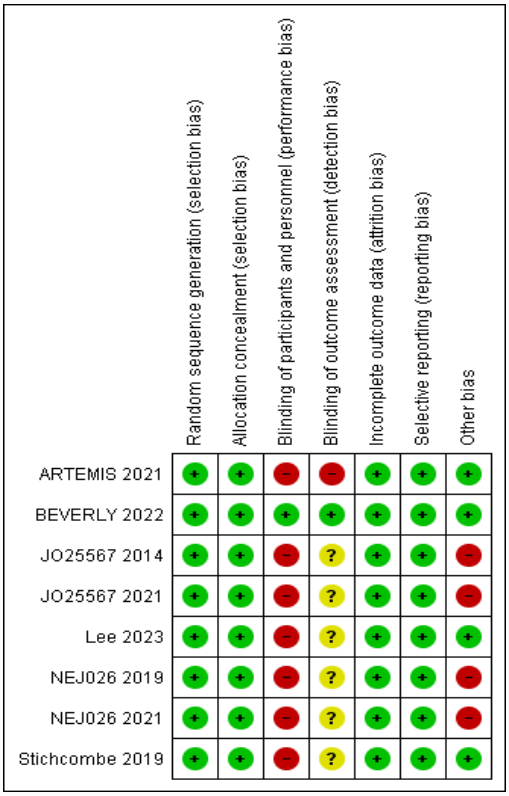

Table 2: Risk of individual bias of clinical trials that involve bevacizumab-erlotinib in first-line of *EGFRm* advanced NSCLC.

evaluated different combinations that could be safe and effective in this population, and the combination of angiogenesis inhibitors and TKI obtained discordant results [21-24]. Currently, Osimertinib is the agent of choice for first-line treatment, due to its greater penetrance in the CNS. However, the economic cost of Osimertinib limits its access to clinical practice. Economic analysis reported that Osimertinib in first-line of treatment is not cost-effective in high-income countries [30-32]. Subsequent studies have evaluated possible combinations that could be options of therapy [3].

Our results report a statistically significant benefit in terms of Progression-Free Survival (PFS) (HR=0.63; 95% CI, 0.54-0.73). This result is consistent with those obtained in clinical trials and is like those obtained by other recently published meta-analyses [33-36]. The studies JO25567, ARTEMIS, NEJ026 and Stinchcombe et al. obtained positive results in progression-free survival when evaluating the addition of an angiogenic inhibitor (Bevacizumab) to the TKI (erlotinib) compared to a TKI given as a monodrug in first-line treatment for advanced NSCLC with *EGFRm* [9]. In 2014, one of the first clinical trials that was phase II (JO25567) showed that the addition of bevacizumab to erlotinib in patients with NSCLC improved PFS from 9.7 to 16.0 months in Japanese patients, with a HR of 0.54 (0.36 to 0.81). Another phase II clinical study (Stinchcombe 2019) was the only study that did not report a statistical benefit of bevacizumab on PFS (HR: 0.81; 95% CI: 0.50-1.31), however, this study found a clinical benefit in mPFS of 17.9 *vs.* 13.5 months, for the group of bevacizumab with erlotinib *vs.* erlotinib alone respectively; similar to the phase II study by Lee et al. [37], which found no statistical benefit but observed a higher median PFS months (17.5 *vs.* 12.4 months).

Another statistically significant result was ORR which was higher with the bevacizumab-erlotinib combination (RR=0.79, 95% CI; 0.64-0.97, p=0.03). However, higher ORR has not been replicated in all meta-analysis, probably because heterogeneity [33-39]. Our analysis only included clinical trials where the combination bevacizumab and erlotinib was used to maintain a homogeneous population (I^2=0%, p=0.66).

Finally, no statistically significant benefit in Overall Survival (OS) was demonstrated (HR=0.93; 95% CI; 0.78-1.10). It should be noted that bevacizumab-erlotinib combination did not improve OS in clinical trials [21-24]. The consistent lack of benefit in OS could be explained by the subsequent line of treatment. Patients with

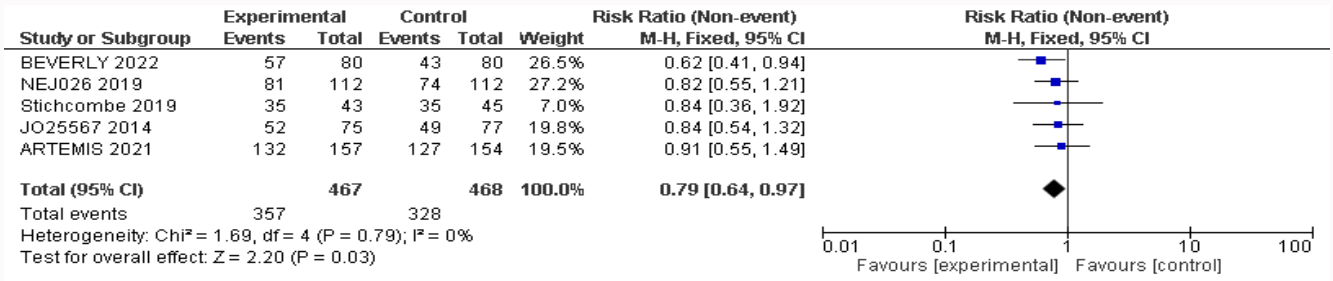

Figure 4: Forest plot of the secondary outcome; Overall Respond Rate (ORR).

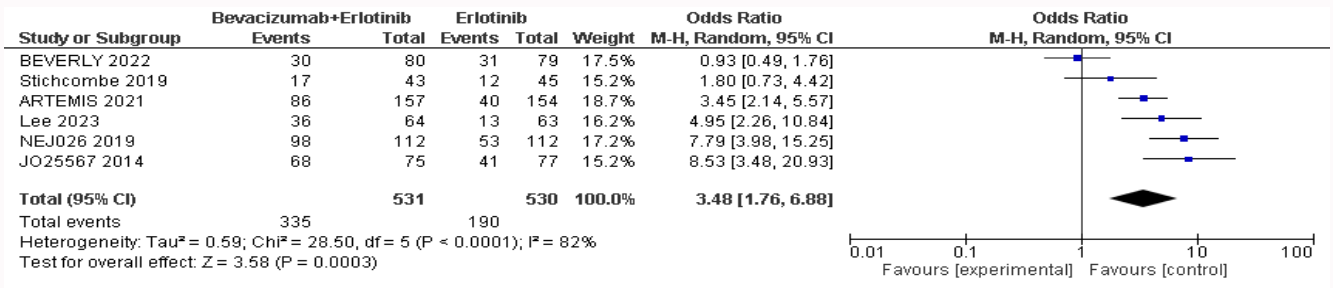

Figure 5: Forest plot of the secondary outcome; Serious Adverse Event (SAE).

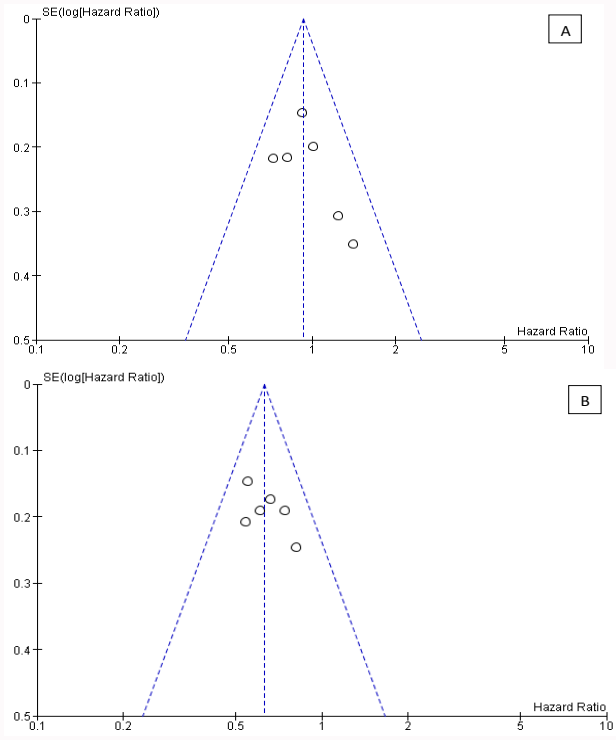

Figure 6: Funnel plot of clinical studies on erlotinib and bevacizumab. A: Funnel plot of overall survival. B: Funnel plot of progression free survival.

progression of disease received Osimertinib as second line when T790M mutation was detected in blood or tumoral tissue. Patients were treated with Osimertinib after progression of disease 29.2%, 57.1%, and 43% of patients in the erlotinib group and 17.2%, 49%, and 45% of patients in the bevacizumab-erlotinib group in the ARTEMIS, BEVERLY, and NEJ026 trials, respectively [21,40,41]. Based on the above, we believe that there could be a methodological limitation that affects the accuracy of the OS results; this could affect the accuracy of OS results due to the difference in the intensity of subsequent therapy between the two groups.

SAEs were more common with bevacizumab-erlotinib combination. However, despite of higher toxicity, clinical trials conclude that bevacizumab-erlotinib is safe, with manageable toxicity [21-23]. Other meta-analysis indicates that the angiogenesis inhibitors and TKI combination is safe in NSCLC patients [36,42]. Using the combination in first-line of therapy may lead to the sequency of treatment with Osimertinib in second-line. Clinical trials report a similar prevalence of T790M mutation after first-generation TKIs and the combination progression of disease. In addition, economic analysis report that Osimertinib is cost-effective in second-line [43,44].

In subgroups analysis, results indicate that the bevacizumab-erlotinib combination is associated with longer PFS in *exon19 deletion* or *exon21 L858R mutations*, suggesting that this combination may be similarly effective in both molecular subtypes. This result is consistent with that obtained in a recently published meta-analysis, suggesting that *L858R mutations* may be as much benefited as *exon19 deletion* [36]. Further investigation is needed to conclude if this combination of treatment is the best option in *L858R mutations*.

The presence of brain metastasis is a recognized adverse prognostic factor and a frequent site of disease progression in EGFR-mutated NSCLC. Previous research has shown that the anti-VEGF medication bevacizumab is a successful treatment for brain metastases and can also significantly decrease their incidence [45]. We present results from three clinical trials that evaluated PFS according to brain metastasis, finding that the combination significantly prolonged PFS in this subgroup of patients.

Grade ≥ 3 AEs were more commonly reported with bevacizumab-erlotinib combination (diarrhea, rash, hypertension, and proteinuria). Grade ≥ 3 toxicity described is mainly secondary to bevacizumab. The toxicity of the combination therapy should be considered according to the patient's comorbidities when making treatment choices. Patients with not controlled chronic hypertension or chronic kidney disease may not be candidates for the bevacizumab-erlotinib combination. In addition, the implementation of a strict monitoring program of blood pressure measurement and urinalysis in patients receiving bevacizumab must be done when treating these patients.

Recently conducted clinical trials on Osimertinib and bevacizumab have failed to demonstrate any improvement in either PFS or OS as compared to Osimertinib alone among patients suffering from NSCLC with an *EGFR mutation*, regardless of whether they are undergoing first-line [46] or second-line treatment [47]. Despite the existence of only phase II studies, the potential for combination therapy appears to be unpromising.

The enhanced PFS value observed when utilizing erlotinib-plus-bevacizumab may be attributed to modifications in tumor vessel physiology caused by bevacizumab, ultimately leading to greater intratumoral drug uptake and improved drug delivery [48].

The present meta-analysis has limitations that should be

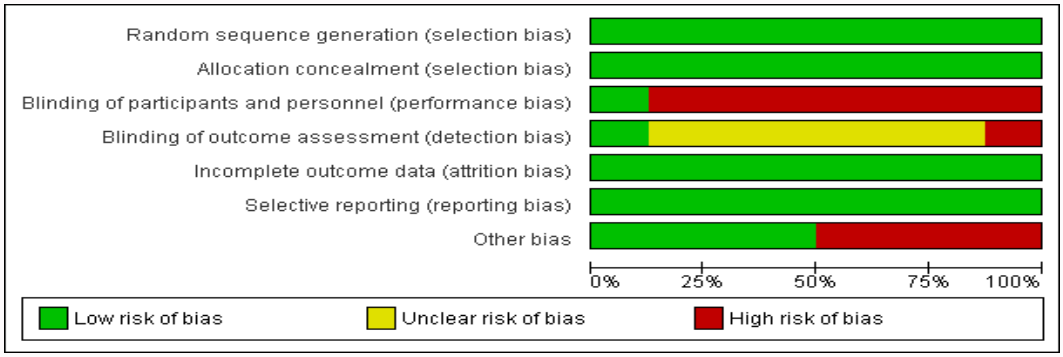

Table 3: Bias assessment of the included primary studies.

considered. Firstly, the quantitative synthesis comprised 6 studies, some with little sample sizes, phases of clinical trials, and follow-up periods as previously stated. This heterogeneity may affect the results. Secondly, the meta-analysis was conducted at the trial level rather than the individual patient level. A sensitivity analysis was infeasible due to a limited number of eligible studies, many of which were open-label. Therefore, potential prognostic factors, patient comorbidities, extent of disease, and other genetic mutations were not examined in our study, potentially constraining our analyses. Despite the study's limitations, the rigorous process of selecting studies enabled a comprehensive evaluation of the available evidence related to the topic of interest. We adhered to the PRISMA, Cochrane, and PROSPERO guidelines.

In conclusion, the study shows that the bevacizumab-erlotinib combination significantly improves PFS and ORR in *EGFRm* metastatic NSCLC. Bevacizumab-erlotinib is also associated with higher grade ≥ 3 adverse events. Although toxicity is manageable, patient's comorbidities must be strongly considerate when treatment with bevacizumab-erlotinib combination. In addition, the combination may be an option in first-line in countries without access to Osimertinib. Prospective trials are needed to validate the benefit in *L585R mutations*.

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