Front-line treatment for advanced non-small-cell lung cancer and ALK fusion: a network meta-analysis

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Yaokai Wen*, Tao Jiang*, Xiangrong Wu, Haoxin Peng, Shengxiang Ren and Caicun Zhou

Abstract

Background: It remains unknown what is the optimal front-line choice for advanced non-small-cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) fusion.

Methods: We conducted a systematic review and network meta-analysis of randomized phase III clinical trials comparing two or more treatments as the front-line setting for patients with advanced ALK-positive NSCLC.

Results: Nine phase III randomized clinical trials with 2367 patients were included. As to efficacy, lorlatinib had the most favorable progression-free survival [PFS; surface under the cumulative ranking curve (SUCRA) = 98.4%] in the first-line setting, with noticeable outcome benefits *versus* chemotherapy [hazard ratio (HR): 0.12; 95% confidence interval (CI): 0.08–0.19], crizotinib (HR: 0.28; 95% CI: 0.19–0.41), ceritinib (HR: 0.22; 95% CI: 0.13–0.37), and brigatinib (HR: 0.58; 95% CI: 0.35–0.96), as well as beneficial trends when compared with alectinib (HR: 0.66; 95% CI: 0.41–1.04) and ensartinib (HR: 0.62; 95% CI: 0.36–1.08). Meanwhile, alectinib showed the optimal overall survival (OS; SUCRA = 91.2%), with significant improvements over chemotherapy (HR: 0.47; 95% CI: 0.30–0.72) and crizotinib (HR: 0.58; 95% CI: 0.41–0.82). Similarly, brigatinib also displayed prolonged OS compared with crizotinib after adjustment for crossover by the marginal structural model (HR: 0.54; 95% CI: 0.31–0.92). In terms of safety, alectinib had the fewest grade 3–5 adverse events (SUCRA = 98.9%), with marked advantages *versus* crizotinib [odds ratio (OR): 0.67; 95% CI: 0.46–0.97], ceritinib (OR: 0.21; 95% CI: 0.10–0.43), brigatinib (OR: 0.37; 95% CI: 0.20–0.69), ensartinib (OR: 0.48; 95% CI: 0.27–0.89), and lorlatinib (OR: 0.30; 95% CI: 0.16–0.54).

Conclusions: Lorlatinib may have advantageous PFS compared with other agents but a greater risk of severe toxicity. Second-generation inhibitors, including alectinib, brigatinib, and ensartinib, provide major efficacy with less toxicity and remain appropriate regimens in the front-line setting.

Keywords: anaplastic lymphoma kinase, front-line therapy, indirect comparison, network meta-analysis, non-small-cell lung cancer

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Correspondence to:
Shengxiang Ren
Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, No. 507, Zheng Min Road, Shanghai 200433, China.
harry_ren@126.com

Caicun Zhou
Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, No. 507, Zheng Min Road, Shanghai 200433, China.
caicunzhou_dr@163.com

Yaokai Wen
Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai, China

Tao Jiang
Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, Shanghai, China

Xiangrong Wu
Haoxin Peng
Nanshan School, Guangzhou Medical University, Guangzhou, China

*These authors contributed equally

Introduction

Lung cancer is now the second most common cancer and the leading cause of cancer-related death globally,[1] and approximately 85% of them are non-small-cell lung cancer (NSCLC).[2] It is estimated that about 4–5% of patients with NSCLC harbor chromosomal rearrangements in the anaplastic lymphoma kinase (ALK) gene,[3] especially in those with young age, never/light smoking history, and adenocarcinoma.[4] Pemetrexed-based chemotherapy (PbCT) used to be the standard front-line therapy. Nonetheless, in the past decade, the therapeutic landscape tremendously changed with the development of

ALK-tyrosine kinase inhibitors (TKIs). Crizotinib is the first ALK-TKI approved by Food and Drug Administration, exhibiting a significant improvement in progression-free survival (PFS) over PbCT in this setting.[5] So far, six ALK-TKIs[5–16] have been evaluated for their front-line application in phase III randomized clinical trials. All next-generation ALK-TKIs showed significant PFS benefits *versus* crizotinib or conventional PbCT[7–17] as the front-line setting. Nevertheless, all control arms of first-line comparisons in existing clinical trials were designed as either PbCT or crizotinib, while direct comparisons between any two kinds of next-generation ALK-TKIs were still absent. Under this circumstance, network meta-analysis (NMA) is a possible approach to compare these treatments across trials for the reason that it can synthesize the outcomes of both direct and indirect comparisons.

In this systematic review and NMA, we aimed to comprehensively investigate the efficacy and safety of current front-line treatment regimens in patients with advanced NSCLC and ALK fusion.

Methods

Study objective

This study aimed to compare the efficacy and safety of multiple front-line therapies in patients with advanced NSCLC and ALK fusion.

Eligibility criteria

The inclusive criteria were listed as follows: (i) studies designed as phase III randomized head-to-head clinical trials; (ii) studies comparing two or more therapies in the first-line setting for advanced ALK-positive NSCLC; (iii) studies reporting at least one of the following target outcomes: PFS, overall survival (OS), objective response rate (ORR) (including intracranial ORR), disease control rate (DCR), grade 3–5 adverse events (AEs), AEs-related treatment discontinuation, dose reduction and interruption, and common AEs among ALK-TKIs; AND (iv) studies published or accepted in English. Studies that did not meet these criteria were subsequently excluded.

Data sources and search strategies

Adhering to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Supplemental Table 1),[18] we performed a comprehensive online search of literature from electronic databases including PubMed, Embase, Web of Science, and Cochrane Library as of April 7, 2022. Detailed search strategies are listed in Supplemental Table 2. In addition, information from ClinicalTrials.gov and important international oncology conferences, including the American Society of Clinical Oncology Annual Meeting, European Society for Medical Oncology (ESMO) Congress, World Conference on Lung Cancer, European Lung Cancer Congress, and ESMO Asia Congress, was also inspected to identify related studies. The protocol of this study has been registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42021238310).

Study selection

Three investigators (Y.W., X.W., and H.P.) identified relevant studies by screening both titles and full texts independently. Divergence among them was resolved through discussions with a senior investigator (T.J.), and a consensus was eventually reached.

Data extraction

Three investigators (Y.W., X.W., and H.P.) extracted the data from included studies individually and finally reached an agreement through discussions. Baseline data consisted of ethnicity, sample size, median age, sex, the condition of brain metastases, and the description of intervention and control arms. Primary outcomes were PFS, OS, and grade 3–5 AEs. Secondary outcomes encompassed ORR (including intracranial ORR), DCR, AEs-related treatment discontinuation, dose reduction and interruption, and common AEs among ALK-TKIs. The independent review committee (IRC)-assessed survival data were preferred rather than investigator-assessed ones in our study to reduce the possible assessment bias. Once the IRC-assessed data were not provided, the investigator-assessed ones were used. Likewise, we preferred treatment-related AEs rather than all-cause AEs to evaluate the safety of treatment regimens more precisely.

Assessment of assumptions and risk of bias

Three issues of comparability for NMA should be considered in our study, including homogeneity, similarity, and consistency assumptions.[19] Homogeneity assumption was tested using the

Cochran Q test and the I^2 statistic.[20] Similarity assumption could be further divided into methodological similarity and clinical similarity,[19] mainly examined through study design and patients' characteristics, respectively. Eventually, we assessed global inconsistency by comparing the model fit based on the deviance information criterion (DIC) of the consistency and inconsistency models.

We evaluated the risk of bias in included studies using the Cochrane Collaboration's tool,[21] which contained the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. The assessment graphs were generated by Review Manager version 5.4.

Statistical analysis

This NMA was performed in the overall population, and subgroup analyses for PFS were further conducted according to sex, age, race, and the condition of brain metastases. The hazard ratio (HR) for survival outcomes (PFS and OS), the odds ratio (OR) for binary outcomes (ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, dose reduction and interruption, and common AEs among ALK-TKIs), and their 95% confidence intervals (CIs) were utilized to compare the efficacy and safety of first-line treatments for advanced ALK-positive NSCLC. The detailed analysis process was presented as follows.

Initially, the network diagram of each target outcome was built separately to elucidate which regimens were directly or indirectly compared in the included studies, using Stata software version 15. Then, a Bayesian NMA was conducted with R version 3.6.3 (R Project for Statistical Computing; gemtc package) to calculate the comparative effect of each pair of agents in the network. The fixed effects consistency model was utilized in our NMA since most direct comparisons in the network included only one trial. Simultaneously, the convergence of iterations was assessed based on the trace features and the Gelman–Rubin–Brooks plots (Supplemental Figure 1). In addition, forest plots and league tables were used to present the results. Eventually, the ranking of treatments in each outcome was established through a rankogram and the surface under the cumulative ranking curve (SUCRA) value.[22] SUCRA was deemed a more precise approach to rank each agent. A larger SUCRA value indicated a better outcome for both efficacy and safety in our analysis.

Results

Study selection and characteristics

A total of 2460 studies were initially identified, and nine studies with 2367 patients were included for analysis eventually. The detailed retrieval process was elucidated in the PRISMA flow chart in Figure 1. This NMA encompassed nine studies for PFS[5–9,12,13,15–17,23]; eight studies for OS,[6,7,10,12,13,15–17,23,24] ORR,[5–8,12,13,15–17] and AEs-related treatment discontinuation[6,7,10,12,13,15–17,23,24]; seven studies for grade 3–5 AEs[7,10,12,13,16,17,23,24]; six studies for DCR[5–8,13,17] and AEs-related dose reduction[10,12,13,15–17,23,24]; five studies for intracranial ORR[7,8,12,13,17]; and four studies for AEs-related dose interruption[10,13,17,23] in the overall population (Figure 2, Supplemental Figures 2–4). The main characteristics of each included study are presented in Table 1.

NMAs for efficacy

With regard to PFS (Figure 3, Supplemental Figure 5), all ALK-TKIs showed noticeable outcome benefits over PbCT. All next-generation ALK-TKIs had superior PFS than crizotinib except ceritinib (HR: 1.28; 95% CI: 0.90–1.81). Lorlatinib (HR: 0.22; 95% CI: 0.13–0.37), ensartinib (HR: 0.35; 95% CI: 0.21–0.60), alectinib (HR: 0.33; 95% CI: 0.22–0.51), and brigatinib (HR: 0.38; 95% CI: 0.23–0.60) also exhibited statistically significant improvements *versus* ceritinib. Furthermore, lorlatinib even prolonged PFS markedly over brigatinib (HR: 0.58; 95% CI: 0.35–0.96), along with favorable trends *versus* alectinib (HR: 0.66; 95% CI: 0.41–1.04) and ensartinib (HR: 0.62; 95% CI: 0.36–1.08). As to subgroup analyses (Supplemental Figures 6 and 7), similar outcomes to the overall population were observed in female patients and those aged <65 years and without brain metastases, while several differences were found in other subgroups. In terms of OS (Figure 3, Supplemental Figure 5), only alectinib manifested a substantial outcome advantage compared with either PbCT (HR: 0.47; 95% CI: 0.30–0.72) or crizotinib (HR: 0.58; 95% CI: 0.41–0.82), while the nonsignificant differences were observed among other comparisons. Nonetheless, the final results of the ALTA-1L trial[23] demonstrated that brigatinib also exhibited remarkably improved OS compared with crizotinib after adjustment for

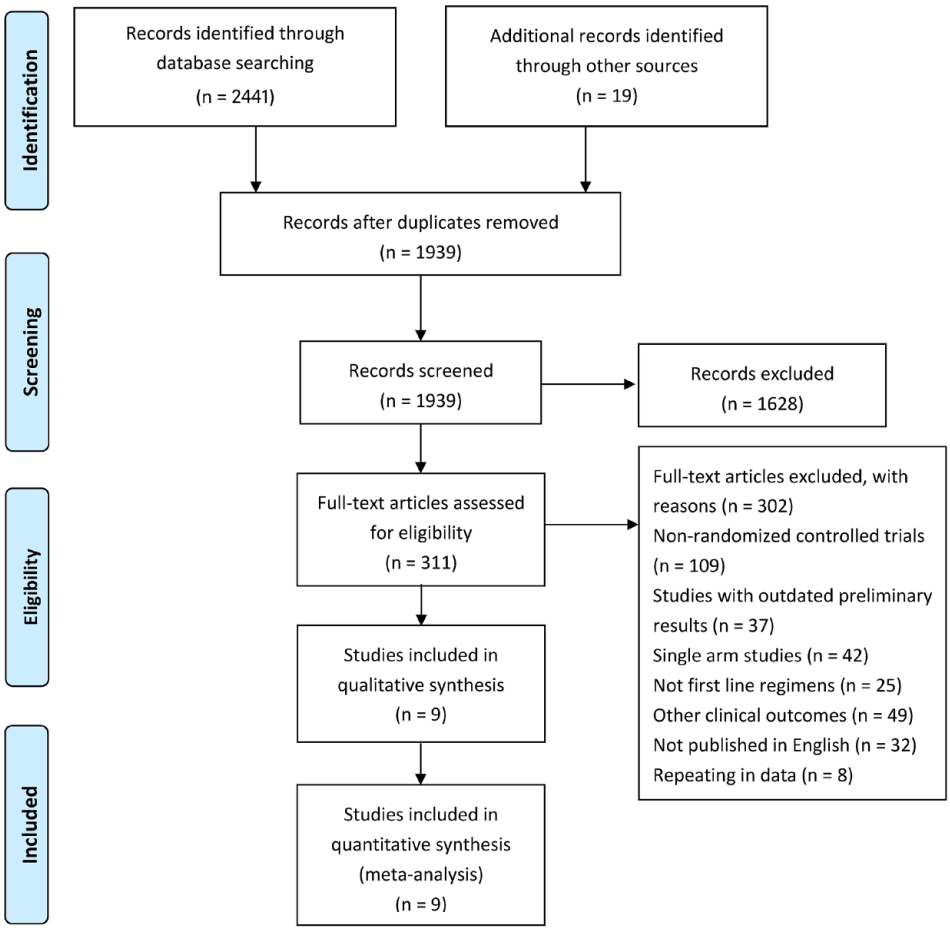

Figure 1. Flowchart of study selection and design.

crossover utilizing the marginal structural model (HR: 0.54; 95% CI: 0.31–0.92) or inverse probability of censoring weight approach (HR: 0.50; 95% CI: 0.28–0.87). Among patients with brain metastases, both brigatinib (HR: 0.43; 95% CI: 0.21–0.89) and alectinib (HR: 0.58; 95% CI: 0.34–1.00) have been reported to prolong OS markedly *versus* crizotinib.[10,23] In addition, the ORR and DCR outcomes are detailed in Supplemental Figures 5 and 8.

NMAs for safety

As regards grade 3–5 AEs (Figure 3, Supplemental Figure 5), alectinib was related with substantial outcome advantages over crizotinib (OR: 0.67; 95% CI: 0.46–0.97), ceritinib (OR: 0.21; 95% CI: 0.10–0.43), brigatinib (OR: 0.37; 95% CI: 0.20–0.69), ensartinib (OR: 0.48; 95% CI: 0.27–0.89), and lorlatinib (OR: 0.30; 95% CI: 0.16–0.54). Brigatinib (OR: 1.82; 95% CI: 1.11–2.98), ceritinib (OR: 3.16; 95% CI: 1.73–5.79), and lorlatinib (OR: 2.26; 95% CI: 1.39–3.72) were related with remarkably increased incidence of grade 3–5 AEs *versus* crizotinib. Ceritinib was also associated with significantly more grade 3–5 AEs compared with ensartinib (OR: 2.30; 95% CI: 1.07–4.88). Besides, ceritinib (OR: 2.81; 95% CI: 1.84–4.32) and lorlatinib (OR: 2.01; 95% CI: 1.05–3.86) even had more toxic effects than PbCT. Concerning AEs-related treatment discontinuation (Figure 3, Supplemental Figure 5), the results indicated that only ceritinib could markedly reduce such events compared with PbCT (OR: 0.43; 95% CI: 0.18–0.92), while no differences were observed among other treatments. The detailed outcomes of common AEs among ALK-TKI as well as AEs-related dose reduction and interruption are reported in Supplemental Figures 5 and 8.

Rank probabilities

Based on the SUCRA value, the results indicated that alectinib was associated with the highest

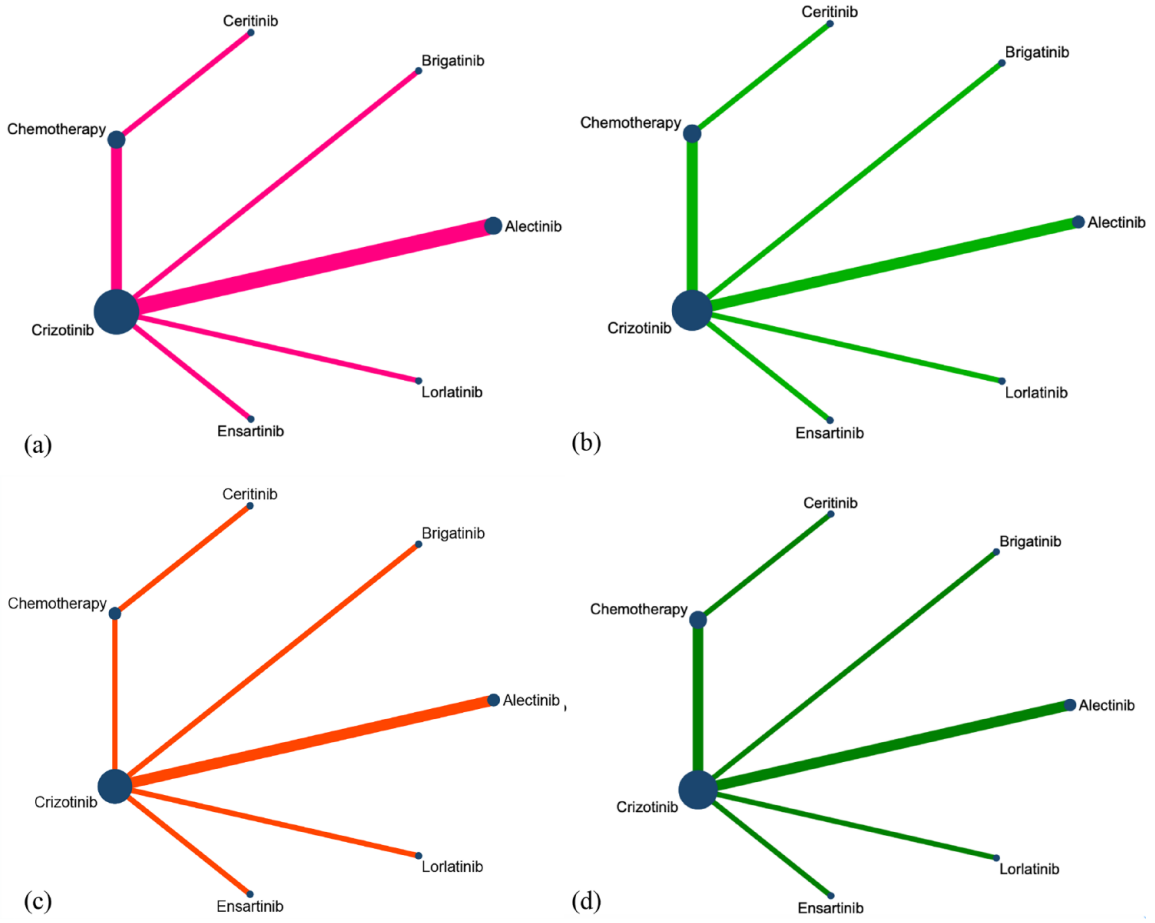

Figure 2. Network plots of (a) PFS, (b) OS, (c) grade 3–5 AEs, and (d) AEs-related treatment discontinuation of first-line treatments for advanced ALK-positive NSCLC in the overall population.
AEs, adverse events; ALK, anaplastic lymphoma kinase; PFS, progression-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival.

probability of ranking first for OS (SUCRA = 91.16%) and grade 3–5 AEs (SUCRA = 98.94%), while lorlatinib was most likely to provide the best PFS (SUCRA = 98.37%), ORR (SUCRA = 86.36%), and DCR (SUCRA = 80.46%) among first-line treatments. Lorlatinib also had the greatest probability of ranking second for OS (SUCRA = 69.73%). In the subgroup analyses of PFS, lorlatinib was related with the best ranking in most subgroups except Asian patients, which was replaced by ensartinib (SUCRA = 86.79%). Alectinib ranked second for PFS in the overall population and most subgroups except the Asian patients and patient groups with brain metastases and without brain metastases, superseded by brigatinib (SUCRA = 79.97%), brigatinib (SUCRA = 81.76%), and ensartinib (SUCRA = 78.97%), respectively. In addition, brigatinib could provide the best intracranial ORR (SUCRA = 82.95%), while ceritinib was related with the lowest incidence of AEs-related treatment discontinuation (SUCRA = 84.87%). Nevertheless, ceritinib (SUCRA = 4.90%) and lorlatinib (SUCRA = 19.43%) ranked last and second to last for grade 3–5 AEs, respectively. The detailed ranking of each outcome is provided in Figure 4, Supplemental Figures 9 and 10, and Supplemental Tables 3 and 4.

Assessment of assumptions and risk of bias

Minimal to low overall heterogeneity ($I^2 \leqslant 25\%$) was detected in most outcomes of both overall and subgroup populations, while moderate heterogeneity was observed for OS ($I^2 = 27\%$) and anemia ($I^2 = 26\%$) in the overall population and PFS in male patients ($I^2 = 57\%$), patients aged <65 years ($I^2 = 44\%$) and with brain metastases ($I^2 = 42\%$). Only strictly designed phase III randomized clinical trials were included in our analysis

Table 1. Main characteristics of included studies.

Study	Ethnicity	Sample size (no); median age	Male (%)	Asian (%)	Brain metastases (%)	Intervention arm	Control arm	Reported outcomes
PROFILE-1014[5,24]	Multiple	172/171; 52/54	40/37	45/47	26/27	Crizotinib 250 mg twice daily	PbCT [pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC = 5–6 every 3 weeks (≤6 cycles)]	PFS, OS, ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, common AEs
PROFILE-1029[6]	Asian	104/103; 48/50	48.1/41.7	100/100	20.2/31.1	Crizotinib 250 mg twice daily	PbCT [pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC = 5–6 every 3 weeks (≤6 cycles)]	PFS, OS, ORR, DCR, AEs-related treatment discontinuation, common AEs
ASCEND-4[7]	Multiple	189/187; 55/54	46/39	40/44	31/33	Ceritinib 750 mg daily	PbCT [pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC = 5–6 every 3 weeks (4 cycles) followed by maintenance pemetrexed]	PFS, OS, ORR, intracranial ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, common AEs
ALEX[8,10]	Multiple	152/151; 58/54	45/42	45/46	42/38	Alectinib 600 mg twice daily	Crizotinib 250 mg twice daily	PFS, OS, ORR, intracranial ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, AEs-related dose interruption, common AEs
J-ALEX[9]	Asian	103/104; 61/59.5	40/39	100/100	14/28	Alectinib 300 mg twice daily	Crizotinib 250 mg twice daily	PFS*
ALESIA[17]	Asian	125/62; 51/49	51/55	100/100	35/37	Alectinib 600 mg twice daily	Crizotinib 250 mg twice daily	PFS, OS, ORR, intracranial ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, AEs-related dose interruption, common AEs
ALTA-1L[11,12,23]	Multiple	137/138; 58/60	50/41	43/36	29/30	Brigatinib 180 mg once daily	Crizotinib 250 mg twice daily	PFS, OS, ORR, intracranial ORR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, common AEs
eXalt3[15,16]	Multiple	143/147; 54/53	50/52	54/57	33/39	Ensartinib 225 mg once daily	Crizotinib 250 mg twice daily	PFS, OS, ORR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, common AEs
CROWN[13]	Multiple	149/147; 61/56	44/38	44/44	26/27	Lorlatinib 100 mg daily	Crizotinib 250 mg twice daily	PFS, OS, ORR, intracranial ORR, DCR, grade 3–5 AEs, AEs-related treatment discontinuation, AEs-related dose reduction, AEs-related dose interruption, common AEs

Data are displayed as intervention/control.
AEs, adverse events; AUC, area under the concentration–time curve; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PbCT, pemetrexed-based chemotherapy; PFS, progression-free survival.
*Only the data of subgroup analysis of PFS in the first-line setting were included and analyzed.

(a)

PFS \ OS

Chemotherapy	1.25 (0.95 to 1.63)	1.37 (0.93 to 2.01)	**2.14 (1.38 to 3.32)**	1.54 (0.94 to 2.53)	1.37 (0.76 to 2.47)	1.73 (0.93 to 3.22)
0.43 (0.35 to 0.53)	Crizotinib	1.10 (0.69 to 1.75)	**1.72 (1.21 to 2.43)**	1.23 (0.81 to 1.88)	1.10 (0.65 to 1.85)	1.39 (0.79 to 2.42)
0.55 (0.42 to 0.72)	1.28 (0.90 to 1.81)	Ceritinib	1.56 (0.87 to 2.80)	1.13 (0.60 to 2.11)	1.00 (0.50 to 2.03)	1.26 (0.61 to 2.63)
0.18 (0.13 to 0.26)	**0.43 (0.33 to 0.55)**	**0.33 (0.22 to 0.51)**	Alectinib	0.72 (0.42 to 1.24)	0.64 (0.34 to 1.20)	0.81 (0.42 to 1.56)
0.21 (0.14 to 0.30)	**0.48 (0.35 to 0.66)**	**0.38 (0.23 to 0.60)**	1.12 (0.75 to 1.69)	Brigatinib	0.89 (0.45 to 1.74)	1.12 (0.56 to 2.26)
0.19 (0.12 to 0.30)	**0.45 (0.30 to 0.67)**	**0.35 (0.21 to 0.60)**	1.05 (0.66 to 1.68)	0.94 (0.57 to 1.55)	Ensartinib	1.26 (0.59 to 2.72)
0.12 (0.08 to 0.19)	**0.28 (0.19 to 0.41)**	**0.22 (0.13 to 0.37)**	0.66 (0.41 to 1.04)	**0.58 (0.35 to 0.96)**	0.62 (0.36 to 1.08)	Lorlatinib

Treatment Hazard ratio (95% confidence interval)

(b)

Grade 3–5 AEs \ AEs-related treatment discontinuation

Chemotherapy	1.29 (0.59 to 2.89)	**2.34 (1.09 to 5.43)**	1.41 (0.53 to 3.72)	0.81 (0.26 to 2.45)	0.95 (0.29 to 3.06)	1.84 (0.56 to 6.08)
0.89 (0.58 to 1.36)	Crizotinib	1.82 (0.60 to 5.71)	1.09 (0.62 to 1.91)	0.62 (0.28 to 1.35)	0.73 (0.30 to 1.73)	1.42 (0.60 to 3.44)
2.81 (1.84 to 4.32)	**3.16 (1.73 to 5.79)**	Ceritinib	0.60 (0.17 to 2.10)	0.34 (0.08 to 1.33)	0.40 (0.09 to 1.65)	0.78 (0.18 to 3.28)
0.59 (0.33 to 1.05)	**0.67 (0.46 to 0.97)**	**0.21 (0.10 to 0.43)**	Alectinib	0.57 (0.21 to 1.48)	0.67 (0.24 to 1.88)	1.30 (0.47 to 3.74)
1.61 (0.84 to 3.11)	**1.82 (1.11 to 2.98)**	0.57 (0.26 to 1.25)	**2.72 (1.45 to 5.06)**	Brigatinib	1.17 (0.36 to 3.83)	2.27 (0.71 to 7.61)
1.22 (0.65 to 2.31)	1.38 (0.86 to 2.20)	**0.43 (0.21 to 0.94)**	**2.06 (1.13 to 3.75)**	0.76 (0.38 to 1.49)	Ensartinib	1.95 (0.57 to 6.78)
2.01 (1.05 to 3.86)	**2.26 (1.39 to 3.72)**	0.72 (0.33 to 1.56)	**3.39 (1.84 to 6.30)**	1.24 (0.62 to 2.51)	1.64 (0.83 to 3.26)	Lorlatinib

Treatment Odds ratio (95% confidence interval)

Figure 3. League table showing the main outcomes of indirect comparisons of efficacy and safety in the overall population: (a) PFS and OS and (b) Grade 3–5 AEs and AEs-related treatment discontinuation.
AEs, adverse events; PFS, progression-free survival; OS, overall survival.
Abbreviation: AEs, adverse events.
Data in cells are hazard or odds ratios (95% confidence intervals) for the pairwise comparisons of row-defining treatments versus column-defining treatments. For overall survival and progression-free survival, hazard ratios less than 1 favor row-defining treatments. For AEs-related treatment discontinuation and grade 3-5 AEs, odds ratios less than 1 favor row-defining treatments. Bold indicates the result with significant difference.

to ensure methodological similarity and clinical similarity was supported by mostly comparable patients' characteristics (Supplemental Figure 11). Notably, the eXalt3 and ALTA-1L trials also enrolled patients receiving prior chemotherapy while others did not, which might influence the similarity assumption to some extent. The model fit based on the DIC of the consistency model was close to that of the inconsistency model in each target outcome (the difference in DIC between the two groups was less than 5), indicating that the consistency assumption was not likely to be violated in our analysis (Supplemental Tables 5–7).

The assessment of the risk of bias is detailed in Supplemental Figure 12. Overall, the risk of bias was low to moderate in our analysis. Most notably, performance bias should be of great concern since all included studies were designed as open-labeled trials.

Discussion

This systematic review and NMA suggested that lorlatinib had the most superior PFS while three second-generation ALK-TKIs, including alectinib, brigatinib, and ensartinib, also displayed satisfactory PFS outcomes, which were similar to each other. Alectinib and brigatinib were most likely to provide the optimum OS among front-line treatment regimens for advanced ALK-positive NSCLC. On the other hand, the safety analysis indicated that alectinib was correlated with the lowest incidence of grade 3–5 AEs.

In a previous NMA, Elliott *et al.*[25] illustrated that alectinib and brigatinib were preferred options for PFS in the first-line setting. Nonetheless, our updated analysis with the addition of the CROWN and eXalt3 trials demonstrated that lorlatinib had statistically substantial PFS advantages over crizotinib, ceritinib, and brigatinib and trends toward better PFS with lorlatinib compared with alectinib and ensartinib were also observed as the first-line setting for advanced ALK-positive NSCLC, which might be contributed by its potent inhibition of all known single ALK rearrangements.[13,26,27] Meanwhile, it had a higher blood–brain barrier penetration and could regress or prevent brain metastases.[13,26,28] Previously, a phase II clinical study reported an impressive ORR of 90% in patients without prior treatments,[29] and the latest CROWN trial further validated this finding.[13] On the other

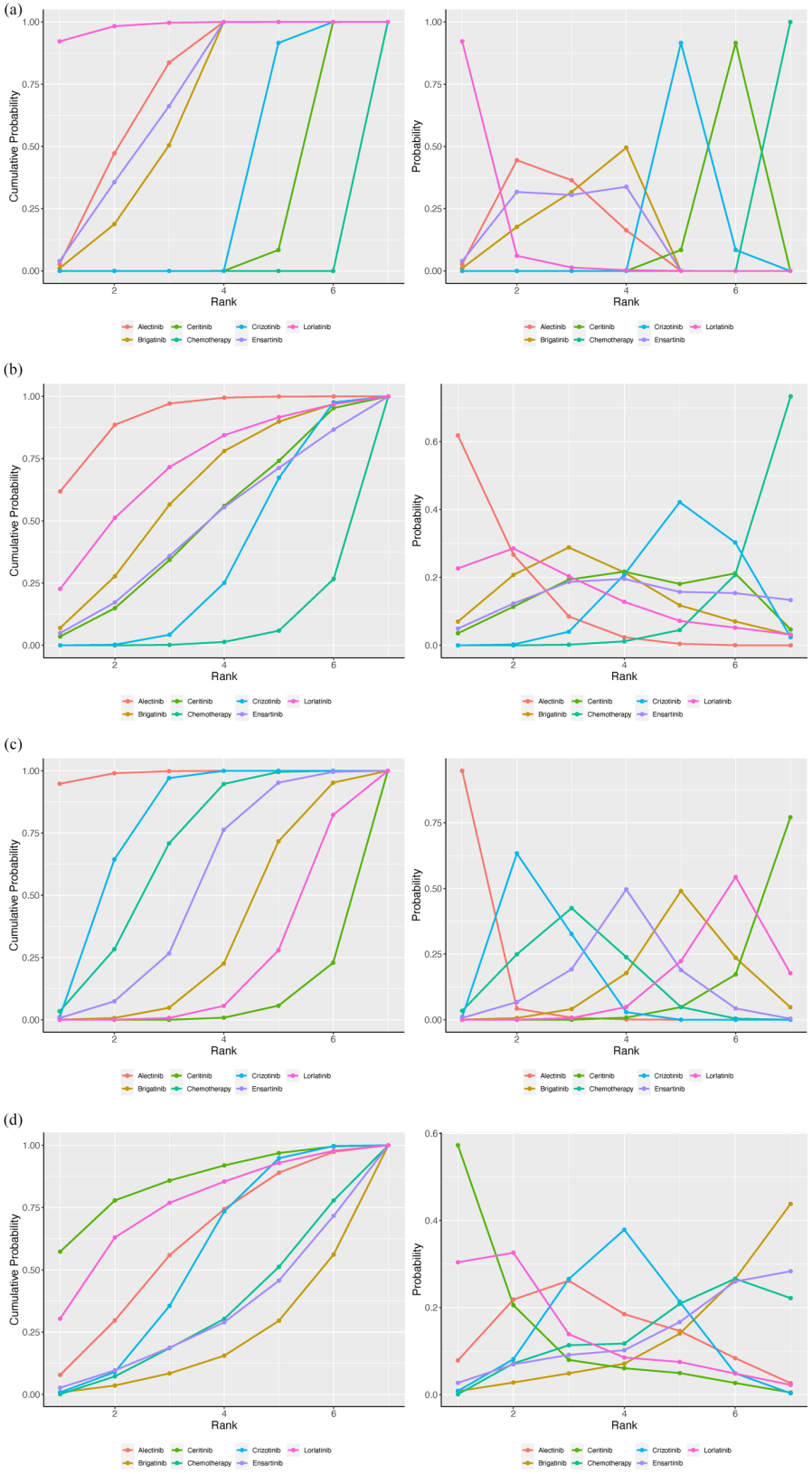

Figure 4. Ranking probabilities based on the SUCRA value (left) and rankogram (right) for main outcomes of efficacy and safety in the overall population: (a) PFS, (b) OS, (c) grade 3–5 AEs, and (d) AEs-related treatment discontinuation.
AEs, adverse events; PFS, progression-free survival; OS, overall survival; SUCRA, surface under the cumulative ranking curve.

hand, ensartinib also demonstrated competitive PFS in our analysis, next to lorlatinib and alectinib. Nonetheless, the PFS outcomes among ensartinib, alectinib, and brigatinib were actually similar for their approximate SUCRA values and HRs derived from their comparisons. These three agents also had statistically marked improvements regarding PFS over PbCT, crizotinib, and ceritinib.

Subgroup analyses of PFS according to clinical characteristics were further performed. The results indicated that lorlatinib correlated with the best PFS, while alectinib displayed sub-optimal outcomes among most subgroups. Nevertheless, it was noteworthy that lorlatinib provided the optimal outcome in non-Asian patients, with remarkable survival benefits over alectinib (second) and brigatinib (third), while it only ranked the fourth in PFS among Asian patients, inferior to ensartinib (first), brigatinib (second), and alectinib (third). In patients with brain metastases, brigatinib manifested a better outcome than alectinib, while in patients without brain metastases, ensartinib was deemed a better option rather than alectinib, although the differences above were insignificant either. Consistent with previous findings that brigatinib exhibited favorable intracranial efficacy than other second-generation ALK-TKIs in pretreated patients,[30–33] our study indicated a better intracranial ORR with brigatinib *versus* alectinib in the first-line setting, which might account for its favorable PFS outcome *versus* alectinib in patients with brain metastases.

Although PFS has been widely utilized as a surrogate primary endpoint thus far, OS is still considered the gold standard.[34–37] Our results indicated that alectinib provided the ideal OS among all front-line therapies for advanced ALK-positive NSCLC. It was also the only option that displayed a statistically substantial OS advantage *versus* either PbCT or crizotinib. Considering the high frequency of brain metastases among ALK-positive NSCLC patients,[38,39] particular attention should be attached to the intracranial efficacy of agents. Among patients with brain metastases, currently, brigatinib[23] and alectinib[10] have been reported to notably prolong OS compared with crizotinib, consistent with their excellent PFS among such population. The OS benefits of other next-generation ALK-TKIs *versus* PbCT or crizotinib were also not observed. Immature OS data and crossover therapy in the control groups might be the possible explanations. For example, after adjustment for treatment crossover in the control arm, brigatinib was also demonstrated to improve OS significantly *versus* crizotinib.[23] Our analysis illustrated that brigatinib, alectinib, and ensartinib exhibited similar PFS results. Consequently, in the absence of crossover, all three agents might have substantial OS benefits *versus* crizotinib, and their efficacy should be considered at the same level. The same principle applied to lorlatinib as well. Meanwhile, future updated OS data of the next-generation ALK-TKIs should be further analyzed to guide their clinical utility in the near future.

Safety analysis revealed that alectinib had the fewest grade 3–5 AEs, with notable advantages over crizotinib, ceritinib, brigatinib, ensartinib, and lorlatinib, while ceritinib had the highest incidence of grade 3–5 AEs. It needs to mention that the incidence of grade 3–5 AEs of both lorlatinib and ceritinib was remarkably higher when compared with PbCT and crizotinib. Simultaneously, a higher incidence of grade 3–5 AEs was observed with brigatinib *versus* crizotinib and ceritinib *versus* ensartinib. Notably, the rate of grade 3–5 AEs of lorlatinib was over 70%. This is of concern in clinical practice as this agent appears to have the highest rate of severe toxicity among current agents, despite its substantial clinical efficacy. We also found that PbCT, crizotinib, and alectinib ranked the first three for AEs-related dose reduction, while ceritinib, lorlatinib, and alectinib were the top three priorities for AEs-related treatment discontinuation. Overall, alectinib demonstrated great safety among these three main indicators, especially when compared with other next-generation ALK inhibitors. While PbCT and crizotinib obtained favorable outcomes on both grade 3–5 AEs and AEs-related dose reduction, their high incidence of AEs-related treatment discontinuation should be of great concern. Common AEs among ALK-TKIs contained constipation, diarrhea, nausea, vomiting, elevated alanine/aspartate aminotransferase, hypercholesterolemia, etc., while each ALK-TKI also owned its specific spectrum of AEs. For example, the most common grade 3–5 AEs induced by lorlatinib encompassed elevated triglyceride and cholesterol levels, hypertension, and increased weight, while hypertension, increased blood creatine, and lipase were the most common ones in the brigatinib group. We conducted NMA for some common AEs based on existing data. Notably, patients receiving ceritinib experienced the highest incidence of vomiting, nausea, and vision disorder, consistent with its high frequency of gastrointestinal toxicity reported previously.[7] Recently, the

ASCEND-8 trial[40] demonstrated that ceritinib 450 mg/day with food gained comparable efficacy and effectively reduced the incidence of gastrointestinal AEs when compared with ceritinib 750 mg/day in the fasted state, providing a mitigation strategy for clinical utilization of ceritinib.

Limitations

There existed several limitations in our study. First, the OS data remained immature in this analysis, which would weaken the strength of our results. Second, since all the included studies were designed as open-labeled, the performance bias resulting from the unblinded process of participants and personnel was inevitable. Third, owing to the nature that most first-line treatments were compared indirectly, the outcomes should be interpreted with caution. Fourth, the different clinical settings of trials might also introduce bias to the results to some extent. For example, receiving previous systemic therapy was not allowed in the ALEX, ALESIA, and CROWN, while it was permitted in the J-ALEX, ALTA-1L, and eXalt3. Simultaneously, the influence of different treatment crossover across trials should be considered cautiously. For instance, brigatinib treatment would have been associated with improved OS if treatment crossover from crizotinib to brigatinib had not been permitted in the ALTA-1L.[23] Fifth, chemotherapy strategies differed across trials, with the use of pemetrexed maintenance in the ASCEND-4 but not in the PROFILE-1014/1029 trials.

Notwithstanding the limitations mentioned above, our study still provided the most extensive evidence regarding the efficacy and safety of first-line therapies for advanced ALK-positive NSCLC. To our knowledge, this is the first NMA offering a ranking profile for each target outcome, not just pairwise comparisons among the treatments. Also, with the progress of newly developed ALK-TKIs such as ensartinib and lorlatinib, the therapeutic pattern of advanced ALK-positive NSCLC might have varied, and an updated analysis was, therefore, necessary to guide clinical practice. Simultaneously, a comprehensive set of clinical indicators was evaluated in this NMA, ranging from ORR, DCR, PFS, OS, grade 3–5 AEs, AEs-related treatment discontinuation, dose reduction, and interruption to common AEs among ALK-TKIs. Moreover, for the first time, we performed subgroup analyses of PFS according to different clinical characteristics, aiming to make more accurate recommendations in specific populations since the efficacy of therapeutic agents might not always be in line with the overall population.

Conclusions

This NMA showed that lorlatinib may yield the greatest efficacy in terms of PFS. However, considering the issue of toxicity, second-generation ALK inhibitors, including alectinib, brigatinib, and ensartinib, may have favorable safety profiles and would continue to be considered standard therapies in the front-line setting.

Declarations

Ethics approval and consent to participate

None.

Consent for publication

All authors reviewed the final version of the manuscript and approved it for publication.

Author contribution(s)

Yaokai Wen: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing – original draft.

Tao Jiang: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – original draft.

Xiangrong Wu: Formal analysis; Investigation; Resources; Software; Validation.

Haoxin Peng: Formal analysis; Investigation; Resources; Software; Validation.

Shengxiang Ren: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Caicun Zhou: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

None.

ORCID iD

Caicun Zhou https://orcid.org/0000-0002-1072-9941

Supplemental material

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