CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Anaplastic Lymphoma Kinase Inhibitors for Genetically Rearranged Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 1, 2018
Report Length:	32 Pages

CADTH

Authors: Saadul Islam, Charlene Argáez

Cite As: Anaplastic lymphoma kinase inhibitors for genetically rearranged non-small cell lung cancer: a review of the clinical effectiveness. Ottawa: CADTH; 2018 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALKI	Anaplastic lymphoma kinase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice-daily
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CTCAE	Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
EGFR	Epidermal growth factor receptor
EPHPP	Effective Public Health Practice Project Tool
GGT	Gammaglutamyltransferase
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HRQoL	Health-related quality of life
HTA	Health technology assessments
IC	Intracranial
IRC	Independent review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NMA	Network meta-analyses
NOS	Newcastle-Ottawa scale
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PRO	Patient-reported outcomes
QD	Once-daily
SR	Systematic reviews
TKI	Tyrosine kinase inhibitors
RCT	randomized controlled trial
RECIST	Response evaluation criteria in solid tumours
RoB	Risk of Bias

Context and Policy Issues

Lung cancer is associated with the highest incidence and cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) being the most frequent type.[1] Patients with advanced or metastasized NSCLC have a poor prognosis, with 5-year survival post-diagnosis less than 5%, and typical survival being 8 to 10 months.[1] A small group of NSCLC patients (3% to 5%) harbors a rare genetic rearrangement in the anaplastic lymphoma kinase (*ALK*) gene, resulting in a novel fusion oncogene *EML4-ALK* that, in turn, leads to constitutive expression of intracellular signaling pathway that promotes tumour growth and survival.[1,2] Patients with *ALK*-positive NSCLC have distinct clinicopathologic features such as adenocarcinoma with signet ring or acinar histology, and it is typically seen in those with a relatively young age, and who are never or light smokers.[2] Additionally, patients with the following clinicopathologic features have a progressively higher likelihood of *ALK* rearrangement: those with clinical features commonly associated with epidermal

growth factor receptor (*EGFR*) mutation (13%), never or light smokers within this subset of patients (22%), and the never or light smokers subset without *EGFR* mutation (33%).[2]

ALK tyrosine kinase inhibitors (TKIs), herein referred to as ALKIs, are a group of targeted therapies for patients with *ALK*-positive NSCLC. Treatment with ALKIs is generally limited to patients with *ALK* rearrangement confirmed with molecular or histological tests.[2] Crizotinib was the first-generation ALKI, and was used as the first-line therapy in the past in *ALK*-positive NSCLC patients.[3] However, patients eventually develop resistance, primarily progressing in the central nervous system (CNS), resulting from poor drug penetration into the brain. Because brain metastases are seen in approximately 30% to 40% of advanced *ALK*-positive NSCLC patients, the intracranial (IC) activity of ALKIs is important to consider. Ceritinib, a second-generation ALKI, was first approved in the second-line setting, but has since received approval as a first-line therapy. Ceritinib has been shown to have activity against IC disease, particularly compared with crizotinib.[3] Alectinib is another second-generation ALKI that was approved for first-line use, with favorable clinical and safety profile compared with crizotinib.[3]

In addition to first-line settings, alectinib and ceritinib have been found to be efficacious as second-line treatments in patients who developed resistance or had disease progression after crizotinib.[3] Brigatinib is one of the newer ALKIs that has received approval for crizotinib-refractory *ALK*-positive NSCLC, with trials underway comparing its benefits against crizotinib and following alectinib and ceritinib failure. Even newer ALKIs are awaiting regulatory approval for third or subsequent-line treatment, lorlatinib being the most prominent one.[3]

With all the ALKIs available in the market, it is important to understand the comparative clinical effectiveness and safety profile of the different ALKIs in relation to each other, particularly in the first-line and second-line setting. This report was undertaken to examine the current evidence surrounding the comparative clinical benefits of first-line ALKIs among patients naive to previous ALK treatment (ALK-naive), and second-line ALKIs among patients who have been pretreated with other ALKIs and had disease progression (ALK-pretreated).

Research Questions

1. What is the comparative clinical effectiveness of Anaplastic Lymphoma Kinase inhibitors as first-line therapy for patients with non-resectable Non-Small Cell Lung Cancer?
2. What is the clinical effectiveness of Anaplastic Lymphoma Kinase inhibitors in patients with non-resectable Non-Small Cell Lung Cancer whose disease has progressed on one or more previous treatments with Anaplastic Lymphoma Kinase (ALK) inhibitors?

Key Findings

One health technology assessment report, one network meta-analysis, one systematic review with meta-analyses, and two randomized controlled trials were included in this review.

Based on findings from a well-conducted indirect comparison that did not account for first and second-line treatment, alectinib was associated with a longer progression free survival and lower toxicity followed by ceritinib and crizotinib; however, these benefits were not seen

in improving objective response rate and disease control rate. Direct comparison using meta-analyses indicated all ALK-inhibitors, regardless of used in patients who were ALK-naive or pretreated, resulted in an improved objective response rate, disease control rate, progression free survival and toxicity; findings did not change with brain metastases. These results, however, were pooled from a mixed group of patients who were ALK-naive and pretreated.

Findings from two well-conducted randomized controlled trials showed alectinib to be more clinically efficacious than crizotinib in both ALK-naive and pretreated settings, significantly improving progression free survival, delaying disease progression to the brain, and maintaining a similar or better safety profile.

Ceritinib demonstrated clinical benefits in patients pretreated with ALK inhibitors. As reported in a well-conducted meta-analysis, patients refractory to crizotinib had an improvement in objective response rate following ceritinib treatment; however, no improvements were seen in progression free survival or intracranial response.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and October 5, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Adult patients with non-resectable, ALK-positive NSCLC who have not previously been treated with an ALK inhibitor (failure with chemotherapy and have not been treated with an ALK inhibitor) Q2: Adult patients with non-resectable, ALK-positive NSCLC whose disease has progressed on one or more ALK inhibitors
Intervention	ALK Inhibitors (entrectinib, ceritinib, crizotinib, lorlatinib, alectinib, and brigatinib)
Comparator	Q1: Other ALK inhibitors Q2: Placebo, chemotherapy, immunotherapy, other ALK inhibitors, no comparator
Outcomes	Q1, Q2: Clinical effectiveness i.e., benefit (e.g., overall survival, progression-free survival, objective response rate, health-related quality of life), harm (e.g., safety, adverse events, discontinuation)
Study Designs	HTA/Systematic Reviews/Meta-Analyses, RCTs

ALK = anaplastic lymphoma kinase; HTA = health technology assessment; NSCLC = non-small cell lung cancer; RCT = Randomized Controlled Trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2016. Studies included in a selected systematic review were also excluded. Due to multiple overlapping systematic reviews, systematic reviews were excluded if there was full or nearly full overlap with an included systematic review, or if the results were not provided separately for each ALKI. Subsequent publications of trials that were included in one of the SRs included in our review were excluded if they did not provide unique or additional data that would change the results of the findings. Excluded publications that may be of interest are included in Appendix 6.

Critical Appraisal of Individual Studies

All studies were critically appraised by one reviewer. The included HTA and SRs were critically appraised using AMSTAR 2,[4] the NMA was critically appraised using the ISPOR questionnaire,[5] and RCTs were critically appraised using the Downs and Black checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 278 citations were identified in the literature search. Following screening of title and abstracts, 238 citations were excluded and 40 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, 44 potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 79 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised one health technology assessments (HTAs),[1] two systematic reviews (SR), one with meta-analyses[7] and another with a network meta-analyses (NMA),[8] and two RCTs.[9,10] Appendix 1 presents the PRISMA[11] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Five studies met the inclusion criteria for this review, including one HTA, two SRs (one NMA, one meta-analyses), and two phase 3 RCTs.

An HTA report, published by EUnetHTA and supported by the European Commission, was identified that assessed the clinical effectiveness and safety of alectinib first-line therapy in comparison with crizotinib and ceritinib using direct and indirect comparison from three phase 3 active-controlled RCTs on patients who were ALK-naive, of which one RCT (the ALEX trial) was relevant for this review.[1] An NMA consisting of 33 clinical trials (including eight RCTs and 25 single-arm trials) was included for direct and indirect comparison of several ALKIs in patients who were ALK-naive and pretreated.[8] A systematic review with meta-analyses consisting of seven clinical trials evaluated the clinical effectiveness and safety of ceritinib, of which five trials reporting results in patients pretreated with crizotinib were relevant.[7] Two multicenter, open-label, phase 3 RCTs were included, namely the

ALUR trial comparing the efficacy and safety of alectinib versus standard chemotherapy in patients pretreated with crizotinib-pretreated[10], and the ALEX trial comparing the CNS efficacy between alectinib and crizotinib in patients who were ALK-naive.[9]

All studies included in this report were published between January and August in 2018. The literature search period ranged from inception to December 2017 for the EUnetHTA report,[1] March 2018 for the NMA,[8] and August 2017 for the meta-analyses by Zhao et al.[7]

Country of Origin

The EUnetHTA report was created in partnership with several EU organizations, including the Dental and Pharmaceutical Benefits Agency (TLV), Sweden; Main Association of Austrian Social Security Institutions (HVB), Austria; and Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ), Croatia.[1]

Authors of two systematic reviews were based in China.[7,8] The ALEX trial was conducted in 98 centres across countries in North America, Europe, Latin America, Asia, and Australia,[9] and the ALUR trial was conducted at 40 centres in Europe and Asia.[10]

Patient Population

All included studies consisted of adults with histologically confirmed *ALK*-positive, locally advanced or metastatic (stage IIIB or IV) NSCLC. Patients in the ALEX trial (N = 303) that constituted the evidence base for Gadgeel et al.[9] and the direct comparison in the EUnetHTA report were ALK-naive.[1] The NMA by Fan et al. consisted of a mix of patients who were ALK-naive and pretreated (N = 5,507).[8] The systematic review by Zhao et al. included patients who were crizotinib-naive and pretreated (N = 1,015).[7] Finally, patients in the ALUR trial (N = 107) had prior treatment with crizotinib.[10]

The median age of patients across the studies ranged from 44 to 72 years. The proportions of patients with CNS/brain metastases at baseline varied across the studies: approximately 40% in the ALEX trial,[1,9] between 31% and 80% in the systematic review by Zhao et al,[7] between 65% and 75% in the ALUR trial[10], and this data was not available in the NMA by Fan et al.[8] Additionally, approximately 14% to 17% of patients in the ALEX trial and 60% to 82% patients in the ALUR trial received prior radiotherapy.[1,9,10]

Interventions and Comparators

Patients in the ALEX trial received either alectinib 600 mg twice-daily (BID) or crizotinib 250 mg BID (randomized in a 1:1 ratio).[1,9] In the ALUR trial, patients received alectinib 600 mg BID or chemotherapy [pemetrexed 500 milligram/square-meter (mg/m^2) or docetaxel 75 mg/m^2] every 3 weeks, at the investigators' discretion (randomized in a 1:1 ratio).[10] In both the ALEX and ALUR trial, patients in the crizotinib and chemotherapy arm, respectively, were permitted to crossover to alectinib if progression occurred. Furthermore, all patients were treated until disease progression, toxicity, withdrawal, or death. [1,9,10] The 33 trials included in the NMA had a number of ALKIs with varying dosages: alectinib 300 to 900 mg BID, crizotinib 250 mg BID, ceritinib 300 to 750 mg once-daily (QD), brigatinib 30 to 300 mg QD, lorlatinib 10 to 200 mg QD or BID, and ensartinib 225 mg QD, in addition to different dosages of chemotherapy (not listed).[8] In the systematic review by Zhao et al., all patients received ceritinib and five of the seven included trials included participants who had received crizotinib as prior treatment, although the dosages in each trial were not provided.[7]

Outcomes

In the EUnetHTA report, the primary efficacy outcome was progression-free survival (PFS); secondary endpoints included time to CNS progression, objective response rate (ORR), overall survival (OS), health-related quality of life (HRQoL), other patient-reported outcomes (PRO), CNS objective response rate (CNS ORR), and CNS duration of response (DOR). In addition, any adverse events (AE) reported during the 17 to 18-month follow-up period were reported.[1]

The NMA by Fan et al. reported the following outcomes for clinical efficacy: overall ORR, DCR, PFS, and discontinuation rate, as well as CNS ORR, CNS DCR.[8]

The systematic review by Zhao et al. pooled the following outcomes: ORR, PFS, DCR, and ORR for intracranial metastasis.[7]

Outcomes in the ALUR trial included PFS (primary), CNS ORR, in patients with measurable baseline CNS disease, ORR, DCR, DOR, time to CNS progression by baseline CNS disease; CNS DCR and CNS DOR in patients with baseline CNS metastases, overall survival (OS), and safety.[10]

The long-term CNS efficacy results of ALEX, reported by Gadgeel et al., included an analysis of PFS, CNS ORR, and time to CNS progression by patients with/without baseline CNS metastases and by patients with/without prior radiotherapy.[9]

In all cases, response was determined by the investigator or the independent review committee (IRC) using the response evaluation criteria in solid tumours (RECIST) version 1.1 criteria;[12] which include physical examinations, computed tomography (CT) scans, and magnetic resonance imaging (MRI). Definitions of the outcomes were available for the ALEX and the ALUR trial and are as follows:

- PFS: Time from the randomization to first documentation of disease progression or death (from any cause), whichever occurred first, in the whole body.
- OS: The time from randomization to death from any cause.
- Time to CNS progression: The time from randomization until first radiographic evidence of CNS progression by independent review.
- CNS progression: Progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions.
- ORR: The proportion of patients with a complete response (CR) or partial response (PR) since the date of the treatment according to RECIST v1.1. CNS ORR was defined as the proportion of patients who achieved a CR or PR in CNS metastases.
- DCR: The proportion of patients with CR, PR, or stable disease of at least five weeks, as determined using RECIST v1.1. CNS DCR was defined as the proportion of patients who achieved a CR, PR, or stable disease of at least five weeks in CNS metastases.
- DOR: The time from when the response criteria (CR or PR) were first met to the occurrence of a PFS event. CNS DOR was defined as the time from when CR or PR was first documented to disease progression in the CNS or death, whichever occurred first.

- Time to CNS progression: The time from randomization to the first documented progressive disease in the CNS.
- Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and were classified according to the Medical Dictionary for Regulatory Activities.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

HTA, systematic review and NMA

The EUnetHTA report[1] and systematic review by Zhao et al.[7] were critically appraised using AMSTAR 2[4]; the ISPOR questionnaire[5] was used to appraise the NMA by Fan et al.[8]

These publications were conducted and reported in accordance with established guidelines for systematic reviews. All three reports had a clearly defined objective and rationale, incorporated a comprehensive and thorough literature review, included at least three databases, provided keywords for the literature search, placed no restrictions on publication date, and had clear inclusion and exclusion criteria. Description of important characteristics of the included studies was adequately provided. Study selection, data extraction, and study quality assessment were done in duplicate for all three reports. Assessment of study quality and quality of evidence were done at the individual study and outcome level using a variety of established tools, including the Cochrane Risk of Bias (RoB) tool, Grading of Recommendations, Assessment, Development and Evaluation (GRADE), Effective Public Health Practice Project Tool (EPHPP), and Newcastle-Ottawa scale (NOS). Even though the systematic reviews were conducted with high scientific rigour, the quality of included studies within each systematic review varied. In general, the publications by EUnetHTA and Zhao et al. consisted of relatively fewer studies, and the quality of evidence was moderate to high. The NMA, on the other hand, consisted of 33 trials of varying quality. The quality of the studies and evidence was adequately considered in interpreting results and formulating conclusions.

The statistical methods for pooling results for direct (pairwise meta-analyses) or indirect (NMA) comparison were well-established and appropriately done. In the two systematic reviews with meta-analyses, statistical heterogeneity was assessed using Tau or Cochrane Q and I^2 statistic and extracted results of studies were weighted. In both cases, a random-effects model was used when $I^2 \geq 50\%$ and Cochrane Q test/Tau P value was < 0.05 indicating moderate to significant heterogeneity, otherwise a fixed-effects model was used. Publication bias was assessed using Begg's and Egger's test in two systematic reviews, but not in the EUnetHTA report. No evidence of a publication bias was reported in the two systematic reviews, and this was not assessed in the EUnetHTA report.

The NMA included in this review had a number of limitations, including a lack of assessment of the consistency between direct and indirect contrasts, and no sensitivity analysis for potential confounders or testing various model assumptions. The statistical rigour of the indirect comparison was therefore limited, despite using a well-established Bayesian method. Finally, the study pooled data from a mixed population of ALK-naive and pretreated patients. Therefore, the effects of any particular ALKI could not be determined in a purely ALK-pretreated population, and no comparative data between two or more ALKI in a purely ALK-naive population was available.

Randomized controlled trials

Strengths common to both RCTs were that the study objective, inclusion and exclusion criteria, and interventions being compared were described clearly. In addition, the main outcomes, potential confounders, baseline patient characteristics, and main findings were also clearly described. Since both trials were open-label, patients and investigators were not blinded. However, an independent review committee assessed several outcomes in both trials and was blinded; results from both groups were comparable. Statistical tests conducted in both RCTs were appropriate and accounted for loss to follow-up. Both RCTs were sufficiently powered to demonstrate superiority for the primary outcome(s). Overall, external validity was a common limitation in the RCTs, since no information was provided if patients were representative of the populations from which they were recruited and staff, places, and facility were representative of the treatment received by the source population. However, the findings are likely to be generalizable, as both trials were conducted in various countries and settings across the world.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions. Table 9 in Appendix 5 provides a detailed description of the overlap in the primary studies between the SRs.

Clinical Effectiveness of ALK inhibitors as first-line therapy for non-resectable NSCLC patients naive to ALK inhibitors

Comparative clinical effectiveness of ALK-inhibitors (Indirect and direct comparison from Fan et al.)

Fan et al.[8] conducted an NMA to provide comparative clinical and safety benefits of three ALKIs; however, the results were not separated by previous ALKI treatment history. Indirect comparison showed that patients treated with alectinib had a statistically significantly longer PFS when compared with ceritinib and crizotinib. Alectinib and crizotinib preceeded ceritinib in the ranked probabilities for prolonging the PFS. Alectinib was also associated with a statistically significantly lower discontinuation rate compared with ceritinib and crizotinib; this pattern was consistent in the ranked probabilities. None of the three ALKIs showed significant differences in improving ORR and DCR using indirect comparisons. Ranked probabilities favored alectinib to have the highest probability for improving ORR, followed by ceritinib, and then crizotinib. Alectinib also ranked the highest for improving DCR.[8] The data were pooled from a mix of ALK-naive and pretreated population and should therefore be taken into consideration when interpreting the results.

Direct comparison using pairwise meta-analyses indicated that all analyzed ALKIs significantly improved the ORR and DCR among patients who were ALK-naive, including those with baseline CNS metastases. As well, significantly longer pooled PFS and lower discontinuation rates were reported in this group of patients.[8] However, the trials included for these pooled estimates were less likely to compare two ALKIs. In addition, the number of available trials and heterogeneity among them varied significantly across different ALKIs.

Clinical effectiveness of alectinib versus crizotinib (ALEX trial, direct comparison in the EUnetHTA report)

The direct comparison in the ALEX trial showed a statistically significant increase in PFS (both investigator and IRC-assessed) among patients treated with alectinib, and the PFS benefit was consistent for patients with and without CNS metastases. A median increase of

15.3 months was reported in the alectinib arm using IRC-assessed PFS, while the median PFS was not reached for investigator-assessed PFS.[1] In contrast, neither arm had a statistically significant difference in OS. However, this was an interim analysis, the median OS was not reached in either arm. Therefore, a future analysis after 50% of events would be more informative.[1]

More patients in the alectinib arm were considered responders in the ALEX trial; however, the difference was not statistically significant.[1] Patients receiving alectinib had longer DOR compared with crizotinib, as demonstrated by fewer cases of disease progression or death among responders in the alectinib arm.[1] Alectinib also showed clear superiority over crizotinib in extending the time to CNS progression. Other exploratory CNS endpoints favored alectinib, although no comparative statistical tests were performed.

QoL was assessed in the ALEX trial only; however, those who were treated with alectinib did not have a statistically significant improvement compared with crizotinib. Overall, the evidence for the QoL outcomes was associated with a high risk of bias due to the open-label nature of the trial and low baseline values of completed questionnaires at baseline.[1]

Safety results showed a similar toxicity profile between alectinib and crizotinib.[1]

Clinical effectiveness of alectinib versus crizotinib (CNS efficacy results from the ALEX study)

CNS efficacy data were partially presented in the earlier publication of the ALEX trial (summarized in the EUnetHTA report),[1] and much of the results in Gadgeel et al.[9] were presented by subgroups of patients on the basis of prior radiotherapy; therefore results relevant from this publication were the time to CNS and non-CNS disease progression among patients with and without brain metastases. Results showed the time to CNS progression was significantly longer with alectinib, and comparable between patients with and without CNS metastases at baseline. However, the benefit of alectinib in non-CNS progression was restricted to patients with baseline CNS metastases. A similar pattern was seen with 24-month CIR in the two subgroups.[9]

Clinical effectiveness of ALK inhibitors in patients with non-resectable NSCLC whose disease has progressed on one or more previous treatments with ALK inhibitors

Comparative clinical effectiveness of ALK-inhibitors (direct comparison from Fan et al.)

Pairwise meta-analyses of trials including patients pretreated with ALKIs showed a trend similar to that found among patients who were ALK-naive. All analyzed ALKIs significantly improved the ORR and DCR among patients pretreated with ALKIs, including those with baseline CNS metastases. As well, significantly longer pooled PFS and lower discontinuation rates were reported in this group of patients.[8] Notably, a greater proportion of trials included for these pooled estimates had mixed or fully ALK-pretreated patients compared with pooled estimates from patients who were ALK-naive. However, the number of available trials and heterogeneity among them varied significantly across different ALKIs, limiting the interpretability of the results.

Clinical effectiveness of ceritinib in crizotinib-pretreated patients (meta-analyses results from Zhao et al.)

Results from Zhao et al.[7] showed that among patients pretreated with crizotinib, ceritinib treatment led to a statistically significant improvement in ORR, but not in PFS or IC ORR. The IC DCR in those pretreated with crizotinib was not reported.

Safety endpoints were pooled from crizotinib-naive and pretreated populations, therefore, the comparative safety of ceritinib among ALKI-pretreated patients could not be ascertained. Within the studies that included participants who were pretreated with crizotinib, the most common AEs included diarrhea, nausea, vomiting, fatigue, decreased weight, decreased appetite, and increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gammaglutamyltransferase (GGT) concentrations. The rates of treatment discontinuation across the studies were low(≤6%). Finally, the pooled incidence of grade 3 or 4 AEs were generally low, ranging from approximately 5% for fatigue to approximately 25% for increased ALT concentration.[7]

Clinical effectiveness of alectinib in crizotinib-pretreated patients (phase 3 ALUR trial results from Novello et al.)

In the ALUR trial,[10] participants in the alectinib arm who were pretreated with crizotinib had a statistically significantly longer mean PFS compared with those in the chemotherapy arm, regardless of whether the assessment was done by the investigators or IRC; and the PFS benefits were seen among patients with and without CNS metastases. With the exception of OS, all other outcomes showed statistically significant clinical benefits with alectinib treatment compared with chemotherapy; including improving the ORR, DCR, time to CNS progression. However, neither arm reached a 50% event rate and over one-third of those in the chemotherapy arm crossed over to alectinib following progression.

Safety results showed a greater frequency of AEs and grade 3 to 5 AEs with chemotherapy. In the alectinib arm, AEs with a frequency of ≥ 5% were dyspnea, increased blood bilirubin; and the frequency of treatment discontinuation and dose reduction was low (≤ 6%). Of the AEs considered grade 3 or higher, pneumonia, syncope, and acute kidney injury occurred more frequently in the alectinib arm.[10]

Limitations

A major limitation of this report is the relative scarcity of evidence from studies that met the inclusion criteria entirely. Specifically, few original RCTs and systematic reviews were found that compared clinical effectiveness between two or more ALKIs in patients who were ALK-naive, or clinical benefits of ALKI alone or in combination with any standard of care in patients pretreated with ALKIs. Additionally, several systematic reviews were excluded because they provided results by ALKIs as a group and not by separate drugs, further limiting the evidence base.

The NMA included in this report consisted of the most comprehensive list of trials; however, the indirect comparison and ranking of treatment were done using pooled data from a mix of patients who were ALK-naive and pretreated. While results from pairwise meta-analyses were reported separately for ALK-naive and pretreated populations, data pooled for ALK-pretreated subgroups sometimes consisted of a mix of ALK-naive and pretreated patients. Furthermore, pairwise meta-analyses for ALK-naive subgroups did not always compare two or more ALKIs; and pairwise meta-analyses for ALK-pretreated subgroups compared a

particular ALKI against all ALKIs as a group. These factors should be taken into account when interpreting the results.

The ALEX and ALUR trials provided head-to-head data on alectinib versus crizotinib in both ALK-naive and ALK-pretreated settings. The systematic review by Zhao et al. pooled data from trials comparing ceritinib alone or in combination with chemotherapy in patients pretreated with crizotinib. However, no head-to-head trial was identified comparing alectinib with ceritinib (for either participants who had or had not been pretreated with an ALK) or ceritinib with crizotinib in participants who were ALK-naive. Evidence for newer ALKIs such as brigatinib, lorlatinib, and ensartinib was even more limited, not more than two trials for each drug were identified.

Conclusions and Implications for Decision or Policy Making

A total of five relevant publications were included, which comprised of one HTA,[1] two systematic reviews, one with a meta-analysis[7] and one with an NMA,[8] and two open-label, phase 3 RCTs.[9,10] The studies were well-conducted overall, with robust methodology; however, the studies included in the two systematic reviews were of varying quality.

Findings from two head-to-head trials demonstrated alectinib to have superior clinical benefits compared with crizotinib in both first-line (ALK-naive) and second-line (ALK-pretreated) settings; with improved progression free survival, slowed disease progression in the brain, and a manageable toxicity profile. The clinical benefits of ceritinib as a second-line therapy was demonstrated in a meta-analysis of five trials, which showed an improvement in tumour response among those who had been pretreated with crizotinib; however, the benefits did not translate to an improvement in progression free survival or intracranial response.

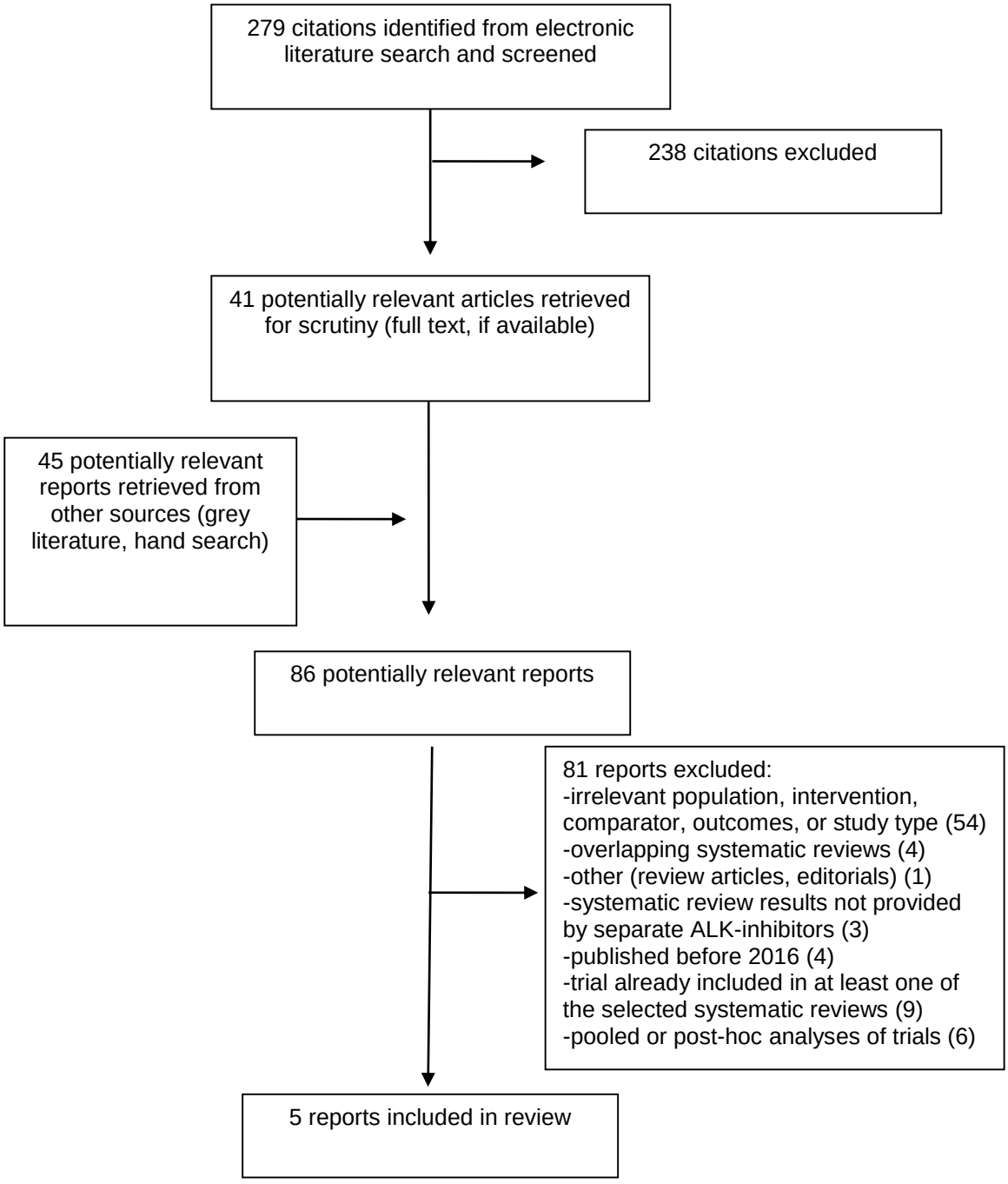
One study reported clinical benefits associated with all ALK-inhibitors in both first and second-line settings using direct pairwise meta-analyses. Through indirect comparisons, the study also showed alectinib to have a superior clinical and safety profile over ceritinib and crizotinib. The indirect comparison did not account for prior treatment history with ALKIs, thereby increasing uncertainty in the findings. While both alectinib and ceritinib were shown to be more efficacious compared with crizotinib, irrespective of the line of treatment, there was a lack of head-to-head RCT comparing alectinib and ceritinib. Results from the indirect comparisons provided evidence regarding the comparative efficacy of alectinib, ceritinib, and crizotinib, and were limited by the fact that data was pooled from patients with and without prior exposure to ALK-inhibitors.

Alectinib and ceritinib were found to be clinically more efficacious compared with crizotinib in both first-line and second-line settings. Alectinib also appeared to have a superior efficacy and safety profile followed by ceritinib and crizotinib based on indirect evidence, irrespective of prior treatment history. However, head-to-head trials comparing second or newer generation ALKIs are lacking or still underway, presenting a significant challenge in creating a treatment sequence or algorithm based on current evidence.

References

1. Dental and Pharmaceutical Benefits Agency, Main Association of Austrian Social Security Institutions, Agency for Quality and Accreditation in Health Care and Social Welfare. Alectinib as monotherapy for the first-line treatment of adult patients with *ALK*-positive advanced non-small cell lung cancer. *Rapid assessment on pharmaceutical technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment*. Sweden: EUnetHTA; 2018 Jan: https://www.eunethta.eu/wp-content/uploads/2018/01/PTJA03-Alectinib-Final-Assessment-Report.pdf. Accessed 2018 Oct 26.
2. Shaw A, Solomon BJ, Lilenbaum R, Vora S. Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancer. In: Post, TW, ed. *UpToDate.* Waltham (MA): UpToDate; 2018: www.uptodate.com. Accessed 2018 Oct 3.
3. Melosky B. Rapidly changing treatment algorithms for metastatic nonsquamous non-small-cell lung cancer. *Curr Oncol.* 2018;25(Suppl 1):S68-s76.
4. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017 Sep 2017;358:j4008.
5. Jansen J, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR task force on indirect treatment comparisons good research practices: part 1. *Value Health.* 2011 Jun;14(4):417-428.
6. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2018 Oct 26.
7. Zhao X, Feng Z, Wang G, Pang H, Wang M. Ceritinib alone for crizotinib-naive versus crizotinib-pretreated for management of anaplastic lymphoma kinase-rearrangement non-small-cell lung cancer: a systematic review. *Clin Lung Cancer.* 2018 Aug;18(30207-9):S1525-7304.
8. Fan J, Fong T, Xia Z, Zhang J, Luo P. The efficacy and safety of ALK inhibitors in the treatment of ALK-positive non-small cell lung cancer: a network meta-analysis. *Cancer medicine.* 2018 Sep;7(10):4993-5005.
9. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol.* 2018.
10. Novello S, Mazieres J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Ann Oncol.* 2018;29(6):1409-1416.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
12. Eisenhauera E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer Clin Oncol.* 2008(45):228-247.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Technology Assessment				
EUnetHTA (TLV, HVB, AAZ) 2018,[1] Europe	3 phase III, OL, RCTs : ALEX, ASCEND-4, and PROFILE 1014 ASCEND-4 and PROFILE 1014 trials were not relevant for this report.	ALEX: N=303 total; n=152 alectinib, n=51 crizotinib All patients had- • Previously untreated with systemic therapy for advanced NSCLC • Histologically confirmed *ALK*-rearrangement. • ECOG performance score 0 to 2 • Non-squamous NSCLC	ALEX: alectinib (600 mg BID) and crizotinib (250 mg BID)	**Effectiveness domain** Primary endpoint: PFS (investigator-assessed), OS Secondary endpoint: PFS[a] (IRC assessed), time to CNS progression, ORR, HRQoL, other PROs, CNS ORR, CNS DOR **Safety domain** Any AEs, SAEs, WDAEs **Follow-up** ALEX: 17.6 to 18 months (median)
Systematic Reviews				
Fan et al., 2018,[8] China[b]	33 clinical trials (8 RCTs, 25 single-arm non-RCTs)	N=5507 (2,042 in the eight RCTs, 3,465 in the 25 non-RCTs) *ALK*+ NSCLC patients ALK inhibitor-naive and pretreated	ALK inhibitors (alectinib, brigatinib, ceritinib, crizotinib, entrectinib, ensartinib, and lorlatinib	Overall ORR, DCR, PFS, and discontinuation rate, CNS ORR, CNS DCR **Follow-up:** approximately 4 to23 months (median range)
Zhao et al. 2018,[7] China	7 phase 1-3 trials (8 reports) [9 single-arm studies (5 relevant)]	N=1,015 Patients with *ALK*-rearrangement NSCLC or metastases to the brain pretreated with and without crizotinib (mixed)	Ceritinib	Primary: ORR, PFS, IC ORR, and IC DCR Secondary: AEs (included toxicity and dose reduction or cessation because of ceritinib) **Follow-up:** NR

AAZ = Agency for Quality and Accreditation in Health Care and Social Welfare, Croatia; (S)AE = (serious) adverse event; ALK = anaplastic lymphoma kinase; BID = twice daily; CNS = central nervous system; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; HTA = health technology assessment; HR = hazard ratio; HVB = Main Association of Austrian Social Security Institutions, Austria; IC = intracranial; NR = not reported; NSCLC = non-small cell lung cancer; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival (investigator and/or independent review committee-assessed); PRO = patient-reported outcomes; RCT = randomized controlled trial; TLV = Dental and Pharmaceutical Benefits Agency, Sweden; WDAE = withdrawal due to adverse event

[a] IRC-assessed PFS /tumour response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

[b] Network meta-analyses

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gadgeel et al. 2018,[9] USA **ALEX**	Phase 3 OL, multi-center RCT	N=303 (alectinib, n= 152; crizotinib, n=151), Patients with stage III/IV *ALK*+ NSCLC, ALK inhibitor-naive.	Alectinib 600 mg BID Crizotinib 250 mg BID	PFS, CNS efficacy endpoint (IRC-assessed): CNS ORR, CIR, DOR, and time to CNS progression **Follow-up:** 17.6 months for crizotinib and 18.6 months for alectinib (median)
Novello et al. 2018,[10] Italy **ALUR**	Phase 3 OL, multi-center RCT	N=107 (alectinib, n=72; chemotherapy, n=35) Patients with advanced/metastatic *ALK*+ NSCLC previously treated with platinum-based doublet chemotherapy and crizotinib	Alectinib 600 mg BID Chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2, both every 3 weeks)	Primary: PFS (investigator-assessed) Secondary: PFS (IRC-assessed), OS, ORR, DCR, DOR (investigator and IRC-assessed), (by baseline CNS disease) CNS ORR, time to CNS progression, (in patients with baseline CNS metastases) CNS DCR and CNS DOR, safety **Follow-up:** 6.5 months for alectinib, 5.8 months for chemotherapy (median)

(S)AE = (serious) adverse event; ALK = anaplastic lymphoma kinase; BID = twice daily; CNS = central nervous system; DCR = disease control rate; DOR = duration of response; IC = intracranial; NR = not reported; NSCLC = non-small cell lung cancer; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival (investigator and/or independent review committee-assessed); RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[4]

Strengths	Limitations
EUnetHTA, 2018[1]	
• A systematic and comprehensive literature search was conducted, with predefined search strategy; an update of the literature search was also performed. The authors checked and validated the search strategy and sources for inclusion. The reporting of the search strategy followed the EUnetHTA guidelines and the requirements of PRISMA-P statement. • The scope of the systematic review was clear, with predefined inclusion/exclusion criteria for patient population, interventions, comparators, outcomes and study design. • Data extraction and study quality assessment was done independently by multiple authors, although there was no information on how disagreements were resolved. • The Cochrane Risk of Bias tool and the GRADE approach was used to assess the risk of bias and quality of evidence. In general, all included trials including the ALEX trial had low risk of bias across different dimensions at the study level and outcome level, with the exception of dimensions affected by the open-label nature of the trial (e.g. blinding). Likewise, the quality of evidence for alectinib vs crizotinib comparison was generally moderate to high; however, outcomes associated with immature data (OS) or low baseline values (HRQoL) were assigned low in quality. • The Bucher method was used for the indirect comparison and NMA; however, this will not be appraised further since results from the indirect comparisons were not used in this report. • Both direct and indirect comparisons were available to assess the consistency assumption for the NMA; however, the qualitative assessment of the consistency assumption was out of scope for this report. • Study and patient characteristics of each included trial were provided with adequate details. • All authors and reviewers of the report declared no conflicts of interest. The source of funding for the report was provided; however, it was not available for the individual studies.	• An assessment of publication bias was not done.
Zhao 2018[7]	
• The study was registered at the International Prospective Register of Systematic Reviews, and reporting was done in accordance with the PRISMA statement. • A systematic and comprehensive literature search was conducted, with predefined search strategy. • Inclusion/exclusion criteria were clearly defined. • Study selection, data extraction, and study quality assessment were done in duplicate; disagreements were resolved by consensus or through consultation with a third reviewer. The EPHPP tool was used to evaluate the internal and external validity of the included studies. Of the 5 trials relevant for this review, 2 were rated weak or	

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[4]

Strengths	Limitations
moderate quality, the remaining studies were of strong quality. • Study and patient characteristics of each included trial was provided with adequate details. • The method for pooling mean effect sizes in meta-analyses was appropriate, and accounted for statistical heterogeneity. Heterogeneity was defined based on Cochran Q test and the I^2 value; random-effects model was used in case heterogeneity was moderate to high, otherwise fixed-effects model was applied. • Publication bias was evaluated using the Begg's test and the Egger's test; no evidence of such bias was found for the primary outcomes. • The authors of the report declared no conflicts of interest. However, the source of funding was not available for the individual studies.	

EPHPP = Effective Public Health Practice Project Tool; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HRQoL = health-related quality of life; NMA = network meta analyses; OS = overall survival; PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-analysis Protocols statement (slightly modified by the authors of this assessment)

Table 5: Strengths and Limitations of Network Meta-analysis using ISPOR checklist[5]

Strengths	Limitations
Fan 2018[8]	
Introduction • The rationale and objective of the review was clearly stated. **Methods** • A comprehensive and systematic search of the literature was conducted in accordance with the PRISMA statement and PRISMA extension statement for NMAs. • The search strategy and the study selection criteria were clearly stated. • Data extraction and study quality assessment was done independently by two reviewers; inconsistencies were resolved by a third reviewer. The Cochrane collaboration risk of bias tool and the Newcastle-Ottawa scale were used to appraise the methodological quality of RCTs and non-RCTs, respectively. The quality of the included studies varied, with low, medium, and high risk of bias found depending on the trial. • The outcome measures were selected appropriately and clearly described. • The choice of fixed or random effect was justified and based on I^2 value of <50% as a cutpoint for statistical heterogeneity. • Both direct pairwise and indirect comparisons were performed to assess the consistency assumption, as well as the results from consistency and inconsistency models of NMA. • Assessment of publication bias was done visually using Funnel plots and quantitatively using the Begg's test and Egger's test. Other than the pooled PFS and discontinuation rate, publication bias was unlikely for other outcomes. • The methods for indirect comparison (Bayesian network meta-analyses) and ranking treatment probabilities for each line of therapy were appropriate. • The methods for pooling Kaplan-Meier curves and other binary outcome measures were appropriate. **Results** • Identification and selection of full-text studies for the NMA were well reported, as well as presented in a PRISMA flowchart. Additionally, a network diagram was provided. • Although not in great detail, a table with study and patient characteristics was provided; and summary effect estimates from each included trial was available. • Convergence of all models using the MCMC method was shown with a PSRF value of 1.00. **Discussion** • A description of the main findings was presented that highlighted the potential limitations of the results as well as possible explanations for discrepancies across studies. • The authors did not provide a discussion on the generalizability of findings; however, given the included studies combined a high number of patients, all available ALK-inhibitors, and trials conducted across the world in various settings, the generalizability of the results is not likely to be a concern.	**Methods** • The models were conducted without covariate adjustment for patient or study characteristics, and hence control of potential bias could not be assessed. • There was no information on prior distributions for model parameters, and whether priors were informative or non-informative. • No sensitivity analyses were performed to assess the effect of different covariate distributions or model assumptions. **Discussion:** • Between-study heterogeneity was high for a number of pairwise comparisons, due primarily to differences in doses of treatment, baseline parameters of enrolled patients, and follow-up duration. • Overall, the original trials used to pool results for direct and indirect comparisons included a mix of ALK inhibitor-naive and pretreated patients, therefore the combined results should be interpreted with caution. However, this was not a limitation of the NMA per se, rather limited the usability of the results given the research questions in this Rapid Response report.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MCMC = Markov chain Monte Carlo; NMA = network meta-analyses; PRISMA = preferred reporting items for systematic reviews and meta-analysis; PSRF = potential scale reduction factor; RCT = randomized controlled trial

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black[6]

Strengths	Limitations
Gadgeel et al. 2018[9]	
Reporting • The objective of the study, main outcomes, inclusion and exclusion criteria, interventions being compared, potential confounders, and main findings are clearly described • 95% confidence intervals and exact P values are reported for the main outcomes **Internal validity** • This was an open-label trial, therefore investigators and patients were unblinded. However, the external and independent review committee in charge of assessing a number of outcomes was blinded. • Randomization method was clear and appropriate. • The statistical tests for different outcomes were appropriate, differential loss to follow-up was taken into account using survival analyses; the effect of potential confounders was limited using relevant stratification factors during randomization as well as by subgroup analyses. • The outcomes measured were valid and reliable, and outcome definitions were consistent with widely accepted criteria. **Sample size/power** • The trial had sufficient power to detect a clinically important effect for the primary endpoint, according to a formal sample size calculation.	**External validity** • Patients receiving any previous ALK inhibitor other than crizotinib were excluded. • There was no information if staff, places, and facilities were representative of the treatment received by the source population. **Internal validity** • Post-hoc analyses were pre-specified in the protocol; however, several subsequent publications were based on the ALEX trial including this. Therefore, it was not possible to evaluate if outcomes in this publication were originally planned. • There was no information if control for multiple comparisons was done for secondary outcomes.
Novello et al. 2018[10]	
Reporting • The objective of the study, main outcomes, inclusion and exclusion criteria, interventions being compared, potential confounders, and main findings are clearly described • 95% confidence intervals and exact P values are reported for the main outcomes **External validity** • Participants in the trial were generally representative of the population from which they were recruited **Internal validity** • This was an open-label trial, therefore investigators and patients were unblinded. However, all staff performing the primary analysis were blinded until after database lock. • Randomization method was clear and appropriate. • Post-hoc analyses were pre-specified in the protocol. • The statistical tests were appropriate, differential loss to follow-up was taken into account using survival analyses; the effect of confounders was limited using relevant stratification factors. • Control for multiple comparisons was in place with *a priori* statistical hierarchy for secondary outcomes. • The outcomes measured were valid and reliable, and outcome	**External validity** • Patients receiving any previous ALK inhibitor other than crizotinib were excluded. • This was a multicenter trial in various countries in Europe and Asia; however, there was no information if staff, places, and facilities were representative of the treatment received by the source population. **Internal validity** • There were minor stratification imbalances between treatment arms; patients in the alectinib arm were slightly younger, healthier as per ECOG PS scale, and had a lower proportion of patients with no baseline CNS metastases. • There was a large difference between the two arms in treatment duration.

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black[6]

Strengths	Limitations
definitions were consistent with widely accepted criteria. **Sample size/power** • The trial had sufficient power to detect a clinically important effect for the primary endpoint, according to a formal sample size calculation based on a prior phase 2 trial.	

ECOG PS = Eastern Cooperative Oncology Group performance status

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
EUnetHTA, 2018[1]	
Clinical effectiveness **Alectinib vs crizotinib (ALEX trial): Direct comparison** **Disease progression:** • PFS (investigator assessed): HR 0.47 (95% CI, 0.34 to 0.65, *P* < 0.0001) • PFS (IRC-assessed): HR 0.50 (95% CI, 0.36 to 0.70, *P* < 0.001) • Median PFS not reached in the alectinib arm for the investigator-based PFS; however, IRC showed a difference in medians of 15.3 months (25.7 vs 10.4 months, respectively) Patients with CNS metastases: HR 0.40 (95% CI, 0.25 to 0.64) Patients without CNS metastases: HR 0.51 (95% CI, 0.33 to 0.80) **Morbidity (whole-body and CNS-related outcomes):** **ORR (investigator):** • Response rate: 82.9% (76.0% to 88.5%) for alectinib vs 75.5% (67.8% to 82.1%) for crizotinib • Difference percentage points 7.40 (95% CI, –1.71 to 16.50), *P* = 0.09 • Patients (responders) with disease progression/death: 40 (32%) for alectinib vs 73 (64%) for crizotinib • DOR (investigator): HR 0.36 (95% CI, 0.24 to 0.53), *P* < 0.0001 **Overall survival:** • HR 0.76 (95% CI, 0.48 to 1.20, *P* = 0.2) • 1-year survival rate 84.3% and 82.5%, respectively • Median OS not reached in either treatment arm **CNS results:** • Time to CNS progression: cause-specific HR 0.16 (95% CI, 0.10 to 0.28, *P* < 0.001) • 12-month CIR of CNS progression (IRC): 9.4% (95% CI, 5.4% to 14.7%) for alectinib vs 41.4% (95% CI, 33.2% to 49.4%) for crizotinib • CNS ORR: 29 (45%) for alectinib (95% CI, 46.4 to 71.5) vs 5 (9%) for crizotinib (95% CI, 15.3 to 39.0) • CNS DOR (median): 17.3 months (95% CI, 14.8 to NE) for alectinib vs 5.5 months (95% CI, 2.1 to 17.3) for crizotinib **Health-related quality of life[a]:** • Time to deterioration in patient-reported global HRQoL: HR 0.72, (95% CI, 0.38 to 1.39) • Time to deterioration in cognitive functioning: HR 0.85 (95% CI, 0.55 to 1.33) ***Safety***	"*From direct comparison, based on high quality of evidence, alectinib demonstrated a substantial and statistically significant increase in PFS. It is also associated with a statistically significant longer time to CNS progression compared to crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients. The OS data are immature and therefore preclude firm conclusions.*" "*From direct comparison, the serious adverse events and adverse events leading to treatment discontinuation occurred at similar frequencies for both alectinib and crizotinib. Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious adverse events that tend to affect quality of life, as well as severe (grade ≥3) events. This notion is supported by the lower frequencies of treatment interruptions and dose reductions observed for alectinib in the direct comparison to crizotinib. Thus markedly lower frequencies for alectinib were reported for diarrhoea, vomiting and nausea. For any grade adverse event, myalgia and anaemia were reported more frequently for alectinib than crizotinib.*" "*Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. Overall a trend favouring alectinib was observed in HRQoL, but the difference was not statistically significant*." (p15)

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>Alectinib vs crizotinib (ALEX trial): Direct comparison
• Total proportion of patients with ≥ 1 AE: 97% in both arms
• Total proportion of patients with SAE: 28% vs 29%
• Grade ≥ 3 AE: 41% vs 50%
• AE leading to treatment discontinuation: 11% vs 13%.
• AE leading to dose reduction: 16% vs 21%
• AEs with higher incidence with crizotinib: GI AEs, liver enzyme abnormalities
• AEs with higher incidence with alectinib: anemia, myalgia, increased blood bilirubin level, increased weight, musculoskeletal pain and photosensitivity reaction
• AEs with similar incidence (≤ 5% absolute difference): Constipation, fatigue, arthralgia, and rash</td><td></td></tr>
<tr><td colspan="2">Fan et al., 2018[8]</td></tr>
<tr><td><u>Results from indirect multiple-treatment comparison</u>

PFS:
• Alectinib vs ceritinib: HR 0.66 (95% CI, 0.56 to 0.78)
• Alectinib vs crizotinib: HR 0.70 (95% CI, 0.61 to 0.80)
• Ceritinib vs crizotinib: HR 1.07 (95% CI, 0.95 to 1.20)

ORR:
• Alectinib vs ceritinib: HR 1.49 (95% CI, 0.39 to 5.99)
• Alectinib vs crizotinib: HR 1.94 (95% CI, 0.85 to 4.70)
• Ceritinib vs crizotinib: HR 1.31 (95% CI, 0.45 to 3.78)

DCR:
• Alectinib vs ceritinib: HR 1.25 (95% CI, 0.05 to 53.47)
• Alectinib vs crizotinib: HR 1.87 (95% CI, 0.33 to 13.85)
• Ceritinib vs crizotinib: HR 1.48 (95% CI, 0.07 to 23.58)

Discontinuation rate:
• Alectinib vs ceritinib: HR 0.81 (95% CI, 0.17 to 3.57)
• Alectinib vs crizotinib: HR 0.59 (95% CI, 0.24 to 1.39)
• Ceritinib vs crizotinib: HR 0.74 (95% CI, 0.21 to 2.68)

Rank probabilities of each treatment by outcome measures:
<table>
<tr><th>Rank/drug</th><th>Alectinib</th><th>Ceritinib</th><th>Crizotinib</th><th>Chemotherapy</th></tr>
<tr><td>PFS</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Rank 1</td><td>100%</td><td>0%</td><td>0%</td><td>0%</td></tr>
<tr><td>Rank 2</td><td>0%</td><td>14%</td><td>86%</td><td>0%</td></tr>
<tr><td>Rank 3</td><td>0%</td><td>86%</td><td>35%[b]</td><td>0%</td></tr>
<tr><td>Rank 4</td><td>0%</td><td>0%</td><td>0%</td><td>100%</td></tr>
<tr><td>ORR</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Rank 1</td><td>76%</td><td>22%</td><td>2%</td><td>0%</td></tr>
<tr><td>Rank 2</td><td>20%</td><td>52%</td><td>28%</td><td>0%</td></tr>
<tr><td>Rank 3</td><td>3%</td><td>26%</td><td>70%</td><td>0%</td></tr>
<tr><td>Rank 4</td><td>0%</td><td>0%</td><td>0%</td><td>100%</td></tr>
<tr><td>DCR</td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>"ALK+ NSCLC patients treated with ALKi tend to have longer PFS than those treated with chemotherapy.
ALKi-naive patients tended to response better than their ALKi-pretreated counterparts.
Alectinib appeared to be preferable for treating brain metastases due to its high intracranial efficacy.
Patients treated with alectinib or ceritinib tended to have higher ORR and DCR than patients with similar baselines treated with crizotinib or chemotherapy.
No significant differences in discontinuation rate were found for alectinib, ceritinib, crizotinib, and chemotherapy." (p1)</td></tr>
</table>

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings					Authors' Conclusion
Rank 1	51%	41%	8%	0%	
Rank 2	33%	25%	41%	1%	
Rank 3	13%	28%	49%	10%	
Rank 4	3%	6%	2%	89%	
Discontinuation rate					
Rank 1	3%	6%	14%	76%	
Rank 2	6%	23%	52%	18%	
Rank 3	30%	34%	31%	5%	
Rank 4	61%	36%	3%	1%	

Results from direct pairwise treatment comparison

ORR:

- Alectinib (ALKi-naive): 0.86 (95% CI, 0.81 to 0.92, *P* < 0.00001) [4 trials, I^2=42%]
- Alectinib (ALKi-pretreated): 0.51 (95% CI, 0.45 to 0.57, *P* < 0.00001) [5 trials, I^2=42%]
- Brigatinib (ALKi-naive): 1.00 (95% CI, 0.40 to 1.60, *P* < 0.001) [1 trial, I^2=NA]
- Brigatinib (ALKi-pretreated): 0.60 (95% CI, 0.38 to 0.83, *P* < 0.00001) [2 trials, I^2=92%]
- Ceritinib (ALKi-naive): 0.71 (95% CI, 0.66 to 0.75, *P* < 0.00001) [4 trials, I^2=0%]
- Ceritinib (ALKi-pretreated): 0.50 (95% CI, 0.38 to 0.62, *P* < 0.00001) [6 trials, I^2=87%]
- Crizotinib (ALKi-naive): 0.66 (95% CI, 0.58 to 0.7, *P* < 0.00001) [13 trials, I^2=91%]
- Lorlatinib (ALKi-naive): 0.90 (95% CI, 0.79 to 1.01, *P* < 0.00001) [1 trial, I^2=NA]
- Lorlatinib (ALKi-pretreated): 0.47 (95% CI, 0.41 to 0.54, *P* < 0.00001) [2 trials, I^2=0%]

ORR in patients with baseline CNS metastases:

- Alectinib (ALKi-naive): 0.59 (95% CI, 0.47 to 0.71, *P* < 0.00001) [1 trial, I^2=NA]
- Alectinib (ALKi-pretreated): 0.48 (95% CI, 0.37 to 0,59, *P* < 0.00001) [3 trials, I^2=25%]
- Brigatinib (ALKi-pretreated): 0.46 (95% CI, 0.36 to 0.57, *P* < 0.00001) [2 trials, I^2=10%]
- Ceritinib (ALKi-naive): 0.50 (95% CI, 0.41 to 0.59, *P* < 0.00001) [3 trials, I^2=0%]
- Ceritinib (ALKi-pretreated): 0.29 (95% CI, 0.17 to 0.40, *P* < 0.00001) [3 trials, I^2=68%]
- Crizotinib (ALKi-naive): 0.51 (95% CI, 0.01 to 1.01, *P* < 0.04) [2 trials, I^2=97%]

DCR:

- Alectinib (ALKi-naive): 0.95 (95% CI, 0.89 to 1.00, *P* < 0.00001) [3 trials, I^2=79%]
- Alectinib (ALKi-pretreated): 0.82 (95% CI, 0.62 to 1.03, *P* < 0.00001)

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
[2 trials, I^2=75%] • Brigatinib (ALKi-naive): 0.88 (95% CI, 0.65 to 1.11, P < 0.00001) [1 trial, I^2=NA] • Brigatinib (ALKi-pretreated): 0.85 (95% CI, 0.81 to 0.89, P < 0.00001) [2 trials, I^2=0%] • Ceritinib (ALKi-naive): 0.90 (95% CI, 0.86 to 0.94, P < 0.00001) [2 trials, I^2=0%] • Ceritinib (ALKi-pretreated): 0.77 (95% CI, 0.73 to 0.80, P < 0.00001) [5 trials, I^2=0%] • Crizotinib (ALKi-naive): 0.86 (95% CI, 0.82 to 0.90, P < 0.00001) [12 trials, I^2=80%] • Ensartinib (ALK-naive): 0.88 (95% CI, 0.65 to 1.11, P < 0.00001) [1 trial, I^2=NA] • Ensartinib (ALK-pretreated): 0.75 (95% CI, 0.60 to 0.90, P < 0.00001) [1 trial, I^2=NA] • Lorlatinib (ALKi-pretreated): 0.90 (95% CI, 0.79 to 1.01, P < 0.00001) [1 trial, I^2=NA] **DCR in patients with baseline CNS metastases:** • Alectinib (ALKi-pretreated): 0.88 (95% CI, 0.82 to 0,94, P < 0.00001) [3 trials, I^2=0%] • Brigatinib (ALKi-pretreated): 0.87 (95% CI, 0.80 to 0.93, P < 0.00001) [2 trials, I^2=53%] • Ceritinib (ALKi-naive): 0.88 (95% CI, 0.82 to 0.93, P < 0.00001) [3 trials, I^2=0%] • Ceritinib (ALKi-pretreated): 0.73 (95% CI, 0.64 to 0.82, P < 0.00001) [3 trials, I^2=47%] • Crizotinib (ALKi-naive): 0.85 (95% CI, 0.74 to 0,96, P < 0.00001) [1 trials, I^2=NA] **PFS:** • Alectinib (ALKi-pretreated): 8.90 (95% CI, 6.77 to 11.02, P < 0.00001) [2 trials, I^2=0%] • Brigatinib (ALKi-pretreated): 12.51 (95% CI, 9.39 to 15.63, P < 0.00001) [2 trials, I^2=0%] • Ceritinib (ALKi-naive): 17.81 (95% CI, 13.40 to 22.22, P < 0.00001) [2 trials, I^2=0%] • Ceritinib (ALKi-pretreated): 6.42 (95% CI, 5.80 to 7.03, P < 0.00001) [4 trials, I^2=0%] • Crizotinib (ALKi-naive): 9.47 (95% CI, 8.46 to 10.49, P < 0.00001) [10 trials, I^2=57%] • Lorlatinib (ALKi-pretreated): 10.00 (95% CI, 3.39 to 16.61, P < 0.003) [1 trial, I^2=NA] **Discontinuation rate:** • Alectinib (ALKi-pretreated): 0.07 (95% CI, 0.04 to 0.10, P < 0.00001) [7 trials, I^2=48%] • Brigatinib (ALKi-pretreated): 0.07 (95% CI, 0.03 to 0.11, P < 0.0005) [2 trials, I^2=49%] • Ceritinib (ALKi-pretreated): 0.08 (95% CI, 0.06 to 0.09, P < 0.00001) [9 trials, I^2=25%]	

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
• Crizotinib (ALKi-pretreated): 0.08 (95% CI, 0.05 to 0.11, *P* < 0.00001) [8 trials, I^2=81%] • Lorlatinib (ALKi-pretreated): 0.03 (95% CI, 0.01 to 0.06, *P* < 0.007) [1 trial, I^2=NA]	
Zhao 2018[7]	
Clinical effectiveness **Ceritinib in crizotinib-pretreated patients** • ORR: 0.48 (95% CI, 0.43 to 0.52, *P* = 0.02), I^2=65% • IC PFS: 6.32 months (95% CI, 5.61 to 7.15 months *P* = 0.56), I^2=0% • IC ORR: 0.33 (95% CI, 0.26 to 0.42, *P* = 0.78), I^2=0% ***Safety*** **Ceritinib (pooled analyses with crizotinib-naive and pretreated patients)** • Most common AEs: diarrhea (83.7%), nausea (74.9%), vomiting (61.5%), fatigue (33.3%), decreased weight (27.2%), decreased appetite (40.5%), and increase in ALT (46.9%), AST (38.1%), ALP (22.0%), and GGT(20.1%) concentration • Rate of treatment discontinuation due to AEs: 3.1% (95% CI, 1.4% to 7.1%) • Dose reduction: 38.4% (95% CI, 19.0% to 62.4%) • Grade 3 or 4 AEs: diarrhea (5.9%; 95% CI, 4.5% to 7.8%), nausea (5.9%; 95% CI, 4.3% to 7.9%), vomiting (7.5%; 95% CI, 2.5%- to 20.2%), fatigue (5.1%; (95% CI, 3.7% to 7.1%), increased ALT (25.5%; 95% CI, 22.5% to 28.6%), increased AST (11.1%; 95% CI, 7.8% to 15.5%), increased blood ALP (5.7%; 95% CI, 4.2% to 7.8%), and increased GGT (12.6%; 95% CI, 5.4% to 26.7%)	"*The results of the present systematic review have shown that the second-generation ALK-TKI ceritinib might be the preferential choice for patients with advanced or metastatic ALK-rearrangement NSCLC, especially crizotinib-naive patients. The adverse events of ceritinib have been mild to moderate. Although further studies are required to determine the optimal approach for the sequence of treatment lines in clinical practice, our findings lend support to the use of ceritinib for crizotinib-naive patients with better results compared with its use for crizotinib-pretreated patients with ALK-rearrangement NSCLC*." (p11)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CIR = cumulative incidence rate; CNS = central nervous system; CrI = credible interval; DCR=disease control rate; DOR = duration of response; GGT = gammaglutamyltransferase; GI = gastrointestinal; HR = hazard ratio; IC= intracranial; IRC = independent review committee; NA = not applicable; NE = not estimable; NMA = network meta analyses; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; (S)AE = (serious) adverse event

[a] Measured using the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire QLQ-C30 and its lung cancer module QLQ-LC13

[b] Ranked probabilities added up to 100%, except under this particular instance

N.B: In Fan et al. 2018, the relative effect of crizotinib versus chemotherapy may be overestimated and thus the effect of alectinib versus ceritinib may be overstated because of the inclusion of pemetrexed maintenance therapy in the ASCEND-4 chemotherapy arm.

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Gadgeel et al. 2018[a9]	
Time to CNS progression (without prior non-CNS progression): • Patients with CNS metastases: HR 0.18 (95% CI, 0.09 to 0.36, *P* < 0.0001) • Patients without CNS metastases: HR 0.14 (95% CI, 0.06 to 0.33, *P* < 0.0001) (interaction ***P*** < 0.0001) **24-month CIR for CNS progression (without prior non-CNS progression):** • Patients with CNS metastases: 19.4% (95% CI, 10.6 to 30.2) with alectinib vs 62.9% (95% CI, 47.2 to 75.1) with crizotinib • Patients without CNS metastases: 7.2% (95% CI, 2.9 to 14.2) with alectinib vs 45.3% (95% CI, 32.0 to 57.7) with crizotinib **Non-CNS progression:** • Patients with CNS metastases: HR 0.35 (95% CI, 0.15 to 0.84, *P* = 0.01) • Patients without CNS metastases: HR 1.16 (95% CI, 0.64 to 2.11, *P* = 0.63) **24-month CIR for non-CNS progression (without prior non-CNS progression):** • Patients with CNS metastases: 22.1% (95% CI, 8.1 to 40.4) with alectinib vs 26.2% (95% CI, 15.1 to 38.8) with crizotinib • Patients without CNS metastases: 29.1% (95%CI, 19.8 to 39.0) with alectinib vs 24.4 % (95%CI, 14.8 to 35.4) with crizotinib	"*Alectinib demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in patients with previously untreated, advanced ALK+ NSCLC, irrespective of prior CNS disease or radiotherapy*." (p 2)
Novello 2018[10]	
Clinical effectiveness (alectinib vs chemotherapy) • Investigator-assessed PFS: Unadjusted HR: 0.15 (95% CI, 0.08 to 0.29, ***P*** < 0.001); results consistent in adjusted analyses. Median PFS was 9.6 months (95% CI, 6.9 to 12.2) with alectinib and 1.4 months (95% CI, 1.3 to 1.6) with chemotherapy • IRC-assessed PFS: HR 0.32 (95% CI, 0.17 to 0.59) HR in patients with CNS metastases: 0.12 (95% CI, 0.03 to 0.45) HR in patients without CNS metastases: 0.21 (95% CI, 0.07 to 0.64) • ORR: Difference 0.34 (95% CI, 0.15 to 0.53) • DCR: Difference 0.52 (95% CI, 0.33 to 0.69) • Time to CNS progression: Cause-specific HR 0.14 (95% CI, 0.06 to 0.36) • 12-month cumulative incidence of CNS progression: Alectinib 21 (95% CI, 11 to 39) vs Chemotherapy NE (95% CI, NE to NE) • OS: HR 0.89 (95% CI, 0.35 to 2.24) ***Safety (alectinib vs chemotherapy)*** • AEs (all grades): 54 (77.1%) vs 29 (85.3%) • SAEs: 13 (18.6%) vs 5 (14.7%)	"*Our data support the efficacy and tolerability of alectinib, and demonstrate that alectinib shows clinically relevant superiority to chemotherapy for extra- and intracranial disease in patients who have been pretreated with crizotinib and PDC*." (p1415)

Table 8: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
• Fatal AEs: 0 (0%) vs 1 (2.9%) • AEs leading to treatment discontinuation: 4 (5.7%) vs 3 (8.8%) • AEs leading to dose reduction: 3 (4.3%) vs 4 (11.8%) • Grade 3 to 5 AEs: 19 (27.1%) vs 14 (41.2%) • Grade ≥ 3 AEs occurring with higher frequency with alectinib vs chemotherapy: pneumonia, syncope, and acute kidney injury • Grade ≥ 3 AEs more common with chemotherapy than alectinib: neutropenia, anemia, febrile neutropenia, fatigue, and stomatitis	

CI = confidence interval; CIR = cumulative incidence rate; CNS = central nervous system; CR=disease control rate; DOR = duration of response; HR = hazard ratio; IC= intracranial; IRC = independent review committee; NE = not estimable; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; (S)AE = (serious) adverse event

[a] Only relevant and non-overlapping results presented

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation, trial name, phase	Fan 2018[8]	Zhao 2018[7]
Bang 2010* Phase 2	X	
Blackhall 2017* (PROFILE 1005) Phase 2	X	
Cadranal 2015[$] Phase 1	X	
Camidge 2012* (NCT00585195) Phase 1	X	
Camidge 2011* Phase 1	X	
Cho 2017* (ASCEND-8) Phase 1	X	
Crino 2016 (ASCEND-2) Phase 2	X	X
Cui 2015* Phase 2	X	
Felip 2016* (ASCEND-3) Phase 2	X	X
Fujiwara 2016* Phase 1	X	
Gadgeel 2014 (AF-002JG) Phase 1/2	X	
Gettinger 2016[$] (NCT01449461) Phase1/2 (a, b)	X	
Hida 2017(J-ALEX) Phase 3	X	X
Hida 2016[$] (JP28927) Phase 1/2	X	
Horn 2017[$] (NCT01625234) Phase 1/2	X	
Iwama 2017[$] Phase 2	X	
Kim 2017 (ALTA) Phase 2	X	
Kim 2016[$] (ASCEND-1) Phase 1	X	X
Lu 2016* (NCT01639001) Phase 3	X	
Nishio 2015[$] (NCT01634763)	X	

Phase 1		
Ou 2016 (NP28673) Phase 2	X	
Peters 2017 (ALEX) Phase 3	X	
Seto 2013* (AF‐001JP) Phase 1/2	X	
Shaw 2014 (a,b) Phase 1		X
Shaw 2017[$] (NCT01970865) Phase 1	X	
Shaw 2017 (ASCEND-5) Phase 3	X	X
Shaw 2016 (NP28761) Phase 2	X	
Shaw 2013* (PROFILE 1007) Phase 3	X	
Solomon 2017 (NCT01970865) [$] Phase 2	X	
Solomon 2014* (PROFILE 1014) Phase 3	X	
Soria 2017* (ASCEND-4) (a,b) Phase 3	X	X
Wu 2015* Phase 2	X	
Zhang 2016 (ASCEND-6) Phase 1/2	X	
Zhao 2015* Phase 3	X	

Note: Observational studies or trials consisting of patients without *ALK*- NSCLC within systematic reviews not listed

* Trial/study did not meet PICO; either ALK inhibitor was not the comparator in a population of ALK-naive patients, or the study population did not include ALK-pretreated patients

[$] Trial/study consisted of a mixed population of ALK-naive and pretreated patients, results not separated by ALK-status

Appendix 6: Additional References of Potential Interest

Additional Publications of Studies Included in SRs

Camidge DR, Kim DW, Tiseo M, et al. Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain Metastases in Two Clinical Trials. J Clin Oncol. 2018 Sep 10;36(26):2693-2701: https://www.ncbi.nlm.nih.gov/pubmed/29768119

Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. NEJM. 2018 Sep 25. https://www.ncbi.nlm.nih.gov/pubmed/30280657

Post-Hoc Analysis

Reckamp K, Lin HM, Huang J, et al. Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer. Cur Med Res Opin. 2018 Oct 5:1-8. https://www.ncbi.nlm.nih.gov/pubmed/30286627