Meta-Analysis

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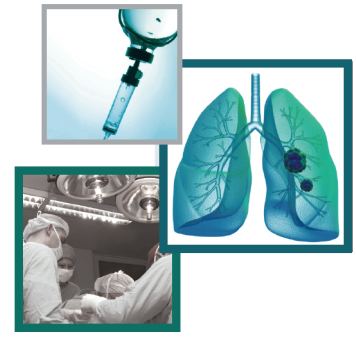
Lung Cancer Management



# Alectinib for treating patients with metastatic *ALK*-positive NSCLC: systematic review and network metanalysis

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**Aim:** To compare the efficacy and safety of alectinib with other ALK inhibitors in treating patients with metastatic or locally advanced *ALK*-positive NSCLC. **Methods:** A systematic literature review was conducted up to November 2021. Network meta-analyses were performed using the frequentist method (random effects). GRADE evidence profile was conducted. **Results:** 13 RCTs were selected. For overall survival, alectinib was found to reduce the risk of death compared with crizotinib. In progression-free survival, alectinib reduced the risk of death or progression compared with crizotinib and ceritinib. Subgroup analysis by brain metastasis at baseline showed the superiority of alectinib over crizotinib and a similar effect compared with second-and third-generation inhibitors. Alectinib showed a good safety profile compared with the other ALK inhibitors.

**Plain language summary:** This article reports the results of a systematic literature review with network meta-analysis (NMA) that aimed to compare the efficacy and safety of alectinib with other ALK inhibitors in treating patients with metastatic or locally advanced *ALK*-positive NSCLC. The results show that alectinib reduces the risk of death and the risk of progression compared with crizotinib. For progression-free survival, further significant reductions were observed when compared with ceritinib. For the other ALK inhibitors, no statistically significant differences were found. Subgroup analysis according to the presence of CNS metastases at baseline were consistent in showing the superiority of alectinib over crizotinib and the absence of statistically significant differences compared with second-and third-generation inhibitors. Alectinib showed a good safety profile compared with the other ALK inhibitors, reducing the frequency of adverse events (AEs) compared with ceritinib, and with no statistically significant differences compared with lorlatinib, brigatinib, ensartinib and crizotinib for the frequency of serious AEs or discontinuation of treatment due to AEs. The results of this study suggest clinically relevant insights in decision-making based on patient survival and progression-free survival. Furthermore, considering the importance of reducing the risk of intracranial progression and the need for available therapies for patients who will inevitably progress, alectinib could be considered as a first-line treatment for patients with *ALK*-positive NSCLC.

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**Keywords:** anaplastic lymphoma kinase • carcinoma • neoplasm metastasis • network meta-analysis • non-small-cell lung

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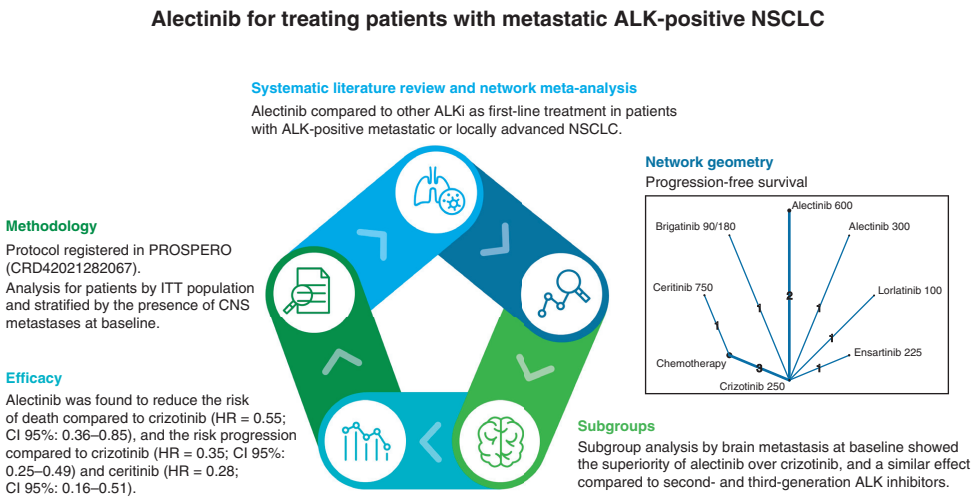
**Graphical abstract:**




Lung cancer is the third most incident cancer worldwide [1]. Lung cancer is widely divided into small-cell lung cancer (SCLC) and non-SCLC (NSCLC), the latter being the most common type (80–85%) [2]. In patients with regional lung cancer, the 5-year survival rate is estimated between 33% and 35%, while in patients with distant lung cancer, the estimated 5-year survival is close to 6% [3,4].

In NSCLC, chromosomal rearrangements involving the *ALK* gene on chromosome 2 are found in approximately 5% of tumors; these rearrangements have been found primarily on young and non-smoking patients with advanced cancer [5].

Identifying the mechanisms underlying the growth of NSCLC cells has allowed the development of new drugs to target these alterations. *ALK* inhibitors (*ALKi*) are recommended to treat patients with metastatic or locally advanced *ALK*-positive NSCLC because of their efficacy in reducing the tumor size in people whose advanced lung cancers have the *ALK* gene rearrangement [6].

Recommendations for first-line treatment of metastatic or locally advanced *ALK*-positive NSCLC are based on the results of head-to-head comparative studies among second-generation ALKi (alectinib, brigatinib and ceritinib) or third-generation inhibitors (lorlatinib) with crizotinib [7,8], the first *ALKi* available on the market. There are currently no published head-to-head clinical studies evaluating second-and third-generation inhibitors among themselves. This is particularly relevant considering the risk of newly diagnosed patients with advanced NSCLC to develop brain metastases, and the increased intracranial efficacy reported in studies of some of the new inhibitors [9].

Previously, network meta-analysis for *ALKi* have been published [10–13]; however, these studies used outdated results of the ALEX study [14]. The final results of progression-free survival (PFS) and overall survival (OS) of the ALEX study were published in 2020 [15]. Additionally, none of those meta-analysis assessed the time to CNS progression, nor estimated overall survival, time to CNS progression or response rates among subgroups with and without CNS metastases at baseline.

The objective of this study is to compare the efficacy and safety of alectinib with other commercially available *ALKi*, as first-line treatment in patients with *ALK*-positive metastatic or locally advanced NSCLC, analyzing the outcomes in patients with and without brain metastases at baseline.

## Methods

A systematic review and network meta-analysis (NMA) was conducted following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [16]. This study was conducted according to the protocol published in PROSPERO (CRD42021282067).

A systematic search was carried out up to November 2021 in Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS databases. The search was complemented using the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov databases. The lists of bibliographic references of the selected studies also were reviewed (reverse snowball search). The search strategies are presented in Supplementary Table 1.

Inclusion criteria were: i) adult patients with *ALK*-positive metastatic or locally advanced NSCLC, ii) studies evaluating the comparative efficacy and safety of alectinib 600 mg, lorlatinib 100 mg, brigatinib 90/180 mg, ceritinib 750 mg, ensartinib 225 mg and crizotinib 250 mg, and iii) randomized controlled phase II and III clinical trials available as a full-text publication. Three reviewers independently carried out an initial screening of the title and abstract (DS/LP/CV), and then two reviewers (DS/CV) assessed the full text of the remaining publications. Differences were resolved by consensus.

The selection and screening processes are documented in a flow diagram following the PRISMA methodology [17]. A data extraction form was designed for recording the effect size estimates of the included studies. One reviewer (DS) conducted the entire process, and it was backed up with quality control by a second reviewer (CV).

One reviewer (DS) conducted the risk of bias assessment, with quality control by a second reviewer (CV), using the Cochrane Risk of Bias tool [18]; disagreements were solved by consensus. The certainty of the evidence for each outcome was assessed with GRADE methodology for NMA, using the GRADE profile tables [19,20].

The included outcomes were OS, PFS, objective response rate (ORR), partial response rate (PRR), complete response rate (CRR), time to CNS progression (TTP-CNS), second PFS (PFS-2), time to response (TTR) and health-related quality of life. Safety outcomes included any adverse events (AE), serious adverse events (SAE), and discontinuation of treatment due to adverse events (DTAE). Definitions for efficacy and safety outcomes are presented in the registered protocol (CRD42021282067). For studies reporting the same outcome with different follow-up times, the results with the longest follow-up time were used for the analysis.

Efficacy analysis included only studies evaluating the benefit of *ALKi* as first-line treatment options. Safety analysis included all studies that assessed the risks of *ALKi* in the target population (including the first and second line of treatment).

## Statistical analysis

Due to the lack of direct comparisons among all interventions, a NMA was performed. Considering that the studies were developed by different researchers in different settings, a frequentist random-effects model was used for OS, PFS, TTP-CNS, ORR, PRR, CRR and safety outcomes. For PFS-2, TTR and health-related quality of life, a NMA analysis was not possible due to lack of data or heterogeneity in the results.

The clinical and methodological homogeneity of the studies was verified. Due to similarities in the distribution of the included studies characteristics (effect modifiers), a NMA was developed (transitivity assumption).

Three independent NMA were planned for efficacy outcomes according to the characteristics of the population:

- Base case A: Intention-to-treat population in each of the included studies.
- Base case B: Patients with CNS metastasis at baseline.
- Base case C: Patients without CNS metastasis at baseline.

The safety outcomes were evaluated with the population included in the safety analysis in each of the included studies, without distinction on the therapeutic line. This was funded under the assumption that harmful AEs are linked to the mechanisms of action of the active treatments, regardless of the line of treatment.

The appropriate comparison measure (hazard ratio, risk ratio) of each study was extracted with its CI. The effect size estimators for the most updated data for each outcome were inputted to the statistical program R v4.1.2 through the R Studio interface. The R "netmeta" package v1.2.2 and the "Meta" package 4.15.1 were used [21,22].

Model consistency was verified using the Cochran Q test [23]. Heterogeneity was assessed using the $I^2$ test, using used the categories suggested by the Cochrane group for its interpretation: non-important or low heterogeneity (from 0 to 40%), moderate heterogeneity (from 30 to 60%), substantial heterogeneity (from 50 to 90%), considerable heterogeneity (75 to 100%) [16].

The results were presented graphically by forest plots, using alectinib 600 mg as the reference. The results were expressed as relative risk (RR) or hazard ratio (HR) with their respective 95% CI. The rankings were estimated, along with the P-score, the frequentist approach to estimate the likelihood of being the best intervention for each outcome [24].

To obtain a network to connect all interventions defined in the protocol, we included studies where at least one of the intervention arms evaluated one of the comparators of interest. However, the results presented are limited to the interventions prioritized in the research question (PROSPERO CRD42021282067).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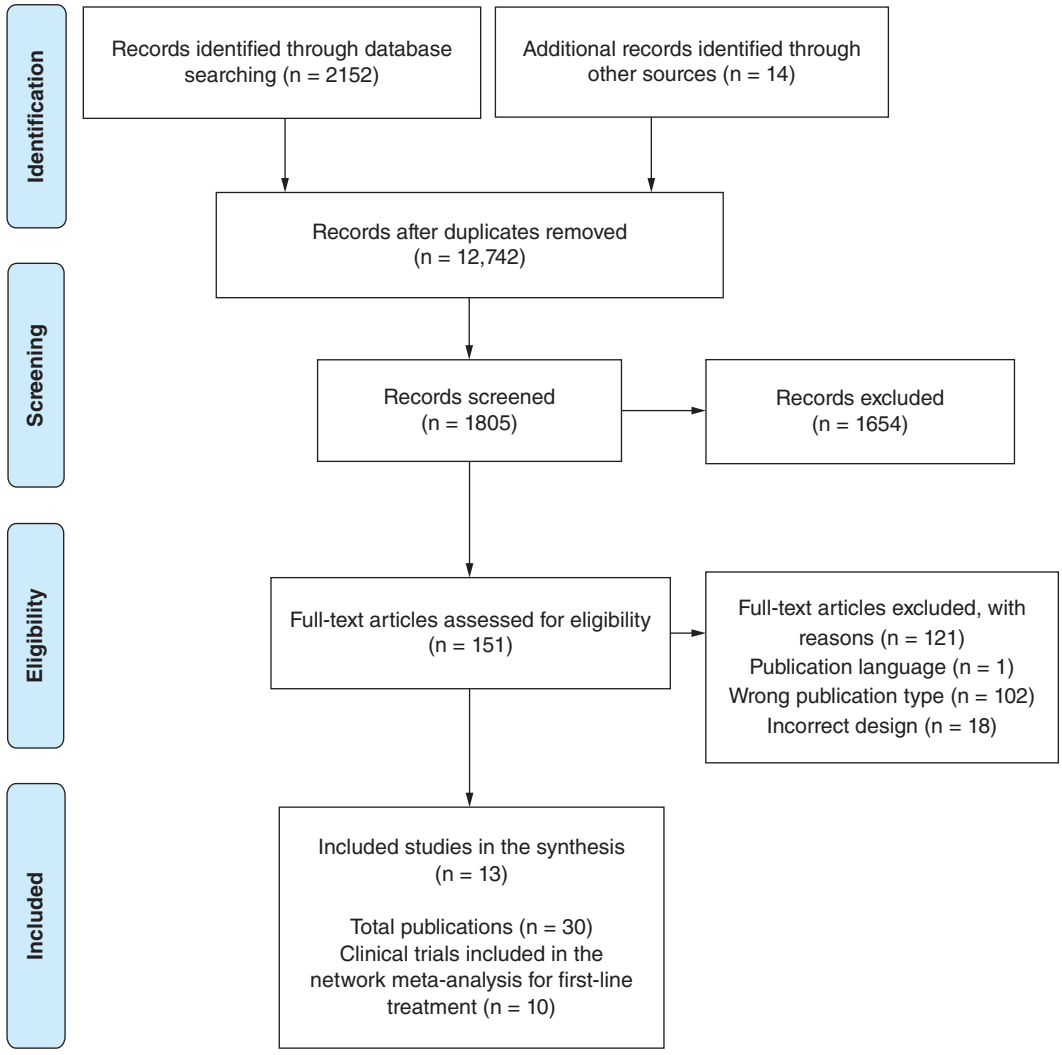


**Figure 1. Flow diagram for the evidence identification and selection process.**

## Results

### Description of the studies

Thirteen randomized clinical trials were included, with 30 publications from 13 RCTs (Figure 1 ). Supplementary Table 2 presents the list of included and excluded publications, along with the reason for exclusion. The characteristics of the included studies are detailed in Supplementary Table 3.

### Risk of bias assessment

All studies included in this review were open-label studies; however, considering the objective measure for the outcomes (mainly RESIST criteria) and the assessment by independent reviewers, we considered that participants' knowledge of the allocation group did not affect the study results. Seven studies were classified as having a low risk of bias, as their methodology is rigorous for the entire process of selection, performance, and reporting of results. The remaining six studies were rated at unclear risk of bias, primarily for lack of information to judge the selection and attrition domains. Risk of bias assessment is presented in Figure 2.

### Network meta-analysis

Efficacy analysis included up to ten studies for first-line treatment for *ALK*-positive metastatic or locally advanced NSCLC. Safety analysis included all thirteen studies included in the systematic review. NMA was viable for OS, PFS, TTP-CNS, ORR, PRR, CPP and all three safety outcomes. Among subgroups of patients with and without

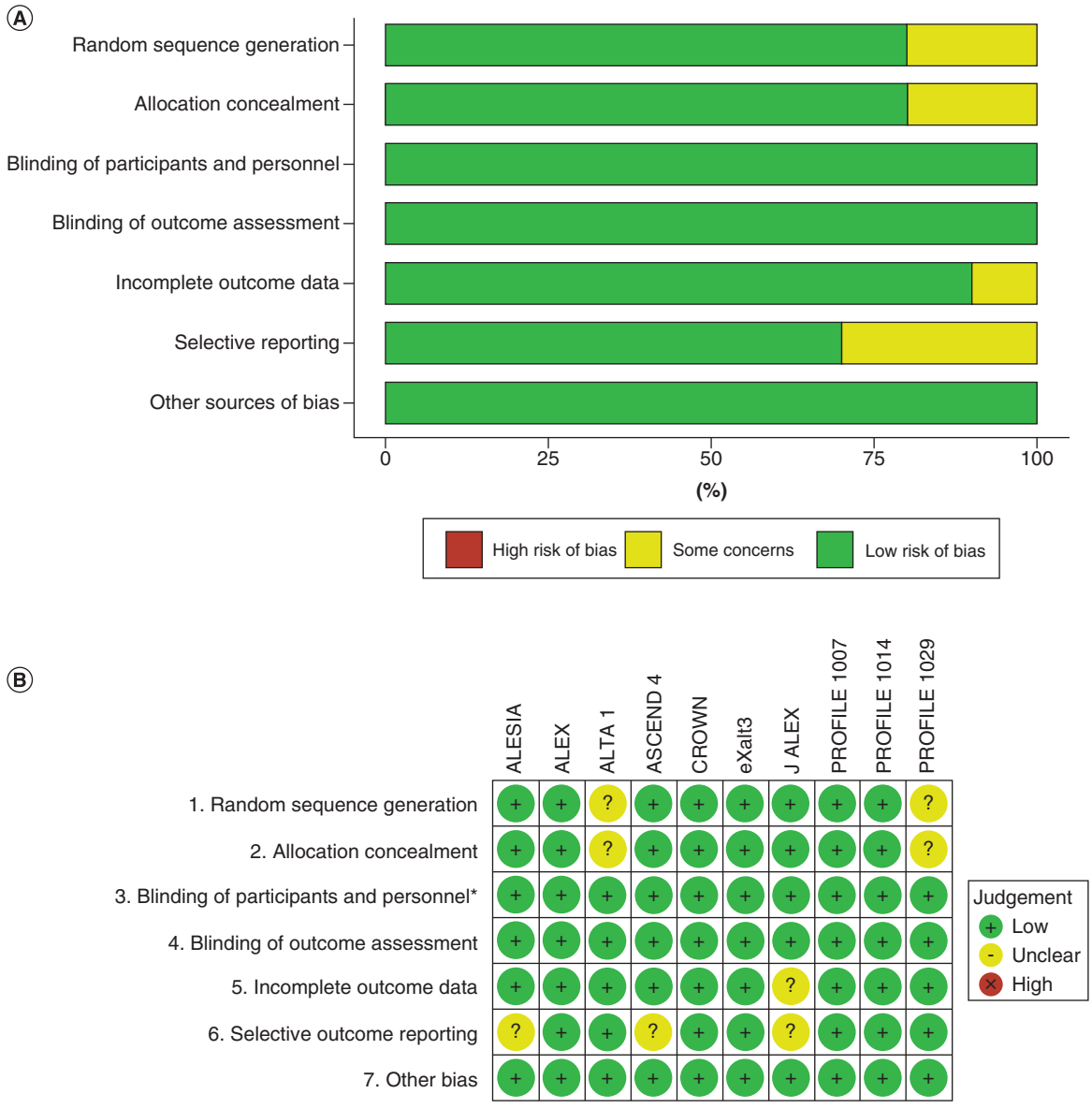


**Figure 2. Risk of bias assessment.**
**(A)** Risk of bias summary. **(B)** Risk of bias graph. All studies included in this assessment were open-label studies; however, considering the objective nature of the outcomes and assessment by independent reviewers, participants' knowledge of the allocation group was judged not to affect the study results.

CNS metastasis at baseline, NMA was viable for OS, PFS, TTP-CNS and ORR. The sources of information used for the construction of each network by outcome are reported in Supplementary Table 4.

Supplementary Tables 5–19 show the quality of the evidence for the network estimators using GRADE methodology for NMA, including the ranking estimation (p-score).

## Efficacy

### *Overall survival*

Base case A NMA for OS included ten studies with 2831 patients (Figure 3A) [15,25–33]. Heterogeneity was non-important ($I^2$ = 33.1%). Consistency could not be evaluated due to the lack of closed loops. Patients in the alectinib 600 mg group at any time point during the study period were 45% less likely to die than patients in the crizotinib 250 mg group. (HR = 0.55; 95% CI: 0.36–0.85) (Figure 3B). The comparison between alectinib 600 mg and the other *ALKi* showed no statistically significant differences. The treatments with the best placement within the


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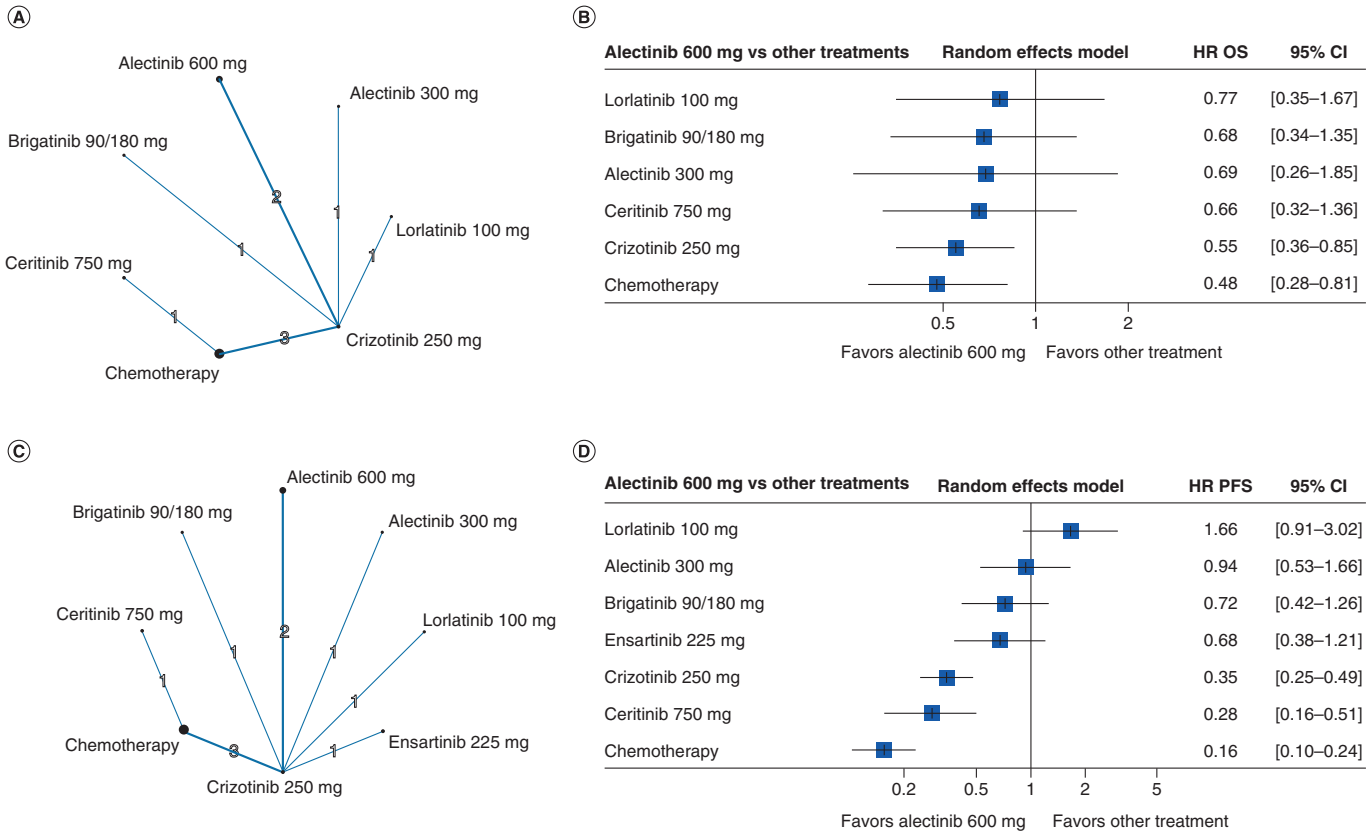


**Figure 3. Network geometry and forest plot for overall survival and progression-free survival comparing alectinib 600 mg with the other ALK inhibitors. (A)** Network geometry for OS. **(B)** Forest plot for OS for alectinib 600 mg compared to other ALK inhibitors. **(C)** Network geometry for PFS. **(D)** Forest plot for PFS for alectinib 600 mg compared to other ALK inhibitors.
HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

ranking (classification according to the probability of being the best treatment) were alectinib 600 mg and lorlatinib 100 mg, with probabilities of 0.87 and 0.64, respectively. The certainty of the evidence supporting these findings was mostly moderate (Supplementary Table 5).

### *Progression-free survival*

Base case A NMA for PFS also included ten studies with 2831 patients (Figure 3C) [15,25–29,31–34]. Heterogeneity was moderate ($I^2$ = 44%). Consistency could not be evaluated due to the lack of closed loops. Alectinib 600 mg achieved a statistically significant reduction in the instantaneous rate of progression or death compared with crizotinib 250 mg (HR = 0.35; 95% CI: 0.25–0.49) and ceritinib 750 mg (HR = 0.28; 95% CI: 0.16–0.51), with risk reductions of 65% and 72%, respectively (Figure 3D). For the other *ALKi* included in the analysis, alectinib 600 mg showed no statistically significant differences. The best placement within the ranking treatments was for alectinib 600 mg and lorlatinib 100, with 0.98 and 0.77 probabilities, respectively. The certainty of the evidence supporting these findings is moderate and high (Supplementary Table 6).

### *Time to CNS progression*

Base case A NMA for TTP-CNS included five studies with 1336 patients [14,28,32–34] (Supplementary Figure 1). Heterogeneity was non-important ($I^2$ = 25%). Consistency could not be evaluated due to the lack of closed loops. Results showed no statistically significant differences in the reduction of the CNS progression between alectinib 600 mg and lorlatinib 100 mg (HR = 2.19; 95% CI: 0.77–6.22); meanwhile, alectinib 600 mg showed a statistically significant reduction in the hazard of CNS progression showing that patients in the alectinib 600 mg group were 85% less likely to have a CNS progression than patients in the crizotinib 250 mg group. (HR = 0.15; 95% CI: 0.09–0.25) (Supplementary Figure 1). The best placement within the ranking treatments were lorlatinib 100 mg

(p = 0.98), and alectinib 600 mg (p = 0.69). The certainty of the evidence supporting these findings was moderate and high (Supplementary Table 7).

### *Response rates*

Base case A NMA analysis for response rates (ORR, PRR, CRR) included ten studies with 2831 patients [25,26,28,29,31–33,35–37] (Supplementary Figure 2). ORR and PRR showed considerable heterogeneity ($I^2$ ~77%). CRR showed non-important heterogeneity ($I^2$ = 0%). Consistency could not be evaluated due to the lack of closed loops in the response rates networks. NMA showed no statistically significant differences among *ALKi* for achieving ORR, PRR or CRR. The treatments with the best placement within the ranking were lorlatinib 100 mg for ORR (p = 0.73), ceritinib 750 mg for PRR (p = 0.76), and lorlatinib for CRR (p = 0.86). Certainty of evidence was low for all comparisons within the ORR and PRR analysis and moderate in the CRR analysis (Supplementary Table 8–10).

## Subgroup analysis

### *Patients with CNS metastasis at baseline (Base case B)*

Base case B NMA for OS included three studies with 295 patients [15,25,30] (Supplementary Table 11). Heterogeneity and consistency could not be evaluated due to the absence of multiple studies within each edge of the network and the lack of closed loops. Alectinib 600 mg significantly decreased the instantaneous death rate compared with crizotinib 250 mg, with a relative reduction of 42% (HR = 0.58; 95% CI: 0.34–0.99). For comparing alectinib 600 mg and brigatinib 90/180 mg, no statistically significant differences were found (HR = 1.35; 0.55 to 3.32). Alectinib 600 mg was in the second position at the ranking (p = 0.67). The certainty of the evidence was moderate to high (Supplementary Table 11).

For PFS, the NMA included ten studies with 867 patients (Figure 4) [15,25,26,28,29,31–33,36,37]. Heterogeneity was substantial ($I^2$ = 54%). Alectinib 600 mg showed a statistically significant reduction in the risk of progression or death in patients with intracranial lesions at baseline compared with crizotinib 250 mg (HR = 0.24; 95% CI: 0.13–0.45) and ceritinib 750 mg (HR = 0.20; 95% CI: 0.07–0.60), with reductions of the probability that patients would experience progression or death up to 80%. For the comparisons between alectinib 600 mg with lorlatinib 100 mg, brigatinib 90/180 mg, and ensartinib 225 mg, NMA showed no statistically significant differences. Alectinib 600 mg occupied the second position at the ranking (p = 0.78) among the six *ALKi*, and the certainty of the evidence was low and moderate (Supplementary Table 12).

For TTP-CNS, the NMA included three studies with 254 patients [32,34,38]. Heterogeneity was non-important ($I^2$ = 0%) (Supplementary Table 13). For Base Case B, it was only possible to compare alectinib 600 mg and crizotinib 250 mg because the other *ALKi* did not report an effect size for CNS progression risk. Patients with previous CNS lesions receiving alectinib 600 mg were 82% less likely to have a CNS progression than patients receiving crizotinib 250 mg. These differences were statistically significant (HR = 0.18; 95% CI: 0.09–0.36). Alectinib occupied the first position at the ranking (p = 1.00), and the certainty for the NMA estimations was high (Supplementary Table 13).

### *Patients without CNS metastasis at baseline (Base case C)*

NMA for OS included three studies with 626 patients [15,25,30] (Supplementary Table 14). Heterogeneity or consistency could not be evaluated. In patients without CNS metastases at baseline, the results showed no statistically significant differences between alectinib 600 mg and crizotinib 250 mg or brigatinib 90/180 mg for the instantaneous death rate (HR = 0.76; 95% CI: 0.45–1.27; HR = 0.66; 95% CI: 0.32–1.36, respectively). Alectinib 600 mg was in the first position at the ranking (p = 0.90), and the certainty of the evidence was moderate (Supplementary Table 14).

NMA for PFS included ten studies with 1921 patients (Figure 4) [15,25,26,28,29,31–33,36,37]. Heterogeneity was non-important ($I^2$ = 0%). In patients without CNS metastases at baseline, alectinib 600 mg showed a statistically significant reduction in the risk of progression or death compared with crizotinib 250 mg (HR = 0.42; 95% CI: 0.30–0.59) and ceritinib 750 mg (HR = 0.38; 95% CI: 0.22–0.64), with hazard reductions close to 60%. Between alectinib 600 mg and the other *ALKi*, NMA found no statistically significant differences (Figure 4). Alectinib 600 mg occupied the third position at the ranking (p = 0.79) among the six *ALKi*, and the certainty of the evidence was moderate and high (Supplementary Table 15).


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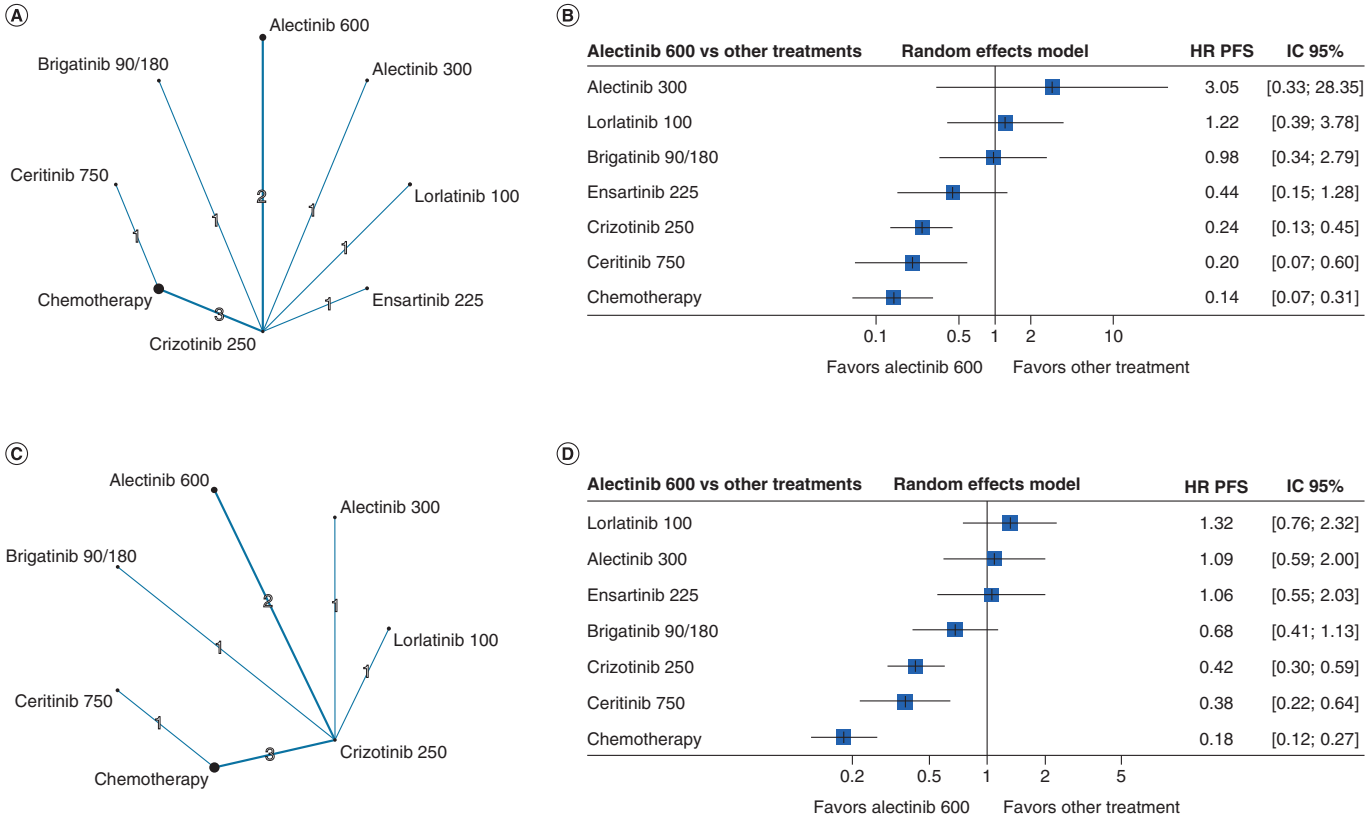


**Figure 4. Network geometry and forest plot for progression-free survival comparing alectinib 600 mg with the other ALK inhibitors among subgroups with/without CNS metastasis at baseline. (A)** Network geometry for progression-free survival of patients with CNS metastasis at baseline. **(B)** Forest plot for PFS for alectinib 600 mg compared to other ALK inhibitors among patients with CNS metastasis at baseline. **(C)** Network geometry for PFS of patients without CNS metastasis at baseline. **(D)** Forest plot for PFS for alectinib 600 mg compared to other ALK inhibitors among patients without CNS metastasis at baseline.
HR: Hazard ratio; PFS: Progression-free survival.

For TTP-CNS, the NMA included forth studies with 755 patients [26,32,34,38]. Heterogeneity was substantial ($I^2$ = 68.3%) (Supplementary Table 16). Alectinib 600 mg showed a statistically significant reduction in the risk of CNS progression compared with crizotinib 250 mg (HR = 0.14; 95% CI: 0.04–0.48). Between alectinib 600 mg and ensartinib 225 mg, the NMA found no statistically significant differences in reducing the hazard of CNS progression (HR = 0.44; 95% CI: 0.08–2.29). Alectinib occupied the first position at the ranking (p = 0.95), and the certainty for the NMA estimations was low and moderate (Supplementary Table 16).

## Safety

### *Any AE*

NMA for AEs included twelve studies with 3082 patients (Supplementary Figure 3) [15,25,27,28,31–33,37,39–42]. Heterogeneity was non-important ($I^2$ = 0%). Cochrane Q test results showed no inconsistency between direct and indirect evidence (Q = 1.08; p = 0.29). NMA showed that alectinib 600 mg reduced the risk of any AE compared with ceritinib 750 mg (RR = 0.96; 95% CI: 0.93–0.99). Regarding the other *ALKi*, the results showed no statistically significant differences in the risk of AEs between alectinib 600 mg compared with brigatinib 90/180 mg (RR = 0.99; 95% CI: 0.97–1.01), lorlatinib 100 mg (RR = 0.98; 95% CI: 0.96–1.00), and crizotinib 250 mg (RR = 0.99; 95% CI: 0.97–1.00) (Supplementary Figure 3).

Table 1 presents the most frequent AEs reported for the intervention groups of the randomized controlled trials included in the analysis [14,26,28,29,31–33,36,37,40–43]. Although the NMA showed no significant differences in the risk of AEs between ALKi, the individual results of the RCTs suggest that the proportion of most frequent AEs was lower in patients treated with alectinib 600 mg (>50%) than in patients treated with other ALKi (70% in the case of lorlatinib 100 mg, or even 85% in the ceritinib 750 mg group).

**Table 1. Summary of most frequent adverse events in the included randomized clinical trials.**

| Study | Intervention group[†] (n) | Control group (n) | Adverse event | Proportion in the intervention group | Proportion in the control group | Ref. |
|---|---|---|---|---|---|---|
| ALTA-1 L (NCT02737501) | Brigatinib 90/180 mg (137) | Crizotinib 250 mg (138) | Diarrhea | 49% | 55% | [43] |
| | | | Increased creatine level | 39% | 15% | |
| | | | Nausea | 26% | 56% | |
| ASCEND-4 (NCT01828099) | Ceritinib 750 mg (189) | Chemotherapy (187) | Diarrhea | 85% | 11% | [31] |
| | | | Nausea | 69% | 55% | |
| | | | Vomit | 66% | 36% | |
| ALEX (NCT02075840) | Alectinib 600 mg (152) | Crizotinib 250 mg (151) | Anemia | 20% | 5% | [14] |
| | | | Myalgia | 16% | 2% | |
| | | | Increased bilirubin in the blood | 15% | 1% | |
| CROWN (NCT03052608) | Lorlatinib 100 mg (149) | Crizotinib 250 mg (147) | Hypercholesterolemia | 70% | 4% | [28] |
| | | | Hypertriglyceridemia | 64% | 6% | |
| | | | Edema | 55% | 39% | |
| PROFILE 1014 (NCT01154140) | Crizotinib 250 mg (172) | Chemotherapy (171) | Vision disorder[‡] | 71% | 9% | [37] |
| | | | Diarrhea | 61% | 13% | |
| | | | Edema | 49% | 12% | |
| PROFILE 1029 (NCT01639001) | Crizotinib 250 mg (104) | Chemotherapy (103) | Increased level of transaminases | 69.2% | 43.6% | [32] |
| | | | Diarrhea | 58.7% | 8.9% | |
| | | | Vision disorder[‡] | 55.8% | 5.0% | |
| ALESIA (NCT02838420) | Alectinib 600 mg (125) | Crizotinib 250 mg (62) | Increased alanine aminotransferase | 42% | 57% | [33] |
| | | | Constipation | 36% | 50% | |
| | | | Increased creatine phosphokinase | 44% | 29% | |
| PROFILE 1007 (NCT00932893) | Crizotinib 250 mg (172) | Chemotherapy (171) | Vision disorder[‡] | 60% | 9% | [29] |
| | | | Diarrhea | 60% | 19% | |
| | | | Nauseas | 55% | 37% | |
| eXalt3 (NCT02767804)[§] | Ensartinib 225 mg (143) | Crizotinib 250 mg (147) | Rash | 59.4% | 10.3% | [26] |
| | | | Increased alanine aminotransferase | 46.2% | 39.7% | |
| | | | Increase in aminotransferase aspartate | 37.1% | 36.3% | |
| J-ALEX (JapicCTI-132316) | Alectinib 300 mg (103) | Crizotinib 250 mg (104) | Constipation | 35% | 44% | [36] |
| | | | Nasopharyngitis | 20% | 23% | |
| | | | Dysgeusia | 18% | 52% | |
| ALTA (NCT02094573)[§] | Brigatinib 90/180 mg (110) | Brigatinib 90 mg (112) | Nauseas | 40% | 33% | [40] |
| | | | Diarrhea | 38% | 19% | |
| | | | Increased creatine phosphokinase | 30% | 11% | |
| ASCEND-5 (NCT01828112) | Ceritinib 750 mg (115) | Chemotherapy (116) | Diarrhea | 68% | 17% | [42] |
| | | | Nausea | 58% | 21% | |
| | | | Vomit | 44% | 4% | |
| ALUR (NCT02604342) | Alectinib 600 mg (70) | Chemotherapy (34) | Constipation | 18.6% | 11.8% | [41] |
| | | | Dyspnea | 8.6% | 0% | |
| | | | Fatigue | 5.7% | 26.5% | |

[†]Most common adverse events in the intervention arm foreach of the included studies in the safety analysis.
[‡]Visual impairment, photopsia, blurred vision, floaters, decreased visual acuity, diplopia, and photophobia.
[§]Treatment-related adverse events.


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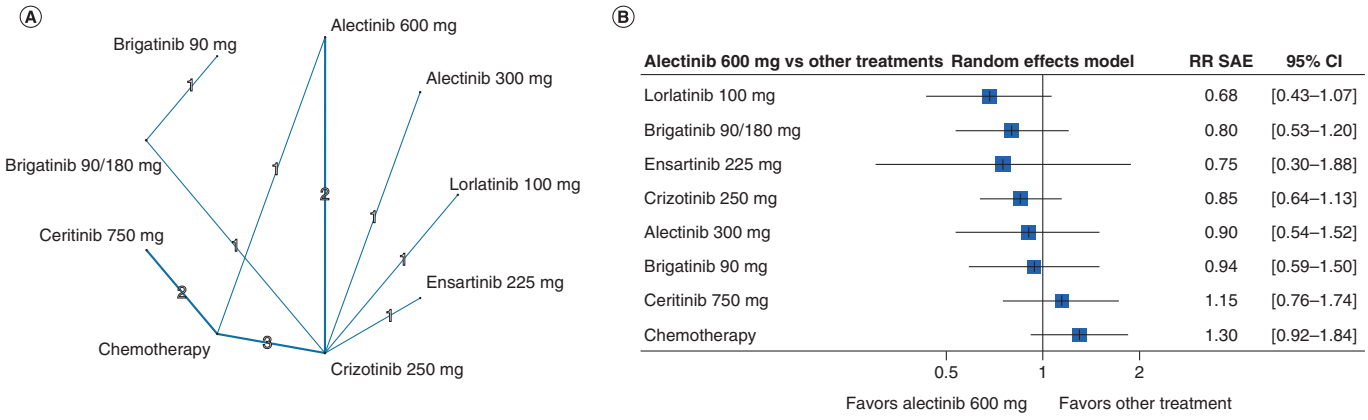


**Figure 5. Network geometry and forest plot for serious adverse events comparing alectinib 600 mg with the other ALK inhibitors. (A)** Geometry for the network for SAEs. **(B)** Forest plot for SAEs for alectinib 600 mg compared to other ALK inhibitors.
RR: Relatvie risk; SAE: Serious adverse event.

The treatments with the highest probability of leading to AEs were ceritinib 750 mg (p = 0.95), lorlatinib 100 mg (p = 0.75), and crizotinib 250 mg (p = 0.55). Alectinib 600 mg was in the last position at the ranking, suggesting the safest intervention among the *ALKi* evaluated (p = 0.27). The certainty of the evidence supporting these findings was mostly moderate and high (Supplementary Table 17).

### *SAEs*

NMA for SAE included thirteen studies with 3274 patients (Figure 5) [25–28,31–33,35,37,39–42]. Heterogeneity was non-important ($I^2$ = 0.1%). Cochrane Q test results showed no inconsistency between direct and indirect evidence (Q = 0; p = 0.94). The analysis showed no statistically significant differences between alectinib 600 mg and other *ALKi* for the risk of SAEs (Figure 5). The treatments with the highest probability of leading to SAEs were lorlatinib 100 mg (p = 0.86), brigatinib 90/180 mg (p = 0.72), and ensartinib 225 mg (p = 0.67). Alectinib 600 mg occupied the fifth position among the six included *ALKi* (p = 0.38). The certainty of the evidence supporting these findings was moderate (Supplementary Table 18).

### *Discontinuation due to AEs*

NMA for TDAE included thirteen studies with 3237 patients (Supplementary Figure 3) [15,25–28,31–33,37,39–42]. Heterogeneity was moderate ($I^2$ = 46.9%). Cochrane Q test results showed no inconsistency between direct and indirect evidence (Q = 0.3; p = 0.58). The analysis showed no statistically significant differences between alectinib 600 mg and other *ALKi* for the risk of discontinuation of treatment due to AEs (Supplementary Figure 3). The treatments with the highest probability of discontinuation of treatment due to AEs were brigatinib 90/180 mg (p = 0.82), ensartinib 225 mg (p = 0.79) and crizotinib 250 mg (p = 0.65). Alectinib 600 mg occupied the fourth position at the ranking (p = 0.51). The certainty of the evidence supporting these findings was moderate (Supplementary Table 19).

## Discussion

NSCLC with *ALK* rearrangement (*ALK*+), present in approximately 5% of tumors, is a disease for which various targeted pharmaceutical alternatives have emerged. Advances in research have allowed a remarkable understanding of the mutations underlying the development of tumors in NSCLC [44]; evaluating the therapies targeting specific mutations is vital for the timely treatment of this condition.

Patients with *ALK*-positive NSCLC treated with crizotinib, the first ALK inhibitor (ALKi) showed a remarkable treatment response compared with platinum-based double chemotherapy, also improving overall survival, progression-free survival, patient-reported outcomes, and the frequency of AEs. This allowed crizotinib to be considered the preferred option for first-line treatment of patients with *ALK*- positive NSCLC [44].

Subsequently, the second-generation inhibitors alectinib, brigatinib, and ensartinib, due to their lower mean inhibitory concentrations (CI50) for the native *ALK*-kinase, and because they cover more *ALK* resistance mutations, while achieving better penetration into the CNS, demonstrated their superiority over crizotinib, positioning

themselves as the preferred options in the first-line treatment [9]. Likewise, lorlatinib, a third-generation *ALK* inhibitor specifically designed to have greater potency against *ALK* rearrangement and all known *ALK* resistance mutations, was also shown to be superior to crizotinib, suggesting its possible use in newly diagnosed patients [9].

The objective of the present systematic review was to evaluate the clinical efficacy and safety of alectinib, compared with other commercially available *ALKi*, as the first-line option in patients with *ALK*-positive metastatic or locally advanced NSCLC, with sub-analysis on clinical efficacy in patients with and without the presence of CNS metastases at baseline.

Due to the absence of direct comparisons between all interventions of interest, we performed a network meta-analysis (NMA) with information obtained from 13 RCTs. Comparative assessment using NMA was possible for overall survival, progression-free survival, time to CNS progression, response rates, and AEs.

In this NMA, alectinib that patients treated with alectinib were 45% less likely to die than patients treated with crizotinib. Similarly, for progression-free survival, alectinib showed a 65% and 72% reduction in the instantaneous death or progression rate compared with crizotinib and ceritinib, respectively. NMA showed no statistically significant differences in comparing alectinib and the other *ALKi* (lorlatinib, brigatinib and ensartinib) for both survival outcomes.

Our results are consistent with evidence published in other NMA. Elliott *et al.* found that both alectinib and brigatinib showed a significant benefit in progression-free survival compared with crizotinib and ceritinib, with risk reductions between 50% and 70% (alectinib vs crizotinib HR = 0.34; 95% CI: 0.17–0.70); alectinib versus ceritinib HR = 0.30; 95% CI: 0.14–0.64; brigatinib versus crizotinib HR = 0.49; 95% CI: 0.33–0.73; brigatinib versus ceritinib HR = 0.43; 95% CI: 0.27–0.70) [10]. Similarly, these authors found no statistically significant differences between alectinib and brigatinib for overall and progression-free survival; however, their NMA omitted lorlatinib [10].

Contrary, the NMA by Chuang *et al.*, which succeeded in including all five *ALKi*, found that while lorlatinib showed a more significant benefit in progression-free survival compared with brigatinib or ensartinib when compared with alectinib, there was no statistically significant difference (HR = 0.68; 95% CI: 0.42–1.08) [13].

Regarding the subgroups analysis, our study found that alectinib, compared with crizotinib, results in a significant reduction of the instantaneous death rate (42%) and the progression rate (76%) among patients with CNS metastases at baseline. Also, alectinib demonstrated additional superiority against ceritinib in progression-free survival (80% reduction). For the other comparisons, we found no statistically significant differences.

Concerning patients with no CNS lesions at baseline, alectinib showed no significant differences in overall survival compared with brigatinib or crizotinib. It showed superiority in reducing the probability that patients would experience progression or death in up to 80% when compared with crizotinib and ceritinib. In this subgroup analysis, we found again no statistically significant differences between alectinib and lorlatinib, brigatinib or ensartinib.

Our results for patients with and without CNS metastasis are consistent with previous research that assessed progression-free survival between different ALKi. For example, Wang *et al.* found that in patients with *ALK*+ NSCLC without prior treatment with ALKi, lorlatinib and alectinib showed no statistically significant differences in patients with baseline brain metastases (HR = 0.67; 95% CI: 0.29–1.56), nor in patients without brain metastases at baseline (HR = 0.72; 95% CI: 0.40–1.28) [11]. Likewise, the study of Ando *et al.* (76) found no statistically significant differences in progression-free survival between lorlatinib and alectinib in patients with baseline CNS metastases (HR = 0.54; 95% CI: 0.23–1.28), and no intracranial metastases reported at baseline (HR = 0.70; 95% CI: 0.40–1.23) [12].

Regarding the CNS time-to-progression, our results showed no statistical differences in the risk of CNS progression between alectinib and lorlatinib (HR = 2.19; 95% CI: 0.77–6.22); while compared with crizotinib, alectinib showed a significant risk reduction of 85% (HR = 0.15; 95% CI: 0.09–0.25). In our study, the superiority of alectinib against crizotinib was maintained in the patients with or without of CNS metastasis at baseline; however, this analysis did not include comparisons against lorlatinib or ceritinib due to the lack of information in these subgroups. None of the meta-analysis published to date have evaluated this outcome in the population according to their CNS metastasis status at baseline.

Finally, regarding the objective, partial and complete response rates, we found no statistically significant differences between alectinib and the other interventions included in the NMA. The response rate analysis could only be performed in the total population due to a lack of data in the subgroups of interest. Our results are consistent with the findings of Chuang *et al.*, which showed no significant differences between lorlatinib and other *ALKi* for


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objective response rate: (ensartinib: RR = 1.18; CI%95% 0.94 to 1.48; brigatinib: RR = 1.11, 95% CI: 0.88 to 1.42, alectinib: RR = 1.16, 95% CI: 0.96–1.40) [13].

Findings from published NMAs on the clinical efficacy of *ALKi*, particularly alectinib, have been consistent with information reported in real-world studies. For example, the study by Davies *et al.*, which included 183 patients treated with alectinib in real-life settings (propensity score-adjusted cohorts), found that the overall survival with alectinib is superior to that of ceritinib (HR = 0.65; 95% CI: 0.48–0.88) [45]. Likewise, with 355 patients treated with alectinib, Wilkinson's study, found that alectinib showed a greater instantaneous death rate reduction of compared with patients treated with ceritinib (HR = 0.46; 95% CI: 0.29–0.63) [46].

The absence of statistically significant differences between the different *ALKi* is relevant when considering the choice of therapeutic sequence or treatment lines for newly diagnosed patients with metastases or advanced disease. While the results of clinical trials and secondary studies coincide in showing the superiority of second-and third-generation inhibitors compared with crizotinib, the choice between new inhibitors should consider both comparative efficacy and available post-treatment therapeutic options when second-and third-generation inhibitors fail.

The second-generation inhibitors alectinib and brigatinib have shown high intracranial efficacy. In contrast, lorlatinib, the only available third-generation inhibitor, has been specifically designed to be effective against all *ALK* resistance mutations [9]. Determining the available alternatives for post-resistance treatment on the first line is important because resistance to treatment is virtually inevitable and leads to patient relapse [47], estimated in approximately 50% of cases [47–49]. Additionally, the need to reduce the risk of intracranial progressions becomes relevant when considering that these progressions occur mainly in young patients, who can achieve a high survival, which may require the use of different treatment sequences [9,50].

Currently, there are no recommendations on the post-progression targeted treatment of patients who progressed with lorlatinib. Its use as a second-line treatment, and its specific design to respond to potential resistant *ALK* mutations, suggest reserving it as a post-failure option for second-generation inhibitors [50].

Concerning the safety evaluation, our findings showed that alectinib significantly reduced the risk of AEs when compared with ceritinib; whereas, concerning the other *ALKi*, the results showed no statistically significant differences in the risk of AEs, the risk of SAEs or the risk of abandoning treatment due to adverse events. However, alectinib position at the ranking suggests its potential to be the safest intervention among the evaluated *ALKi* (p = 0.27).

Other published NMA have evaluated the comparative safety between treatment options available for patients with *ALK*+ NSCLC; however, the primary outcome evaluated in these studies has been the frequency of grade ≥3 AEs, finding differences in the safety profile, mainly between alectinib and lorlatinib. For example, the NMA by Chuang *et al.* found that lorlatinib was associated with an increased risk of grade 3–5 AEs than alectinib (RR = 1.62; 95% CI: 1.24–2.12) [13]. Likewise, Peng *et al.* found that lorlatinib significantly increased the risk of presenting grade ≥3 AEs when compared with alectinib (RR = 4.26; 95% CI: 1.22–15.53) [51]. Finally, the study by Elliot *et al.* found that the incidence of grade 3 AEs was more frequent in the lorlatinib treated group than in the alectinib group (RR = 1.92; 95% CI: 1.48–2.5), concluding that among *ALKi*, alectinib was the most favorable treatment in terms of safety, while lorlatinib was the most unfavorable, precisely because of the increased risk in the frequency of any AE, grade 3 AEs, SAEs events of any grade and SAEs of grade 3 or more [10].

Additionally, the comparative safety between alectinib and lorlatinib should consider the most frequent events that have been reported, specifically, the events reported in clinical studies of lorlatinib, which are related to changes in cognitive functions and mood, requiring significant interruptions or dose reductions [52]. The possible impact on effectiveness has not been evaluated, which is relevant when considering that in real-life scenarios the percentage of patients requiring dose reductions is usually higher than that reported in clinical studies [53].

Consequently, the high frequency of grade 3 or higher AEs, and the specific AEs requiring interruptions or dose reduction for lorlatinib, suggest that alectinib presents a better safety profile for the first-line treatment of patients with metastatic or locally advanced *ALK*+ NSCLC.

Some limitations should be acknowledged. This study prioritized the outcomes assessed by the independent committees and the reports with extended follow-up time; however, in cases such as ALEX, PFS results with extended follow-up were only evaluated by the investigators [15]. This may have had an impact when considering possible variations between the investigator and committee estimates; however, the original report by Peters *et al.* showed highly similar estimates between the investigator and independent committee evaluations in the ALEX study [14], thus lessening the possible impact.

Similarly, study design and extended reporting can generate variations; for example, some studies, such as ALEX, did not allow post-progression treatment [14], while studies, such as ALTA1, did [43]. This variability may have an impact in that the number of events (progression or death) may change at longer follow-ups.

The results of this study should be interpreted cautiously due to the limitations inherent in an analysis of indirect comparisons since the estimators obtained from this analysis rely upon the transitivity and consistency assumptions. While we were able to assess the transitivity assumption, due to the absence of loops in the evidence networks (related to the lack of head-to-head comparisons between interventions), it was not possible to assess consistency for most analysis performed. Similarly, some of the planned analysis of this study could not be conducted due to the heterogeneity of the report or the absence of a common comparator.

## Conclusion

This NMA was based on the quantitative synthesis of 13 RCTs evaluating *ALK* inhibitors in patients with *ALK*+ NSCLC. Due to the similarity of the RCTs, the heterogeneity of the analysis mainly was low or moderate. Likewise, due to the methodological quality of the included studies, the risk of bias was considered low in most cases, which allowed the network estimates to have a moderate to high certainty of the evidence.

Regarding overall survival and progression-free survival, alectinib was found to reduce the hazard rate of death and the hazard rate of progression compared with crizotinib. For progression-free survival, a further significant reduction was observed compared with ceritinib. Compared with the other *ALKis* included in the analysis (lorlatinib, brigatinib and ensartinib), the results showed no statistically significant differences, suggesting comparable efficacy between alectinib and the other second-and third-generation *ALK* inhibitors.

Subgroup analysis according to the presence of CNS metastases at baseline was consistent in showing the superiority of alectinib over crizotinib and the absence of statistically significant differences when compared with second-and third-generation inhibitors. Comparable clinical efficacy between alectinib and other *ALK* inhibitors was found for the time to CNS progression, objective response rate, partial response rate, and complete response rate.

Evidence suggests that alectinib has a good safety profile compared with other *ALK* inhibitors available for the treatment of patients with *ALK*+ NSCLC.

## Future perspective

*ALK*-positive NSCLC is a distinct subset of lung cancer with a diverse natural history and response to therapies. Since disease progression is practically inevitable, defining the best option for first-line treatment is essential, as determining the available alternatives for post-resistance treatment on the first line.

Targeted therapy and immunotherapy are fast-developed fields in oncology. Future studies will likely focus on treating resistance to ALK inhibitors currently on the market, allowing the availability of new lines of treatment for metastatic disease progression.

### Summary points

- Recommendations for first-line treatment of metastatic or locally advanced *ALK*-positive NSCLC are based on the results of head-to-head studies comparing second-generation *ALKi* or third-generation inhibitors with crizotinib.
- This network meta-analysis compares the efficacy and safety of alectinib with other commercially available *ALKi*, as first-line treatment in patients with *ALK*-positive metastatic or locally advanced NSCLC.
- Comparable efficacy between alectinib and the other second-and third-generation ALK inhibitors was found in overall survival, progression-free survival and response rates.
- The second-generation inhibitor alectinib showed statistical reductions in the risk of death or disease progression compared with crizotinib and ceritinib.
- NMA showed no statistically significant differences in the reduction of the central nervous system progression between alectinib and third-generation ALK inhibitor.
- Results suggest that alectinib has a good safety profile compared with other ALK inhibitors indicated for patients with *ALK*-positive NSCLC.
- Alectinib showed favorable results in reducing the risk of progression to the nervous system, even in patients with brain metastases at baseline.
- Since progression to the nervous system occurs mainly in young patients, who can achieve high survival and may require different treatment sequences, our results suggest that alectinib could be considered as a first-line treatment in patients with brain metastases at baseline.


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### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/lmt-2022-0018

### Author contributions

All authors had substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be 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 resolve.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.



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