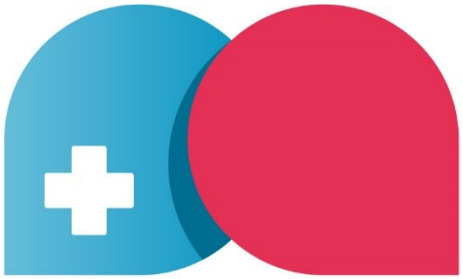
# Evidence report

# ALK inhibitors
# in ALK+ advanced non-small-cell lung cancer

Version 2



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## CONTENTS

## LIST OF ABBREVIATIONS

ALK: anaplastic lymphoma kinase
AMNOG: Reform of the Market for Medicinal Products Act
ASCO: American Society of Clinical Oncology
BIRC: Blinded independent review committee
CI: Confidence interval
DA: Decision aid
EMA: European Medicines Agency
FAQs: Frequently asked questions
HR: Hazard ratio
ICP: Intracranial progression
IQWiG: Institute for Quality and Efficiency in Health Care
NSCLC: non-small-cell lung cancer
ORR: Overall response rate
OS: Overall survival
PFS: Progression-free survival
PICOS: Participants, intervention, comparators, outcomes, and study design
RCT: Randomised controlled trial
SDM: Shared decision making

## PROJECT OBJECTIVES

A key aim is to inform patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) and an alteration in the gene anaplastic lymphoma kinase (ALK-positive) on the different therapy options with ALK inhibitors as part of shared decision making (SDM). This evidence report is prepared to form the scientific basis for an online patient decision aid (DA). The report was developed in cooperation with clinical experts from German university and non-university medical centres and patient representatives from patients' organisations.

This report is an update of the previously published evidence report. The original evidence report version 1 was prepared by Share to care in March 2023. As data with longer follow-up has become available, the present report (version 2) aims to update the evidence and to adapt the previous report where necessary.

## INTRODUCTION TO THE DISEASE

NSCLC is a heterogeneous disease. In some cases, genetic alterations can be identified which allow targeted treatments. Therefore, molecular testing is recommended in current guidelines [1].

One of the driver mutations is a change in the ALK gene. About 3% to 4% of all cases with adenocarcinoma NSCLC are ALK positive [1].

Therapy for early stages of NSCLC is usually multimodal with surgery, chemoradiotherapy and/or systemic therapy. However, NSCLC is often only diagnosed in the advanced or even metastatic stage. For stage IV of ALK-positive NSCLC without an curative intention, current guidelines recommend the ALK inhibitors alectinib, brigatinib or lorlatinib as first-line therapy [1,2].

Further therapy for metastases (such as radiotherapy or surgery) or supportive therapy might be required for symptom control. These options, however, are beyond the scope of the DA and are only mentioned in the background information.

It should be noted that the marketing authorisations of the ALK inhibitors are broader than the guideline recommendations and do not only include metastatic, but also advanced NSCLC. They also include second-line therapy, for lorlatinib also further lines of therapy. Alectinib is also authorised for adjuvant therapy after surgery in high-risk patients in earlier stages of the disease. The data in this evidence report, however, focusses on first-line therapy in stage IV patients.

## THE DECISION PROBLEM

Current guidelines point out that lorlatinib might be preferred in terms of efficacy, especially with regard to intracranial progression. However, the profiles of adverse

events are different between the ALK inhibitors with serious adverse events being less common with alectinib. Therefore, alectinib, brigatinib and lorlatinib are listed as first-line agents from which the most appropriate therapy option should be chosen on an individual basis [1,2].

## METHODS

For the first version of this evidence report, we conducted a scoping process with the clinical experts. Together we defined the characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), used as inclusion criteria for the evidence report, as well as the frequently asked questions (FAQs) which the DA should answer. The FAQs were checked against the needs assessment conducted with patients and adapted where necessary.

This version of the report relies on the scoping process and the needs assessments for the previous report. However, we consulted recent guidelines to confirm the treatment options and scanned recent research on the preferences of patients [3–5] with ALK-positive NSCLC for further refinement of the FAQs (see below).

### INCLUSION CRITERIA

For this version of the evidence report, we slightly adapted the inclusion and exclusion criteria, according to PICOS, from the previous version:

- For the population, we included the specification for the disease that there is no indication for multimodal therapy as detailed in the guidelines.
- We omitted best supportive therapy as comparator as the current guidelines do not recommend this option and the previous version of this report found no trials for these comparisons. Instead, we focus on the comparisons of the ALK inhibitors. However, the DA can describe best supportive therapy if patients do not want therapy.
- As outcomes, we omitted overall response rate (ORR), which had been reported in the previous version in the absence of mature data for disease progression. As these are available with longer follow-up in the trials, ORR is no longer necessary. We also omitted the development of resistance as an outcome as there is no indication of a difference between the options. However, we included intracranial progression as an additional outcome. This has been confirmed as an important outcome for patients in studies of patient preferences [3–5] because intracranial progression is associated with more symptoms and a lower quality of life.

The PICOS for this version are described in Table 1.

Table 1: Inclusion and exclusion criteria

| | Included | Excluded |
|---|---|---|
| Population | Patients with advanced ALK-positive NSCLC without indication for multimodal therapy | Other than the specified |
| Intervention / Comparator | Alectinib, Brigatinib, and Lorlatinib | Other than the specified |
| Outcomes | Overall survival (OS), progression-free survival (PFS), intracranial progression, quality of life, adverse events | Other than the specified |
| Study design | Randomised controlled trials (RCT) | Other than the specified |
| ALK: anaplastic lymphoma kinase, NSCLC: non-small-cell lung cancer, OS: overall survival, PFS: progression-free survival, RCT: randomised controlled trial | | |

### Frequently asked questions

The frequently asked questions (FAQs) were adopted from the previous version of the report and adjusted as described above:

1. What do the treatments involve?
2. What is the impact on my life expectancy?
3. What is the impact on the progression of the disease?
4. What is the impact on intracranial progression?
5. What is the impact on my quality of life?
6. What are the risks or side effects?

### Literature searches

The previous version searched for systematic reviews and used the study pool identified in a Cochrane Review from 2022 with the latest searches in January 2021 [6]. As there was no more recent version of this Cochrane Review available, we searched for recent evidence-based guidelines with a systematic search of the literature. We supplemented this search with more recent publications for the identified RCTs or more recently published trials.

For additional data and the risk of bias assessments, we used the documents for the early benefit assessments according to the Reform of the Market for Medicinal Products Act (AMNOG) documents which have been identified in the previous version [7–9].

For FAQ 1 and qualitative information on risks and adverse events, the summary of product characteristics for the relevant medicines were used.

#### *Search sources*

- Information on medicines: Handsearching the websites of the European Medicines Agency (EMA) on 05.08.2026

- Guidelines: Handsearching websites of relevant national and international medical societies and organisations on 05.08.2026
- Additional publications and trials: PubMed (for detailed search strategy see appendix)
- Where necessary and available: identification of additional results in the US trial registry by handsearching.

### *Handling of citations*

Identified references from the bibliographic database searches were downloaded as RIS files and transferred into Rayyan App for abstract screening. Excluded references were tagged with the reasons for exclusion. Results of the abstract screening were exported as RIS file. Results of the full text screening were documented in the appendices.

### *Quality assurance within the search process*

One reviewer (IH) developed the search strategy, a second reviewer (FS) checked the appropriateness (for rationale, see Appendix).

## Methods of study selection

One reviewer (IH) inspected the title and abstract of each reference identified by the search and documented reasons for exclusion. For potentially relevant articles, the full article was obtained, inspected, and inclusion criteria applied. Reasons for exclusion were documented. All decisions were checked by a second reviewer (FS). Any disagreements were resolved through discussion.

For each trial, we included the publications with the longest follow-up or the follow-up which allows for the best comparison of the treatment options. We included more than one publication per trial when the data was scattered over several publications, e.g. for the different outcomes. For the decision, which publication to include, we started scanning the publication pool with the most recent publications and stopped, when all necessary data had been collected. Additionally, publications were included which report the study protocol of the respective trial.

## Methods of data extraction

For each study, data were extracted by one reviewer (IH) and checked by another (FS). Any disagreements were resolved through discussion.

## Methods for appraising risk of bias and certainty of the evidence

For the risk of bias (RoB) assessment, we adopted the ratings in the identified reports by the Institute for Quality and Efficiency in Health Care (IQWiG) reports [7–9], where available (see Appendix). In the absence of direct comparisons, GRADE was not used for rating the certainty of the evidence.

# RESULTS

## Literature searches and inclusion assessment

For the update, we identified two recent evidence-based guidelines [1,2]. We preferred the American Society of Clinical Oncology (ASCO) guideline due to the recent systematic search. Therefore, we used the trial and publication pool identified in this guideline as a base for this version of the evidence report. We reconciled the trial pool with the trials identified in the previous version of the evidence report and found good concordance. The only exception is the J-ALEX trial of alectinib (JapicCTI-132316) which is mentioned in the ASCO guideline but not in the previous version of the evidence report. However, this trial used a lower dose of alectinib than currently authorised in the EU. Therefore, this trial is not included in this version, either. A supplementary search for more recent publications or trials retrieved a journal publication for the CROWN study with a follow-up of 7 years [10].

As the ASCO guideline does not contain a "Characteristics of studies" table or evidence profiles for the outcomes, we extracted the data mainly from the journal publications. We did not include all identified publications for the identified trials (see Appendix), but only the most relevant for the data extraction. For the majority of publications, no sufficient data on quality of life was included. We extracted these data therefore from the AMNOG documents [7–9].

## Quality assessment

Risk of bias has been assessed as high for all trials and all outcomes except for overall survival. The details are reported in the appendix.

In the absence of direct comparisons, the certainty of the evidence is rated as very low.

## Overview of the evidence

Compared to the previous version of the evidence report, we did not identify additional trials, but newer publications with more recent follow-up.

Besides updating the evidence report with longer follow-up data, we also use the opportunity to provide background information for the trials and to include additional data on intracranial progression.

An overview of the trials can be found in Table 2. For the drugs brigatinib and lorlatinib, only one trial is available each, whereas there are two trials testing alectinib. In all trials, the drugs were tested against the first-generation ALK inhibitor crizotinib. There are no head-to-head trials for the therapy options of interest.

The trials ALEX, ALESIA and ALTA-1L are completed, whereas CROWN is ongoing until 2028. Final analyses have been only published for ALEX [11] and ALTA-1L [12] so far.

Patients in the trials predominantly had stage IV ALK-positive NSCLC. In all trials, patients had not received prior therapy with the exception of the ALTA-1L, where up to one previous regimen of systemic therapy (no ALK inhibitor) for advanced or metastatic disease was allowed. The proportion of patients with brain metastases at baseline was about 40 % in the trials ALEX and ALESIA and about 30% in the trials ALTA-1L and CROWN.

Table 2: Overview of the trials

| **Trial Identifier Study size** | **Intervention Comparator** | **Important inclusion and exclusion criteria** | **Important baseline characteristics** |
|---|---|---|---|
| ALEX [13]<br>NCT02075840<br><br>n = 303 completed | Alectinib vs. Crizotinib | *Inclusion:* advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC, ECOG PS 0–2<br>*Exclusion:* prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC | Stages: 3-4% IIIB, 96-97% IV<br>Brain metastases: 38-42% |
| ALESIA [14]<br>NCT02838420<br><br>n = 187 completed | Alectinib vs. Crizotinib | *Inclusion:* advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC; only patients from China, South Korea or Thailand, ECOG PS 0–2<br>*Exclusion:* prior systemic treatment for advanced, recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK-positive NSCLC | Stages: 7-10% IIIB, 90-94% IV<br>Brain metastases: 35-37% |
| ALTA-1L [15]<br>NCT02737501<br><br>n = 275 | Brigatinib vs. Crizotinib | *Inclusion:* stage IIIB (and not a candidate for definitive multimodality therapy) or stage IV ALK-positive NSCLC, ECOG PS 0–2<br>*Exclusion:* Previously received any prior TKI, including ALK-targeted TKIs; previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease. | Stages: 7% IIIB, 93% IV<br>Brain metastases: 29%<br><br>Previous chemotherapy in patients with locally advanced or metastatic disease: 27% |
| CROWN [16]<br>NCT03052608<br><br>n = 296 ongoing | Lorlatinib vs. Crizotinib | *Inclusion:* locally advanced or metastatic ALK-positive NSCLC, ECOG PS 0–2<br>*Exclusion:* prior systemic NSCLC treatment, including molecularly targeted agents, angiogenesis inhibitors, immunotherapy, or chemotherapy. | Stages: 0-1% IIIA, 5-8% IIIB, 91-95% IV<br><br>Brain metastases: 26-27% |

ALK: anaplastic lymphoma kinase, ECOG: Eastern Cooperative Oncology Group Performance Status, NSCLC: non-small-cell lung cancer, TKI: tyrosine kinase inhibitor

### FAQ 1: What do the treatments involve?

In ALK-positive NSCLC, the genetic mutations result in an active ALK fusion kinase protein which stimulates pathways resulting in the proliferation of cancer cells and angiogenesis. The ALK inhibitors inhibit the activity of ALK and therefore show antitumour activity. Alectinib, brigatinib and lorlatinib show central nervous system (CNS) activity.

#### *Mode of application*

All three ALK inhibitors are available as tablets for oral application. The details for the mode of application are shown in Table 3.

Table 3: Mode of application

| **Drug** | **Mode of application** |
|---|---|
| Alectinib | 600 mg (4 capsules of 150 mg each) twice daily with food, resulting in a daily dose of 1200 mg |
| Brigatinib | One tablet of 90 mg once daily in the first 7 days, then one tablet of 180 mg once daily, with or without food |
| Lorlatinib | One tablet of 100 mg once daily, with or without food |
| The data have been extracted from the summary of product characteristics. | |

#### *Consequences for everyday life*

- Due to possible interactions, patients should avoid grapefruit and grapefruit juice as well as supplements with St. John's wort during treatment with any of the ALK inhibitors.
- When side effects occur, this may affect the ability to drive, e.g. visual disturbances with alectinib or brigatinib or CNS effects with lorlatinib.
- Alectinib and brigatinib may increase photosensibility, adequate protection should be used.

### FAQ 2: What is the impact on my life expectancy?

In all trials, overall survival (OS) was not the primary outcome and hence, the trials were not powered to detect a difference in OS. In the first version of the evidence report, the median OS for all trials had not been reached yet.

Updated OS data is only available for the ALEX and the ALESIA trial (Table 4Table 4: Overall survival data). Although there are publications with longer follow-up for the CROWN trial, they do not report on OS. Risk of bias has been assessed as low for overall survival for all trials.

Median OS has only been reached in the ALEX trial at about 80 months for alectinib. However, the difference between the intervention and the comparator is not statistically significant in any of the trials. This might change in the future for the CROWN trial which is still on-going.

Based on these results, it is not possible to draw definitive conclusions about the relative effectiveness of the ALK inhibitors in terms of OS. However, the comparison of OS proportions at 24 months in the Kaplan-Meier curves indicates that OS might be at least as high with brigatinib and lorlatinib as with alectinib. It should be noted, however, that the estimate for lorlatinib is rather uncertain due to the relatively short median follow-up of 18.3 months, indicating that only a small proportion of participants (about 20% of the full study population) contributed to OS data at 24 months.

Table 4: Overall survival data

| Trial | Median OS (months) | Median follow-up (months) | OS proportion at 24 months |
|---|---|---|---|
| ALEX (Alectinib) [11] | 81.1 [a] | 53.5 | 74% [b] |
| ALESIA (Alectinib) [17] | Not reached [c] | 61 | 85% [d] |
| ALTA-1 (Brigatinib) [12] | Not reached [e] | 40.4 | 75% [f] |
| CROWN (Lorlatinib) [16] | Not reached [g] | 18.3 | 85% [h] |

CI: confidence interval, HR: hazard ratio, NE: not estimable, OS: overall survival
[a] Median OS was 81.1 months [95% CI 62.3 months-not estimable (NE)] in the alectinib arm and 54.2 months (95% CI 34.6-75.6 months) in the crizotinib arm (HR 0.78, 95% CI 0.56-1.08, P = 0.13)
[b] Estimated from Fig. 1
[c] 95% CI median OS was NE in the alectinib arm (95% CI: NE–NE) and in the crizotinib arm (95% CI: 45.5–NE)
[d] Fig. 2
[e] HR = 0.81, 95% CI: 0.53–1.22, log-rank p = 0.331
[f] Estimated from Fig. 2A. At 4 years, the KM-estimated OS (95% CI) was 66% (56%–74%; seven patients at risk) in the brigatinib arm and 60% (51%–68%; five patients at risk) in the crizotinib arm.
[g] The hazard ratio for death was 0.72 (95% CI, 0.41 to 1.25)
[h] Estimated from Fig. 2D. At the data cut-off, 23 patients [15%] in the lorlatinib group and 28 patients [19%] in the crizotinib group had died.

### *Conclusion for the decision aid*

- It is unclear which of the therapy options leads to a longer life expectancy. The main reasons are: 1) There are no trials directly comparing the treatment options. 2) The trials did not run long enough to capture enough deaths for a valid estimate.
- The previous version of the evidence report stated that more than half of the patients survive 36 months, based on data for alectinib and brigatinib. Based on the updated data, overall survival might be even longer: With alectinib, median overall survival is about 80 months. Based on the indirect comparison, it is plausible that median overall survival with brigatinib and lorlatinib might be at least in the same order of magnitude.

### FAQ 3: What is the impact on the progression of the disease?

In all trials, progression-free survival (PFS) was the primary outcome. It should be noted that in all trials, PFS was assessed in two modes at least at some length of follow-up: In ALTA-1L and CROWN, the primary outcome was PFS assessed by a blinded independent review committee (BIRC) whereas in ALEX and ALESIA, investigator-assessed PFS was the primary outcome and BIRC-assessed PFS only a secondary outcome. In both of these trials, IRC-assessed PFS is only reported for the primary analysis but not for the reports with longer follow-up. In the CROWN trial, BIRC assessment stopped after 3 years. The previous version of the evidence report only included data on investigator-assessed PFS. As the BIRC assessment is more reliable and usually leads to more conservative estimates, we report both data, where available, in this version of the evidence report.

In the first version of the evidence report, median PFS was reported for all trials except the intervention arms in ALESIA and CROWN. We updated the data for all trials except ALTA-1 for which no more recent publication is available (

Table 5). Median PFS data is now available for the intervention arms in ALEX, ALESIA and ALTA-1L. It should be noted that the median PFS for the comparator crizotinib is quite similar across the trials indicating a certain comparability of the populations.

Risk of bias has been assessed as high for PFS for all trials.

Table 5: Progression-free survival data

| Trial | Median PFS (months) [a] | | Median follow-up (months) [b] | PFS proportion at 36 months |
|---|---|---|---|---|
| | BIRC | Investigator | | Investigator |
| ALEX (Alectinib) | -- | 34.8 vs 10.9 | 37.8 [18] | 46 per 100 [c] |
| | 25.7 vs 10.4 | NR vs 11.1 | 17.6 [13] | -- |
| ALESIA (Alectinib) | -- | 41.6 vs 11.1 | 61 [17] | 56 per 100 [d] |
| | NR vs 10.7 | NR vs 11.1 | 16.2 [14] | -- |
| ALTA-1 (Brigatinib) | 24.0 vs 11.1 | 30.8 vs 9.2 | 40.4 [12] | 45 per 100 [e] |
| CROWN (Lorlatinib) | -- | NR vs 9.1 f | 83 [10] | 65 per 100 [g] |
| | NR vs. 9.3 | NR vs 9.1 | 36.7 [19] | -- |

All data refer to the ITT population. BIRC: blinded independent review committee, NE: not estimable, NR: not reached
[a] Compared to crizotinib
[b] For the intervention arm
[c] Fig. S1
[d] Estimated from Fig. 1A
[e] Fig. 1B
[f] 95% confidence interval for lorlatinib 68.5-NE
[g] Fig. 2A

In the indirect comparison of the ALK inhibitors, the proportion for investigator-assessed PFS seems longer in the CROWN trial at a follow-up of 3 years. However, due to the heterogenous results in the ALEX and ALESIA trial, these data do not allow for reliable conclusions.

In the CROWN trial, median PFS is not reached yet, although the follow-up of 83 months is considerably longer than in the other trials. The lower limit of the confidence interval for investigator-assessed PFS is about 69 months.

Overall, the data indicate that PFS with lorlatinib might be longer than with alectinib and brigatinib. Based on the results for median PFS, it is unclear if there is a difference between alectinib and brigatinib. The same conclusion applies to the subgroup of patients with brain metastases at baseline for which median PFS is reached in all trials (Table 6).

Table 6: PFS data in patients with brain metastases at baseline

| | Median PFS (months) |
|---|---|
| ALEX (Alectinib) [18] | 25.4 vs 7.4 [a] |
| ALESIA (Alectinib) [17] | 41.6 vs 9.2 [a] |
| ALTA-1 (Brigatinib) [20] | 24.0 vs 5.6 [b,c] |
| CROWN (Lorlatinib) [10] | 86.3 vs 6.0 [b] |

All interventions have been compared to crizotinib. PFS: Progression-free survival
[a] Assessment by investigator
[b] Assessment by blinded independent review committee
[c] Fig 3A

*Conclusion for the decision aid*

- The available evidence indicates that PFS might be higher with lorlatinib than with alectinib and brigatinib. It is unclear whether there is a difference between alectinib and brigatinib. However, this conclusion relies on indirect comparisons as there are no head-to-head trials and is therefore rather uncertain.
- With alectinib and brigatinib, it might take 24 to 42 months (2 to 3.5 years) until half of the patients experience progression or death. With lorlatinib, it might take 86 months for patients with brain metastases and even longer for patients without brain metastases at the start of treatment.

### FAQ4: What is the impact on intracranial progression?

Intracranial progression has been assessed in the trials by regular radiography and been defined as new brain metastases in patients without brain metastases at baseline or progression of existing brain metastases.

It should be noted that progression was not only assessed by the investigator, but by a blinded independent review committee (BIRC) at least for the first phase of the trial. In the CROWN trial, BIRC assessment stopped at 3 years, in ALEX and ALESIA, BIRC assessment was not applied to data cut-offs after the primary analysis. Where available, we preferred BIRC-assessed data.

As the proportion of patients with brain metastases at baseline is different in the trials of alectinib and brigatinib/lorlatinib, respectively, we report the data separately for patients with and without brain metastases at baseline, where available (Table 1

Table 7).

Data on intracranial progression in the ALEX trial is only reported for a relatively short follow-up of 19 months. Median intracranial progression has been only reached in the trials ALTA-1L and in the crizotinib arm of the CROWN trial for which data at a follow-up of 7 years is available. Therefore, we additionally extracted data for the proportions of patients without event of intracranial progression at 18 months and at 36 months which are available for all medicines. Risk of bias has been assessed as high for intracranial progression for all trials.

Table 7: Intracranial progression-free survival data

| | **ALESIA (Alectinib)** [17] [a] | **ALEX (Alectinib)** [13] [b] | **ALTA-1 (Brigatinib)** [12] [c] | **CROWN (Lorlatinib)** [10] [d] |
|---|---|---|---|---|
| **Median follow-up (months)** | **61** | **19** | **40.4** | **83** |
| **ITT population** | | | | |
| Median time to event (months) | Not reached | Not reached | 44.1 vs 21.2 | NR vs 16.4 |
| Proportion without event at 18 months | 95 per 100 vs 70 per 100 | 88 per 100 vs 55 per 100 | 75 per 100 vs 55 per 100 | 95 per 100 vs 45 per 100 |
| Proportion without event at 3 years | 88 per 100 vs 66 per 100 | Not reported | 57 per 100 vs 38 per 100 | 92 per 100 vs 25 per 100 |
| Proportion without event at 5 years | 86 per 100 vs 63 per 100 | Not reported | Not reported | 92 per 100 vs 21 per 100 |
| **Brain metastases at baseline** | | | | |
| Median time to event (months) | Not reached | Not reported | 24 vs 5.5 | NR vs 7.2 months |
| Proportion without event at 18 months | 95 per 100 vs 44 per 100 | Not reported | 60 per 100 vs 18 per 100 | 95 per 100 vs 12 per 100 |
| Proportion without event at 3 years | 84 per 100 vs 44 per 100 | Not reported | 31 per 100 vs 9 per 100 | 83 per 100 vs 0 per 100 |
| Proportion without event at 5 years | 77 per 100 vs 29 per 100 | Not reported | Not reported | 83 per 100 vs 0 per 100 |
| **No brain metastases at baseline** | | | | |
| Median time to event (months) | Not reached | Not reported | Not reported | NR vs 23.9 months |
| Proportion without event at 18 months | 95 per 100 vs 85 per 100 | Not reported | Not reported | 96 per 100 vs 55 per 100 |
| Proportion without event at 3 years | 91 per 100 vs 77 per 100 | Not reported | Not reported | 96 per 100 vs 33 per 100 |
| Proportion without event at 5 years | 91 per 100 vs 74 per 100 | Not reported | Not reported | 96 per 100 vs 27 per 100 |

All data compared to crizotinib. CNS: central nervous system, ITT: intention to treat

[a] Cumulative incidence for CNS progression Fig. 3: a) at 18 months ITT 5% vs 30%, brain metastases at baseline: 5% vs 56%, no brain metastases at baseline: 5% vs 15% b) at 36 months: ITT 11.6% vs 34.0%; brain metastases at baseline: 16.2% vs 55.7%; without brain metastases at baseline: 9.1% vs 23.1%; c) at 60 months: ITT 14.2% vs 37.4%, brain metastases at baseline: 23.2% vs 61.0%; without brain metastases at baseline: 9.1% vs 25.6%

[b] At a follow-up of about 18 months, 12 per 100 patients with alectinib and 45 per 100 patients with crizotinib had intracranial progression (ITT).

[c] Fig. 1E and 1F

[d] Fig. 3 and Suppl. Fig. S3. Probability of being free of intracranial progression at 7 years: ITT 92% vs 16%, brain metastases at baseline: 83% vs 0 %, without brain metastases at baseline: 96% vs 22%. At 5 years [21]: ITT 92% vs 21%; with brain metastases at baseline 83% vs not evaluable (all patients progressed in the brain or were censored within 2 years, Fig 3B); without brain metastases at baseline 96% vs 27% (Fig 3C).

Whereas the median time to intracranial progression as well as the proportions in the crizotinib arm are in the same order of magnitude for brigatinib and lorlatinib, the results for alectinib are heterogenous at 18 months. Additionally, the results in the crizotinib arm of the ALESIA trial show a slower CNS progression than in the respective arm of the CROWN trial, indicating differences in the study population. However, with lorlatinib, the proportions do not increase beyond 3 years up to 7 years, whereas there is a small increase with alectinib in the ALESIA trial beyond 3 years up to 5 years in the ITT population. The difference is especially pronounced for patients with brain metastases at baseline. These results indicate that lorlatinib might be more effective than brigatinib and alectinib in terms of intracranial progression.

*Conclusion for the decision aid*

- Lorlatinib seems to be more effective in slowing progression of brain metastases than brigatinib and alectinib.
- With lorlatinib, about 83 per 100 patients with brain metastases and about 96 per 100 patients without brain metastases do not experience intracranial progression within 7 years. The proportions might be lower with alectinib or brigatinib. The difference, however, cannot be reliably quantified.
- There is high uncertainty of the evidence as there are no trials which compare the treatment options directly.

### FAQ5: What is the impact on my quality of life?

There is an association between the patient-reported outcomes quality of life and symptoms: When the disease progresses, symptoms may increase and therefore quality of life may decrease. When a treatment stabilises or even improves symptoms, at least temporarily, quality of life may increase. Some aspects of quality of life, however, might be more affected by symptoms than others. Quality of life may also be impacted by treatment effects, such as adverse events or treatment burden.

In the first version of the evidence report, data was only available for the ALTA-1L trial. The conclusion was: "Whether one of the ALK inhibitors improves the quality of life more than the other two has not yet been sufficiently investigated."

For this version of the evidence report, we used the data reported in the IQWiG assessments or the AMNOG documents for the early benefit assessments [7–9]. In all trials, quality of life has been assessed at least by the generic EORTC-QLQ-C30 questionnaire and the lung cancer specific questionnaire EORTC-QLQ-LC13 and a difference of 10 points was considered to be clinically relevant. As the lengths of follow-up differ, we report only median time to deterioration (TTD), where available, and due to limited resources, only for the subscale global health scale

(GHS). When different operationalisations were available, we preferred median time to confirmed deterioration (Table 8).

Risk of bias has been assessed as high for quality of life for all trials.

Table 8: Median time to deterioration of global health status

| Trial | Intervention (months) | Comparison (months) | Median follow-up (months) |
|---|---|---|---|
| ALEX [7] [a] Alectinib | Not reached | Not reached | 19 |
| ALTA-1L [8] [b] Brigatinib | 26.7 | 8.3 | 24 |
| CROWN [9] [c] Lorlatinib | 24.0 | 12.0 | 18 |

In all trials, the interventions have been compared to crizotinib.
[a] IQWiG report 28.03.2018, Table 14; Kaplan-Meier curve in Fig. 16. The median follow-up for the data cut-off 09.02.2017 is not available in the IQWiG report but the corresponding journal publication (18.6 months for alectinib) [13].
[b] IQWiG report 30.07.2020, Table 14; median follow-up in Table 10
[c] AMNOG dossier, Module 4A, Table 4-81; median follow-up is only reported for the outcome PFS: 18.3 months (p. 126)

With brigatinib and lorlatinib, the median time to deterioration for GHS was in a similar order of magnitude (about 2 years). However, the median has not been reached in the ALEX trial with alectinib or crizotinib. As the Kaplan-Meier curve (Fig. 16) in the IQWIG report shows, the decline in GHS is much slower with crizotinib as in the trials with brigatinib or lorlatinib. This indicates that there might be differences in the trial populations. Therefore, it is questionable if quality of life can be meaningfully compared between the trials. This is further supported by the fact that in all trials, there is no significant difference in median time to relevant worsening of GHS compared to crizotinib for alectinib and lorlatinib with the exception for brigatinib, for which there is a marginally significant effect ($p = 0.049$).

### *Conclusion for the decision aid*

- With brigatinib and lorlatinib, it takes about 2 years until half of the patients experience a relevant worsening of their overall quality of life. For some aspects of quality of life or some symptoms, the time to worsening might be shorter.
- It is not known if overall quality of life is in a similar order of magnitude with alectinib.
- The conclusion does not change that it is not possible to compare the ALK inhibitors in terms of quality of life.

## FAQ 6: What are the risks or side effects?

Qualitative data on side effects have been updated based on the summary of product characteristics, where not otherwise noted. We extracted very common side effects and summarised them where possible (Table 9). It should be noted that the description is not exhaustive. Also, the quantitative data on serious adverse events (Table 10), severe adverse events (Table 11) and permanent treatment discontinuation due to adverse events (Table 12) have been updated. Risk of bias has been assessed as high for all safety outcomes for all trials.

### Table 9: Very common and common side effects

| | Alectinib | Brigatinib | Lorlatinib |
|---|---|---|---|
| Respiratory symptoms (e.g. cough, dyspnoea) and infections | Pneumonitis △ | ○/ Pneumonitis ○/▲ | Pneumonitis △ |
| Anaemia | ○/▲ | ○ | ○/▲ |
| Metabolic and electrolyte disturbances | Hyperuricaemia △ | ○ | ○/ **Hypercholesterinaemia, hypertriglyceridaemia** ● |
| Gastrointestinal problems | ○/ Diarrhoea ▲ | ○ / Nausea and diarrhoea ▲ | ○ / Diarrhoea ▲ |
| Weight gain | ○ | -- | ● |
| Vision problems | △ | ○/▲ | ○ |
| Hypertension | -- | ● | ○/▲ |
| Increased liver enzymes | ○/▲ | ○/▲ | ○/▲ |
| Rash | ○/▲ | ○/▲ | ○ |
| Myalgia and/or arthralgia | ○ | ○ | ○ |
| Fatigue | ○ [a] | ○/▲ | ○/▲ |
| Oedema | ○ | ○ | ○/▲ |
| Bradycardia | ○ | △ | -- |
| Photosensitivity | △ | △/▲ | -- |
| Psychiatric side effects | -- | Insomnia △ | Depression ○/▲, hallucinations △ |
| Neurological side effects | Dysgeusia △ | Peripheral neuropathy ○ /▲, headache ○ /▲, dizziness ○, dysgeusia △ | Cognitive effects ○/▲, peripheral neuropathy ○/▲, headache ○ |
| Renal side effects | Elevated creatinine ○, acute kidney injury △ | Elevated creatinine ○ | Proteinuria △ |

●: very common, Grade ≥ 3; ○: very common, any grade; ▲ common, Grade ≥ 3; △: common, any grade. [a] [11] Suppl. Tab. 2

With all ALK inhibitors, pneumonitis, gastrointestinal problems, metabolic and electrolyte disturbances, vision problems, increased liver enzymes, rash, myalgia, arthralgia, fatigue and oedema are common or very common adverse events.

With lorlatinib, dyslipidaemia (hypercholesterinaemia and hypertriglyceridaemia) and weight gain are particularly pronounced. Weight gain is no common problem with brigatinib.

Hypertension is particularly pronounced with brigatinib and is a very common adverse event with lorlatinib, but not with alectinib.

Bradycardia and photosensitivity, which are common or very common with alectinib and brigatinib, are no concern with lorlatinib.

Only with lorlatinib, depression and cognitive effects are a special concern. Peripheral neuropathy and headache can occur with both lorlatinib and brigatinib and are not common with alectinib. With brigatinib, dizziness is very common, but not with the other two ALK inhibitors.

For the decision aid, quantitative data have been extracted for three safety outcomes: serious AE, severe AE and permanent treatment discontinuation due to AE.

As the proportions are affected by the length of follow-up, we extracted data from publications reporting on comparable lengths of follow-up across the trials.

Table 10: Serious adverse events

| **Trial** | **Proportion and follow-up (months)** | | |
|---|---|---|---|
| | **> 4 years** | **Up to 4 years** | **Up to 2 years** |
| **ALEX (Alectinib)** | 46 per 100<br>54 [11] [a] | 39 per 100<br>48 [18] [b] | 28 per 100<br>18 [13] [c] |
| **ALESIA (Alectinib)** | 28 per 100<br>61 [17] [d] | No publication | 15 per 100<br>16 [14] [e] |
| **ALTA-1L (Brigatinib)** | No publication | 41 per 100<br>40.4 [f] | Not reported<br>11 [15] |
| **CROWN (Lorlatinib)** | 44 per 100<br>60 [21] [g] | 38 per 100<br>37 [19] [h] | 34 per 100<br>18 [16] [i] |

[a] Tab. 3
[b] Tab. 3
[c] Tab. S4
[d] Tab. 2
[e] Tab. 5
[f] https://clinicaltrials.gov/study/NCT02737501?tab=results#outcome-measures
[g] Tab. 2
[h] Tab. 2
[i] Tab. S3

Table 11: Severe adverse events

| Trial | Proportion and follow-up (months) | | |
|---|---|---|---|
| | **> 4 years** | **Up to 4 years** | **Up to 2 years** |
| **ALEX (Alectinib)** | 58 per 100<br>54 [11] [a] | 52 per 100<br>48 [18] [b] | 41 per 100<br>18 [13] [c] |
| **ALESIA (Alectinib)** | 48 per 100<br>61 [17] [d] | No publication | 29 per 100<br>16 [14] [e] |
| **ALTA-1L (Brigatinib)** | No publication | 70 per 100<br>40.4 [12] [f] | 61 per 100<br>11 [15] [j] |
| **CROWN (Lorlatinib)** | 77 per 100<br>60 [21] [g] | 76 per 100<br>37 [19] [h] | 72 per 100<br>18 [16] [i] |

[a] Tab. 3, Grade 3-5
[b] Tab. 3, Grade 3-5
[c] Tab. S4, Grade 3-5
[d] Tab. 2, Grade 3-5
[e] Tab. 5, Grade 3-5
[f] Tab. 2, Grade 3 and 4
[g] Tab. 2, Grade 3 and 4
[h] Tab. 2, Grade 3 and 4
[i] Tab. 3, Grade 3 and 4
[j] Tab. 3, Grade ≥ 3

Table 12: Permanent treatment discontinuation due to AE

| Trial | Proportion and follow-up (months) | | |
|---|---|---|---|
| | **> 4 years** | **Up to 4 years** | **Up to 2 years** |
| **ALEX (Alectinib)** | 18 per 100<br>54 [11] [a] | 15 per 100<br>48 [18] [b] | 11 per 100<br>18 [13] [c] |
| **ALESIA (Alectinib)** | 11 per 100<br>61 [17] [d] | No publication | 7 per 100<br>16 [14] [e] |
| **ALTA-1L (Brigatinib)** | No publication | 13 per 100<br>40.4 [12] [f] | 12 per 100<br>11 [15] [j] |
| **CROWN (Lorlatinib)** | 11 per 100<br>60 [21] [g] | 7 per 100<br>37 [19] [h] | 7 per 100<br>18 [16] [i] |

[a] Tab. 3
[b] Tab. 3
[c] Tab. 3
[d] Tab. 2
[e] Tab. 5
[f] Tab. 2
[g] Tab. 2
[h] Tab. 2
[i] Discontinuation of treatment because of adverse events occurred in 7% and 9% of the patients, respectively.
[j] A total of 12% of patients who received brigatinib and 9% of patients who received crizotinib discontinued treatment owing to adverse events.

*Conclusion for the decision aid*

- The qualitative data for adverse events should be updated according to Table 9 and the conclusions for serious and severe adverse events as well as permanent discontinuation of treatment as detailed below.
- It is not clear if serious adverse events are more common with any of the ALK inhibitors. Within 4 years, about 40 per 100 patients may experience serious adverse events.
- Severe AE seem to be more common with brigatinib and lorlatinib than with alectinib. Within about 4 years, severe adverse events affect about 52 per 100 patients with alectinib and 70 to 76 per 100 with brigatinib or lorlatinib.
- It is unclear whether permanent treatment discontinuation is more common with one of the ALK inhibitors. Within about 4 years, up to 18 per 100 patients permanently discontinue treatment due to AE.

# DISCUSSION

### SUMMARY OF MAIN FINDINGS

For the comparison of the three ALK inhibitors alectinib, brigatinib and lorlatinib, the main conclusions are:

- It is unclear if there is a difference in terms of life expectancy.
- The available evidence indicates that PFS might be higher with lorlatinib than with alectinib and brigatinib.
- Lorlatinib seems to more effective in slowing progression of brain metastases than brigatinib and alectinib.
- It is not possible to compare the ALK inhibitors in terms of quality of life.
- It is not clear if serious adverse events are more common with any of the ALK inhibitors.
- Severe AE seem to be more common with brigatinib and lorlatinib than with alectinib.
- It is unclear whether permanent treatment discontinuation is more common with one of the ALK inhibitors.

### STRENGTH, LIMITATIONS AND UNCERTAINTIES

The main strength of this evidence report is the comprehensive base of up-to-date evidence and the discussion of the main treatment options as recommended in current guidelines.

However, there are several limitations:

- As the ALK inhibitors have not been directly compared in trials, all conclusions rely on indirect comparisons. The certainty is therefore very low.
- In all trials, there is a high risk of bias for all outcomes except overall survival.
- Median overall survival has not been reached in 3 of the 4 included trials. As the CROWN trial is still ongoing, it might be possible that our conclusion on comparative overall survival might change with more mature data.
- For some outcomes, only selected data have been reported in the publications which limited some conclusions.
- Due to limited resources, we used evidence triangulation rather than a formal network meta-analysis or adjusted indirect comparisons. Therefore, there is added uncertainty.

Our main conclusions are concordant with the assessments in current guidelines:

- In the German guideline for the treatment of lung cancer, lorlatinib is preferred over alectinib or brigatinib which are listed as alternatives [1].
- The ASCO guideline recommends alectinib, brigatinib or lorlatinib and discusses some differences between the drugs which might guide the treatment decision: As the guideline (Version 2026.3.3) points out, alectinib might be more favourable in terms of tolerability whereas lorlatinib is favourable in disease control (systemic and in the CNS). However, serious adverse events are more common with lorlatinib which require monitoring and frequently dose modifications. Therefore, lorlatinib is preferred in patients with good performance status, no comorbidities and high risk of progression. Especially in frail, older adults with cardiac and CNS morbidities, alectinib or brigatinib can be considered as alternatives [2].

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# APPENDIX

## LITERATURE SEARCHES

### *Guidelines*

Handsearching websites of relevant organisations 05.08.2026

Inclusion criteria: Published 2026

| Organisation | Retrieval |
|---|---|
| Leitlinienprogramm Onkologie [a] | https://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom (Version 5.1) |
| ASCO [b] | https://ascopubs.org/guidelines/treatment-multiple-myeloma-asco-living-guideline (Version 2026.3.2) |
| [a] https://www.leitlinienprogramm-onkologie.de/leitlinien/<br>[b] https://ascopubs.org/topics/asco-guidelines/thoracic-cancer | |

As both guidelines contain comparable recommendations and rely on the same evidence, we assumed sufficient saturation and no other organisation websites were searched.

### *RCT*

As the ASCO guideline had very broad search terms, we did not use this search strategy. Instead, we focussed on RCTs with the three medicines of interest. As the medicines are only used for advanced ALK-positive NSCLC, no search terms for the populations were used. For a more specific search, only the title and abstract fields were searched for the interventions and title, abstract and publication type fields for the study type. The search period was restricted to publications as of April 1, 2026, or later, corresponding to the latest search for the ASCO guideline allowing for some overlap.

**PubMed 05.08.2026**

#1: "alectinib"[Title/Abstract] OR "brigatinib"[Title/Abstract] OR "lorlatinib"[Title/Abstract]

#2: "random*"[Title/Abstract] OR "randomized controlled trial"[Publication Type]

#3: #1 AND #2

#4: 2026/04/01:3000/12/31[Date - Publication]

#5: #3 AND #4

## SELECTION OF THE EVIDENCE

### *Guidelines*

Criteria and results of the guideline selection are presented in Table 13.

Table 13: Guideline selection

| Guideline | Suitable for PICO? | Suitable for data extraction? | Decision |
|---|---|---|---|
| Leitlinienprogramm Onkologie 2026 | Y | N (due to the incremental reporting of the systematic searches it is not sufficiently clear when the latest search for the relevant PICO questions was conducted) | Included to inform PICO |
| ASCO Version 2026.3.2 | Y | N (systematic searches sufficiently transparent, but no evidence profiles) | Included to inform PICO and for study pool |

After completion of the searches, an update of the ASCO guideline has been published (2026.3.3). However, the recommendations for ALK inhibitors are unchanged. Changes in the trial and publication pool are discussed below.

### *Trial and publication pool*

Trials and publications have been identified via the ASCO guideline (Version 2026.3.2) and the previous version of the evidence report. However, not all publications were necessary to inform this version of the evidence report (Table 14).

Table 14: Trial and publication pool

| Trial | Publication | ASCO guideline | Evidence report | |
|---|---|---|---|---|
| | | | Previous version | This version |
| ALEX | Peters 2025 PMID 41110693 [11] | x | -- | x |
| | Mok 2020 PMID 32418886 [18] | x | -- | x |
| | Camidge 2019 PMID 30902613 | -- | x | -- |
| | Peters 2017 PMID 28586279 [13] | x | -- | x |
| J-ALEX | Nakagawa 2024 PMID 31812890 | x | -- | -- |
| | Hotta 2022 PMID 35843080 | x | -- | -- |
| ALESIA | Zhou 2024 PMID 39282663 [17] | x | -- | x |
| | Zhou 2019 PMID 30981696 [14] | x | x | x |
| ALTA-1L | Camidge 2021 PMID 34537440 [12] | x | x | x |
| | Camidge 2020 PMID 32780660 | x | -- | -- |
| | Camidge 2018 PMID 30280657 [15] | -- | -- | x |
| CROWN | Shaw 2026 PMID 42217582 [10] | -- | -- | x |

| Trial | Publication | ASCO guideline | Evidence report | |
|---|---|---|---|---|
| | | | Previous version | This version |
| | Solomon 2024 PMID 38819031 [21] | x | -- | x |
| | Solomon 2023 PMID 36535300 [19] | x | -- | x |
| | Shaw 2020 PMID 33207094 [16] | -- | x | x |

In the version 2026.3.3 of the ASCO guideline, which was published after completion of the searches, a new publication has been included for the CROWN trial. This is the same publication which we identified in the additional searches for RCTs (see below). Therefore, the trial and publication pool is still in concordance with the guideline.

*Additional search for RCTs*

**Abstract-Screening**

Screened: n = 8 (see separate Rayyan file)

Excluded: n = 7

Included for full-text screening: n = 1

**Full-text screening**

Shaw 2026 https://pubmed.ncbi.nlm.nih.gov/42217582/

7-year update of CROWN (lorlatinib) – included

## RISK OF BIAS ASSESSMENT

*ASCO Guideline (version 2026.3.2)*

Table 15: Methodological guideline assessment

| Domain | Aspects | Notes |
|---|---|---|
| **Systematic search of the literature** | x Information available on the databases searched<br><br>x Information available on search terms and/or search strategy<br><br>x Information available on the date of the search | Data Supplement 3: Search Strategy String<br><br>Ovid MEDLINE<br><br>Searches running on a biweekly frequency – version 2026.3.2 literature search end date: April 22, 2026 |
| **Inclusion and exclusion of trials/ publications** | x Inclusion and exclusion criteria defined<br><br>x Information available on the selection process<br><br>O Information available on excluded trials/publications | Data Supplement 4: Summary of Inclusion and Exclusion Criteria<br><br>Guideline Development process: This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a representative from Ontario Health, a patient representative, and an ASCO guidelines staff member with health research methodology expertise (Additional Information Table A1).<br><br>The recommendations were developed using a systematic review of evidence identified through routinely scheduled searches of PubMed. […] Members were asked to provide ongoing input on the guideline development protocol, quality and assessment of the evidence, generation of recommendations and draft content.<br><br>No information on excluded trials. However, the resulting study pool is the same as in the Cochrane Review used in the previous version of the evidence report |

| | | |
|---|---|---|
| | | and in the German S3 Guideline. Therefore, it is unlikely that relevant trials have been omitted. |
| **Assessment of the evidence** | n.a. | GRADE final assessments in the recommendations, but no details |
| **Presentation of the evidence** | n.a. | Only narrative description of the results, no evidence profiles |
| **Summary** | x Methodical rigour sufficient<br>O Suitable for data extraction<br>x Update of the body of evidence necessary<br>x Additional information from trial publications necessary | Methodical rigour refers to the search process; use study pool, check for newer trials; extract data from journal publications |

*Trials*

Risk of bias assessments can be found in Table 16. Where available, risk of bias assessments have been adopted from the IQWiG reports. Otherwise, the rationales for the rating are described in the footnotes.

Table 16: Risk of bias assessments

| Trial | OS | PFS | ICP | QoL | AE |
|---|---|---|---|---|---|
| ALEX/ALESIA [7] [a] | Low | High | High | High | High |
| ALTA-1L [8] [b] | Low | High | High | High | High |
| CROWN [9] [c] | Low | High | High | High | High |

AE: Adverse events, ICP: intracranial progression, OS: overall survival, PFS: progression-free survival

[a] IQWiG report 22.12.2017, Table 13. The ALESIA trial is not included in the IQWiG report. As the protocols of ALESIA and ALEX are very similar, the risk of bias assessments of the ALEX trial are adopted for the ALESIA trial as well. QoL: missing data, lack of blinding, possibly informative censoring; AE: serious and severe AE possibly informative censoring, discontinuation due to AE: lack of blinding. PFS and ICP have not been assessed in the IQWiG report but as the conclusions in this evidence report rely mainly on investigator-assessed progression, risk of bias is rated as high.

[b] IQWiG report 30.07.2020, Table 13. QoL: lack of blinding, missing data; AE: serious and severe AE informative censoring, discontinuation due to AE: lack of blinding. PFS and ICP have not been assessed in the IQWiG report. PFS: Conclusions in this report rely mainly on investigator-assessed progression, therefore risk of bias is rated as high. ICP: possibly informative censoring as patients were not followed for this outcome until the end of study and censoring occurred at systemic progression; therefore, risk of bias is rated as high.

[c] IQWiG report, Table 15, rating only available for OS. The description of censoring and lack of blinding corresponds to the ALTA-1L trial; therefore, the ratings are adopted for the CROWN trial.