BMJ Open

Correlation between ALK+ non-small cell lung cancer targeted therapy and thrombosis: a systematic review and network meta-analysis

Yaopu Qi, Xiuhuan Wang, Tai Guo, Tiebin You, Ping Wang

To cite: Qi Y, Wang X, Guo T, *et al*. Correlation between ALK+ non-small cell lung cancer targeted therapy and thrombosis: a systematic review and network meta-analysis. *BMJ Open* 2024;**14**:e078173. doi:10.1136/bmjopen-2023-078173

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-078173).

Received 27 July 2023
Accepted 12 September 2024

Department of Respiratory Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Correspondence to
Dr Ping Wang;
pingwang1393@163.com

ABSTRACT

Objective The main adjuvant therapies for anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer include ALK tyrosine kinase inhibitors (TKI) and chemotherapy. We aimed to compare differences in the incidence of thromboembolism (TE) among different treatment options.

Design Using a systematic review and Bayesian network meta-analysis (NMA).

Data sources We searched PubMed, Embase, Cochrane Library, ClinicalTrials.gov and Web of Science databases before 10 June 2023.

Eligibility criteria We included published randomised controlled trials (RCT) involving comparisons of treatments between chemotherapy and ALK-TKI drugs.

Data extraction and synthesis Assessed risk bias with Cochrane tool. Conducted NMA with GEMTC in R, we evaluate the model fit using the deviation information criteria. Estimated posterior distribution using Markov Chain Monte Carlo, 4 chains, 10 fine-tuned iterations, 10 000 iterations per chain, total 50 000 iterations. Monitored potential scale reduction factor for convergence. And checked convergence with Gelman-Rubin statistics and trace plot. Provided surface under the cumulative ranking, lower values indicate less TE event probability.

Results Analysis of eight RCTs showed that, compared with that for crizotinib, there was a lower risk of total TE with chemotherapy (OR, 0.28; 95% credible intervals (CrI) 0.11 to 0.63), brigatinib (OR 0.31; 95% CrI 0.11 to 0.79) and ceritinib (OR 0.13; 95% CrI 0.03 to 0.45). In addition, analysis of venous TE (VTE) showed similar results, with a lower occurrence for chemotherapy (OR 0.27; 95% CrI 0.1 to 0.62), brigatinib (OR 0.18; 95% CrI 0.04 to 0.6) and ceritinib (OR 0.1; 95% CrI 0.02 to 0.43) compared with that for crizotinib. There were no significant differences in the occurrence of arterial TE among the different treatment options.

Conclusion Compared with chemotherapy, alectinib, lorlatinib, brigatinib and ceritinib, crizotinib significantly increased the risk of TE and VTE.

PROSPERO registration number CRD42023373307.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first to specifically compare the risk of thrombosis among different treatments for anaplastic lymphoma kinase+non-small cell lung cancer using a Bayesian network meta-analysis.
⇒ Only clinical trials that could limit bias were considered, and the conclusions were relatively reliable.
⇒ Only English language publications were retrieved, which may have led to language bias.
⇒ There was a risk of bias to some extent because of the small number of included samples.

INTRODUCTION

Lung cancer is one of the most common malignant tumours worldwide.[1 2] Approximately 70% of non-small cell lung carcinoma (NSCLC) cases are diagnosed at an advanced stage, and the 5-year survival rate is only 23%.[3] Thromboembolism (TE) is recognised as one of the leading factors contributing to the increased mortality in these patients.[4–6] Abufarhaneh *et al* found that the incidence rate of venous TE (VTE) in patients with advanced NSCLC was as high as 8%–15%.[7] Furthermore, studies showed a higher risk of death in subjects with cancer-related venous thrombosis than in those with cancer or venous thrombosis.[1 8]

With the rapid progress of molecular biology, our understanding of NSCLC has gradually deepened, and its treatment methods have been enriched on the basis of traditional chemotherapy, such as targeted therapy (such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), ROS proto-oncogene 1, etc), immunotherapy and radiotherapy. In particular, immunotherapy, as a novel cancer treatment method, has demonstrated its remarkable efficacy in many types of cancer therapy.[9] Tartarone *et al*'s study analysis shows that the effect of treating anti-programmed cell death protein-1 (PD-1) and anti- programmed cell death-Ligand-1 (PD-L1) drugs in advanced patients is better than docetaxel in the treatment of NSCLC.[10] The EGFR mutation is a common mutation in lung cancer and other

solid tumours. EGFR-tyrosine kinase inhibitors (TKIs) have shown significant results in delaying the disease process in elderly patients with advanced EGFR mutant NSCLC.[11] With the in-depth exploration of the mechanism of the role of ALK in the occurrence and development of cancer, targeted therapy for ALK has gradually become a key direction in the field of cancer therapy. Targeted therapy for ALK rearrangement (ALK+) patients not only improves the quality of life of patients but also extends their survival time.

Of note, an in-depth study of NSCLC molecular subtypes and targeted therapy in recent years found that ALK+NSCLC and its treatment may also increase the risk of thrombosis to some extent.[12] In NSCLC, a somatic gene rearrangement involving the fusion of ALK and echinoderm microtubule-associated protein-like 4 (EML4) (EML4-ALK) is observed, initially described in a small number of lung cancers in Japan in 2007 by Soda *et al*.[13]

Many other ALK fusions have been reported, such as Recombinant Kinesin Family Member 5B (KIF5B) -ALK, TRK-fused gene (TFG)-ALK and Recombinant Kinesin Light Chain 1(KLC1)-ALK. EML4-ALK is the most common ALK fusion in patients with NSCLC,[4 13–20] with an incidence of approximately 2%–7%.[13] The population characteristics of patients with ALK+NSCLC include younger age, history of non-smoking or mild smoking and adenocarcinoma histology.[21] Recent retrospective studies found that the risk of VTE associated with ALK+ was significant.[22–24] An increased risk of VTE in patients with ALK+NSCLC was confirmed in a prospective cohort study. ALK+patients had a significantly higher VTE recurrence rate (ALK+vs ALK–: 13.5% vs 3.1%), which increased the risk of death by 4.85-fold.[25]

Crizotinib was the first small-molecule ALK-TKI approved by the US Food and Drug Administration in 2011 for treating patients with advanced ALK+NSCLC[26–28]; however, it was initially developed as a potent cellular-mesenchymal epithelial transition factor inhibitor.[29] A trial by Solomon *et al* demonstrated that the first-generation ALK-TKI, crizotinib, had better efficacy in ALK+patients than platinum-based and pemetrexed chemotherapy.[27] This finding laid the foundation for crizotinib as the standard first-line treatment for advanced ALK+NSCLC. Subsequently, several randomised phase III studies have demonstrated the superior efficacy of second-generation ALK-TKI drugs as first-line therapy compared with crizotinib. These studies included alectinib and brigatinib as representatives of second-generation ALK-TKI drugs.[30 31] In summary, the new generation of targeted drugs significantly improved patients' overall progression-free survival time and quality of life compared with crizotinib. However, a study by Roopkumar *et al* found that compared with ALK+patients who did not receive TKIs, those who did receive TKIs had a significantly higher risk of coagulation events (HR=0.1, 95% credible intervals (CrI) 0.03 to 0.2, p<0.0001).[32] Therefore, it is crucial to study the risk of thrombosis associated with a range of drugs used for the treatment of ALK+NSCLC. Owing to the limited number of head-to-head studies comparing different treatment measures for ALK+and the absence of clear conclusions regarding their impact on the risk of thrombosis, this study provides a reliable reference for reaching effective conclusions in the mentioned research.

In this study, we compared crizotinib with chemotherapy and next-generation ALK inhibitors (including alectinib, brigatinib, lorlatinib and ceritinib) to determine the risk of thrombotic events in patients with ALK+advanced NSCLC. In addition, we used a network meta-analysis (NMA) approach to compare and rank the risk of induced thrombosis for clinical interventions that have not been directly compared. Compared with other studies, this study used the NMA method to make indirect comparisons of treatment outcomes that had not been compared in a head-to-head study and to rank the risk of thrombosis. This study aimed to provide a more reliable theoretical basis for the comprehensive management of ALK+NSCLC and drug selection by studying the risk of thrombosis caused by different ALK-TKI.

METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses.[33 34] This systematic traditional and NMA is registered in PROSPERO (CRD42023373307).

Data source and search strategy

We searched for publications on the use of TKI for the treatment of ALK+NSCLC. Two investigators independently searched multiple electronic databases (PubMed, Embase, Cochrane Library, ClinicalTrials.gov and Web of Science). We used the following terms: carcinoma, non-small-cell lung; lung carcinoma, non-small-cell; crizotinib or PF-02341066; alectinib or Alecensa; ceritinib or Zykadia; brigatinib or Alunbrig; lorlatinib; randomised controlled trial (RCT). The search included studies proposed or published up to 10 June 2023, and only English-language publications were retrieved. We identified additional articles that may be eligible for this analysis by reviewing the articles listed in the references of the included studies (online supplemental table S1).

Study selection

All included studies met the following criteria: (1) histologically or cytologically confirmed advanced NSCLC that was ALK+, as assessed by immunohistochemistry or fluorescence in situ hybridisation; (2) a phase III randomised controlled trial (RCT); (3) TE OR and 95% CrI and (4) incidence rate of TE during the treatment of ALK+NSCLC, even if this was not the main focus of the report. (The reported incidences of VTE in these treatment trials are not necessarily the true incidence of VTE in patients treated with ALK inhibitors and chemotherapy). Studies that met the following criteria were excluded: (1) the use of other treatments such as immunotherapy; (2) no

data relating to TE and (3) experimental animal studies. When the same information was reported in more than one article, we analysed only the publications relevant to the study, which was the most informative.

Data extraction and quality assessment

The information that had to be extracted from our included studies were as follows: ClinicalTrials.gov Identifier; year of publication; race, age and sex of patients; treatment used in the intervention and control groups; occurrence of TE; the first-line treatment for ALK+; TE, including VTE and other venous thromboses (such as pelvic venous thrombosis) and occurrence of cerebrovascular accident and myocardial infarction, which were considered as arterial thrombosis (ATE). One author extracted and entered the relevant data from each publication, and the other reviewed the extracted data. Disagreements between the two investigators were resolved by discussion. If the disagreement could not be resolved, a third researcher was consulted, and the decision was made. We used the Cochrane risk-of-bias tool to explore the sources of bias in randomised trials.

Statistical analysis

The included studies contained TE events that could be extracted. The NMA focused on serious TE events, which included outcomes such as death, life-threatening situations, hospitalisation, extended hospital stays, significant incapacity and interference with normal life functions. All data are presented as OR with 95% CrIs.

A meta-analysis with direct comparison of TE events (VTE and ATE), random effects or fixed models were selected based on their heterogeneity. In addition, we used NMA to compare the effects of interventions not directly compared in clinical trials, NMA was performed using the R software GEMTC software package in a Bayesian framework. During the analysis, non-informative prior distribution was applied to all model parameters, the deviation information criteria were used to evaluate the model fit, the Markov Chain Monte Carlo method was used to estimate the posterior distribution of parameters, establish four Markov chains, and tune 10 times, 10 000 iterations, a total number of 50 000 iterations. By monitoring the change trend of the Potential Scale Reduction Factor, which is close to 1, then the convergence of the simulation results is good.[35] Furthermore, we will use the Gelman-Rubin statistics and the trace plot for the convergence check of the Markov chains (online supplemental figures S1 and S2). For the empirical assessment of network consistency, NMA will employ node-splitting methods to compare direct and indirect evidence. If the obtained p value is greater than 0.05, this would indicate that there is no significant difference between the direct and indirect evidence.

In terms of results presentation, in addition to the OR or mean presented at 95% CrIs, we will provide a surface under the cumulative ranking (SUCRA) of treatment measures, lower SUCRA values indicating a lower probability of a thrombotic event. Funnel plot and funnel plot asymmetry tests included at least 10 studies, therefore, no publication bias analysis was performed.[36 37] Sensitivity analysis was conducted by comparing the Bayesian and the frequentist model, and if the results are not changed, the results are robust. The quality of evidence from this study was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) method Using grade of evidence level: the node segmentation method is used to divide the nodes into direct comparison and indirect comparison and select the ones with higher evidence level as the final result (the results are shown in online supplemental tables S2–S4).

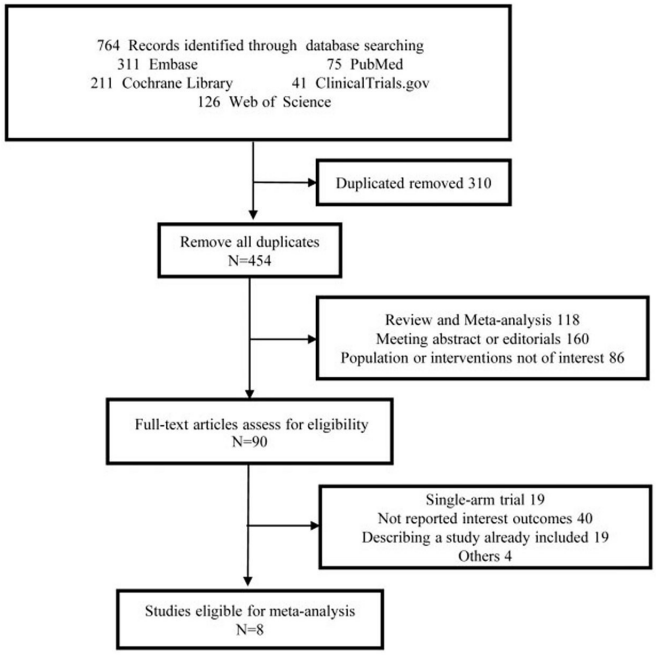

Figure 1 Flow chart of literature screening.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Characteristics of the included studies

A total of 764 articles (75 from PubMed, 311 from Embase, 211 from the Cochrane Library, 41 from Clinical Trials.gov and 126 from Web of Science) were retrieved according to the established search strategy. After deleting duplicate articles, we briefly reviewed the titles and abstracts of 764 articles. We excluded 646 records, including 118 meta-analyses and review articles. After careful reading of the remaining 90 articles, 82 were excluded for the reasons described in figure 1. Risk assessment by the Risk bias assessment tool RoB 2 protocol for the remaining eight phase III RCTs graded three as having 'some concerns' and five as 'low risk'[38] (figure 2). Table 1 summarises the specific characteristics of the included studies.[25 28 31 39–43] Eight eligible studies were international multicentre phase III RCTs that included a total of 2080 patients with

ALK+NSCLC. Six studies evaluated the treatment effect of crizotinib in the control group, four studies assessed the treatment effect of chemotherapy in the control group and two studies compared crizotinib with chemotherapy treatment. We compared the aggregated OR of NMA with the corresponding OR of traditional direct comparison meta-analysis. Using NMA, we compared eight different drug regimens (online supplemental figure S3).

Incidence of total thromboembolism

The consistency between the traditional meta-analysis and the NMA results was good. The NMA results showed a significant difference in the incidence of total thromboembolism (TTE) between crizotinib and chemotherapy, brigatinib or ceritinib. Compared with that of crizotinib, the incidence of TTE was lower with chemotherapy (OR 0.28; 95% CrI 0.11 to 0.63), brigatinib (OR 0.31; 95% CrI 0.11 to 0.79) and ceritinib (OR 0.13; 95% CrI 0.03 to 0.45). The results of the indirect comparison of crizotinib with chemotherapy and brigatinib were relatively consistent with the direct comparison results, with OR 0.33 (95% CrI 0.14 to 0.75) and OR 0.33 (95% CrI 0.12 to 0.85), respectively. However, the consistency of the results could not be determined because of the lack of direct comparison between ceritinib and crizotinib. Using the Bayesian NMA statistical method, the SUCRA curve value ranged between 0 and 1 (0≤SUCRA ≤ 1). When SUCRA is 1, the intervention measures have a higher risk of adverse events. In contrast, when the SUCRA is 0, it suggests that the intervention measures have a lower risk of adverse events. According to the size of the SUCRA, the ranking of TTE probabilities for different intervention measures was as follows: ceritinib (SUCRA=0.16), lorlatinib (0.26), chemotherapy (0.50), brigatinib (0.52), alectinib (0.56) and crizotinib (0.99). The figures are shown in figure 3A, figure 4A and online supplemental figure S4A. The results are shown in online supplemental table S5.

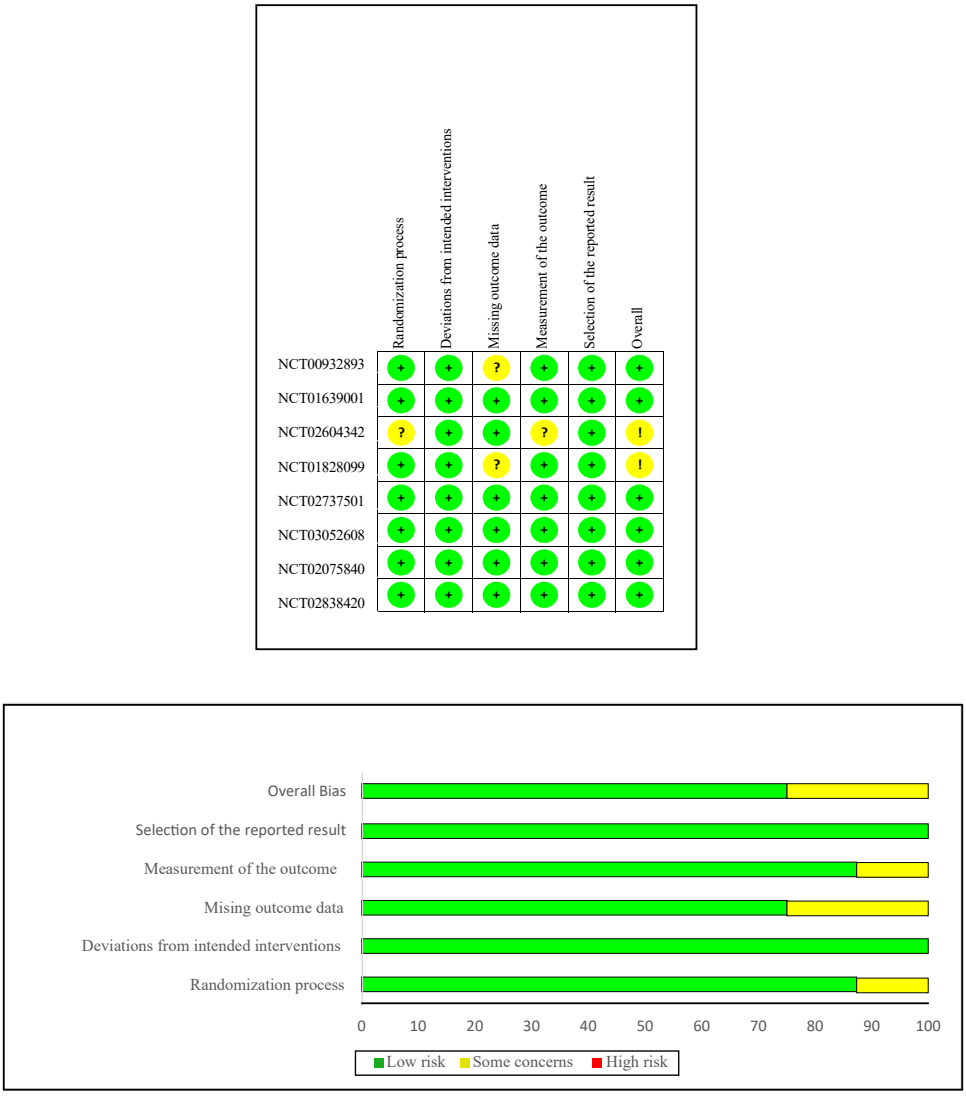

Figure 2 Results of the risk of included randomised trial bias was assessed using the Cochrane risk-of-bias tool for randomised trials. High-risk trials are shown in red, low-risk trials in green, while trials with some concerns are shown in yellow.

Incidence of VTE

A comparative analysis of the traditional meta-analysis and NMA results showed that the results were relatively consistent. Chemotherapy, brigatinib and ceritinib had a lower incidence of VTE than crizotinib, with OR 0.27 (95% CrI 0.1 to 0.62), OR 0.18 (95% CrI 0.04 to 0.60) and OR 0.1 (95% CrI 0.02 to 0.43), respectively. The results of the indirect comparison of crizotinib with chemotherapy and brigatinib were relatively consistent with the direct comparison results, with OR 0.32 (95% CrI 0.13 to 0.78) and OR 0.18 (95% CrI 0.04 to 0.60), respectively. However, owing to the lack of a direct comparison between ceritinib and crizotinib, the consistency of the results could not be determined. According to the results of the Bayesian NMA statistical method, crizotinib was associated with the highest risk of VTE (SUCRA=0.97), whereas ceritinib was associated with the lowest risk (SUCRA=0.16). The figures are shown in figure 3B, figure 4B and online supplemental figure S4B. The results are shown in online supplemental table S6.

Incidence of ATE

Traditional meta-analysis of ATE events did not show significant differences between crizotinib, chemotherapy, lorlatinib, brigatinib and ceritinib. Therefore, NMA was not conducted to assess the risk of ATE occurring during different drug treatments. The figures are shown in online supplemental figure S5.

Incidence of serious TTE

The occurrence of serious TTE can interfere with the delivery of continuous treatment and reduce the quality of life. The majority of TTE events were found to be serious adverse events; therefore, this study further analysed serious TTE events. NMA showed that crizotinib

Table 1 The characteristics of the included studies

Study	Year	Age median	Race	Male sex	Treatment		Number of patients	
					Experimental	Control	Experimental	Control
NCT00932893(26)	2017	50	Multiraces	193 (55.6%)	Crizotinib	Chemotherapy	172	171
					250 mg	Pemetrexed 500 mg/m^2 Docetaxel 75 mg/m^2		
NCT03052608(27)	2022	57.4	Multiraces	175 (59.1%)	Lorlatinib	Crizotinib	149	142
					100 mg	250 mg		
NCT01639001(28)	2020	48.5	Asian	114 (55.1%)	Crizotinib	Chemotherapy	104	101
					250 mg	Pemetrexed 500 mg/m^2+cisplatin 75 mg/m^2		
						Pemetrexed 500 mg/m^2+carboplatin AUC 5–6		
NCT02604342(39)	2019	56	Multiraces	53 (44.5%)	Alectinib	Chemotherapy	77	37
					600 mg	Pemetrexed 500 mg/m^2 Docetaxel 75 mg/m^2		
NCT01828099(404)	2022	53.9	Multiraces	216 (57.4%)	Ceritinib	Chemotherapy	189	175
					750 mg	Pemetrexed 500 mg/m^2+cisplatin 75 mg/m^2 Pemetrexed 500 mg/m^2+carboplatin AUC 5–6		
NCT02737501(41)	2021	58.2	Multiraces	150 (54.5%)	Brigatinib	Crizotinib	136	137
					90 mg	250 mg		
NCT02075840(42)	2022	55.1	Multiraces	171 (56.4%)	Alectinib	Crizotinib	152	151
					600 mg	250 mg		
NCT02838420(43)	2019	50.7	Asian	89 (47.6%)	Alectinib	Crizotinib	125	62
					600 mg	250 mg		

AUC, area under the curve.

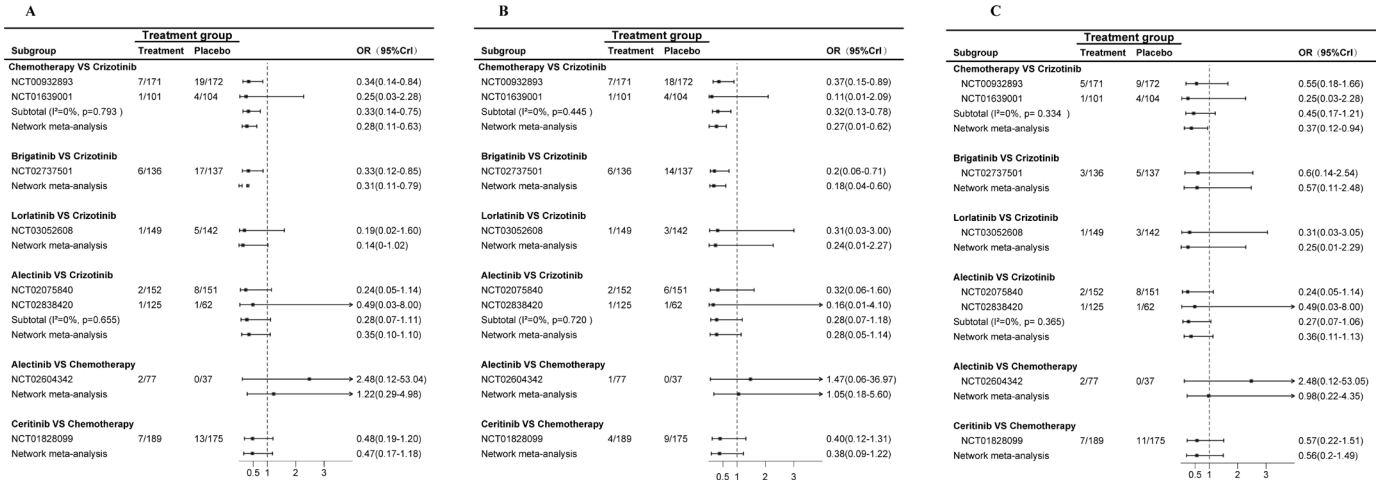

Figure 3 Direct comparison versus indirect comparison of forest plots of TTE, VTE and serious TTE outcome. (A) Direct comparison of TTE versus indirect comparison of forest plot. (B) Direct comparison of VTE versus indirect comparison of forest plot. (C) Direct comparison of serious TTE versus indirect comparison of forest plot. TTE, total thromboembolism; VTE, venous thrombosis.

was associated with a higher incidence of serious TTE than chemotherapy (OR 0.37; 95% CrI 0.12 to 0.94) and ceritinib (OR 0.2; 95% CrI 0.05 to 0.8). From low to high, for the risk of serious TTE, based on the magnitude of SUCRA, was ceritinib (SUCRA=0.21), lorlatinib (0.34), alectinib (0.44), chemotherapy (0.47), brigatinib (0.63) and crizotinib (0.92). The figures are shown in figure 3C, figure 4C and online supplemental figure S4C. The results are shown in online supplemental table S7.

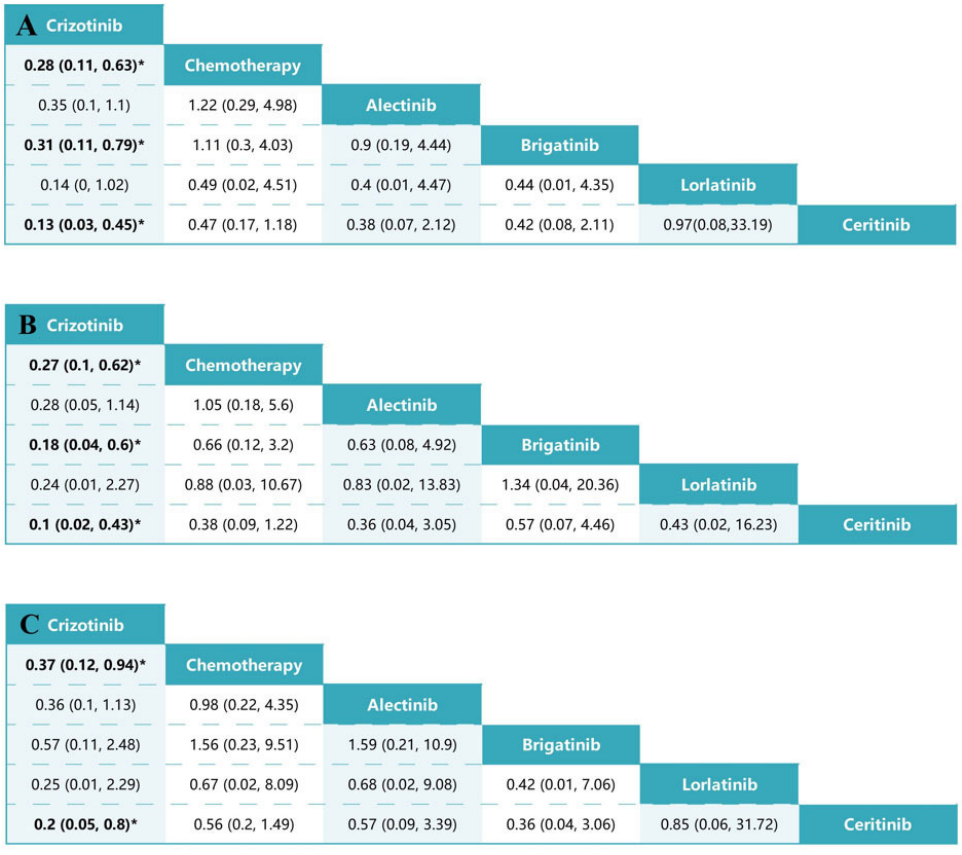

Figure 4 NMA indirectly compares the results of different treatment measures for TTE, VTE and serious TTE outcome events. (A) NMA indirectly compares the results of different treatment measures for TTE outcome events. (B) NMA indirectly compares the results of different treatment measures for VTE outcome events. (C) NMA indirectly compares the results of different treatment measures for serious TTE outcome events. *as there is difference between the two groups. NMA, network meta-analysis; TTE, total thromboembolism; VTE, venous thrombosis.

Evaluation of inconsistency

There was a closed loop in the comparison of interventions for TTE, VTE and serious TTE; for the closed loop created by the intervention, the inconsistency was tested by the node-splitting method, except for serious TTE, both TE and VTE p>0.05, there is no obvious inconsistency. The results are shown in online supplemental table S8.

Sensitivity analysis and publication bias

By comparing the sensitivity analysis between Bayesian and frequentist models, no obvious changes in TTE, VTE or serious TTE results showed good stability. In addition, the sensitivity analysis for ATE showed stable results. Because the number of included studies was <10, we did not assess the publication bias. The results are shown in online supplemental tables S9–S11.

DISCUSSION

Using data from eight RCTs conducted before 10 June 2023, we analysed the relationship between different therapeutic drugs and TE in patients with ALK+NSCLC. Data from a meta-analysis of 2080 patients from 8 randomised trials showed that there were significant differences in the risk of TTE and VTE and serious TTE events between chemotherapy and ALK-TKI regimens; patients treated with crizotinib had a higher risk of TTE, VTE and serious TE than did those treated with chemotherapy and a new generation of targeted therapies, with ceritinib having the least risk. However, based on a traditional meta-analysis of eight existing studies, the results showed no significant difference between different treatment regimens for the risk of ATE in patients with ALK+NSCLC, which may be associated with a lower incidence of ATE.

Crizotinib improves patient survival compared with conventional chemotherapy.[44 45] Although it has been recommended as a first-line drug in the National Comprehensive Cancer Network guidelines,[46] a recent study showed that crizotinib is associated with a higher risk of thrombosis than other treatment measures.[47 48] This result is consistent with our findings. Unlike other studies, we performed an indirect comparison of different treatments using Bayesian NMA and ranked the risk of thrombosis. Our study indicates that chemotherapy and the new-generation targeted drugs, ceritinib and brigatinib, significantly reduced the risk of thrombosis compared with crizotinib. In our study, the lowest risk of TE was observed in patients treated with ceritinib. This difference in the results may be attributed to factors such as whether pulmonary embolism (PE) is included, whether other venous thrombosis grades are included, whether ATE is included and whether the study data are updated. Therefore, based on our current research findings, crizotinib leads to a higher risk of serious TE events in patients, serious TE events may lead to drug reduction or even forced discontinuation of treatment. This may, to some extent, increase the risk of death in patients, and the new generation of targeted drugs may have fewer thromboembolic side effects, suggesting that they might be preferred as first-line treatment. However, considering the inconsistency in the study of serious TE events, this conclusion needs to be limited.

The occurrence of VTE may indicate invasive tumour biology; therefore, the short-term prognosis is poor.[49] In patients with cancer, symptomatic and asymptomatic VTE are associated with lower survival compared with patients without VTE.[50] A recent observational study reported the impact of VTE on the overall survival of patients with ALK+NSCLC0.[51] The use of TKIs in ALK+NSCLC affects the survival of patients with thrombosis, the retrospective study showed that in the ALK fusion subgroup, TE was associated with a lower objective response rate than in patients without TE (65.2% vs 75.0%, p=0.360) and significantly shortened progression-free survival among patients who received crizotinib treatment (HR 4.960; 95% CI 2.627 to 9.365; p<0.0001).[52] Another study showed that prophylactic anticoagulation therapy for patients with ALK+NSCLC treated with crizotinib reduced progression-free and overall survival.[53] This may be because any evolutionary advantage of cancer may manifest upstream of the anticoagulant mechanism, leading to the inability of anticoagulation therapy to reverse adverse clinical outcomes.[53] However, data on whether thrombosis affects the clinical response to TKI treatment are not available. Therefore, the impact of ALK-TKIs on the risk of thrombosis and survival needs to be further confirmed through analysis of large samples and prospective studies.

This study has certain limitations. Owing to the limited number of head-to-head studies on AKI-TKIs, our study could not take into account previous experience with chemotherapy or ALK-TKI treatment failure. The RCTs included in the analysis used two different chemotherapy regimens, and no analysis was conducted on the differences between the two regimens. Different follow-up times and treatment durations were reported in the analysed studies, and the longer the follow-up or duration of medication, the higher the incidence of thromboembolic events[49]; this may have influenced the observed incidence of TE. The number of studies included was relatively small; therefore, there may have been some bias in the data, and it is difficult to draw clear conclusions from indirect comparisons using NMA alone. This may be responsible for the inconsistency in the results of serious TE events. Finally, although we analysed RCTs, the disadvantage of clinical trials is that the included patient populations were rigorously screened, which limits the universality of the results. Therefore, further exploration is needed regarding the risk of thrombosis in NSCLC patients treated with ALK-TKI drugs and chemotherapy.

The relationship between ALK gene expression and TE needs to be thoroughly studied. One study investigated the relationship between ALK expression and tumour characteristics in NSCLC subtypes adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma. The results showed that ALK was more

strongly positive in ADC and ALK were more weakly positive in SCC. ALK expression is more common in ADC with poor prognosis. This suggests that ALK is overexpressed or promotes ADC tumour invasion and progression.[11] Studying the relationship between ALK and TE helps to understand the biological mechanisms of TE.

Our study provides evidence of the risks of thromboembolic events associated with the treatment of ALK+NSCLC with ALK-TKIs. These findings can aid in decision-making concerning the choice of first-line treatment and improve existing risk prediction models.

Contributors PW is the guarantor. PW provides research topics, research ideas, research designs, final manuscript reviews and submission. TG and TY conducted a literature search, literature collation. YQ and XW: literature selection, data collection and other work. YQ conducted a statistical analysis and wrote the manuscript.

Funding This study was supported by Hebei provincial health technology project (No. 20210471), and prevention and treatment of geriatric diseases by Hebei provincial department of finance (No. 20200316).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All data used in this study were extracted from published randomised controlled trials (RCTs); therefore, no ethical approval was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iD

Ping Wang http://orcid.org/0009-0002-7418-8555

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.
2 Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med* 2021;27:1345–56.
3 Miller KD, Nogueira L, Mariotto AB, *et al*. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019;69:363–85.
4 Rikova K, Guo A, Zeng Q, *et al*. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 2007;131:1190–203.
5 Blom JW, Doggen CJ, Osanto S. Malignancies, Prothrombotic Mutations, and the Risk of Venous Thrombosis. *JAMA* 2005;293:715.
6 Khorana AA, Francis CW, Culakova E, *et al*. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632–4.
7 Abufarhaneh M, Pandya RK, Alkhaja A, *et al*. Association between genetic mutations and risk of venous thromboembolism in patients with solid tumor malignancies: A systematic review and meta-analysis. *Thromb Res* 2022;213:47–56.
8 Crobach MJT, Anijs RJS, Brækkan SK, *et al*. Survival after cancer-related venous thrombosis: the Scandinavian Thrombosis and Cancer Study. *Blood Adv* 2023;7:4072–9.
9 Mei X, Chen J, Wang J, *et al*. Immunotoxins: Targeted Toxin Delivery for Cancer Therapy. *Pharm Fronts* 2019;01:e33–45.
10 Tartarone A, Roviello G, Lerose R, *et al*. Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis. *Future Oncol* 2019;15:2423–33.
11 Roudi R, Haji G, Madjd Z, *et al*. Evaluation of anaplastic lymphoma kinase expression in nonsmall cell lung cancer;a tissue microarray analysis. *J Cancer Res Ther* 2016;12:1065–9.
12 Icht O, Leader A, Batat E, *et al*. Arterial and Venous Thromboembolism in *ALK* -Rearrangement-Positive Non-small Cell Lung Cancer: A Population-Based Cohort Study . *Oncologist* 2023;28:e391–6.
13 Soda M, Choi YL, Enomoto M, *et al*. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature New Biol* 2007;448:561–6.
14 Hallberg B, Palmer RH. Mechanistic insight into ALK receptor tyrosine kinase in human cancer biology. *Nat Rev Cancer* 2013;13:685–700.
15 Choi Y-L, Lira ME, Hong M, *et al*. A Novel Fusion of TPR and ALK in Lung Adenocarcinoma. *J Thorac Oncol* 2014;9:563–6.
16 Fang DD, Zhang B, Gu Q, *et al*. HIP1-ALK, a novel ALK fusion variant that responds to crizotinib. *J Thorac Oncol* 2014;9:285–94.
17 Hong M, Kim RN, Song J-Y, *et al*. HIP1-ALK, a novel fusion protein identified in lung adenocarcinoma. *J Thorac Oncol* 2014;9:419–22.
18 Jung Y, Kim P, Jung Y, *et al*. Discovery of ALK-PTPN3 gene fusion from human non-small cell lung carcinoma cell line using next generation RNA sequencing. *Gene Chrom Canc* 2012;51:590–7.
19 Majewski IJ, Mittempergher L, Davidson NM, *et al*. Identification of recurrent FGFR3 fusion genes in lung cancer through kinome-centred RNA sequencing. *J Pathol* 2013;230:270–6.
20 Togashi Y, Soda M, Sakata S, *et al*. KLC1-ALK: a novel fusion in lung cancer identified using a formalin-fixed paraffin-embedded tissue only. *PLoS One* 2012;7:e31323.
21 Shaw AT, Yeap BY, Mino-Kenudson M, *et al*. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247–53.
22 Xiong W, Du H, Ding W, *et al*. The association between pulmonary embolism and the cancer-related genomic alterations in patients with NSCLC. *Respir Res* 2020;21:185.
23 Zer A, Moskovitz M, Hwang DM, *et al*. ALK-Rearranged Non-Small-Cell Lung Cancer Is Associated With a High Rate of Venous Thromboembolism. *Clin Lung Cancer* 2017;18:156–61.
24 Al-Samkari H, Leiva O, Dagogo-Jack I, *et al*. Impact of ALK Rearrangement on Venous and Arterial Thrombotic Risk in NSCLC. *J Thorac Oncol* 2020;15:1497–506.
25 Dou F, Zhang Y, Yi J, *et al*. Association of ALK rearrangement and risk of venous thromboembolism in patients with non-small cell lung cancer: A prospective cohort study. *Thromb Res* 2020;186:36–41.
26 Shaw AT, Kim D-W, Nakagawa K, *et al*. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368:2385–94.
27 Solomon BJ, Mok T, Kim D-W, *et al*. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167–77.
28 Wu Y-L, Lu S, Lu Y, *et al*. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2018;13:1539–48.
29 Cui JJ, Tran-Dubé M, Shen H, *et al*. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). *J Med Chem* 2011;54:6342–63.
30 Ahn M-J, Kim H, Yang J-H, *et al*. Brigatinib (BRG) versus crizotinib (CRZ) in Asian versus non-Asian patients (pts) in the phase III ALTA-1L trial. *J C O* 2019;37:9026.
31 Solomon BJ, Bauer TM, Mok TSK, *et al*. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *Lancet Respir Med* 2023;11:354–66.
32 Roopkumar J, Poudel SK, Gervaso L, *et al*. Risk of thromboembolism in patients with ALK- and EGFR-mutant lung cancer: A cohort study. *J Thromb Haemost* 2021;19:822–9.
33 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

34 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
35 van Valkenhoef G, Lu G, de Brock B, *et al*. Automating network meta-analysis. *Res Synth Methods* 2012;3:285–99.
36 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
37 Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
38 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
39 Novello S, Mazières J, Oh I-J, *et al*. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Ann Oncol* 2018;29:1409–16.
40 Soria J-C, Tan DSW, Chiari R, *et al*. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017;389:917–29.
41 Camidge DR, Kim HR, Ahn M-J, *et al*. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;379:2027–39.
42 Mok T, Camidge DR, Gadgeel SM, *et al*. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol* 2020;31:1056–64.
43 Zhou C, Kim S-W, Reungwetwattana T, *et al*. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *Lancet Respir Med* 2019;7:437–46.
44 Wardak Z, Choy H. Improving Treatment Options for Brain Metastases From ALK-Positive Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016;34:4064–5.
45 Costa DB, Shaw AT, Ou S-HI, *et al*. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. *J Clin Oncol* 2015;33:1881–8.
46 Ettinger DS, Wood DE, Aisner DL, *et al*. Non–Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022;20:497–530.
47 Hou H, Sun D, Liu K, *et al*. The safety and serious adverse events of approved ALK inhibitors in malignancies: a meta-analysis. *Cancer Manag Res* 2019;11:4109–18.
48 Zhao J, Ma Z, Li H, *et al*. Risks of cardiovascular toxicities associated with ALK tyrosine kinase inhibitors in patients with non-small-cell lung cancer: a meta-analysis of randomized control trials. *Expert Opin Drug Saf* 2023;22:581–8.
49 Baron JA, Gridley G, Weiderpass E, *et al*. Venous thromboembolism and cancer. *Lancet* 1998;351:1077–80.
50 Agnelli G, Verso M, Mandalà M, *et al*. A prospective study on survival in cancer patients with and without venous thromboembolism. *Intern Emerg Med* 2014;9:559–67.
51 Zugazagoitia J, Biosca M, Oliveira J, *et al*. Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced *ALK*-rearranged non-small cell lung cancer. *Eur Respir J* 2018;51:1702431.
52 Liu Y, Wang W, Wu F, *et al*. High discrepancy in thrombotic events in non-small cell lung cancer patients with different genomic alterations. *Transl Lung Cancer Res* 2021;10:1512–24.
53 Ng TL, Tsui DCC, Wang S, *et al*. Association of anticoagulant use with clinical outcomes from crizotinib in ALK- and ROS1-rearranged advanced non-small cell lung cancers: A retrospective analysis of PROFILE 1001. *Cancer Med* 2022;11:4422–9.