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Efficacy and safety of anaplastic lymphoma kinase inhibitors for non–small cell lung cancer: A systematic review and network meta-analysis

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Abstract

Background: To assess the efficacy and safety of anaplastic lymphoma kinase inhibitors (ALKIs) for the treatment of advanced-stage ALK rearrangement-positive non–small cell lung cancer (NSCLC).

Methods: We searched PubMed, EMBASE, and the Cochrane Library for randomized controlled trials (RCTs) that included patients with ALK-positive NSCLC receiving ALKIs. The outcomes of the study included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (TRAEs) of grade ≥3.

Results: A total of 12 RCTs consisting of 3169 patients with eight treatment options were included in this study. Our results showed that ALKIs have superior efficacy in OS, PFS, and ORR than chemotherapy or crizotinib (first-generation ALKI). Our study showed that only alectinib has a significant improvement in OS compared to chemotherapy (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.40–0.94). Alectinib appeared to have better OS than crizotinib (HR, 0.66; 95% CI, 0.45–0.95). Ensartinib has a significant PFS advantage over alectinib (HR, 0.62; 95% CI, 0.40–0.96). The surface under the ranking curve indicated that ensartinib (99.0%) was the highest rank regarding PFS. Moreover, both ensartinib and ceritinib showed significantly higher TRAEs of grade ≥3 compared with chemotherapy (risk ratios [RR], 2.74; 95% CI, 1.45–5.18; RR, 1.80; 95% CI, 1.26–2.57, respectively).

Conclusions: These results indicated that alectinib could be associated with the best therapeutic efficacy and well-tolerance AEs in the treatment of ALK-positive NSCLC.

KEYWORDS
anaplastic lymphoma kinase inhibitors, non-small cell lung cancer, objective response rate, overall survival, progression-free survival

INTRODUCTION

Lung cancer is the second most common cancer and the leading cause of death in 2020, with a 5-year survival rate of 15%.[1] Approximately 80%–85% of lung cancers are non–small-cell lung cancer (NSCLC).[2] In the last two decades, significant advances in the treatment of NSCLC have contributed to our understanding of driver mutations and the corresponding advances in therapeutic approaches. Some examples of these are small molecular tyrosine kinase inhibitors (TKIs), anti-angiogenesis agents, and immune checkpoint inhibitors (ICIs).[3] In recent years, the implementation of high-throughput sequencing platforms has led to the identification of uncommon molecular alterations in oncogenic drivers (e.g., *BRAF*, *MET*, *RET*, *HER2*, and *NTRK*). Moreover, newly developed drugs are active against hard-to-target drivers. Specific TKIs targeting these genomic alterations are currently in clinical development.[4] However, immunotherapy has revolutionized the treatment landscape of NSCLC, representing a therapeutic breakthrough in this

field. Along with this, we will also face treatment choices and challenges. For example, the challenge of selecting the optimal first-line therapy has arisen for treatment-naïve advanced NSCLC patients with high programmed death-ligand 1 (PD-L1) expression.[5] Even studies have conducted in-depth discussions, including the possibility that antacid agents may change the anticancer activity of ICIs.[6] Furthermore, ~5% of patients with NSCLC have rearrangements in the anaplastic lymphoma kinase (*ALK*) gene.[7] As targeted therapies for ALK, TKIs have revolutionized the prognosis and management of NSCLC with ALK positivity. Currently, several generations of anaplastic lymphoma kinase inhibitors (ALKIs) have been developed, including crizotinib (first generation); alectinib, brigatinib, ceritinib, ensartinib (second generation); and lorlatinib (third generation).

In randomized controlled trials (RCTs), the efficacy and safety of ALKIs compared to chemotherapy or different ALKIs have been evaluated in patients with advanced ALK-positive NSCLC. Compared to chemotherapy, crizotinib and alectinib improved overall survival (OS) and progression-free survival (PFS) in a previous meta-analysis of ALK inhibitors.[8,9] However, these reviews used a pairwise meta-analysis that compared the two treatments simultaneously. Network meta-analysis (NMA) allows the comparison of multiple treatments and a comprehensive efficacy and safety assessment to provide clinical decision recommendations. In an NMA performed in 2019,[10] the outcomes analyzed were PFS and OS, and the incidence of treatment-related deaths was observed. Because much of the new research has been conducted since the last NMA was published in 2019, we included new evidence on the efficacy and safety of ALKIs treatment in patients with advanced ALK-positive NSCLC in this updated NMA. This study is different from the previous NMA in that its outcomes in terms of OS, PFS, objective response rate (ORR), and treatment-related adverse events (TRAEs) of grade ≥3. Therefore, we conducted an NMA to investigate the efficacy and safety of ALKIs treatment in patients with advanced ALK-positive NSCLC to inform the optimal clinical choice.

MATERIALS AND METHODS

Literature strategy and study selection

We searched PubMed and EMBASE for relevant literature published up to March 24, 2022 without language restrictions. The following search terms were included in the search: "non–small-cell lung cancer," "NSCLC," "non–small-cell lung carcinoma," "ALK," "TKIs," "randomized controlled trial," and "clinical trial." Randomized controlled trials in which OS, PFS, ORR, and TRAEs of grade ≥3 were reported were included in this study. A review of all abstracts, studies, and citations was performed. Additionally, relevant studies were found in the reference sections of the selected articles. The flowchart provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] provides detailed information on the search strategy for eligible studies. Two independent reviewers (T.R.P. and P.F.L.) reviewed the retrieved studies. T.W.W. resolved any discrepancies between the reviewers by consensus.

Inclusion and exclusion criteria

Study eligibility was defined according to the following criteria:

Population: Treatment-naive or experienced participants with phase III or IV ALK-positive NSCLC.

Interventions: Treatment with ALK inhibitors (e.g., crizotinib, ceritinib, alectinib, brigatinib, loratinib, ensartinib, and entrectinib).

Comparators: Treatment with placebo, chemotherapy, radiotherapy, or another ALK inhibitor.

Outcomes: OS, PFS, ORR, and TRAEs of grade ≥3. Hazard ratio (HR) is used to calculate OS and PFS, whereas the odds ratios (ORs) are used to calculate ORR and the risk ratios (RRs) are used to calculate TRAEs of grade ≥3.

Study design: RCTs.

The following studies were excluded: (1) non-RCT studies, such as retrospective, prospective observational cohort studies or reviews, case reports, letters, commentaries, editorials, or meta-analyses; and (2) studies with a lack of information on OS, PFS, ORR, or TRAEs of grade ≥3.

Data extraction and quality assessment

This review was registered with the International Prospective Register for Systematic Reviews (CRD42023390916) and followed the Cochrane Handbook for Systematic Reviews for Interventions and the PRISMA for NMA checklist.[12] We extracted the following information: trial ID, first author, publication year, study design, trial phase, number of patients enrolled, OS, PFS, ORR, and TRAEs of grade ≥3. According to the Cochrane Collaboration recommendation,[13] two reviewers independently assessed the methodological quality of each study using the revised risk of bias 2.0 method (version 2.0). The bias was classified into low, unclear, and high (green, yellow, and red, respectively) in each study. We assigned a judgment of the risk of bias for domain allocation concealment, randomization, blinding, incomplete outcome data, selective outcome reporting, and other biases. The assessment graphs were generated by Review Manager (version 5.4).

Statistical methods and data synthesis

Meta-analysis was performed using RevMan software (Cochrane Review Manager, version 5.4, Oxford, UK). The median PFS was pooled and analyzed in the form of

HR. The corresponding 95% confidence interval (CI) was calculated. The random effects model (DerSimonian–Laird method) was used to calculate the pooled HR.[14] We evaluated heterogeneity using a χ^2 test with $p < 0.10$ considered statistically significant. Heterogeneity was considered low, moderate, or high for I^2 values <25, 25–50, and >50%, respectively. The results were considered statistically significant with a p-value <0.05. In the NMA, the frequentist approach was used. The network and network graphs packages in STATA version 15 (STATA Corporation) were used for the statistical evaluation of inconsistencies and the production of network graphs and figures. An NMA was conducted based on HRs for survival outcomes (PFS and OS), ORs for ORR, and RR for binary outcomes (grade ≥3 adverse events [AEs]) and their respective 95% CIs. The analyses were stratified according to the treatment experience of the patients (naive or experienced) for NMAs. Subgroup analyses were performed by central nervous system (CNS) metastases status. Chemotherapy was selected as the reference group for the NMA comparison. Our comparisons were based on similarity, transitivity, and consistency. The concept of transitivity was evaluated clinically, whereas the concept of consistency was evaluated formally.[15] For each comparison in closed loops, we used a χ^2 test to calculate inconsistency factors to determine whether there were any inconsistencies. We calculated the surface under the cumulative ranking curve (SUCRA) for each treatment to evaluate its relative efficacy. To estimate the probability of being ranked in each possible rank, we calculated the rank of probabilities. To assess publication bias, we used comparison-adjusted funnel plots.

RESULTS

Literature search results

We found 9681 articles from PubMed and EMBASE, of which 2350 studies were removed because of duplication. After excluding duplicate studies, we reviewed the titles and abstracts of 7331 articles, and 7255 were excluded because they were irrelevant. We excluded 64 of the 76 studies after reviewing the full articles. Finally, 12 studies were included according to our inclusion criteria. A flowchart for systematic reviews and meta-analyses (PRISMA) illustrating the study selection process is shown in Figure 1.

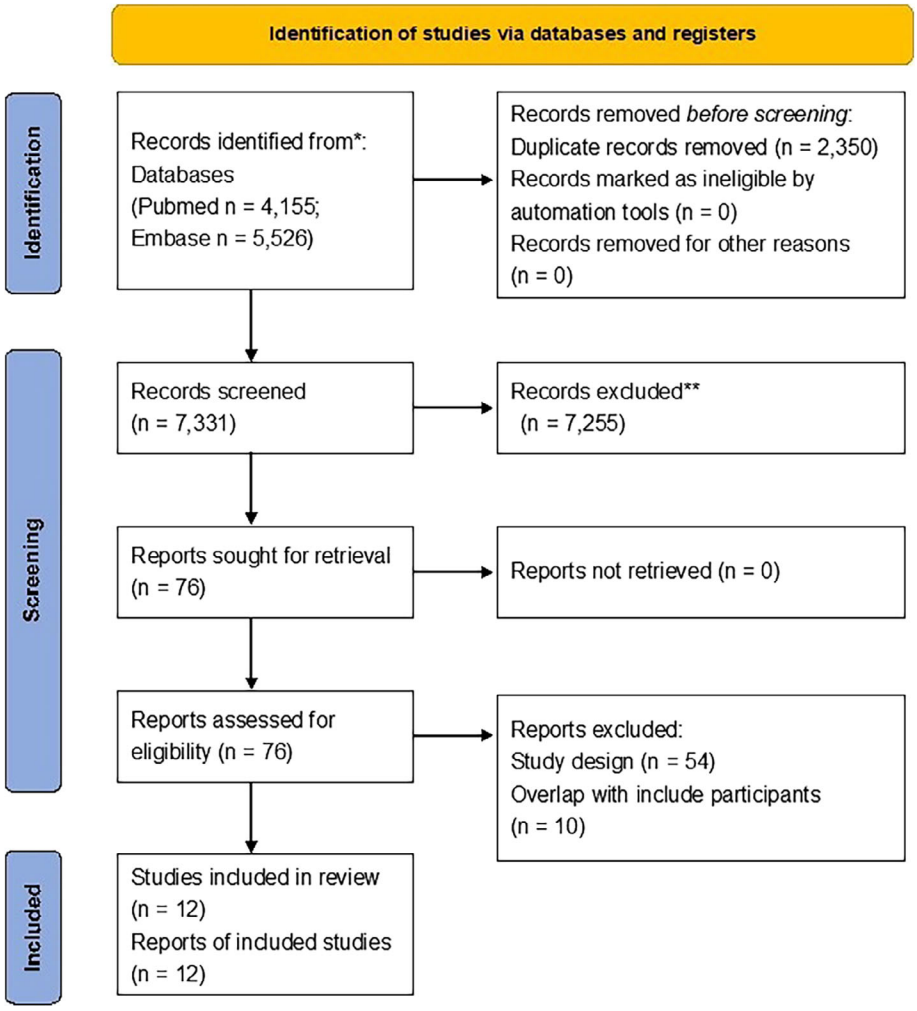

FIGURE 1 Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) 2020 flow diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools

Eligible studies and patient characteristics

The characteristics of selected studies and patients are described in Table 1. RCTs published between 2013 and 2021 were included in the selection. The studies were all phase III clinical trials with a total of 3169 patients. Each of the 12 studies had two arms of intervention. Six of them were head-to-head studies to compare two ALKIs. The risk of bias assessment is shown in Figure S1.

Efficacy evaluation of the meta-analysis

The median OS of the two studies we included was not reached and was immature; the trials were ongoing and will be updated in the future. Therefore, we pooled the HR of PFS according to the first-line or mixed-line ALKI versus crizotinib or chemotherapy. In terms of the first-line ALKI, a statistical significance was found in PFS between ALKI with crizotinib and chemotherapy (HR, 0.43; 95% CI, 0.34–0.54, $I^2 = 45\%$, $p < 0.001$ and HR, 0.48; 95% CI, 0.41–0.55, $I^2 = 0\%$, $p < 0.001$, respectively) (Figure 2(a)). However, similar results were also found with mix-line ALKI (Figure 2(b)).

Network geometry and testing for inconsistency

Figure 3 illustrates the network construction. This NMA included six ALKIs (alectinib, brigatinib, ceritinib, crizotinib, ensartinib, and lorlatinib) and chemotherapy for OS,

TABLE 1 The baseline characteristics of selected studies

Author	Year	Treatment-line of ALKI	Study phase	No. of patients	Treatment	OS, HR (95% CI)	PFS, HR (95% CI)	ORR	Grade 3–5 TRAEs
Novello et al.[16]	2018	Mixed	III	72	Alectinib	0.60 (0.41–0.89)	0.32 (0.17–0.59)	27 (72)	9 (70)
				35	Pemetrexed or docetaxel			1 (35)	14 (34)
Shaw et al.[17]	2017	Mixed	III	115	Ceritinib	1.0 (0.67–1.49)	0.49 (0.36–0.67)	45 (115)	115 (115)
				116	Pemetrexed or docetaxel			8 (116)	57 (113)
Soria et al.[18]	2017	1st	III	189	Ceritinib	0.73 (0.50–1.08)	0.55 (0.42–0.73)	137 (189)	189 (189)
				187	Cisplatin or carboplatin plus pemetrexed			50 (187)	106 (175)
Shaw et al.[19]	2013	1st	III	173	Crizotinib	1.02 (0.68–1.54)	0.49 (0.37–0.64)	113 (173)	90 (172)
				174	Pemetrexed or docetaxel			34 (174)	87 (171)
Solomon et al.[20]	2014	1st	III	172	Crizotinib	0.82 (0.54–1.26)	0.45 (0.35–0.60)	127 (172)	76 (171)
				171	Cisplatin or carboplatin plus pemetrexed			77 (171)	87 (169)
Wu et al.[21]	2018	1st	III	104	Crizotinib	0.89 (0.55–1.44)	0.40 (0.28–0.56)	91 (104)	45 (104)
				103	Cisplatin or carboplatin plus pemetrexed			47 (103)	78 (101)
Hida et al.[22]	2017	Mixed	III	103	Alectinib	NR	0.34 (0.21–0.55)	76 (83)	12 (103)
				104	Crizotinib			71 (90)	51 (104)
Peters et al.[23]	2017	1st	III	152	Alectinib	0.76 (0.48–1.20)	0.50 (0.36–0.70)	126 (152)	28 (152)
				151	Crizotinib			114 (151)	55 (151)
Zhou et al.[24]	2019	1st	III	125	Alectinib	0.28 (0.12–0.68)	0.37 (0.22–0.61)	114 (125)	15 (125)
				62	Crizotinib			48 (62)	29 (63)
Camidge et al.[25,26]	2018, 2021	1st	III	137	Brigatinib	0.81 (0.53–1.22)	0.48 (0.35–0.66)	104 (137)	95 (136)
				138	Crizotinib			101 (138)	77 (137)
Shaw et al.[27]	2020	1st	III	149	Lorlatinib	NR	0.28 (0.19–0.41)	113 (149)	128 (149)
				147	Crizotinib			85 (147)	36 (142)
Horn et al.[28]	2021	1st	III	143	Ensartinib	0.91 (0.54–1.54)	0.52 (0.36–0.75)	106 (143)	72 (143)
				147	Crizotinib			98 (147)	62 (146)

Abbreviations: ALKI, anaplastic lymphoma kinase inhibitors; CI, confidence interval; HR, hazard ratio; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TRAEs, treatment-related adverse events; NR, not reported.

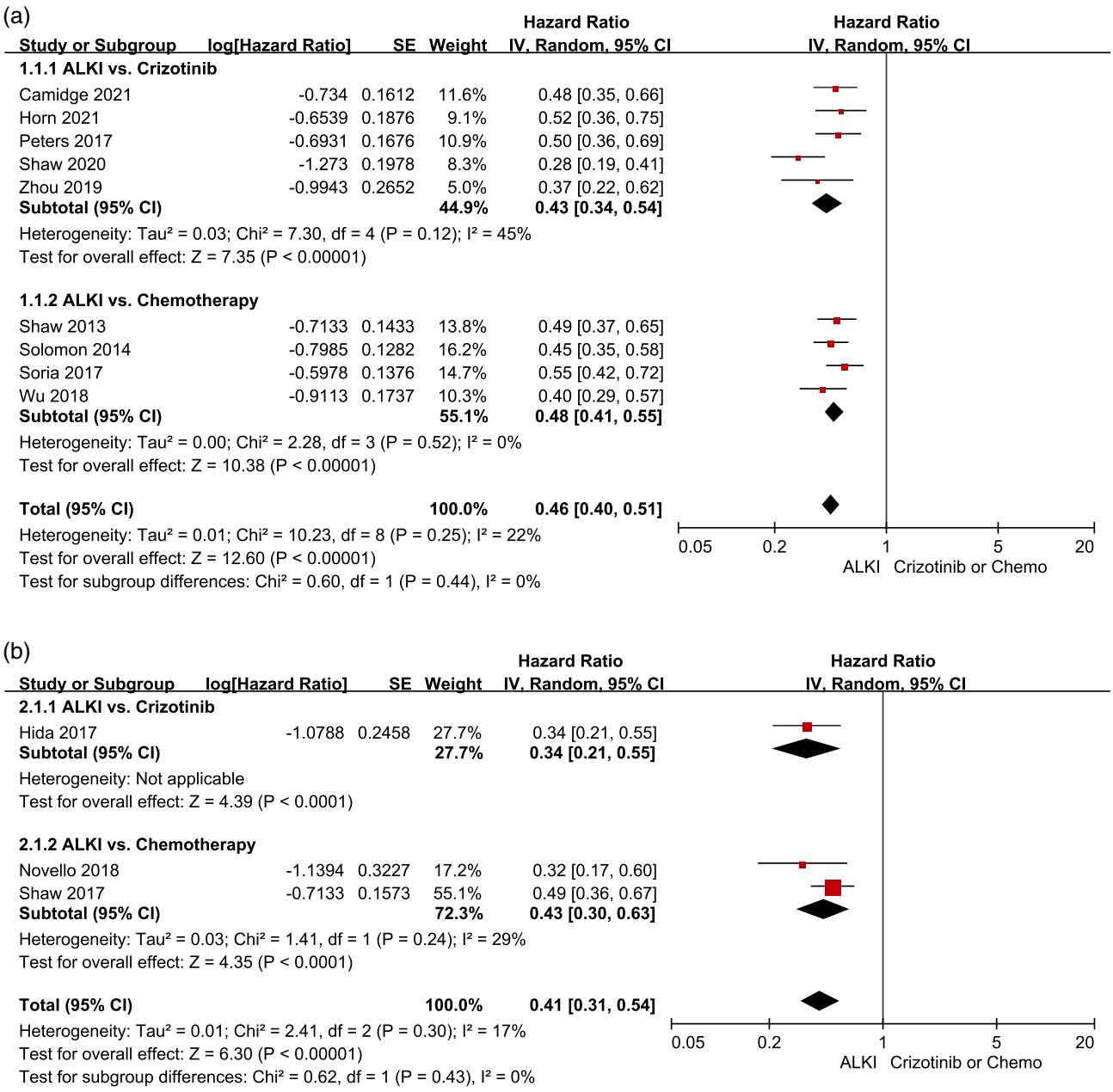

FIGURE 2 Forest plots for progression-free survival (a) ALKI for first-line (b) ALKI for mixed-line. ALKI, anaplastic lymphoma kinase inhibitors.

PFS, ORR, and grade ≥3 AEs. The *p*-value was 0.4849, 0.1760, 0.6881, and 0.7539 for the test of inconsistency in network geometry of OS, PFS, ORR, and TRAEs of grade ≥3, respectively. In this study, all *p*-values for the test of local inconsistency were >0.05. No statistical significance was found in any global or local tests, indicating that the consistency assumption was accepted (Table 2).

Efficacy and safety evaluation of the NMA

Ten RCTs assessed OS. In terms of OS, most studies have a short follow-up period, which may affect the result of our analysis to some extent. Our study showed that only alectinib has a significant improvement in OS compared to chemotherapy (HR, 0.61; 95% CI, 0.40–0.94) (Table 3(a)). Alectinib had better OS than crizotinib (HR, 0.66; 95% CI, 0.45–0.95). The SUCRA indicated that alectinib (92.7%) ranked the highest in terms of OS, followed by ceritinib (54.1%) and ensartinib (50.5%) (Figure 4(a)). PFS was assessed in 12 RCTs. Regarding PFS, six drugs (alectinib, brigatinib, ceritinib, crizotinib, ensartinib, and lorlatinib) significantly improved PFS compared to chemotherapy (Table 3(b)). Two of the highest-ranking drugs (ensartinib and alectinib) had significant differences in PFS, in which ensartinib has a significant PFS advantage over alectinib (HR, 0.62; 95% CI, 0.40–0.96). The SUCRA indicated that ensartinib (99.0%) ranked the highest in terms of PFS, followed by alectinib (73.1%) and brigatinib (66.5%) (Figure 4(b)).

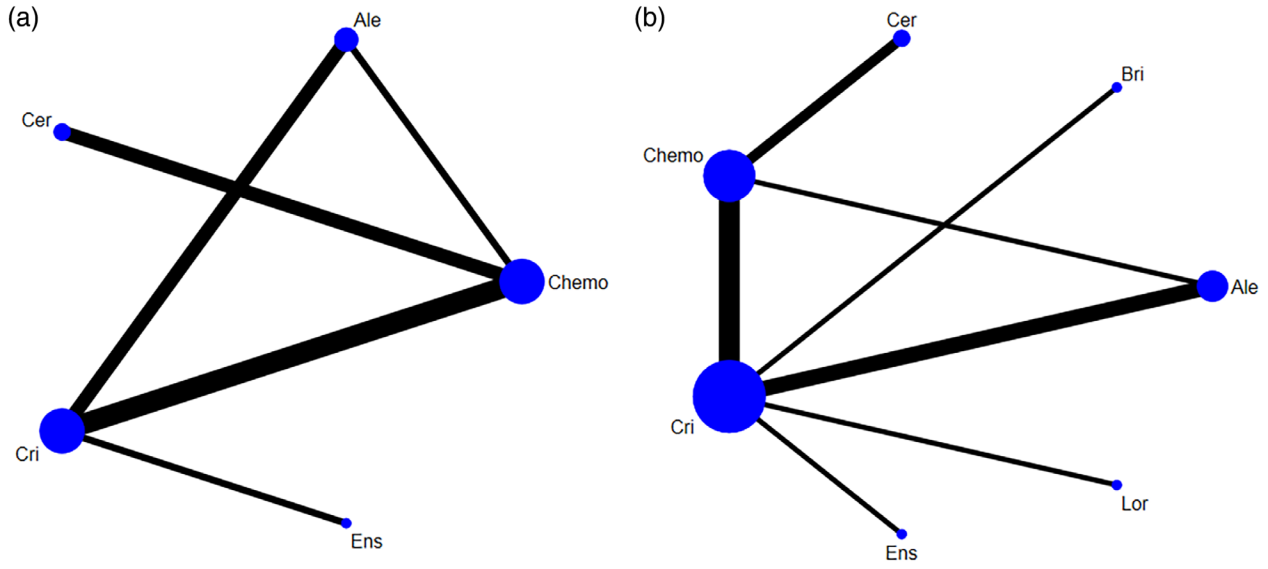

FIGURE 3 Network construction for comparison in (a) overall survival and (b) progression-free survival. Ale, alectinib; Bri, brigatinib; Cer, ceritinib; Chemo, chemotherapy; Cri, crizotinib; Ens, ensartinib; Lor, lorlatinib.

Regarding ORR, six drugs (alectinib, brigatinib, ceritinib, crizotinib, ensartinib, and lorlatinib) showed significantly better ORR than chemotherapy (Table 4(a)). The SUCRA indicated that alectinib (85.4%) ranked the highest in terms of ORR, followed by ensartinib (83.2%) and lorlatinib (56.5%) (Figure 4(c)). In terms of TRAEs of grade ≥3, two drugs (ensartinib and ceritinib) showed a significant increased TRAEs of grade ≥3 compared to chemotherapy (RR, 2.74; 95% CI, 1.45–5.18 and RR, 1.80; 95% CI, 1.26–2.57, respectively) (Table 4(b)). The SUCRA indicated that ensartinib (97.4%) ranked the highest in terms of TRAEs of grade ≥3, followed by ceritinib (83.2%) and brigatinib (54.3%) (Figure 4(d)).

Figure 5 shows a scatterplot of the SUCRA values of all ALKIs for efficacy (PFS) and tolerability (TRAEs of grade ≥3). We indicated the drugs in different colors to cluster them into groups. Alectinib had the most effective treatment (PFS) and has a lower rate of grade ≥3 AEs.

Subgroup analysis by CNS metastasis status

Except for NCT00932893[19] and CROWN,[27] 10 of 12 studies stratified randomization based on CNS metastases (Table 2). For all patients with or without CNS metastases at baseline, only an NMA of PFS could be performed. For patients with CNS metastases at baseline, alectinib and brigatinib were more likely to be beneficial. According to the NMA, alectinib significantly increased PFS compared to chemotherapy (HR, 0.12; 95% CI, 0.06–0.26). Except for ceritinib, all ALKI treatments significantly improved PFS compared to chemotherapy (Table 5(a)). However, alectinib and ensartinib were the most preferred treatment options for patients without CNS metastases at baseline. Furthermore, all ALKI treatments improved PFS compared to chemotherapy. Based on the NMA, alectinib was found to have the greatest benefit compared to chemotherapy in patients without CNS metastases at baseline (HR, 0.18; 95% CI, 0.13–0.26) (Table 5(b)).

Publication bias

Comparison-adjusted funnel plots revealed no evidence of apparent asymmetry (Figure S2). No significant publication bias was found. In this analysis, Begg and Mazumdar rank (Kendall's $\tau = -0.044$ and $p = 0.858$) and Egger's regression intercept approach (intercept, −1.946; two-tailed 95% CI, −4.64 to 0.755; $p = 0.135$) did not indicate any significant publication bias. According to Duval and Tweedie's trim-and-fill analysis, there were no missing studies on either side of the mean effect, with an adjusted standard mean difference of 0.833 (95% CI, 0.71–0.96).

Sensitivity analysis

In this study, we performed a sensitivity analysis. As the three trials that we included in this study were a mix-line of ALKIs, we excluded these studies[16,17,22] from the sensitivity analysis. However, alectinib was still found to be the best option for patients with advanced ALK-positive NSCLC in a similar study. Alectinib has been shown to be the most effective (PFS), but has lower TRAEs of grade ≥3. The scatterplots in Figure S3 show the SUCRA values for sensitivity analysis (PFS) and tolerability (TRAEs of grade ≥3).

DISCUSSION

In several clinical trials, ALKIs treatments in patients with ALK-positive lung cancer have shown superior outcomes

TABLE 2 Extracted progression-free survival by CNS metastases status from all included studies

Author	Year	Trial name	Treatment	No. of patients	Brain metastases n, (%)	CNS metastases PFS, HR (95% CI)	Non-CNS metastases PFS, HR (95% CI)
Novello et al.[16]	2018	ALUR	Alectinib	72	47 (65.3)	0.12 (0.04–0.37)	0.21 (0.07–0.64)
			Pemetrexed or docetaxel	35	26 (74.3)		
Shaw et al.[17]	2017	ASCEND-5	Ceritinib	115	60 (52.2)	0.50 (0.33–0.76)	0.45 (0.28–0.72)
			Pemetrexed or docetaxel	116	59 (50.9)		
Soria et al.[18]	2017	ASCEND-4	Ceritinib	189	59 (31)	0.70 (0.44–1.12)	0.48 (0.34–0.69)
			(Cisplatin or carboplatin) plus pemetrexed	187	62 (33)		
Shaw et al.[19]	2013	NCT00932893	Crizotinib	173	NR	NR	NR
			Pemetrexed or docetaxel	174	NR		
Solomon et al.[20]	2014	PROFILE 1014	Crizotinib	172	45 (26)	0.57 (0.35–0.93)	0.46 (0.34–0.63)
			(Cisplatin or carboplatin) plus pemetrexed	171	47 (27)		
Wu et al.[21]	2018	PROFILE 1029	Crizotinib	104	21 (20.2	0.49 (0.26–0.94)	0.37 (0.25–0.54)
			(Cisplatin or carboplatin) plus pemetrexed	103	32 (31.1)		
Hida et al.[22]	2017	J-ALEX	Alectinib	103	14 (14)	0.08 (0.01–0.61)	0.39 (0.23–0.64)
			Crizotinib	104	29 (28)		
Peters et al.[23]	2017	ALEX	Alectinib	152	64 (42)	0.40 (0.25–0.64)	0.51 (0.33–0.80)
			Crizotinib	151	58 (38)		
Zhou et al.[24]	2019	ALESIA	Alectinib	125	44 (35)	0.11 (0.05–0.28)	0.34 (0.18–0.65)
			Crizotinib	62	23 (37)		
Camidge et al.[25,26]	2018, 2021	ALTA-1L	Brigatinib	137	40 (29)	0.25 (0.14–0.46)	0.62 (0.43–0.91)
			Crizotinib	138	41 (30)		
Shaw et al.[27]	2020	CROWN	Lorlatinib	149	38 (26)	NR	NR
			Crizotinib	147	40 (27)		
Horn et al.[28]	2021	eXALT3	Ensartinib	143	47 (32.9)	0.55 (0.30–1.01)	0.46 (0.27–0.77)
			Crizotinib	147	57 (38.8)		

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; NR, not reported.

compared to chemotherapy in OS, PFS, and ORR. However, most of these trials directly compared ALKI and chemotherapy, and small trials compared two ALKIs for the treatment of patients with ALK-positive lung cancer. This NMA provides updated data and proposed rankings for OS, PFS, ORR, and TRAEs of grade ≥3 for different ALKIs for the treatment of ALK-positive lung cancer. Based on our NMA, we found that alectinib and lorlatinib had better effects and were more well-tolerated AEs. However, other ALK TKIs (e.g., ceritinib, alectinib, and brigatinib) have been developed to overcome resistance to crizotinib.[9] In the first-line setting, a novel generation of ALKIs has shown improved PFS compared to crizotinib.[22–28] This may be related to poorer brain penetration and a lower intracranial response to crizotinib.[29] Unlike first-generation ALKIs, second-generation ALKIs are non-P-glycoprotein substrates with decreased binding to transport proteins, preventing drug excretion from the brain. Although it penetrates the blood–brain barrier (BBB) more easily, with a penetration rate ranging from 63% to 94%, the CNS progression probability is reduced.[30,31] Furthermore, second-generation ALKIs, with improved specificity and efficacy, penetrated the cerebral spinal fluid (CSF) significantly better than first-generation ALKIs, demonstrating significantly higher penetration and CSF:IC_{50} values.[32,33]

Ensartinib (second-generation ALK-TKI) has been evaluated compared to crizotinib in treatment-naïve patients with ALK-positive NSCLC, with promising results as first-line systemic therapy. However, OS results are not available. Ensartinib is not approved by the Food and Drug Administration (FDA) and is available only through clinical trials (eXalt3).[28] Although we included eXalt3 in the evaluation of this study, the results are still to be confirmed by more

TABLE 3 Pooled estimates of the network meta-analysis

(a) Overall survival					
Alectinib					
0.72 (0.44, 1.20)	Ceritinib				
0.72 (0.38, 1.37)	1.00 (0.53, 1.89)	Ensartinib			
0.66 (0.45, 0.95)	0.91 (0.63, 1.31)	0.91 (0.54, 1.54)	Crizotinib		
0.61 (0.40, 0.94)	0.85 (0.64, 1.12)	0.85 (0.48, 1.52)	0.94 (0.73, 1.19)	Chemotherapy	
(b) Progression-free survival					
Ensartinib					
0.62 (0.40, 0.96)	Alectinib				
0.57 (0.33, 1.00)	0.93 (0.58, 1.47)	Brigatinib			
0.54 (0.32, 0.92)	0.87 (0.57, 1.34)	0.94 (0.55, 1.63)	Lorlatinib		
0.28 (0.19, 0.41)	**0.45 (0.36, 0.57)**	**0.49 (0.33, 0.73)**	**0.52 (0.36, 0.75)**	Crizotinib	
0.24 (0.15, 0.39)	**0.39 (0.28, 0.55)**	**0.43 (0.26, 0.69)**	**0.45 (0.29, 0.71)**	0.87 (0.67, 1.13)	Ceritinib
0.13 (0.08, 0.19)	**0.21 (0.16, 0.27)**	**0.22 (0.14, 0.34)**	**0.24 (0.16, 0.35)**	**0.45 (0.39, 0.53)**	**0.52 (0.43, 0.64)** Chemotherapy

Note: (a) Overall survival. (b) Progression-free survival. Data in each cell are hazard ratios (95% confidence intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios <1 favor row-defining treatment. Significant results are in bold ($P < 0.05$).

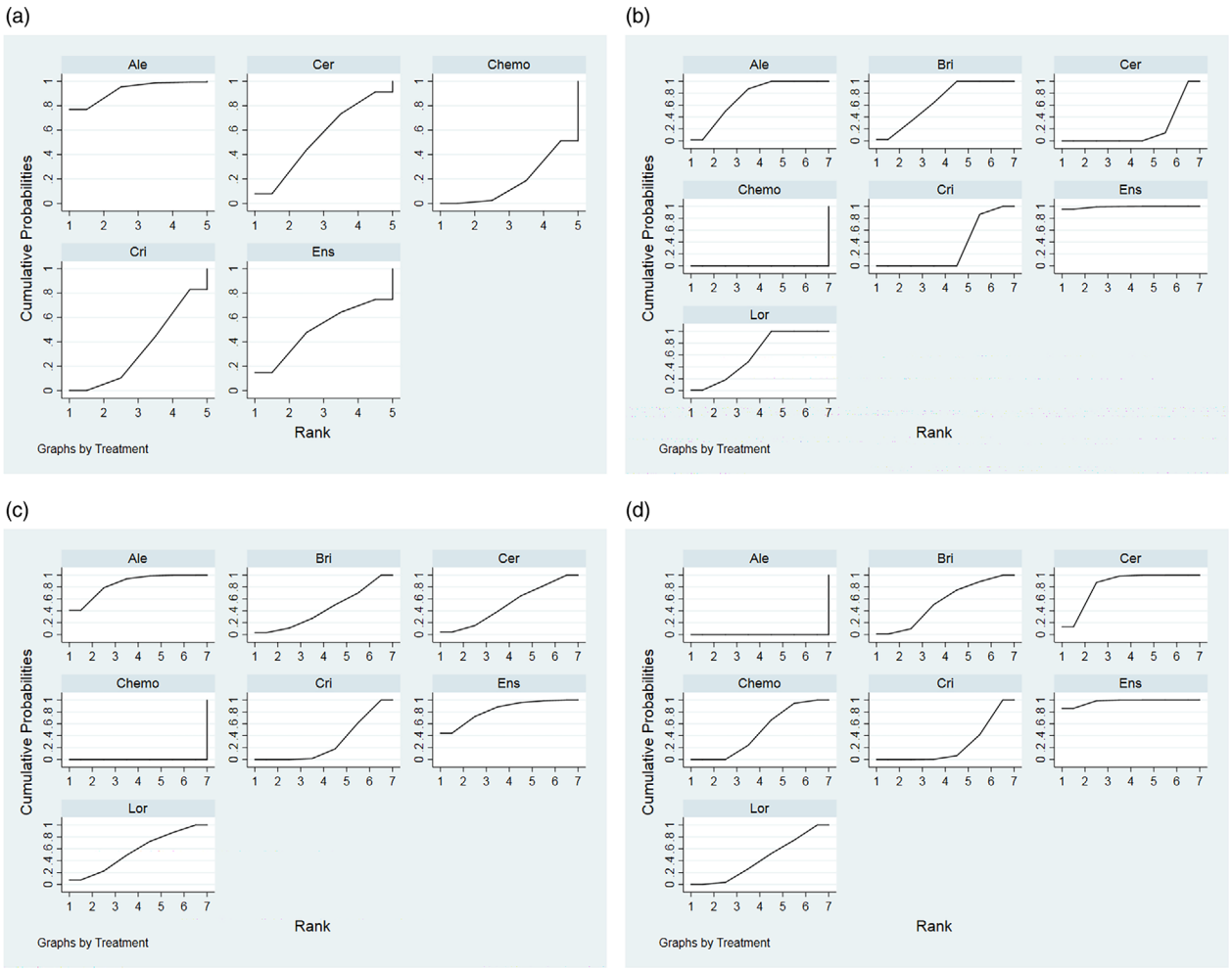

FIGURE 4 Cumulative probability for different treatments: (a) overall survival, (b) progression-free survival, (c) objective response rate, and (d) grade 3–5 adverse events. Ale, alectinib; Bri, brigatinib; Cer, ceritinib; Chemo, chemotherapy; Cri, crizotinib; Ens, ensartinib; Lor, lorlatinib.

TABLE 4 Pooled estimates of the network meta-analysis

(a) Objective response rate						
Alectinib						
0.99 (0.39, 2.57)	Ensartinib					
1.59 (0.61, 4.12)	1.60 (0.53, 4.80)	Lorlatinib				
1.74 (0.70, 4.37)	1.75 (0.60, 5.17)	1.10 (0.37, 3.25)	Ceritinib			
1.97 (0.75, 5.22)	1.98 (0.65, 6.06)	1.24 (0.40, 3.81)	1.13 (0.38, 3.40)	Brigatinib		
2.28 (1.32, 3.93)	**2.29 (1.05, 4.97)**	1.43 (0.66, 3.13)	1.31 (0.61, 2.77)	1.15 (0.52, 2.58)	Crizotinib	
13.45 (6.66, 27.13)	**13.52 (5.50, 33.26)**	**8.46 (3.42, 20.92)**	**7.71 (4.23, 14.06)**	**6.82 (2.70, 17.21)**	**5.91 (3.74, 9.33)**	Chemotherapy
(b) Grade 3–5 adverse events						
Ensartinib						
1.53 (0.74, 3.17)	Ceritinib					
2.46 (1.12, 5.43)	1.61 (0.78, 3.32)	Brigatinib				
2.74 (1.45, 5.18)	**1.80 (1.26, 2.57)**	1.11 (0.60, 2.08)	Chemotherapy			
2.86 (1.30, 6.26)	1.87 (0.92, 3.83)	1.16 (0.53, 2.52)	1.04 (0.56, 1.93)	Lorlatinib		
3.39 (1.93, 5.96)	**2.22 (1.40, 3.53)**	1.38 (0.79, 2.39)	1.24 (0.92, 1.66)	1.19 (0.69, 2.04)	Crizotinib	
9.92 (5.05, 19.47)	**6.50 (3.69, 11.46)**	**4.03 (2.07, 7.83)**	**3.62 (2.33, 5.61)**	**3.47 (1.80, 6.70)**	**2.93 (2.02, 4.23)**	Alectinib

Note: (a) Pooled odds ratios (95% confidence intervals) for objective response rate. (b) Pooled risk ratios (95% confidence intervals) for grade 3–5 adverse events. Data in each cell are odds or risk ratios (95% confidence intervals) for the comparison of row-defining treatment versus column-defining treatment. Odds ratios more than 1 favor row-defining treatment. Significant results are in bold ($P < 0.05$).

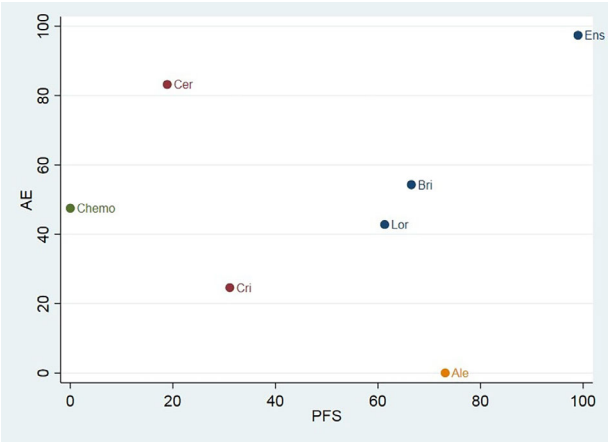

FIGURE 5 Clustered ranking plot for progression-free survival and grade 3–5 adverse events. Cluster techniques (single linkage clustering) were used to cluster interventions in groups defined by different colors. Ale, alectinib; Bri, brigatinib; Cer, ceritinib; Chemo, chemotherapy; Cri, crizotinib; Ens, ensartinib; Lor, lorlatinib.

studies in the future. Furthermore, we found that although ensartinib had a better PFS, its TRAEs of grade ≥3 had the highest rank. However, these were only based on one study, therefore, it needs to be carefully evaluated in the future. The results of eXalt3 were published in September 2021.[28] Therefore, ensartinib was not included in the systematic review before 2021. In a Wu et al. NMA to evaluate first-line ALKI for ALK-positive lung cancer in the Asian population, this study included ensartinib.[34] This result showed that ensartinib may currently be the most effective first-line treatment for Asian patients with ALK-positive NSCLC. However, this study did not evaluate the efficacy and AEs of the drug as a whole, so it can only show that ensartinib has better efficacy than other ALKIs.

AEs and the efficacy of drugs are the evaluation points for drug selection. The AE rate plays an important role in the selection of ALKIs. Our study showed that alectinib has the best safety outcomes, followed by crizotinib and lorlatinib. Although different doses of alectinib (300 mg and 600 mg) were included in our study, the results still showed that it was the safest ALKI. However, it is worth noting clinically that the severe AEs of different ALKIs manifested in different characteristics. A higher percentage of respiratory severe AE occurred with ceritinib (14.2%) and brigatinib (13.5%), whereas a higher percentage of CNS severe AE occurred with ceritinib (8.8%) and brigatinib (7.4%), perhaps because of their CNS-penetrating properties.[35] PFS of ALKIs in ALK-positive NSCLC patients with and without brain metastases was used in our subgroup study. The results show that the effect of alectinib remains the best in patients with or without brain metastases. A possible reason may be that alectinib has a rate of higher apoptosis than crizotinib.[36] In addition, alectinib was also shown to have a higher BBB penetrating ability and higher antitumor activity in mice implanted with intracranial tumors.[37]

There are several limitations to this study. First, this NMA only included 12 studies. However, the comparison-adjusted funnel plots did not reveal publication bias because of symmetry. Second, there may be heterogeneity in the included RCTs; for example, the J-ALEX and ALESIA studies included only Asian populations, which may overemphasize the effect of racial differences. Third, some of the included clinical trials had immature OS with no median

TABLE 5 Pooled estimates of the network meta-analysis

(a) PFS in patients with baseline CNS metastases					
Alectinib					
0.91 (0.31, 2.72)	Brigatinib				
0.42 (0.14, 1.24)	0.45 (0.13, 1.60)	Ensartinib			
0.23 (0.12, 0.43)	**0.25 (0.10, 0.61)**	0.55 (0.22, 1.35)	Crizotinib		
0.21 (0.08, 0.53)	**0.23 (0.07, 0.74)**	0.50 (0.15, 1.65)	0.90 (0.41, 2.00)	Ceritinib	
0.12 (0.06, 0.26)	**0.13 (0.05, 0.38)**	**0.29 (0.10, 0.84)**	**0.53 (0.30, 0.93)**	0.59 (0.34, 1.03)	Chemotherapy
(b) PFS in patients without baseline CNS metastases					
Alectinib					
0.94 (0.52, 1.70)	Ensartinib				
0.70 (0.43, 1.12)	0.74 (0.39, 1.41)	Brigatinib			
0.43 (0.32, 0.57)	**0.46 (0.27, 0.78)**	**0.62 (0.43, 0.90)**	Crizotinib		
0.39 (0.25, 0.62)	**0.42 (0.22, 0.79)**	**0.56 (0.33, 0.95)**	0.91 (0.63, 1.31)	Ceritinib	
0.18 (0.13, 0.26)	**0.20 (0.11, 0.35)**	**0.26 (0.17, 0.41)**	**0.43 (0.34, 0.54)**	**0.47 (0.35, 0.62)**	Chemotherapy

Note: (a) PFS in patients with baseline CNS metastases. (b) PFS in patients without baseline CNS metastases. Data in each cell are hazard ratios (95% confidence intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios less than 1 favor row-defining treatment. Significant results are in bold ($P < 0.05$).
Abbreviations: CNS, central nervous system; PFS, progression-free survival.

OS. If restricted OS data are used as the endpoint to evaluate individual treatment effectiveness, there may be heterogeneity. However, PFS can be considered a surrogate for OS, but has not been validated.[38] Therefore, the scatterplot of our study is a scatterplot showing the SUCRA efficacy (PFS) and tolerability (TRAEs of grade ≥3) values for all ALKIs.

Currently, there are five ALK-TKIs approved by the FDA. Furthermore, clinical trials of novel ALK-TKIs, including ensartinib and fourth-generation ALK-TKI, are ongoing. However, our study evaluated five FDA-approved ALK-TKIs and ensartinib, providing drug treatment options. Furthermore, clinical trials of angiogenesis inhibitors, ICIs, and platinum doublet chemotherapy and ALK-TKI combination therapy are ongoing. Treatment of ALK-rearranged NSCLC with ICI and in combination with angiogenesis inhibitors are expected to be an effective therapeutic strategy. More research is needed in the future, and research on single ALK inhibitors and drugs combined with other mechanisms will make the treatment of lung cancer more selective.

CONCLUSIONS

These results indicated that alectinib could be associated with the best therapeutic efficacy and well-tolerance AEs in the treatment of patients with advanced NSCLC with ALK rearrangement.

AUTHOR CONTRIBUTIONS

Tzu-Rong Peng wrote the first draft of the manuscript. Pei-Fei Liao and Tzu-Rong Peng searched databases and extracted the data. Tzu-Rong Peng and Ta-Wei Wu evaluated the risk of bias. Pei-Fei Liao performed the statistical analysis. Ta-Wei Wu critically revised the manuscript. All authors contributed to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data, models, and code generated or used during the study appears in the submitted article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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