Efficacy and toxicity of combined inhibition of EGFR and VEGF in patients with advanced non-small-cell lung cancer harboring activating EGFR mutations: A systematic review and meta-analysis

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Abstract

Objectives: Dual inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways have demonstrated promising results for treatment of advanced non-small cell lung cancer (NSCLC). We conducted a systematic review and meta-analysis to assess the efficacy and toxicity of the combined treatment with EGFR tyrosine kinase inhibitors (TKIs) and VEGF blockade for patients with advanced NSCLC harboring activating EGFR mutations, in comparison to EGFR TKIs alone.

Methods: The electronic databases PubMed (Medline), Cochrane Library and EMBASE, were searched for relevant randomized trials between 2000 and 2020. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), and grade ≥ 3 adverse events (AEs). Pooled hazard ratios (HR) for OS and PFS, and odds ratios (OR) for ORR, DCR and toxicity were meta-analyzed using the generic inverse variance and the Mantel-Haenszel methods. Subgroup analyses compared PFS by gender, age, smoking status, EGFR mutation, intra-cranial disease and Eastern Cooperative Oncology Group (ECOG) status.

Results: A total of 1,246 patients from 6 trials were evaluated for analyses. The combination treatment decreased the risk of disease progression by 38% (HR=0.62; 95%CI=0.53-0.72) but had no added benefit on OS compared to EGFR inhibition alone (HR=0.93; 95%CI=0.74-1.17). There was no significant difference in ORR or DCR between treatments. There was a significantly increased number of AEs reported in the dual treatment arm (OR=4.41; 95%CI=2.33-8.37), with proteinuria and hypertension being the most significantly increased AEs. The PFS benefit was consistent across all subgroups.

Conclusions: This meta-analysis suggests combined inhibition of EGFR and VEGF pathways significantly improves PFS, with no interim OS benefit, and increases AEs. Mature OS data are needed along with results from trials exploring this strategy with 3rd generation EGFR-TKIs to strengthen these results.

Key Findings

This meta-analysis of EGFR TKI ± VEGF inhibitor in NSCLC with confirmed EGFR mutations showed that combination therapy significantly improves PFS (HR 0.62), but not OS (HR 0.93), and there was no significant difference in ORR or DCR. There were significantly more AEs reported in combination treatment. Data from trials with 3rd gen. EGFR-TKIs are needed to strengthen these results

1.0 Introduction

Approximately 15–40% of patients with advanced non-small-cell lung cancer (NSCLC) harbor epidermal growth factor receptor (EGFR) activating mutations[1]. EGFR tyrosine kinase inhibitors (TKIs) have become first line treatment for patients with these mutations [2, 3]. PFS benefit and duration of response, however, is limited by the development of acquired resistance to EGFR TKIs. The T790M mutation has been identified as an acquired mutation that is responsible for resistance for many of these patients[2]. Osimertinib was approved for use in patients that had acquired this mutation after progressing on an earlier generation TKI. However, there are other mechanisms for tumors to develop resistance to TKIs, and even Osimertinib is limited by the development of acquired resistance. Extending survival further may depend on overcoming alternative pathways of resistance to TKIs.

Vascular endothelial growth factor (VEGF) shares a common downstream pathway with EGFR, and it is postulated that one of the mechanisms of resistance to EGFR blockage is attenuation of this alternate VEGF pathway (Fig. 1)[4]. Prior research has reported that EGFR blockade leads to decreased VEGF activation, and when resistance to EGFR blockade develops, VEGF activation is actually increased. This led to pre-clinical trials utilizing combined inhibition of EGFR and VEGF as a mechanism to overcome resistance, resulting in improved anti-tumor activity[4, 5].

Since then, several clinical studies have investigated the combination of early generation EGFR TKI and VEGF pathway inhibitor therapies in the hopes that it may delay resistance and ultimately extend PFS and overall survival (OS), but results have been mixed. Some studies report an improvement in PFS while others do not[6–13]. Limitations also include relatively small sample sizes and power to detect a significant result. There have been meta-analyses previously conducted on the combination, however the control arms have varied as has the EGFR mutation status[14, 15], resulting in a non-homogenous comparison. Our goal in this systematic review and meta-analysis, therefore, is to examine if there is a significantly improved PFS and OS with combined inhibition of EGFR and VEGF in patients with advanced NSCLC harboring EGFR activating mutations, compared to the standard of care treatment with EGFR TKI alone for a more homogenous comparison. Secondary outcomes are to explore objective response rate (ORR), disease control rate (DCR), and toxicity. Our hypotheses are

that the combination of EGFR and VEGF blockade will improve PFS, and OS compared to single agent early generation TKI alone, with an improved ORR and DCR rate, but at the expense of higher rates of toxicity, as is often seen when multi-agent treatment regimens are utilized.

2.0 Material And Methods

We conducted this review using methods of the Cochrane Database of Systematic Reviews and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16, 17].

2.1 Data sources and search strategy

A systematic review was conducted using medical subject headings (MeSH) terms and text words related to TKI and VEGF inhibitor in lung cancer by searching for relevant publications across PubMed (Medline), Cochrane Library (Centre Register of Controlled Trials), and EMBASE databases, as well as past ASCO and ESMO meeting abstracts, published or presented between January 2009 and December 2020. The detailed search strategy is presented in Appendix 1. The search terms are listed in the appendix. One Clinical Librarian conducted the systematic review and two reviewers independently screened the titles and abstracts of all citations obtained through the literature search. A third independent reviewer adjudicated any disputes between reviewers. The same two reviewers independently screened the full-texts of potentially relevant articles. In the case of duplicate publications, the most recent version of the publication was included, with older publications referred to, only if the primary or secondary outcomes were not reported in the most recent paper.

2.2 Inclusion/Exclusion Criteria

Included trials were phase 2 or 3 randomized controlled trials in advanced (stages IIIB-IV) NSCLC adenocarcinoma in the first line setting where the control arm was an EGFR TKI ± placebo, and the experimental arm was an EGFR TKI plus a VEGF inhibitor.

Trials were excluded if there was no control arm, if the control arm was anything other than an EGFR TKI (such as a VEGF inhibitor or chemotherapy), or if patients did not have pathologically confirmed activating EGFR mutations on exon 19 or 21.

2.3 Primary and Secondary Outcomes

Primary outcomes were PFS, as defined as time from randomization until disease progression or death; and OS as defined by time from randomization until death from any cause. In the event there were both investigator-reported outcomes and independent review committee-reported outcomes, the independent review committee outcomes were chosen to be included in the final analysis. Secondary outcomes were ORR, DCR, and grade 3–4 adverse events (AEs).

Tumor response rates included (a) objective response rates (ORR) defined as the proportion of patients achieving a complete or partial response as best response during treatment time and (b) disease control rate (DCR) defined as the proportion of patients with a complete response, a partial response, or stable disease as best response during treatment time according to the modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1)[18]. Toxicities were defined as any grade 3 and higher toxicity reported. Toxicities experienced by patients during treatment were reported as rates and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3 or 4[19, 20].

To address potential heterogeneity, a pre-specified subgroup analysis was carried out to assess the efficacy (PFS) based upon patient age (over 75 vs. less than or equal to 75), gender (male vs. female), smoking status (smoker vs. non-smoker), ECOG performance status (0 vs. 1), EGFR mutation subtype (exon 19 vs. exon 21), and presence of intracranial disease (present vs. absent).

2.4 Data Extraction

Data from included publications was extracted in accordance with Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) by one investigator while a second investigator reviewed the data for discrepancies. Extracted data included first author, date of publication, therapeutic regimen, and study population size and demography. Clinical data extracted included Hazard Ratios (HRs) of PFS and OS, as well as their 95% confidence intervals. Extracted data also included primary outcomes stratified by patient age over 75, gender, smoking history, ECOG, EGFR mutation subtype, and presence of intracranial disease. We extracted the proportion of patients who demonstrated a response in order to calculate Odds Ratios (ORs) for ORR and DCR. For AEs, we extracted the proportion of patients who experienced a given AE in order to calculate the ORs for that AE.

2.5 Quality Analysis

A risk of bias table was generated for included trials using the Cochrane Risk of Bias domains of random sequence generation, allocation concealment, blinding of participants/physicians, blinding outcome assessment, incomplete outcome data, and selective reporting. Each

domain was rated as high risk or low risk based upon information available within the publication or its clinical trial registry. Domains were rated as unknown risk if insufficient information was available to otherwise rank[21].

2.6 Quality of Evidence

The level of evidence for the pre-specified outcomes of interest was assessed and reported as low, moderate or high based on the GRADE approach developed by the Grading of Recommendations, Assessment, Development, and Evaluations working group[22, 23].

2.7 Statistical Analysis

Results involving time to event (PFS, OS) were expressed as HRs with 95% CIs. For dichotomous outcomes (response rates, toxicity), the number of events was used to calculate Odds Ratios (ORs) estimates of effect. Estimates for HRs and ORs were pooled using the Mantel-Haenszel and Peto method and were weighted using generic inverse variance[24, 25]. To account for between-study heterogeneity, random-effect models were used to compute pooled estimates with two-sided 95%CIs. The I^2 statistic (0–100%) was used to assess the proportion of variability in the results that was attributable to heterogeneity between the trials. Moderate-high heterogeneity was defined as an I^2 statistic > 50%. Potential clinical heterogeneity between trials was addressed, by conducting predefined subgroup analyses using methods described by Deeks et al.[26]. A two-sided P value of < 0.05 was considered significant. The meta-analysis was conducted using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark)[16].

3.0 Results

3.1 Trials Identified

Our search identified a total of 4933 publications. Of these, we identified six trials that met criteria for inclusion into the meta-analysis (Fig. 2).

These six trials represent 1246 patients with individual trial size varying from 16 to 449 patients (Table 1). All trials were randomized with a control arm consisting of an EGFR TKI (erlotinib or gefitinib with or without placebo) and an experimental arm consisting of that same EGFR TKI plus a VEGF pathway inhibitor (bevacizumab or ramucirumab). Five of six trials used erlotinib as their EGFR TKI, and five of six trials used bevacizumab as VEGF inhibitor. Table 1 summarizes the characteristics of the included trials.

Table 1
Summary table of included trials

Study	Primary Endpoint	Primary Outcome Met? Y/N	Year	Phase	Treatment Comparison	Number of Patients (N)	mPFS exp. Vs. control (months)	PFS HR (95% CI)	mOS exp. Vs. control (months)	mOS HR (95% CI)
ARTEMIS[6]	PFS	Y	2019	III	B + E vs E	311	18.0 vs. 11.3	0.55 (0.41–0.75)	NR	NR
BAGEL[13]	PFS	N	2019	II	B + G vs G	16	5.4 vs. 15.1	NR	NR	NR
JO255567[7, 8]	PFS	Y	2014	II	B + E vs E	154	16.4 vs. 9.8	0.52 (0.35–0.76)	47.0 vs. 47.4	0.81 (0.53–1.23)
NCT01532089[9]	PFS	N	2019	II	B + E vs E	88	17.9 vs. 13.5	0.81 (0.50–1.31)	32.4 vs. 52.6	1.41 (0.71–2.81)
NEJ026[10, 11]	PFS	Y	2019	III	B + E vs E	228	16.9 vs. 13.3	0.60 (0.42–0.88)	50.7 vs. 46.2	1.01 (0.68–1.49)
RELAY[12]	PFS	Y	2019	III	R + E vs E + P	449	16.5 vs. 11.1	0.67(0.52–0.87)	NR	0.83 (0.53–1.30)

Abbreviations: B = Bevacizumab 15 mg/kg q3 weeks; E = Erlotinib 150 mg/day; G = Gefitinib 250 mg/day; NR = Not Reported; P = Placebo; R = Ramucirumab 10 mg/kg q2 weeks;

3.2 Assessment of Trial Quality

Trials were evaluated for bias using the Cochrane Risk of Bias Domains (Supplemental Table 1). Most trials were non-blinded with the exception of RELAY, which was a blinded placebo-controlled trial. RELAY was also the only trial with incomplete reporting of outcomes as data regarding mature overall survival remains outstanding. Two trials (NEJ026, ARTEMIS) had high risk of selective reporting due to failure to report OS. The BAGEL trial was closed early due to poor recruitment and had limited data, but it did report PFS and adverse events of participants. Several trials did not disclose sufficient information to adequately assess quality of allocation concealment or blinding of outcome assessment.

3.3 Primary outcome: Overall Survival and Progression Free Survival

Of included studies, five reported PFS, four of which demonstrated statistically significant improvement in PFS with combination therapy compared to EGFR TKI alone. The median PFS ranged from 7.1 to 15.1 months in single agent control arms to 5.4 to 18.0 months in combination therapy patients. Four studies reported OS hazard ratios, none of which were individually statistically significant. The median OS ranged from 46.2 to 52.6 months in monotherapy patients to 32.4 to 50.7 months in combination therapy patients.

Pooled results demonstrated that combination of EGFR TKI plus VEGF inhibitor led to a reduction in the risk of disease progression by 38% compared with EGFR TKI alone (HR 0.62 [0.53–0.72], $p < 0.00001$; Fig. 3A). Pooled results showed that the combination of EGFR TKI plus VEGF inhibitor did not improve OS compared with EGFR TKI alone (HR 0.93 [0.74–1.17]; Fig. 3B).

In our pre-specified subgroup analysis, subgroups demonstrated improved PFS with combination therapy compared with EGFR TKI alone irrespective of age, gender, smoking status, ECOG, or specific EGFR mutation (Table 2; Supplemental Fig. 1A-E). By contrast, patients with intracranial disease did not demonstrate improved PFS with combination therapy (HR 0.86 [0.42–1.76]), while patients without intracranial disease did benefit from combination therapy (HR 0.58 [0.44–0.77]). However, in our testing for subgroup differences this trend did not reach the level of statistical significance ($p = 0.32$) (Table 2; Supplemental Fig. 1F).

Table 2
Pre-specified subgroup analysis of progression free survival

Variable	Subgroup	Hazard Ratio (5% CI)	P-value for test for subgroup differences
Age	Between Subgroups	0.57 (0.47–0.70]	0.31
	> 75 years	0.59 (0.48–0.72)]	
	< 75 years	0.38 (0.17–0.86)	
Gender	Between Subgroups	0.58 (0.49–0.70)	0.51
	Male	0.54 (0.37 – 0.80)	
	Female	0.63 (0.52–0.76)	
Smoking status	Between Subgroups	0.66 (0.55–0.80)	0.74
	Smokers	0.70 (0.49–0.99)	
	Never smokers	0.65 (0.51–0.82)	
ECOG	Between Subgroups	0.63 (0.54–0.73)	0.16
	0	0.53 (0.40–0.72)	
	1	0.68 (0.57–0.82)	
EGFR mutation	Between Subgroups	0.61 (0.53–0.71)	0.65
	Exon 19	0.63 (0.52–0.77)	
	Exon 21	0.59 (0.47–0.73)	
Intracranial Disease	Between Subgroups	0.71 (0.49–1.04)	0.32
	Present	0.86 (0.42–1.76)	
	Absent	0.58 (0.44–0.77)	

According to GRADE criteria, the evidence for the PFS an OS outcome was rated as moderate (Table 4).

3.4 Overall Response Rate and Disease Control Rate

All studies reported ORR. Between studies, ORR ranged from 52–93% in monotherapy, and 58–92% in combination therapy. Pooled ORR was not significantly different between monotherapy and combination therapy groups (OR 0.86 [0.65–1.12]; Supplemental Fig. 2; Supplemental Table 2).

Five studies reported DCR. Across all studies, DCR ranged 91.0–99.0% in monotherapy, and 88.7–98.0% in combination treatment. DCR was not significantly different between groups (OR 0.71 [0.24–2.09]; Supplemental Fig. 3; Supplemental Table 2).

According to GRADE criteria, the evidence for the ORR and DCR outcome was rated as moderate (Supplemental Table 3).

3.5 Adverse Events

All studies reported on significant adverse events, but categories of adverse events varied across trials. Four of the trials reported findings for any grade 3 or 4 toxicity (Table 3; Supplemental Fig. 4A). There were significantly more grade 3–4 adverse events associated with combination treatment compared with EGFR TKI alone OR 4.41 (95% CI 2.33–8.37) (Table 3; Supplemental Fig. 4A) with a number needed to harm of 4.

Table 3
OR and 95% confidence intervals of grade ≥ 3 adverse events

Outcome	OR (95% CI)
Any G3-4 AE	**4.41 (2.33–8.37)**
Hypertension	**6.89 (3.78– 12.56)**
Proteinuria	**13.48 (4.11 – 44.20)**
Dermatitis	1.40 (1.00–1.96)
Diarrhea	2.42 (0.86–6.78)
Stomatitis	1.03 (0.32–3.30)
Bleeding	1.29 (0.40–4.19)
Elevated ALT	0.86 (0.55–1.35)

The most common adverse events associated with combined EGFR TKI and VEGF inhibitor treatment were proteinuria with an OR 13.48 (95% CI 4.11–44.20; Table 3; Supplemental Fig. 4B), and hypertension with an OR 6.89 (95% CI 3.78–12.56; Table 3; Supplemental Fig. 4C). There was no significant difference in the incidence of diarrhea, dermatitis, stomatitis, bleeding, or elevated ALTs (Table 3; Supplemental Fig. 4D-H). Dermatitis verged on the border of significance OR 1.40 (95% CI 1.00–1.96). Too few studies reported incidence of thromboembolism, or interstitial lung disease for inclusion in our meta-analysis.

4.0 Discussion

This meta-analysis was conducted to assess the efficacy in terms of PFS and OS for the combination of EGFR-TKIs and VEGF inhibitors in advanced NSCLC harboring activating EGFR mutations compared to the standard of care treatment with EGFR-TKIs alone. The results of this study demonstrated that combined inhibition of EGFR and VEGF pathways in patients with an EGFR activating mutation in advanced NSCLC significantly prolongs PFS, and was evident across all subgroups. Notably, the BAGEL trial[13] had opposing PFS results compared to the other trials analyzed. The population size for this trial was quite small, and no hazard ratio was reported in the paper which is why it was not included in the forest plot analysis. The reported PFS HR of 0.62 in this meta-analysis can be clinically meaningful; however, the clinical meaningfulness was defined by the American Society of Clinical Oncology[27] for patients with advanced NSCLC as an improvement of at least 4 months in PFS and a hazard ratio for OS of < 0.80 with minimal additional toxicity. In most trials, the 4 months improvement in PFS was met but the OS outcome is not clinically meaningful yet as it did not reach statistical significance.

No difference in OS was observed between the combination treatment and EGFR-TKI alone. Unfortunately, some trials had not reported OS data, or it was not yet mature. In the RELAY trial for example, mOS was not met in either group, but the hazard ratio for interim analysis was still reported and included in our analysis. The lack of mature OS data, as well as treatment with subsequent lines of therapy including patients in the control arms crossing over to receive anti-VEGF treatment, could in part explain why there was no significant difference in mOS between groups. If there truly is no difference in OS between groups, it would raise the question as to whether sequential treatment with single agents may be just as effective as combination treatment, but with reduced toxicity.

Disappointingly, there did not seem to be an improvement in ORR or DCR. One would have hoped that by targeting two separate mechanisms of tumor growth, the number of responders would increase, however, this was not observed. As these trials were examining patients in the first line setting prior to development of resistance, it is possible blockade of dual pathways which share the same downstream effects would not increase response rate. Acquired resistance has not yet developed in patients starting first-line treatment, so the addition of VEGF inhibitors would not have a role in overcoming resistance and increasing response rate for that reason. In the pre-clinical trials, the VEGF pathway is suppressed with EGFR blockade initially, until resistance develops, and the pathway attenuates[4].

Conversely, a large proportion of acquired resistance is due to T790M mutations. It's possible that VEGF attenuation only accounts for a small portion of acquired resistance, with other mechanisms of resistance predominating. Osimertinib was initially utilized in the second line setting as its mechanism is not affected by T790M mutations, and thus could overcome acquired resistance from the development of such a mutation. It is now also approved for use in the first line setting as it was shown to have superior survival outcomes as compared to earlier generation TKIs and had a superior ORR and DCR compared to earlier TKIs[2]. While some of this improvement in response rates could be accounted for by patients with primary resistance due to de-novo T790M mutations, the proportion of patients with de novo mutations was small suggesting Osimertinib may be inherently better than other TKIs for reasons other than overcoming T790M. An early phase I/II open-

label single arm trial examined Osimertinib and bevacizumab for treatment of EGFR mutant advanced NSCLC has found the combination to be safe and tolerable, with an ORR of about 80% and median PFS of 19 months, but the results were not compared to monotherapy Osimertinib in a randomized fashion and cross trial comparisons are difficult[28]. A more recent trial conducted examined the combination of Osimertinib and bevacizumab compared to Osimertinib alone in patients with T790M mutations who had progressed on earlier generation TKIs and found that the addition of bevacizumab did not improve progression-free survival in this setting[29]. Interestingly, response rates improved, but progression free survival was shorter in the combination treatment arm[29]. This could potentially be accounted for by prior exposure to TKIs leading to cross-resistance to anti-VEGF treatments, and the authors noted that they allowed for enrollment of participants that had previously received anti-VEGF treatments[29]. Results in first line setting comparing combination Osimertinib and anti-VEGF treatment to standard first-line Osimertinib are awaited.

In our toxicity analyses, the combination treatment was reasonably well tolerated, although more toxic than EGFR TKI alone, with hypertension, diarrhea and proteinuria being the most frequent cause of grade 3–4 toxicity. Without including information on quality of life, it is unclear whether the improvement in PFS also translated to a meaningfully improved quality of life for patients, or whether the toxicity experienced outweighed the potential benefit of disease stability. One of the trials recently reported quality of life data, however, showing that time to treatment failure was similar between the experimental and control arms, and that the only patient reported symptom that differed was increased hemoptysis in the experimental arm, likely due to the addition of the antiangiogenic agent[30]. The potential benefit in PFS without an OS benefit, and increased toxicity, would also have to be weighed against the expense of adding a VEGF inhibitor when appropriate parties are deciding whether to fund this combined regimen.

A limitation to this analysis is that there were no trials comparing combination VEGF and EGFR inhibition with osimertinib as the control arm, which is the new standard of care based on the FLAURA trial[2]. Since this trial only was published in 2018, there were not any phase III trials with this combination either with osimertinib in the treatment combination arm or as a control arm comparator. There are currently early phase clinical trials and randomized trials underway examining this[28].

Another limitation is that there were some trials in this analysis which included patients with brain metastases and other trials which did not, which could result in heterogeneity in the overall survival analysis. Furthermore, the older generation TKIs do not have substantial blood brain barrier penetration compared to osimertinib, and in theory, including osimertinib in this combination could have improved results.

The subgroup analyses were of course limited by the small number of studies that were included. This was further compounded by varying definitions of variables which did not allow for direct comparison. For example, some studies defined smoking status as non-smokers or smokers, while others include never smoker and past smokers as variables. Moreover, the use of summary data rather than patient-level data weakens the possibility of discovering meaningful associations and reaching stronger conclusions.

A strength of our meta-analysis is that it adds to the literature compared with previous meta-analyses examining this combination in that we have limited our studies to only those with populations whose tumors were screened for EGFR activation mutations, since we know that EGFR TKIs have improved efficacy in those tumors, and we excluded studies whose control arm included VEGF inhibitors or chemotherapy, thereby improving the homogeneity of included trials. Prior meta-analyses included trials that had participants both with and without mutations. Since we know that EGFR TKIs have improved efficacy in those tumors with confirmed activating mutations, trials with mixed populations potentially diluted the efficacy of EGFR TKIs.

In summary, the level of recommendation to support offering a combination treatment with EGFR TKI and VEGF inhibitor is moderate. More research is needed to examine this combination with newer generation EGFR TKIs such as Osimertinib, which has prolonged PFS and improved central nervous system (CNS) penetration, and to also include osimertinib as the new standard of care for the control arm in the first line setting. Furthermore, improved efficacy in PFS alone may not warrant a change in clinical practice without an accompanying overall survival benefit, as sequential treatment could potentially have similar outcomes in survival but with less toxicity[31]. Quality of life data would also be important to consider if there is no change in overall survival benefit. the addition of mature OS data is needed to confirm and strengthen the results of these findings.

In conclusion, combined inhibition of first EGFR TKIs in combination with VEGF inhibitors results in a clinically meaningful benefit in PFS but not OS with mild toxicity. However, given osimertinib is the new standard of care in the first line setting, further research is warranted to assess whether combined inhibition of EGFR with osimertinib and a VEGF inhibitor results in improved survival outcomes in addition to mature OS data from the previously published trials.

Declarations

Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations of interest:

D. Breadner has provided advisory board participation or received honoraria from Amgen Canada, Bristol-Myers-Squibb, AstraZeneca and Takeda.

J. Raphael has provided advisory board participation or received honoraria from Roche, Novartis, Merck, Lilly, and AstraZeneca.

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Figures

Figure 1

Legend not included with this version.

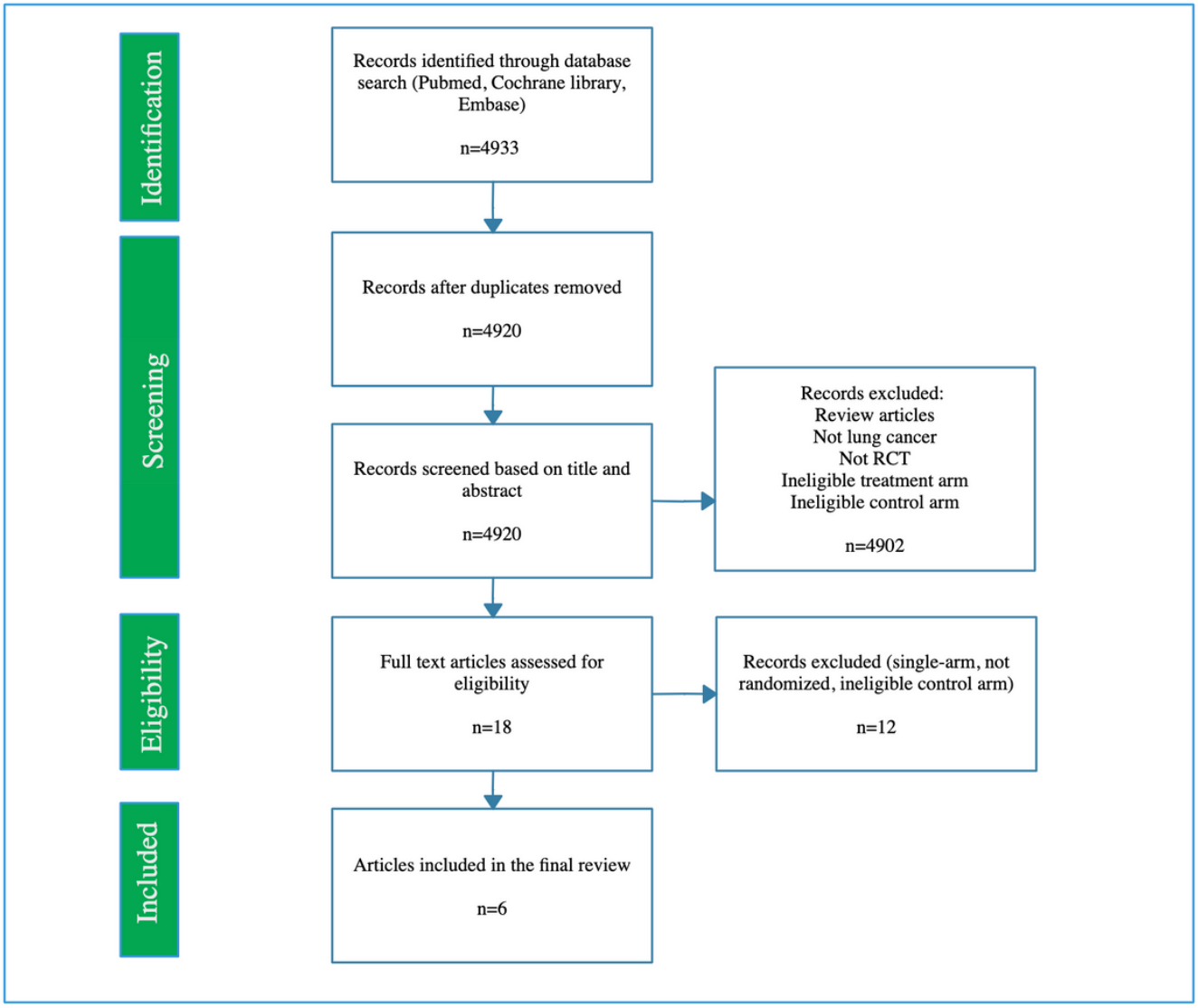

Figure 2

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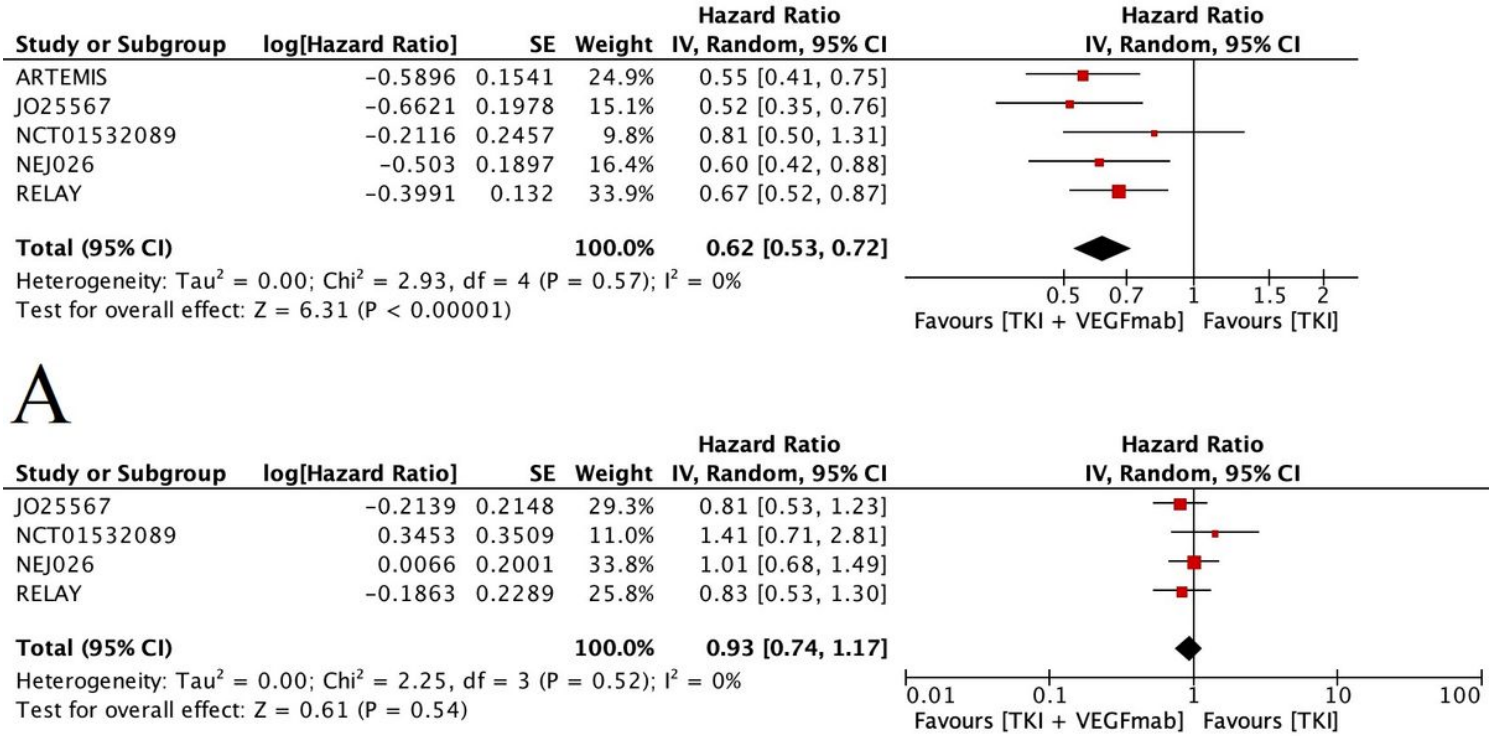

Figure 3

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