Original Article

Efficacy of ALK inhibitors in Asian patients with ALK inhibitor-naïve advanced *ALK*-positive non-small cell lung cancer: a systematic review and network meta-analysis

Xuchang Li, Yangchen Xia, Chengyan Wang, Shanshan Huang, Qian Chu

Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: Q Chu; (II) Administrative support: S Huang; (III) Provision of study materials or patients: X Li, Y Xia, S Huang; (IV) Collection and assembly of data: C Wang, Q Chu; (V) Data analysis and interpretation: X Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shanshan Huang, PhD. Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Qiaokou District, Wuhan 430030, China. Email: hss940424@163.com.

Background: A previous network meta-analysis (NMA) compared the efficacy of anaplastic lymphoma kinase (ALK) inhibitors in *ALK*-positive non-small cell lung cancer (NSCLC). The phase III INSPIRE study of iruplinalkib was published recently. The present study aimed to add the results related to iruplinalkib to the NMA.

Methods: A systematic literature search was performed in PubMed, Embase, Cochrane Library, Google, and Baidu. Randomized controlled trials (RCTs) reporting the independent review committee-assessed progression-free survival (PFS), objective response rate (ORR), or disease control rate (DCR) results of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC were eligible for inclusion in the NMA. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Bayesian fixed-effect models were used for the direct and indirect pairwise comparisons. This study was registered with PROSPERO (CRD42024555299).

Results: Eight studies, involving 1,477 Asian patients and seven treatments (crizotinib, alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib), were included in the NMA. In terms of the overall risks of bias, all of the studies had "some concerns". All the next-generation ALK inhibitors were statistically superior to crizotinib in terms of PFS. Iruplinalkib had the best surface under the cumulative ranking curve (74.0%), followed by brigatinib (69.1%) and ensartinib (63.7%). Most of the pairwise comparisons did not reveal significant differences in the ORR and DCR. In terms of both the ORR and DCR, alectinib ranked first, followed by lorlatinib.

Conclusions: Next-generation ALK inhibitors had better efficacy than crizotinib in the treatment of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC. Iruplinalkib may have more favorable PFS benefit than other ALK inhibitors for Asians.

Keywords: Non-small cell lung cancer (NSCLC); anaplastic lymphoma kinase (ALK); targeted therapy; network meta-analysis (NMA)

Submitted Jul 16, 2024. Accepted for publication Aug 22, 2024. Published online Aug 28, 2024.
doi: 10.21037/tlcr-24-604
View this article at: https://dx.doi.org/10.21037/tlcr-24-604

Introduction

Lung cancer is the most incident tumor, with the highest cancer mortality rate worldwide (1). Anaplastic lymphoma kinase (*ALK*) alterations are a group of driver genes. Of which, *EML4-ALK* is the most frequent alteration, with incidence rates ranging from 3% to 7% in global patients with non-small cell lung cancer (NSCLC) (2-4). In Asians, approximately 9% of NSCLC patients have been reported to have the *ALK*-positive disease (5,6).

ALK tyrosine kinase inhibitors (TKIs) are recommended for the treatment of advanced *ALK*-positive NSCLC (7,8). Crizotinib, a first-generation ALK TKI, has been shown to have better efficacy than chemotherapy (9,10). In randomized controlled trials (RCTs), next-generation ALK TKIs (alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib) result in longer progression-free survivals (PFSs) than crizotinib in patients with ALK TKI-naïve advanced *ALK*-positive NSCLC (11-21). However, no head-to-head RCTs have been conducted to examine different next-generation ALK TKIs in the ALK TKI-naïve setting. A previous network meta-analysis (NMA) indicated that global and Asian patients may have distinct prognoses after ALK TKI treatment in the first-line (treatment-naïve) setting (22). Further, in terms of PFS, lorlatinib has been shown to have the best efficacy for global patients, followed by alectinib and brigatinib (22). While for Asian patients, it is indicated that alectinib has a greater PFS benefit than other ALK TKIs (22).

The results of the phase III INSPIRE study of iruplinalkib were recently published (19,20). The INSPIRE study was not included in the latest NMA. Therefore, we conducted a systematic review and NMA to compare the efficacy of iruplinalkib and other ALK TKIs for Asian patients with TKI-naïve advanced *ALK*-positive NSCLC. The protocol was registered in PROSPERO (CRD42024555299). We present this article in accordance with the PRISMA NMA reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-604/rc).

Highlight box

Key findings

- Next-generation anaplastic lymphoma kinase (ALK) inhibitors had better efficacy than crizotinib in the treatment of Asian patients with ALK inhibitor-naïve advanced *ALK*-positive non-small cell lung cancer (NSCLC). And iruplinalkib was likely to have more favorable PFS benefit in Asians.

What is known and what is new?

- Previous network meta-analysis (NMA) compared ALK inhibitors. However, data of iruplinalkib were not included in the NMA.
- The present NMA provided the results of comparisons of each ALK inhibitors in efficacy.

What is the implication, and what should change now?

- Iruplinalkib showed encouraging PFS benefit for Asian patients with ALK inhibitor-naïve advanced *ALK*-positive NSCLC, and OS data are awaited.

Methods

A systematic literature search was performed in PubMed, Embase, and Cochrane Library to retrieve articles or meeting abstracts published up to December 26, 2023. Search engines (i.e., Google and Baidu) were also used to find eligible studies. The key search terms included "non-small cell lung cancer", "randomized controlled trial", "crizotinib", "alectinib", "brigatinib", "ceritinib", "ensartinib", "envonalkib", "iruplinalkib", and "lorlatinib". The detailed search strategy is summarized in Table S1. Finally, the reference lists of the relevant articles were checked to identify additional reports.

Eligible criteria

Studies were included in the NMA if the following criteria were met: (I) related to articles or meeting abstracts of a RCT written in English; (II) compared ALK TKIs for TKI-naïve advanced *ALK*-positive NSCLC; and (III) reported independent review committee (IRC)-assessed PFS, objective response rate (ORR), or disease control rate (DCR) results for Asian patients. If the full text was not available, the article was not included in the analysis. Two reviewers (X.L. and Y.X.) independently reviewed the titles, abstracts, and full texts of the articles. Any disagreements as to whether an article met the inclusion criteria were resolved through discussion or consultation with a third reviewer (S.H.).

Data extraction and risk of bias assessment

The following data were independently extracted from the eligible reports by two reviewers (C.W. and Q.C.) using a standardized sheet: first author's name, publication year, study name, registration number, country or region, race, number of patients, age, sex, treatment line, regimen,

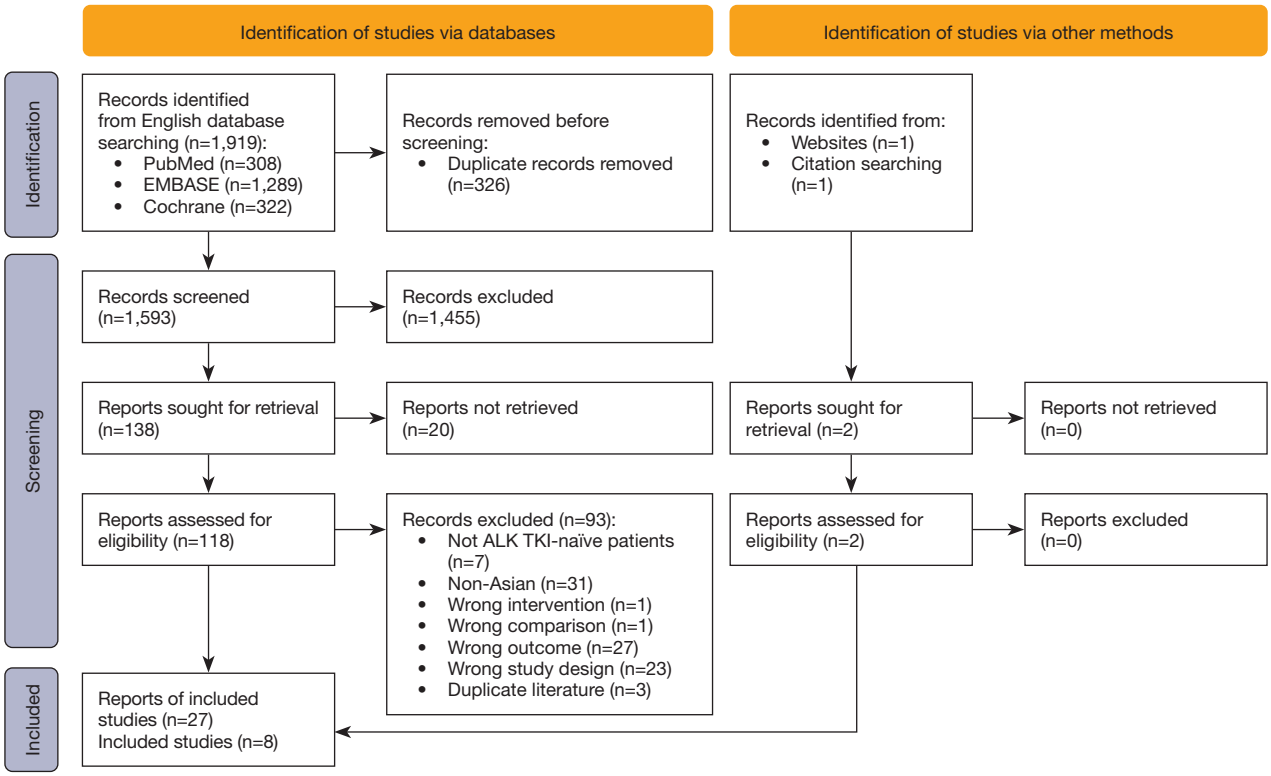

Figure 1 Flow chart of study selection. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

hazard ratio (HR) with confidence interval (CI) for IRC-assessed PFS between the experimental and control groups, and number of patients with an IRC-assessed objective response or disease control. If the results of a study had been reported multiple times, the latest efficacy results for Asian patients were included in the NMA, and the study characteristics were extracted from the latest report or another report at the discretion of the reviewers. If a report had results for global and Asian patients, only the data related to Asians were extracted. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool (23).

Statistical analysis

Bayesian fixed-effects models were used for the direct and indirect pairwise comparisons of the PFS, ORR, and DCR because most of the comparisons were made using only one study. The PFS results were expressed as the HR with the 95% credible interval (CrI). The ORR and DCR results were expressed as the odds ratio (OR) with the 95% CrI. Heterogeneity was not assessed because there were too few studies. As there was no closed loop of treatments, neither local nor global inconsistency was evaluated. If a study only reported the CI of the HR for PFS other than the 95% CI, it was converted to the 95% CI using the Z-score. Cumulative ranking curves were plotted. Each curve represents a treatment. The horizontal axis represents the ranks. The vertical axis is the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. The surfaces under the cumulative ranking curve (SUCRAs) were also estimated. The SUCRA is a value between 0 and 100%. The higher the SUCRA, the more likely the drug is to be the best (24). The statistical analyses were conducted using the R packages "gemtc" and "rjags" of R software (version 4.3.0, R Core Team).

Results

Study selection and characteristics

In the initial search, 1,919 records were retrieved, and 326 duplicated records were removed. After the screening, 27 reports of eight studies, comprising a total of 1,477 Asian patients, were included in the analysis (*Figure 1*).

Table 1 Study characteristics

First author	Trial name/ number	Region	Experimental treatment	Control treatment	Sample size of Asians	No. of Asian patients who previously underwent chemotherapy for advanced disease	HR (95% CI) for PFS in Asians[†]	No. of Asian patients who achieved an objective response[†]	No. of Asian patients who achieved disease control[†]
Mok, 2017 (11)	ALEX	Global	Alectinib 600 mg bid	Crizotinib 250 mg bid	69/69	Not allowed	0.49 (0.30–0.79)	Not reported	Not reported
Nakagawa, 2020/ Hida, 2017 (12,13)	J-ALEX	Japan	Alectinib 300 mg bid		103/104	37/37	0.37 (0.26–0.52)	76 of 83/71 of 90[‡]	80 of 83/83 of 90[‡]
Zhou, 2019 (14)	ALESIA	Asia	Alectinib 600 mg bid		125/62	Not allowed	0.37 (0.22–0.61)	Not reported	Not reported
Ahn, 2022 (15)	ALTA-1L	Global	Brigatinib 180 mg qd with 7-day lead-in at 90 mg qd		59/49	19/12	0.35 (0.20–0.59)	47/35	53/45
Zhou, 2022/Horn, 2021 (16,17)	eXalt3	Global	Ensatinib 225 mg qd		77/84	15 of 73/21 of 78[§]	0.37 (0.23–0.58)	59 of 73/53 of 78[§]	66 of 73/70 of 78[§]
Yang, 2023 (18)	NCT04009317	China	Envonalkib 600 mg bid		131/133	33/32	0.47 (0.34–0.64)	107/94	120/118
Shi, 2023/Shi, 2024 (19,20)	INSPIRE	China	Iruplinalkib 180 mg qd with 7-day lead-in at 60 mg qd		143/149	24/25	0.34 (0.23–0.52)[¶]	133/133	138/142
Zhou, 2023 (21)	CROWN	Global	Lorlatinib 100 mg qd		59/61	Not allowed	0.40 (0.23–0.71)	46/35	53/52[ǀ]

[†], IRC-assessed results; [‡], based on patients with measurable lesions by an IRC; [§], based on modified intent-to-treat population; [¶], 98.02% CI; [ǀ], including one/ two patients with non-complete response or non-progressive disease. No., number; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; bid, twice a day; qd, once daily; IRC, independent review committee.

Four studies were international RCTs. One study was conducted in Asia, two studies in China, and one study in Japan. Treatments included crizotinib, alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib. No eligible study of ceritinib was found. The characteristics of the selected studies are summarized in *Table 1*. All the studies had a "low risk" in terms of the missing outcome data but had "some concerns" in some of the other domains. In terms of the overall risks of bias, all of the studies had "some concerns" (Figure S1).

Efficacy

As Figure S2A shows, all the next-generation ALK TKIs were compared with crizotinib in terms of PFS, but there were no direct comparisons of the next-generation drugs. In terms of IRC-assessed PFS, the pairwise comparisons showed that the next-generation ALK TKIs (alectinib, brigatinib, ensartinib, envonalkib, iruplinalkib, and lorlatinib) had significantly better efficacy than crizotinib in Asians. However, no significant difference was found between each next-generation ALK TKI (*Figure 2*). In the ranking of IRC-assessed PFS, iruplinalkib had the highest SUCRA (74.0%). Thus, iruplinalkib was more likely to have the best efficacy of the drugs in Asians, followed by brigatinib, ensartinib, lorlatinib, and alectinib (SUCRAs: 69.1%, 63.7%, 54.8%, and 54.8%, respectively; *Figure 3*).

Six studies reported the ORR and DCR results (Figure S2B). The ORRs for alectinib, envonalkib, and lorlatinib were significantly better than the ORR for crizotinib. The ORs were 3.00 (95% CrI: 1.22–8.24), 1.86 (95% CrI: 1.04–3.39), and 2.68 (95% CrI: 1.22–6.09), respectively. No significant difference was found in the pairwise comparisons of the other treatments (*Figure 4*). The next-generation ALK TKIs (except brigatinib) had higher DCRs than crizotinib. None of the differences were statistically significant

Alectinib						
1.14 (0.63–2.07)	Brigatinib					
1.08 (0.64–1.82)	0.95 (0.46–1.93)	Ensartinib				
0.85 (0.57–1.26)	0.74 (0.40–1.39)	0.79 (0.45–1.38)	Envonalkib			
1.17 (0.73–1.89)	1.03 (0.52–2.02)	1.09 (0.59–2.01)	1.38 (0.82–2.32)	Iruplinalkib		
0.99 (0.54–1.84)	0.88 (0.40–1.91)	0.93 (0.45–1.91)	1.18 (0.62–2.24)	0.85 (0.42–1.71)	Lorlatinib	
0.40 (0.31–0.51)	**0.35 (0.20–0.60)**	**0.37 (0.23–0.59)**	**0.47 (0.34–0.65)**	**0.34 (0.23–0.51)**	**0.40 (0.23–0.70)**	Crizotinib

Figure 2 NMA of IRC-assessed PFS. The data are expressed as the HR (95% CrI). A HR less than 1 favors the column-defining intervention. The significant results are presented in bold. NMA, network meta-analysis; IRC, independent review committee; PFS, progressive-free survival; HR, hazard ratio; CrI, credible interval.

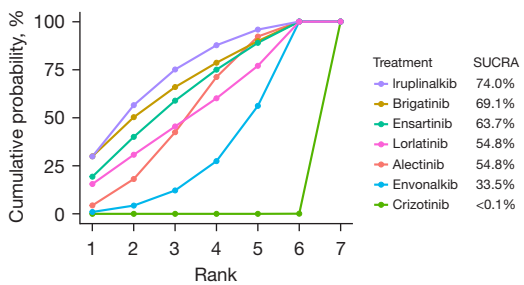

Figure 3 SUCRA of IRC-assessed PFS. SUCRA, surface under the cumulative ranking curve; IRC, independent review committee; PFS, progressive-free survival.

(*Figure 4*). The top three best treatments in terms of the ORR were alectinib, lorlatinib, and ensartinib (SUCRAs: 79.9%, 74.9%, and 56.3%, respectively; *Figure 5A*). In terms of the DCR, alectinib ranked first, followed by lorlatinib and envonalkib (SUCRAs: 78.4%, 61.8%, and 57.0%, respectively; *Figure 5B*).

Discussion

The present systematic review and NMA compared the efficacy of ALK TKIs for TKI-naïve advanced *ALK*-positive NSCLC in an Asian population. After a comprehensive literature search, eight RCTs were included in the NMA. The results indicated that next-generation ALK TKI resulted in longer PFSs than crizotinib. Iruplinalkib had the highest SUCRA. Thus, iruplinalkib may bring better PFS benefit than other ALK TKIs for Asian patients with TKI-naïve advanced *ALK*-positive NSCLC.

Several RCTs have shown that next-generation ALK TKIs are more efficacious than crizotinib. Thus, next-generation ALK TKIs have become the preferred treatment options for *ALK*-positive NSCLC (7,8). However, there is a lack of head-to-head comparisons between each next-generation ALK TKI. In the first-line setting, a previous NMA, for which the cut-off date was December 2022, found that lorlatinib had the best efficacy in terms of PFS for global *ALK*-positive NSCLC patients, followed by alectinib, brigatinib, and ensartinib. For Asian patients, the top three first-line treatments were alectinib, ensartinib, and brigatinib (22). The results of the phase III INSPIRE study of iruplinalkib were first presented at the World Conference of Lung Cancer in September 2023 (19). The full text of the study results was published in January 2024 (20). The HR for IRC-assessed PFS reached 0.34 (98.02% CI: 0.23–0.52), showing its promising anti-tumor activity. In the present study, the efficacy of iruplinalkib and other ALK TKIs were compared. Iruplinalkib resulted in the best PFS benefit, followed by brigatinib, ensartinib, lorlatinib, and alectinib. The rankings of these drugs differ to those reported in the previous NMA. There might be two reasons for this discrepancy. First, the restricted mean survival time model was used in the previous NMA, while the present NMA ranked treatments based on the SUCRA. Second, the previous study included RCTs comparing crizotinib and chemotherapy, and ceritinib and chemotherapy, which were excluded from the present NMA.

In terms of the ORR and DCR, we found that most of the pairwise comparisons did not show any statistically significant differences. This might be because the rates were quite high (ORR: approximately 70–90%; DCR: approximately 90%), and the sample sizes of Asians were too small to detect the minor differences. In the present study, in terms of both ORR and DCR, alectinib ranked first, followed by lorlatinib.

Alectinib	0.31 (0.04–2.19)	0.46 (0.07–2.62)	0.59 (0.10–2.92)	0.58 (0.08–3.66)	0.66 (0.10–4.00)	0.42 (0.09–1.63)
1.91 (0.54–7.22)	Brigatinib	1.44 (0.25–8.74)	1.87 (0.39–9.91)	1.86 (0.30–12.38)	2.09 (0.37–13.04)	1.32 (0.34–5.57)
1.50 (0.45–5.24)	0.79 (0.24–2.52)	Ensartinib	1.30 (0.33–5.17)	1.28 (0.25–6.69)	1.45 (0.30–7.22)	0.92 (0.30–2.75)
1.61 (0.55–5.08)	0.85 (0.29–2.48)	1.07 (0.42–2.86)	Envonalkib	0.99 (0.23–4.42)	1.12 (0.28–4.70)	0.71 (0.30–1.61)
1.85 (0.53–6.61)	0.97 (0.28–3.30)	1.23 (0.40–3.81)	1.14 (0.40–3.11)	Iruplinalkib	1.13 (0.21–5.93)	0.72 (0.20–2.33)
1.12 (0.33–4.04)	0.59 (0.17–1.97)	0.75 (0.25–2.25)	0.69 (0.25–1.86)	0.60 (0.19–1.97)	Lorlatinib	0.64 (0.20–1.92)
3.00 (1.22–8.24)	1.58 (0.65–3.88)	2.00 (0.96–4.39)	**1.86 (1.04–3.39)**	1.63 (0.72–3.87)	**2.68 (1.22–6.09)**	Crizotinib

Figure 4 NMA of the IRC-assessed ORR (lower left) and DCR (upper right). The data are expressed as the OR (95% CrI). An OR greater than 1 favors the column-defining intervention. The significant results are presented in bold. NMA, network meta-analysis; IRC, independent review committee; ORR, objective response rate; DCR, disease control rate; OR, odds ratio; CrI, credible interval.

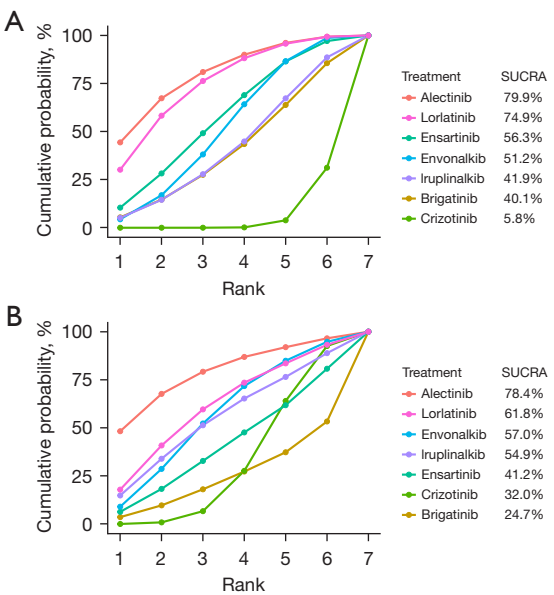

Figure 5 SUCRAs. (A) IRC-assessed ORR; (B) DCR. SUCRAs, surfaces under the cumulative ranking curve; IRC, independent review committee; ORR, objective response rate; DCR, disease control rate.

Due to insufficient data, overall survival (OS) was not analyzed in the present study. As surrogate endpoints, PFS is better correlated with OS, while ORR lacks validity for the surrogacy of OS (25). Thus, iruplinalkib, which results in the best PFS, may have better efficacy for Asians.

Our study had several limitations. First, the efficacy for the subgroups (e.g., patients with or without brain metastasis) and OS of Asians were not analyzed because the international RCT did not report these results (15,21). Additionally, transitivity, which is important for indirect comparisons, might be affected due to differences in the baseline characteristics, protocols, etc. across the studies. Thus, the results of the present NMA should be interpreted with caution.

Conclusions

Next-generation ALK TKIs showed significantly superior efficacy compared to crizotinib in the treatment of Asian patients with ALK TKI-naïve advanced *ALK*-positive NSCLC. Iruplinalkib may provide better PFS benefit than other TKIs for Asians.

Acknowledgments

Funding: This study was supported by the Key Program of National Natural Science Foundation of China (No. 62131009) and the Key-Area Research and Development Program of Hubei Province (No. 2022BCA020).

Footnote

Reporting Checklist: The authors have completed the PRISMA NMA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-604/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-604/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-604/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
2. Dearden S, Stevens J, Wu YL, et al. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol 2013;24:2371-6.
3. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008;14:4275-83.
4. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
5. Jazieh AR, Gaafar R, Errihani H, et al. Real-World Data on the Prevalence of Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer in the Middle East and North Africa. JCO Glob Oncol 2021;7:1556-63.
6. Ying J, Li L, Li W, et al. P1. 09-05 ALK Testing in Chinese Advanced NSCLC Patients: A National-Wide Multicenter Prospective Real-World Data Study (The RATICAL Study). J Thorac Oncol 2019;14:S497.
7. National Comprehensive Cancer Network®. NCCN Guidelines® - Non-Small Cell Lung Cancer V3.2024. [cited 2024 Mar 29]. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
8. Chinese Association for Clinical Oncologists; Medical Oncology Branch of China International Exchange and Promotive Association for Medical and Health Care. China expert recommendations on anaplastic lymphoma kinase-tyrosine kinase inhibitors treatment for advanced non-small cell lung cancer (2024 edition). Zhonghua Yi Xue Za Zhi 2024;104:473-85.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
10. Wu YL, 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.
11. Mok TSK, Peters S, Camidge DR, et al. Alectinib (ALC) vs crizotinib (CRZ) in treatment-naïve ALK+ non-small-cell lung cancer (NSCLC): Asian vs non-Asian subgroup analysis of the ALEX study. Ann Oncol 2017;28:x191.
12. Nakagawa K, Hida T, Nokihara H, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. Lung Cancer 2020;139:195-9.
13. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29-39.
14. Zhou C, Kim SW, 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.
15. Ahn MJ, Kim HR, Yang JCH, et al. Efficacy and Safety of Brigatinib Compared With Crizotinib in Asian vs. Non-Asian Patients With Locally Advanced or Metastatic ALK-Inhibitor-Naive ALK+ Non-Small Cell Lung Cancer: Final Results From the Phase III ALTA-1L Study. Clin Lung Cancer 2022;23:720-30.
16. Zhou Q. eXalt 3 study: First release of Asian population's efficacy in ALK-positive non-small cell lung cancer (NSCLC). 2022. Available online: https://www.liangyihui.net/class/102928
17. Horn L, Wang Z, Wu G, et al. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Randomized Clinical Trial. JAMA Oncol 2021;7:1617-25.
18. Yang Y, Min J, Yang N, et al. Envonalkib versus crizotinib for treatment-naive ALK-positive non-small cell lung cancer: a randomized, multicenter, open-label, phase III trial. Signal Transduct Target Ther 2023;8:301.
19. Shi Y, Chen J, Yang R, et al. OA03. 05 A Randomized, Phase 3 Study of Iruplinalkib (WX-0593) vs Crizotinib in Locally Advanced or Metastatic ALK+ Non-small Cell Lung Cancer (NSCLC). J Thorac Oncol 2023;18:S49-50.

20. Shi Y, Chen J, Yang R, et al. Iruplinalkib (WX-0593) Versus Crizotinib in ALK TKI-Naive Locally Advanced or Metastatic ALK-Positive NSCLC: Interim Analysis of a Randomized, Open-Label, Phase 3 Study (INSPIRE). J Thorac Oncol 2024;19:912-27.
21. Zhou Q, Soo RA, Chang GC, et al. Asian Subgroup Analysis of the Randomized Phase 3 CROWN Study of First-Line Lorlatinib Versus Crizotinib in Advanced ALK-Positive NSCLC. JTO Clin Res Rep 2023;4:100499.
22. Zhao M, Shao T, Shao H, et al. Identifying optimal ALK inhibitors in first- and second-line treatment of patients with advanced ALK-positive non-small-cell lung cancer: a systematic review and network meta-analysis. BMC Cancer 2024;24:186.
23. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). 2023 [cited 2024 Apr 17]. Available online: https://training.cochrane.org/handbook
24. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163-71.
25. Hua T, Gao Y, Zhang R, et al. Validating ORR and PFS as surrogate endpoints in phase II and III clinical trials for NSCLC patients: difference exists in the strength of surrogacy in various trial settings. BMC Cancer 2022;22:1022.

(English Language Editor: L. Huleatt)

Cite this article as: Li X, Xia Y, Wang C, Huang S, Chu Q. Efficacy of ALK inhibitors in Asian patients with ALK inhibitor-naïve advanced *ALK*-positive non-small cell lung cancer: a systematic review and network meta-analysis. Transl Lung Cancer Res 2024;13(8):2015-2022. doi: 10.21037/tlcr-24-604

Supplementary

Table S1 Search strategy

Database name and code number of keywords	Keywords
PubMed	
#1	"Carcinoma, Non-Small-Cell Lung"[MeSH] OR "Adenocarcinoma of Lung"[MeSH] OR non-small-cell lung carcinoma*[tw] OR nonsmall cell lung cancer*[tw] OR NSCLC[tw] OR lung squamous carcinoma*[tw] OR squamous cell lung carcinoma*[tw] OR lung squamous cell carcinoma*[tw] OR pulmonary squamous carcinoma*[tw] OR pulmonary squamous cell carcinoma*[tw] OR lung adenocarcinoma*[tw] OR pulmonary adenocarcinoma*[tw] OR large cell lung cancer*[tw]
#2	"alectinib"[Supplementary Concept] OR alectinib[tw] OR "af 802"[tw] OR alecensa[tw] OR alecensaro[tw] OR "ch 5424802"[tw] OR ch5424802[tw] OR ro5424802[tw] OR "brigatinib"[Supplementary Concept] OR brigatinib[tw] OR "ap 26113"[tw] OR ap26113[tw] OR alunbrig[tw] OR "ensartinib"[Supplementary Concept] OR ensartinib[tw] OR "x 396"[tw] OR "lorlatinib"[Supplementary Concept] OR lorlatinib[tw] OR loratinib[tw] OR "pf 06463922"[tw] OR lorbrena[tw] OR envonalkib[tw] OR "tq-b3139"[tw] OR lruplinalkib[tw] OR wx-0593[tw] OR "ceritinib"[Supplementary Concept] OR zykadia[tw] OR ldk378[tw]
#3	("controlled clinical trial"[pt] OR "Controlled Clinical Trials as Topic"[MeSH] OR "Random Allocation"[MeSH] OR "Double-Blind Method"[MeSH] OR "single-blind method"[MeSH] OR "Control Groups"[MeSH] OR "cross-over studies"[MeSH] OR random*[tiab] OR placebo[tiab] OR trial[tiab] OR groups[tiab] OR crossover[tiab] OR cross-over[tiab]) NOT ("Animals"[Mesh] NOT ("Humans"[MeSH] AND "Animals"[MeSH]))
#4	#1 AND #2 AND #3
Embase	
#1	'non small cell lung cancer'/exp OR 'lung adenocarcinoma'/exp OR 'non small cell lung cancer':ti,ab,kw OR nsclc:ti,ab,kw OR 'squamous cell lung carcinoma':ti,ab,kw OR 'lung squamous cell carcinoma*':ti,ab,kw OR 'lung squamous carcinoma cell line':ti,ab,kw OR 'pulmonary squamous cell carcinoma*':ti,ab,kw OR 'lung adenocarcinoma':ti,ab,kw OR 'pulmonary adenocarcinoma*':ti,ab,kw OR 'large cell lung carcinoma':ti,ab,kw
#2	'alectinib'/exp OR alectinib:ti,ab,kw OR ro5424802:ti,ab,kw OR 'brigatinib'/exp OR brigatinib:ti,ab,kw OR ap26113:ti,ab,kw OR 'ensartinib'/exp OR ensartinib:ti,ab,kw OR 'x 396':ti,ab,kw OR 'lorlatinib'/exp OR lorlatinib:ti,ab,kw OR loratinib:ti,ab,kw OR 'pf 06463922':ti,ab,kw OR envonalkib:ti,ab,kw OR iruplinalkib:ti,ab,kw OR 'wx 0593':ti,ab,kw OR 'ceritinib'/exp OR ceritinib:ti,ab,kw
#3	('controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'double blind procedure'/de OR 'control group'/de OR 'crossover procedure'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR 'placebo'/de OR 'randomization'/exp OR random*:ab,ti,kw OR trial:ab,ti,kw OR groups:ab,ti,kw OR placebo*:ab,ti,kw OR crossover:ab,ti,kw OR 'cross-over':ab,ti,kw) NOT (('nonhuman'/exp OR 'animal'/exp) NOT 'human'/exp
#4	#1 AND #2 AND #3
Cochrane	
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2	MeSH descriptor: [Adenocarcinoma of Lung] explode all trees
#3	non-small-cell lung carcinoma* OR nonsmall cell lung cancer* OR NSCLC OR lung squamous carcinoma* OR squamous cell lung carcinoma* OR lung squamous cell carcinoma* OR pulmonary squamous carcinoma* OR pulmonary squamous cell carcinoma* OR lung adenocarcinoma* OR pulmonary adenocarcinoma* OR large cell lung cancer*
#4	#1 OR #2 OR #3
#5	alectinib OR "af 802" OR alecensa OR alecensaro OR "ch 5424802" OR ch5424802 OR ro5424802 OR brigatinib OR "ap 26113" OR ap26113 OR alunbrig OR ensartinib OR "x 396" OR lorlatinib OR loratinib OR "pf 06463922" OR lorbrena OR envonalkib OR "tq-b3139" OR lruplinalkib OR wx-0593 OR zykadia OR ldk378
#6	#4 AND #5

https://dx.doi.org/10.21037/tlcr-24-604

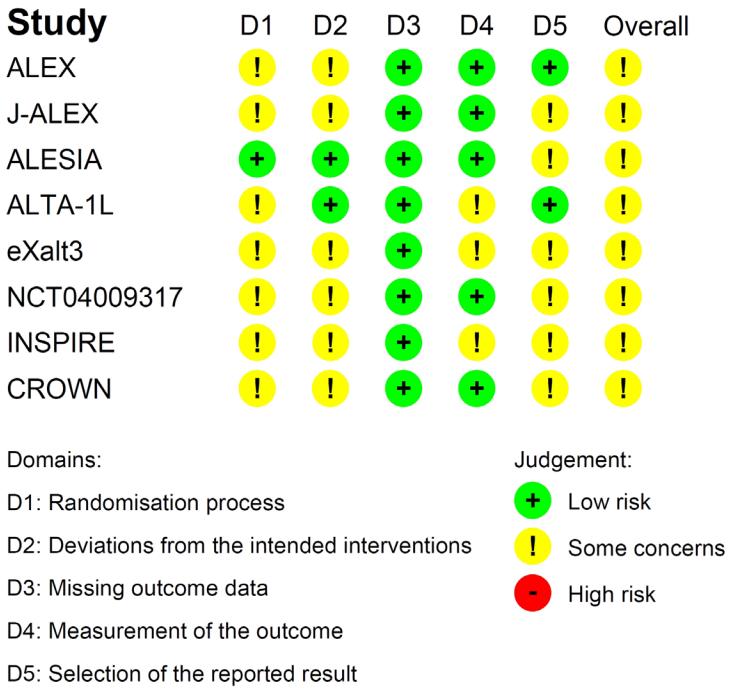

Figure S1 Risks of bias assessed using the Cochrane Risk of Bias 2 tool.

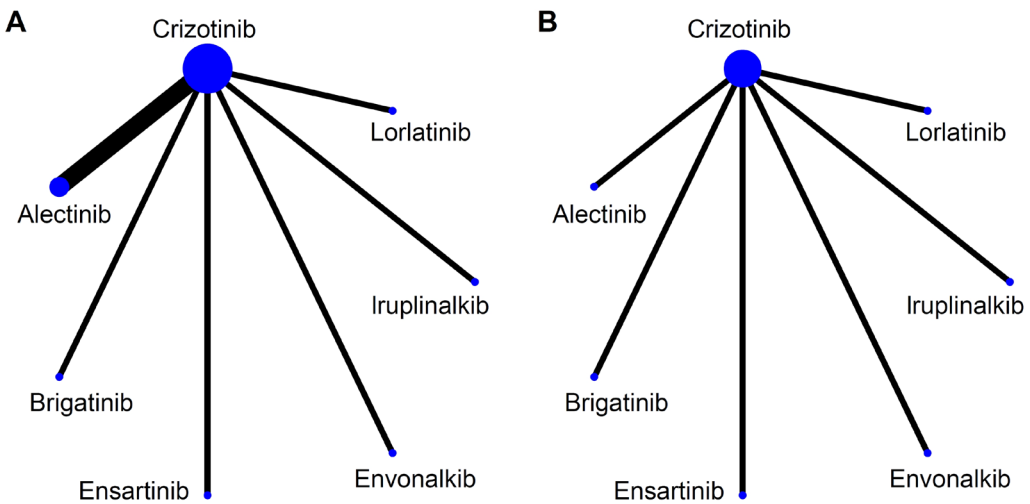

Figure S2 Network diagram of treatments. (A) Comparison on IRC-assessed PFS; (B) comparison on IRC-assessed ORR and DCR. IRC, independent review committee; PFS, progressive-free survival; ORR, objective response rate; DCR, disease control rate.

https://dx.doi.org/10.21037/tlcr-24-604