


BMJ Open ALK inhibitors in ALK-rearranged non-small cell lung cancer with and without brain metastases: systematic review and network meta-analysis

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ABSTRACT

Objectives To systematically evaluate the efficacy and safety of anaplastic lymphoma kinase (ALK) inhibitors in ALK-rearranged positive non-small cell lung cancer (NSCLC) with brain metastases, and update the overall survival (OS) outcomes of the second-generation and third-generation ALK (ALK-2ndG/3rdG) inhibitors versus first-generation (ALK-1stG) inhibitors.

Design The study is in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines. Randomised controlled trials (RCTs) published up to 3 November 2021 were retrieved from PubMed, EMBASE, Cochrane Library and ClinicalTrials.gov.

Setting RCTs from any country and healthcare setting.

Participants Patients with advanced ALK-positive NSCLC with or without brain metastases.

Interventions and comparisons The interventions were ALK-2ndG/3rdG; the control arm was ALK-1stG or crizotinib.

Primary and secondary outcome measures Primary outcomes included median progression-free survival and median OS. Secondary outcomes included systemic objective response rate, intracranial response rate and rate of grade ≥ 3 adverse events (AEs).

Results A total of 12 RCTs involving 3156 patients were analysed. Compared with ALK-1stG (crizotinib), ALK-2ndG (alectinib, brigatinib, ceritinib and ensartinib) significantly improved the OS (HR: 0.72, 95% CI: 0.57 to 0.90, $p=0.004$) and intracranial response of patients with any brain metastases, especially with measurable (diameter ≥ 10 mm) brain metastases. Network meta-analysis demonstrated that ALK-3rdG (lorlatinib) had superior efficacy for patients with brain lesions, but performed a distinct side-effect profile. Moreover, alectinib showed superior efficacy and lower toxicity in ALK-positive NSCLC.

Conclusion Treatment with ALK-2ndG inhibitors significantly improved OS compared with crizotinib, and alectinib has less severe AEs than any other ALK inhibitors with moderate-high efficacy. The limited OS follow-up and inadequate sample sizes might contribute to having no statistically significant difference in OS of lorlatinib versus crizotinib. More high-quality and longer follow-up RCTs are warranted to prove our findings.

PROSPERO registration number CRD42021292245.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The general characteristics of the included trials and patients were provided more comprehensively.
- ⇒ The network meta-analysis provided access to directly compare the efficacy and safety of different anaplastic lymphoma kinase (ALK) inhibitor regimens for non-small cell lung cancer.
- ⇒ This study did not analyse the impact of ALK fusion variants on efficacy of ALK inhibitors.
- ⇒ The recruited studies lacked sufficient randomised controlled trials on third-generation ALK inhibitors (lorlatinib).

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the world, and non-small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancers.¹ Most patients with NSCLC harbour oncogenic driver mutations or fusions such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor, Kirsten rat sarcoma viral oncogene homolog, ROS proto-oncogene 1 receptor tyrosine kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, BRAF and others.^{2–3} ALK rearrangement, first discovered in a subtype of anaplastic large cell lymphoma in 2007, occurs in 2%–7% of patients with NSCLC.⁴ Echinoderm microtubule-associated protein-like 4 and ALK genes (EML4-ALK), the most common ALK fusion variant, are an inversion at the short arm of chromosome 2.⁵ Interestingly, EML4-ALK is usually detected in non-smokers and younger patients with unique pathological features.^{6–8}

With the continuous development and clinical application of ALK inhibitors, the progression-free survival (PFS) of patients with ALK-positive NSCLC has been improved significantly. However, patients with ALK rearrangement are prone to brain

metastasis, which is the most common event for tumour progression.⁹ There are almost 10%–30% of patients with NSCLC who develop brain metastases.^{10–11} A retrospective study showed that the 2-year and 3-year cumulative incidence rates of brain metastases in ALK-positive NSCLC were 45.5% and 58.4%, respectively.¹² Crizotinib, the first-generation ALK (ALK-1stG) inhibitor, is significantly better than chemotherapy for patients with advanced ALK-positive NSCLC.^{13–14} Nevertheless, crizotinib is a target of p-glycoprotein, a membrane protein that pumps exogenous substances out of the central nervous system (CNS), leading the brain as a common site of relapse in patients treated with crizotinib.^{14–15} The second-generation ALK (ALK-2ndG) inhibitors including ceritinib,¹⁶ alectinib,¹⁵ brigatinib¹⁷ and ensartinib,¹⁸ and third-generation ALK (ALK-3rdG) inhibitors such as lorlatinib^{19–20} were designed to cross blood–brain barrier (BBB) and exhibited efficiency in shrinking intracranial lesions, consistently demonstrating a benefit in PFS.

A previous meta-analysis confirmed that ALK-2ndG improved PFS in patients with ALK-positive NSCLC. However, the effect of ALK-2ndG versus crizotinib on overall survival (OS) was not statistically significant due to the limited follow-up time.²¹ Moreover, there is no head-to-head trial to compare the efficacy and safety between ALK-2ndG and ALK-3rdG inhibitors in patients with measurable brain metastases. Therefore, considering the absence of immature OS data and other outcomes for brain metastases from individual randomised controlled trials (RCTs), we conducted this updated meta-analysis and intended to provide the medical evidence for clinical decision-making to patients with ALK-positive NSCLC with brain metastases.

METHODS

Literature search

The study is in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.²² The review protocol has been registered in PROSPERO (CRD42021292245). The PRISMA checklist is available in online supplemental appendix 1.

We searched database of PubMed, EMBASE, Cochrane Library and ClinicalTrials.gov for studies investigating the efficacy and safety of ALK inhibitors in patients with ALK-rearranged NSCLC with CNS metastases. The records were systematically screened up until 03 November 2021 by two independent investigators (JJ and CZ). A combination of searched keywords and medical subject headings was used and these were as follows: “non-small cell lung cancer”, “lung cancer”, “lung neoplasm”, “CNS metastases”, “brain metastases”, “CNS lesions”, “ALK inhibitor”, “ensartinib”, “lorlatinib”, “alectinib”, “brigatinib”, “ceritinib”, “crizotinib”, “chemotherapy”. We also manually searched the literature for further analysis. The search strategy is available in online supplemental appendix 2.

Inclusion and exclusion criteria

Participants

Patients with advanced ALK-positive NSCLC with or without brain metastases according to the Response Evaluation Criteria in Solid Tumors, V.1.1.²³

Interventions and comparisons

The interventions were ALK-2ndG or ALK-3rdG or ALK-1stG inhibitors; the control arm must be either ALK-1stG inhibitor or chemotherapy.

Outcomes

Primary outcomes included median PFS and median OS. Secondary outcomes included systemic objective response rate (ORR), intracranial response rate and rate of grade ≥ 3 adverse events (AEs).

Data extraction and risk of bias assessment

For each study, first author’s name, study design, publication year, country, patients’ characteristics, stage and registration number of clinical trials, ALK inhibitors of intervention and control arms, drug dosage and usage, endpoints and outcomes were extracted. The following patients’ characteristics were retrieved when available: sample size, proportion of women, median age, smoking status, treatment line of ALK inhibitors, pathological type, follow-up duration, median PFS, median OS, ORR, Complete Response (CR), Partial Response (PR), AE and outcomes of brain metastases subgroups. Data were extracted by two reviewers (JJ and CZ) independently from each study with a data extraction form and verified by a third reviewer (YW). Consensus was reached through discussion when any contradiction appeared.

The quality of included RCTs was assessed by Cochrane Collaboration risk of bias tool,^{24–25} which assesses risk of bias in six domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and persons (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.

Data synthesis and statistical analysis

The median PFS and OS were pooled and analysed in the form of HR. AEs and ORR were pooled and analysed in the form of risk ratio (RR) or OR.²⁶ The corresponding 95% CI was calculated. The heterogeneity between studies was evaluated by χ^2 test with I^2 statistics. $I^2 > 50\%$ was considered moderate-high heterogeneity and random-effects models (DerSimonian-Laird estimator) were then used for meta-analysis, and a fixed-effect model was used for analysis when $I^2 < 50\%$, which was considered low heterogeneity.²⁷ The subgroup analysis and sensitivity analysis were needed to use to assess the effect of sex, age, smoking status and CNS response. The direct meta-analysis was performed with Review Manager V.5.3 (Cochrane). Statistical significance was set at $p < 0.05$. Representative forest plots conveyed an overview of the results and details of the included studies.

A network meta-analysis on intracranial response and AEs was performed using STATA V.16.0 software.²⁸ Iteration was performed 50 000 times, with the first 10 000 iterations considered to be burn-in samples in Bayesian model. The Brooks-Gelman-Rubin diagnostic method was used to assess model convergence.²⁹ A network plot map indicated the relationship between different interventions. We used a random-effects model and consistency model to calculate OR/RR and 95% credible intervals from posterior distributions. Global and local inconsistencies were assessed by comparing the pooled OR/RR from the network meta-analysis and pairwise meta-analysis, and by comparing the fit and parsimony of consistency and inconsistency models, respectively. The node splitting method was used to calculate the local inconsistency in the entire network on a particular node.³⁰ $P < 0.05$ indicated existing inconsistency. For each outcome, we additionally used the surface under the cumulative ranking curve (SUCRA),³¹ which summarised the relative ranking probability of the treatment. In case of AEs, numbers in cells are SUCRA values indicating the probability of treatment being ranked highest on toxicity, which is between 0 (certainly the safest treatment) and 1 (certainly the most toxic treatment). Furthermore, publication bias was examined with funnel plots, Begger's test or Egger's test.

Patient and public involvement

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

RESULTS

Characteristic of studies

A total of 1204 records were identified during the preliminary literature search. After removing duplicates and irrelevant studies through abstract screening, 66 articles were chosen to further full-text assessment. Finally, the remaining 12 RCTs were eligible for meta-analysis. The screening process of 12 eligible RCTs was shown in figure 1. Six trials were comparison of ALK-2ndG or ALK-3rdG with crizotinib (Shaw *et al.*,³² Horn *et al.*,³³ Zhou *et al.*,³⁴ Camidge *et al.*,³⁵ Hida *et al.*,³⁶ Camidge *et al.*³⁷), and six trials were comparison of ALK inhibitors with chemotherapy (Novello *et al.*,³⁸ Shaw *et al.*,³⁹ Soria *et al.*,⁴⁰ Solomon *et al.*,⁴¹ Wu *et al.*,⁴² Shaw *et al.*⁴³).

The recruited participants of included RCTs were patients with confirmed ALK-rearranged positive and advanced/metastatic NSCLC. The main characteristics of included studies were shown in table 1 and online supplemental appendix 3, table 1.

Risk of bias assessment

The assessment of risk of bias was performed by Review Manager V.5.3 (online supplemental appendix 4, figure 1). All included eligible studies were open-label, phase III and multicentre randomised clinical trials.

Primary endpoints

Median PFS

The median PFS of ALK-1stG (crizotinib) and ALK-2ndG (ceritinib and brigatinib) was matured, but the

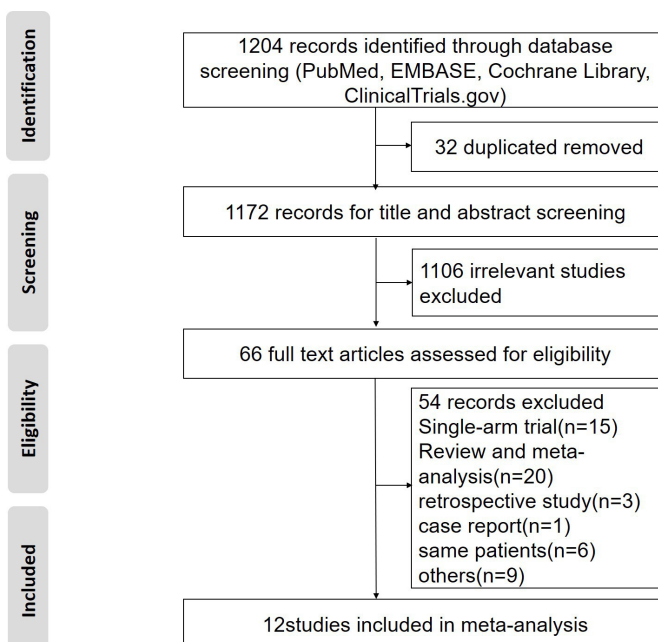


Figure 1 Literature screening results and process following the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines.

median PFS of lorlatinib, ensartinib and alectinib was not reached (table 1). Analysis of six studies comparing ALK-2ndG/3rdG with ALK-1stG (crizotinib) resulted in significant improvement in median PFS (HR=0.37, 95% CI: 0.29 to 0.47), with moderate heterogeneity ($I^2=50%$, $p < 0.001$). Test for overall effect was statistically significant ($Z=8.36$; online supplemental appendix 4, figure 2). Analysis of five studies comparing ALK-1stG/2ndG inhibitors with chemotherapy also resulted in significant improvement in median PFS. The random-effects model showed that the HR of pooled median PFS was 0.41 (95% CI: 0.31 to 0.54), with high heterogeneity ($I^2=73%$, $p < 0.001$).

To analyse PFS of patients with brain metastasis, we included seven trials including 664 patients with any CNS lesions. The median PFS of patients with brain metastasis was significantly improved in ALK-2ndG/3rdG versus crizotinib (HR=0.30, 95% CI: 0.17 to 0.51, $I^2=67%$, $p < 0.001$) and ALK inhibitors versus chemotherapy (HR=0.53, 95% CI: 0.39 to 0.72, $I^2=20%$, $p < 0.001$) (online supplemental appendix 4, figure 3).

Median OS

The median OS of ALK-2ndG and ALK-3rdG was not reached and immature; the trials were ongoing and would be updated in the future. However, the HR of pooled OS in 12 published trials was available. In case of ALK-3rdG, no significant improvements were observed when comparing lorlatinib with crizotinib (HR=0.81, 95% CI: 0.56 to 1.19, $I^2=0%$, $p=0.29$). However, there is statistical significance in OS when comparing ALK-2ndG with crizotinib (HR=0.68, 95% CI: 0.53 to 0.87, $I^2=35%$, $p=0.003$) (figure 2A).

Table 1 Characteristics of open-label, multicentre, phase III, RCT in the meta-analysis of ALK-rearranged NSCLC

First author	Intervention arm					Control arm					HR (95% CI)	
	Median PFS (month) (IQR)	Median OS (month) (IQR)	ORR (%)	≥3 AEs (%)	Median PFS (month) (IQR)	Median OS (month) (IQR)	ORR (%)	≥3 AEs (%)	Median PFS (month) (IQR)	OS		
Horn ³³	NR (20.20–NR)	NR (NR–NR)	74.00%	50.34	12.70 (8.90–16.60)	NR (NR–NR)	67.00%	42.47	0.45 (0.30–0.66)	0.91 (0.54 to 1.54)		
Shaw ³²	NR (NR–NR)	NR (NR–NR)	75.84%	72.00	9.30 (7.60–11.10)	NR (NR–NR)	57.82%	56.00	0.28 (0.19–0.41)	0.72 (0.41 to 1.25)		
Zhou ³⁴	NR	NR	91.00%	29.00	11.10	NR	77.00%	48.00	0.22 (0.13–0.38)	0.28 (0.12 to 0.68)		
Mok ¹⁶	34.80 (17.70–NE)	NR	82.89%	44.70	10.90 (9.10–12.90)	57.40	75.00%	51.00	0.43 (0.32–0.58)	0.67 (0.46 to 0.98)		
Hida ³⁶	NR (20.30–NR)	NR	85.00%	26.00	10.20 (8.20–12.00)	NR	70.00%	52.00	0.34 (0.17–0.71)	0.80 (0.35 to 1.82)		
Camidge ³⁷	24.00 (18.50–43.20)	NR	71.00%	73.00	11.10 (9.00–13.00)	NR	62.00%	61.00	0.48 (0.35–0.66)	0.81 (0.53 to 1.22)		
Novello ³⁸	9.60 (6.90–12.20)	12.60 (9.7–NR)	37.50%	27.10	1.40 (1.30–1.60)	NR (NR–NR)	2.90%	41.20	0.15 (0.08–0.29)	0.89 (0.35 to 2.24)		
Shaw ³⁹	5.40 (4.10–6.90)	20.30	45.00%	43.00	1.60 (1.40–2.80)	22.80	8.00%	32.00	0.49 (0.36–0.67)	1.0 (0.67 to 1.49)		
Soria ⁴⁰	16.60 (12.6–27.2)	NR (29.30–NR)	72.50%	78.00	8.10 (5.80–11.10)	26.20 (29.30–NR)	26.70%	62.00	0.55 (0.42–0.73)	0.73 (0.50 to 1.08)		
Solomon ⁴¹	10.90 (8.30–13.90)	NR (45.80–NR)	74.00%	50.30	7.00 (6.80–15.00)	47.50 (32.20–NR)	45.00%	53.30	0.45 (0.35–0.60)	0.76 (0.55 to 1.05)		
WU ⁴²	11.10 (8.30–12.60)	28.50 (26.40–NR)	87.50%	–	6.80 (5.70–7.00)	27.70 (23.90–NR)	45.60%	–	0.40 (0.29–0.57)	0.90 (0.56 to 1.45)		
Shaw ⁴³	*	21.70	*	*	*	21.90	*	*	*	0.85 (0.66 to 1.10)		

*No access to full text.

AEs, adverse events; ALK, anaplastic lymphoma kinase; NE, not estimated; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

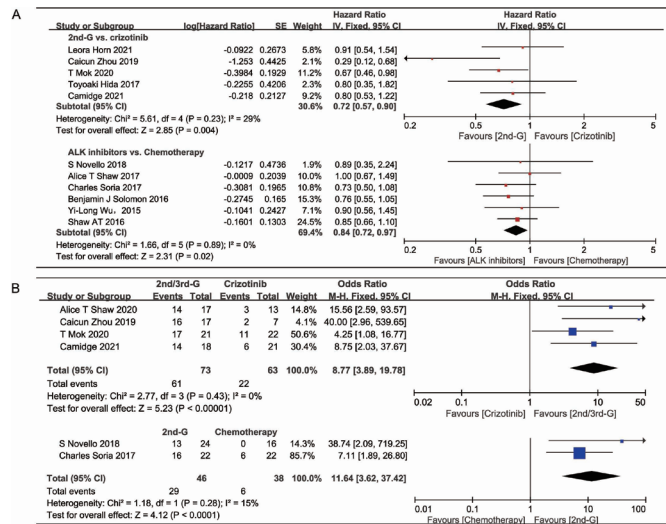


Figure 2 Forest plots for overall survival (A) and intracranial response with measurable brain metastases (B). ALK, anaplastic lymphoma kinase.

Secondary endpoints

Systemic response and intracranial response

In six studies including 1515 patients, the OR of systemic ORR comparing ALK-2ndG/3rdG with crizotinib was 1.85 (95% CI: 1.46 to 1.85), with extremely low heterogeneity (I²=0, p=0.49). In five studies including 1264 patients, the OR of systemic ORR comparing ALK-1stG/2ndG inhibitors with chemotherapy was 6.76 (95% CI: 4.16 to 10.97), with high heterogeneity (I²=61%, p=0.04) (online supplemental appendix 4, figure 4).

Nine studies included 2049 patients with any brain metastases (online supplemental appendix 3, table 2). Comparing ALK-2ndG/3rdG with crizotinib, the OR of ORR with any CNS lesions was 5.62 (95% CI: 2.74 to 11.53), with moderate heterogeneity (I²=62%, p<0.001). In three studies comparing ALK-1stG/2ndG with chemotherapy, the OR of ORR with any CNS lesions was 6.2 (95% CI: 2.26 to 16.99) with low heterogeneity (I²=48%, p<0.001) (online supplemental appendix 4, figure 5).

In case of intracranial response of patients with measurable (diameter ≥10mm) brain metastases, six studies included 220 patients with measurable brain metastases (online supplemental appendix 3, table 3). The OR of ALK-2ndG/3rdG versus crizotinib was 8.77 (95% CI: 3.89 to 19.78), with extremely low heterogeneity (I²=0, p<0.001). Two studies comparing ALK-2ndG with chemotherapy reported that the OR of ORR with measurable CNS lesions was 11.64 (95% CI: 3.62 to 37.42), with low heterogeneity (I²=15%, p<0.001) (figure 2B).

By adopting a network meta-analysis approach, we conducted intracranial response (figure 3) and AE (figure 3B) comparisons between ALK inhibitors and chemotherapy directly or indirectly. The global and local inconsistencies were conducted (p>0.05). In terms of ORR with measurable brain metastases, the ALK-3rdG lorlatinib yielded the best benefit of all ALK inhibitors (figure 4).

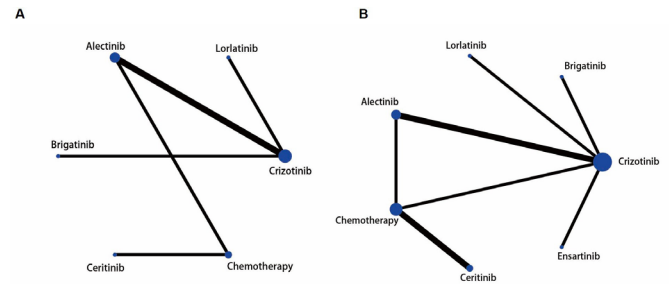


Figure 3 Network diagrams for comparisons on intracranial response (A) and adverse events (B). Each node denotes each treatment. The width of the lines is proportional to the number of trials comparing two treatments.

Adverse events

Ten studies including 1346 patients had reported grade ≥3 AEs (online supplemental appendix 4, figure 6). Despite having favourable efficacy, ALK-3rdG (lorlatinib) was found to have more severe AEs than alectinib and crizotinib. Alectinib was the only ALK-2ndG with less severe AEs than other ALK inhibitors and chemotherapy, while ceritinib showed the highest rate of severe AEs (figure 5).

The network meta-analysis depicted the relative ranking of each treatment based on the SUCRA value (figure 5B). The toxicity ranking of treatment from low to high was as follows: alectinib (SUCRA=0.01), crizotinib (0.24), chemotherapy (0.39), ensartinib (0.60), brigatinib (0.61), lorlatinib (0.79), ceritinib (0.87) for systemic grade ≥3 AEs; and alectinib (0.36), brigatinib (0.38), ensartinib

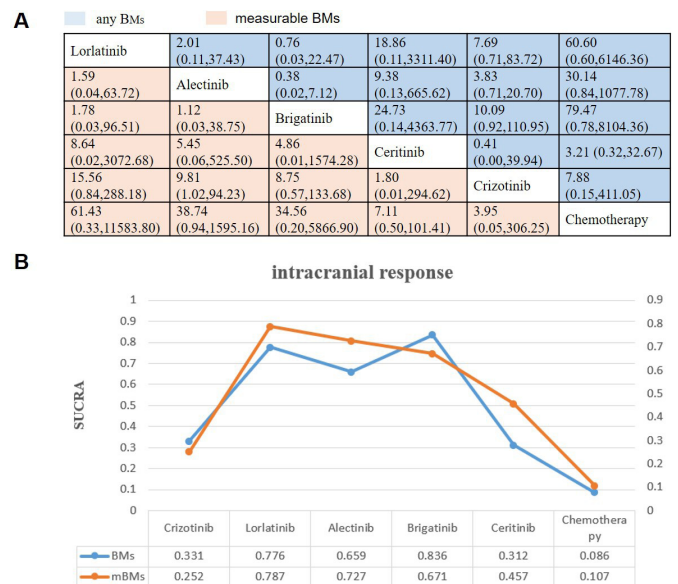


Figure 4 Pooled estimate (A) and relative rankings of ALK inhibitors (B) regarding intracranial response of patients with ALK-positive NSCLC with any brain lesions and mBMs (>10mm). OR and 95% CI for any brain lesions (upper triangle in blue) and measurable brain metastases (lower triangle in red). ALK, anaplastic lymphoma kinase; BMs, brain metastases; mBMs, measurable BMs; NSCLC, non-small cell lung cancer; SUCRA, surface under the cumulative ranking curve.

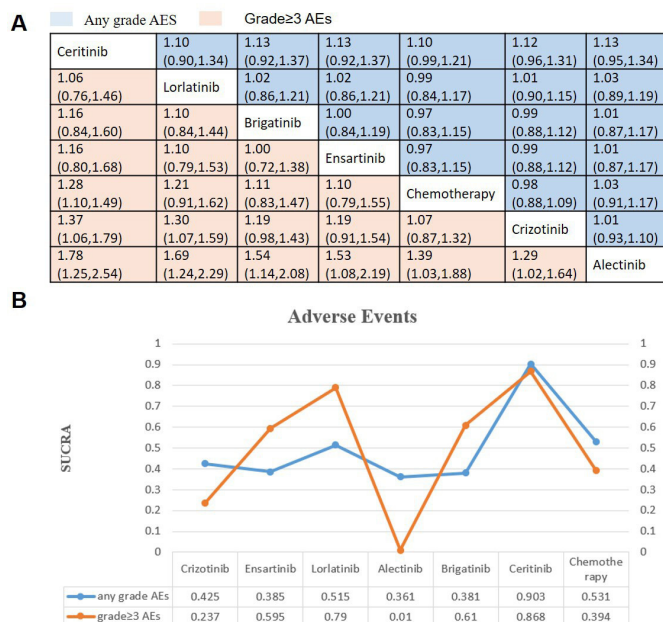


Figure 5 Pooled estimate (A) and relative rankings of ALK inhibitors (B) regarding all-grade AEs and grade ≥ 3 AEs in ALK-positive NSCLC. RR and 95% CI for all-grade AEs (upper triangle in blue) and grade ≥ 3 AEs (lower triangle in red). AE, adverse events; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; RR, relative risk; SUCRA, surface under the cumulative ranking curve.

(0.39), crizotinib (0.43), lorlatinib (0.52), ceritinib (0.90) for systemic any grade AEs.

Assessment of inconsistency

The test of global inconsistency regarding grade ≥ 3 AEs and intracranial response showed a similar or better fit of the consistency model than that of the inconsistency model, and the node splitting analysis showed no evidence of local inconsistency.

DISCUSSION

Throughout the recent randomised clinical trials relating second-generation inhibitors, the median PFS with alectinib in the ALEX Study (34.8 months) was significantly improved,³⁵ followed by ensartinib in the eXalt3 Study (25.8 months),³³ and brigatinib in the ALTA-1L Study (24.0 months).³⁷ However, the OS data of these studies are currently immature, with only HR available. In this meta-analysis, we updated the OS data of ALK-2ndG versus crizotinib, and comprehensively summarised the serious AEs, systemic and intracranial response of patients with brain metastases. Compared with crizotinib, ALK-2ndG inhibitors significantly improved OS of ALK-positive patients (HR=0.72, 95% CI 0.57 to 0.90, $p=0.004$), and the benefit in patients of ALK-3rdG (lorlatinib) versus crizotinib had a trend towards improved OS (HR=0.81, 95% CI 0.56 to 1.19, $p=0.29$).

Nevertheless, how to rationally and effectively use each generation of ALK inhibitors to treat patients with NSCLC

with brain metastases is worth exploring. Therefore, we further conducted a Bayesian network meta-analysis, and network heterogeneity and inconsistency were thoroughly investigated. There is no significant inconsistency in ALK-2ndG/3rdG inhibitors versus crizotinib and ALK inhibitors versus chemotherapy. For ALK inhibitor-naïve patients with brain metastases, it is recommended choosing the second-generation and third-generation ALK-tyrosine kinase inhibitors (TKIs) instead of chemotherapy and first-generation TKI for initial treatment. A significant benefit in intracranial response rate was observed in patients with measurable brain metastasis when ALK-3rdG/2ndG inhibitors versus crizotinib (OR=8.77, 95% CI 3.89 to 19.78, $p<0.001$) were used. In terms of intracranial response for patients with any brain metastases, our study suggested a generally greater efficacy for brigatinib, lorlatinib and alectinib, and moderate efficacy for ceritinib followed by crizotinib. Moreover, we performed the league table of systemic AEs, with detailed grade ≥ 3 AE rankings from high to low: ceritinib, lorlatinib, brigatinib, ensartinib, chemotherapy, crizotinib and alectinib. Considering both CNS and systemic efficacy and tolerability, alectinib seems to be the best choice for untreated ALK-positive NSCLC with longer PFS, higher intracranial ORR and lower toxicity than crizotinib, other ALK-2ndG inhibitors and chemotherapy.

Although ALK-3rdG inhibitors (lorlatinib) have better BBB permeability and better intracranial response rate than alectinib from indirect comparison, lorlatinib has been reported to be downregulating secreted phosphoprotein 1, inhibiting vascular endothelial growth factor, transforming growth factor beta and Claudin subsequently reducing the number of tight junctions between BBB cells.⁴⁴ However, the side-effect profile of lorlatinib was distinct and great. The most common grade ≥ 3 AEs in lorlatinib included hypercholesterolaemia, hypertriglyceridaemia, increased weight and oedema.¹⁹ Although there are no existing clinical studies comparing the efficacy of ALK-2ndG/3rdG inhibitors for advanced NSCLC after crizotinib resistance, lorlatinib was found to be more suitable for the follow-up treatment, with alectinib or crizotinib, with secondary ALK resistance mutations from single-arm phase II trials.^{19 45} Lorlatinib has been found to be retaining potency against all known ALK resistance mutations including G1202R, the most common secondary resistance mutation for ALK-2ndG inhibitors.⁴⁶

Different from Breadner *et al's* study,²¹ we added outcomes of ensartinib (eXalt3 trial, 2021) and lorlatinib (CROWN trial, 2020), and updated the latest OS data of brigatinib (ALTA-1L trial, 2021). As the trials and patient baseline data extracted were more comprehensive, this study indicated superior benefit in OS of the ALK-2ndG inhibitors relative to crizotinib, although further follow-up was required. Additionally, we extracted the measurable (diameter ≥ 10 mm) brain metastases baseline which was more suitable to assess the efficacy of ALK inhibitors on preventing or treating brain lesions. Combined with

previous clinical findings, the above results demonstrated that ALK-2ndG inhibitors had better PFS, OS and intracranial response than crizotinib. The network meta-analysis also indicated that alectinib showed superior efficacy and lower toxicity among ALK-2ndG inhibitors.

Limitations

This study also has some limitations. First, we did not analyse the impact of ALK fusion variants on efficacy of ALK inhibitors. The ALK gene mutation was initially detected by immunohistochemistry⁴⁷ and in situ immunofluorescence hybridisation.⁴⁸ These methods can only tell us that there is a fusion mutation in the ALK gene but cannot tell us which gene is fused with the ALK gene, and where fracture and fusion occurred at the site. With the advancement of next-generation gene sequencing technology, we can now clearly know which gene has a fusion mutation with the ALK gene, and where the break has occurred.⁴⁹ Most ALK fusion mutations occur between EML4 and ALK, accounting for 85% of all ALK fusion mutations. But the fusion between EML4 and ALK also has many fractures and fusion forms. More than 15 EML4-ALK fusion variants have been identified. The global phase III ALEX Study has shown that the EML4-ALK variant type did not influence alectinib treatment benefit, but the impact of non-EML4-ALK variants remains unclear. Second, regarding the few RCTs related to ALK-3rdG inhibitors, inadequate sample size and immature OS data, the efficacy and safety of ALK-3rdG inhibitors remain further to be investigated. Third, there are no direct RCTs that compare between ALK-3rdG and ALK-2ndG, or between ALK-2ndG and ALK-1stG inhibitors, thus it is difficult to draw definitive conclusions from the only indirect comparisons through a network meta-analysis. Cross-trial comparisons are inherently limited due to differences in study designs and populations.

CONCLUSIONS

This meta-analysis indicated that the ALK-2ndG inhibitors significantly improved the OS, systemic and intracranial response of patients with ALK-positive NSCLC. Particularly, alectinib showed superior efficacy and lower toxicity among the ALK-2ndG inhibitors, and further RCTs are needed to directly compare lorlatinib with ALK-2ndG inhibitors.

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analysis. YW—guarantor. YW and XR—conception and design, revision, supervision, approval and funding.

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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.

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