IQWiG Reports – Commission No. A22-31

Lorlatinib (NSCLC) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Lorlatinib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lorlatinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 25 February 2022.

Research question

The aim of the present report was to assess the added benefit of lorlatinib in comparison with the appropriate comparator therapy (ACT) in adults with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of lorlatinib

Therapeutic indication	**ACT**[a]
Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **brigatinib**

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The company followed the ACT specified by the G-BA by choosing brigatinib from the 2 options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

No relevant randomized controlled trial (RCT) was found for the direct comparison of lorlatinib versus the ACT specified by the G-BA. The company presented an adjusted indirect comparison using the common comparator of crizotinib, using the CROWN study on the lorlatinib side and the ALTA-1L study on the brigatinib side of the comparison.

CROWN study (with lorlatinib)

The CROWN study is an open-label RCT comparing lorlatinib with crizotinib. The study included adult patients with previously untreated locally advanced or metastatic ALK-positive

NSCLC. Systemic prior therapies including therapy of the advanced or metastatic disease with a tyrosine kinase inhibitor were disallowed.

A total of 296 patients were randomly allocated in a 1:1 ratio to treatment with lorlatinib (N = 149) or crizotinib (N = 147).

Treatment in both study arms was largely in compliance with the requirements of the respective Summaries of Product Characteristics (SPCs). Patients were treated until disease progression, withdrawal of consent, unacceptable toxicity, lost to follow-up, or study end. However, both study arms allowed continuing treatment beyond disease progression as determined via Response Evaluation Criteria in Solid Tumors (RECIST), provided that the investigator deemed the treatment to still be of clinical benefit to the patient.

The study's primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were mortality, morbidity, health-related quality of life, and side effects outcomes.

ALTA-1L study (with brigatinib)

As described in dossier assessment A20-42, the ALTA-1L study is an open-label RCT comparing brigatinib with crizotinib. The study included adult patients with ALK-positive, locally advanced, recurrent, or metastatic NSCLC. Regarding prior therapy, no more than 1 regimen of prior systemic therapy for advanced or metastatic disease was allowed. This count did not include any prior tyrosine kinase inhibitor therapy.

A total of 275 patients were randomly allocated in a 1:1 ratio to treatment with brigatinib (N = 137) or crizotinib (N = 138).

Both study arms administered treatment without relevant deviation from the requirements of the SPCs. Patients were treated until disease progression, start of new antineoplastic treatment, withdrawal of consent, unacceptable toxicity, or end of study. In line with the SPC; the brigatinib arm allowed continuing treatment beyond disease progression as determined by RECIST, provided that the investigator deemed the treatment to still be of clinical benefit to the patient. At the investigator's discretion and in compliance with approval, patients in the crizotinib arm were allowed to receive brigatinib as subsequent therapy after disease progression.

The study's primary outcome was PFS. Patient-relevant secondary outcomes were mortality, morbidity, health-related quality of life, and side effects outcomes.

Similarity of the studies for the indirect comparison

Overall, the CROWN and ALTA-1L studies exhibit relevant differences in the planned duration of follow-up observation as well as in patients' prior treatment. These differences do not fundamentally call into question a similarity sufficient for conducting an adjusted indirect comparison via the common comparator of crizotinib. However, the differences in the planned duration of follow-up observation leads to insufficient similarity in the operationalizations of

the morbidity, health-related quality of life, and side effects outcomes, whose observation is linked to treatment duration. Hence, no indirect comparison is conducted for said outcomes.

Risk of bias

The risk of bias across outcomes is rated as low for both studies.

In the present scenario, an indirect comparison can be conducted only for the outcome of overall survival. For both studies, this results in a low risk of bias for the results on overall survival.

One RCT was found on each side of the available adjusted indirect comparison. Hence, the check for homogeneity is not needed. As there is no directly comparative study for the comparison of lorlatinib versus the ACT, it is impossible to check the consistency of results. Therefore, the adjusted indirect comparison has at most a low certainty of results. Consequently, at most hints, e.g. of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Results

Mortality

Overall survival

For the outcome of overall survival, the adjusted indirect comparison shows no statistically significant difference between lorlatinib and brigatinib. Hence, there is no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)

Due to insufficient similarity of the outcome operationalizations used in the 2 studies, no usable data are available for an adjusted indirect comparison of symptoms outcomes. For each of the outcomes regarding symptoms, this results in no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven for any of them.

Health status (European Quality of Life – 5 Dimensions [EQ-5D] visual analogue scale [VAS])

The outcome of health status was recorded only in the CROWN study. Therefore, an adjusted indirect comparison is not possible for this outcome. This results in no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven.

Health-related quality of life and side effects

Due to insufficient similarity of the outcome operationalizations used in the 2 studies, no data are available for an adjusted indirect comparison of health-related quality of life and side effects outcomes. This results in no hint of an added benefit of lorlatinib in comparison with brigatinib for either of these outcomes; an added benefit is therefore not proven for either of them.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the presented results, the probability and extent of added benefit of the drug lorlatinib in comparison with the ACT is assessed as follows:

Overall, based on the adjusted indirect comparison using the common comparator of crizotinib, there are neither favourable nor unfavourable effects of lorlatinib in comparison with brigatinib.

However, it should be noted that results usable for an indirect comparison are available only for the outcome of overall survival. For this outcome, there is no hint of an added benefit of lorlatinib because the indirect comparison shows no statistically significant difference. For the outcomes of morbidity, health-related quality of life, and side effects categories, no usable data are available for the indirect comparison. An adequate weighing of benefit and harm is made impossible by the lack of usable results on these outcome categories.

In summary, for adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor, there is no hint of added benefit of lorlatinib in comparison with brigatinib.

Table 3 summarizes the probability and extent of added benefit of lorlatinib.

Table 3: Lorlatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **brigatinib**	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of lorlatinib in comparison with the ACT in adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of lorlatinib

Therapeutic indication	**ACT**[a]
Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **brigatinib**

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The company followed the ACT specified by the G-BA by choosing brigatinib from the 2 options.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on lorlatinib (status: 10 January 2022)
- bibliographical literature search on lorlatinib (last search on 10 January 2022)
- search in trial registries / trial results databases for studies on lorlatinib (last search on 10 January 2022)
- search on the G-BA website for lorlatinib (last search on 10 January 2022)
- bibliographical literature search on the ACT (last search on 10 January 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 10 January 2022)
- search on the G-BA website for the ACT (last search on 10 January 2022)

To check the completeness of the study pool:

- search in trial registries for studies on lorlatinib (last search on 16 March 2022); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 28 March 2022); for search strategies, see Appendix A of the full dossier assessment

In agreement with the company's findings, the check of completeness of the study pool did not identify any studies suitable for a direct comparison of lorlatinib versus the ACT in this therapeutic indication.

Therefore, the company presented an adjusted indirect comparison according to Bucher [3] for assessing lorlatinib versus brigatinib using the common comparator of crizotinib. For the adjusted indirect comparison, the company identified the CROWN study on the intervention side and the ALTA-1L study on the brigatinib side.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: lorlatinib versus brigatinib

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Lorlatinib vs. crizotinib						
CROWN	Yes	Yes	No	Yes [4,5]	Yes [6,7]	Yes [8]
Brigatinib vs. crizotinib						
ALTA-1L	No	No	Yes	No	Yes [9,10]	Yes [11-16]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company. The ALTA-1L study has already been presented and assessed in a previous benefit assessment of brigatinib [12,13].

Figure 1 shows a schematic representation of the indirect comparison.

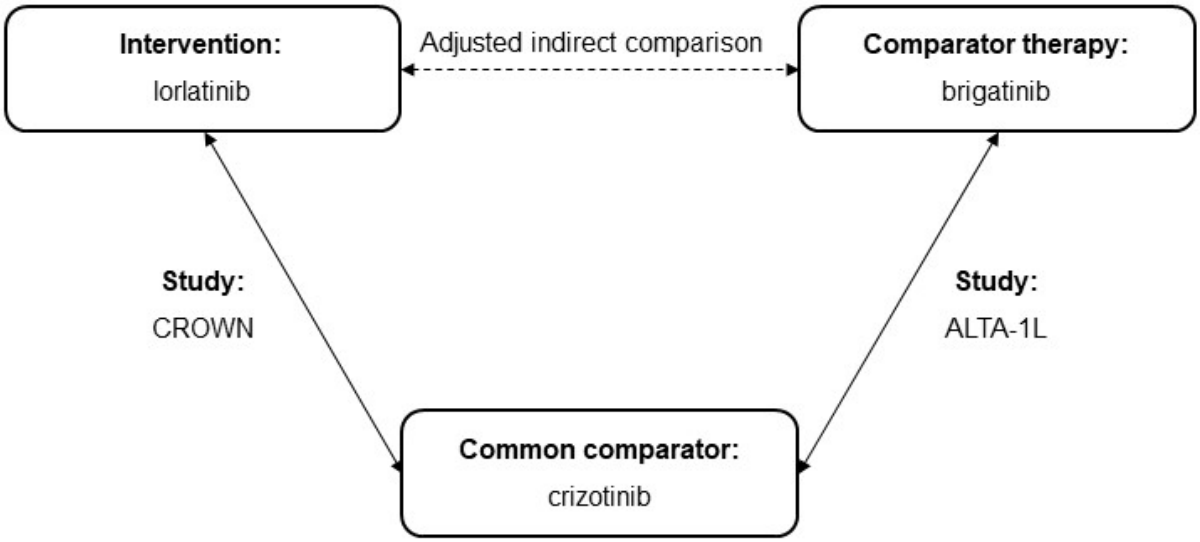

Figure 1: Study pool for the indirect comparison between lorlatinib and brigatinib

2.3.2 Study characteristics

2.3.2.1 Design of the CROWN and ALTA-1L studies

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: lorlatinib versus brigatinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Lorlatinib vs. crizotinib						
CROWN	RCT, open-label, parallel	Adults with ALK-positive[b], untreated[c] locally advanced (stage IIIB[d]) or metastatic (stage IV) NSCLC, with ECOG-PS ≤ 2	Lorlatinib (N = 149) Crizotinib (N = 147)	Screening: ≤ 28 days before randomization Treatment: until progression[e], withdrawal of consent, lost to follow-up, unacceptable toxicity, or end of study Observation[f]: outcome-specific, at most until death or end of study	104 centres in Argentina, Australia, Belgium, Canada, China, Czech Republic, France, Germany, Hong Kong, India, Italy, Japan, Korea, Mexico, Netherlands, Poland, Russia, Singapore, Spain, Taiwan, Turkey, United Kingdom, United States 04/2017 – ongoing Data cut-off[g]: 20 March 2020	Primary: PFS Secondary: mortality, morbidity, health-related quality of life, AEs
Brigatinib vs. crizotinib						
ALTA-1L	RCT, open-label, parallel	Adults with ALK-positive[h] locally advanced or recurrent (stage IIIB[d]) or metastatic (stage IV) NSCLC previously not treated with tyrosine kinase inhibitors (including ALK inhibitors), with ECOG PS ≤ 2	Brigatinib (N = 137) Crizotinib (N = 138)	Screening: ≤ 21 days before randomization Treatment: until disease progression[i], start of new antineoplastic treatment, withdrawal of consent, unacceptable toxicity, or end of study Observation[f]: outcome-specific, at most until death or end of study	92 study centres in Australia, Austria, Canada, Denmark, France, Germany, Hong Kong, Italy, Luxembourg, Netherlands, Norway, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States 05/2016–01/2021 1st data cut-off: 19/02/2018[j] 2nd data cut-off: 28/06/2019[k] Final data cut-off: 29/01/2021[l]	Primary: PFS Secondary: mortality, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: lorlatinib versus brigatinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Determined using the Ventana ALK (D5F3) CDx IHC test.
c. No prior systemic NSCLC therapy for locally advanced (stage IIIB not a candidate for multimodal treatment) or metastatic (stage IV) disease, including targeted molecular therapeutic agents (e.g. ALK tyrosine kinase inhibitor), angiogenesis inhibitors, immunotherapy, or chemotherapy. Prior treatment in a previous stage of NSCLC was allowed only if it had been completed more than 12 months before randomization.
d. and who are not candidates for definitive multimodal therapy.
e. Disease progression assessed by a blinded independent central review committee; patients with disease progression who are deemed by the investigator to exhibit clinical benefit of the study treatment are allowed to continue their allocated treatment, provided the treating physician has determined a favourable benefit-risk ratio.
f. Outcome-specific information is provided in Table 14.
g. First interim analysis was planned to occur after about 133 PFS events (75% of the 177 events expected by the end of the study) and was carried out after 127 PFS events (72%); further analyses are planned at 70% and 100% of the 198 expected events on overall survival (final analysis of overall survival).
h. Presence of at least 1 of the following 2 criteria: (1) documented positive result of a Vysis ALK Break Apart FISH Probe Kit or Ventana ALK (D5F3) CDx assay or (2) ALK rearrangement documented by a different test and adequate tissue available for central laboratory testing by an FDA-approved test; confirmation of central test positivity was not required prior to randomization.
i. Disease progression deemed by the investigator to require alternative therapy, or disease progression assessed by a blinded independent committee; treatment in the brigatinib arm was allowed to be continued beyond disease progression if the patient was deemed by the investigator continue to clinical benefit from it. At the investigator's discretion, patients in the crizotinib arm were allowed to receive brigatinib as subsequent therapy after disease progression.
j. First interim analysis planned to occur after 99 events (progression or death).
k. Second interim analysis planned to occur after 149 events (progression or death).
l. Final analysis about 3 years after inclusion of the last patient (study end).

AE: adverse event; ALK: anaplastic lymphoma kinase; CDx: companion diagnostic; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FISH: fluorescence in situ hybridization; IHC: immunohistochemstry; N: number of randomized patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, indirect comparison: lenvatinib versus brigatinib (multipage table)

Study	Intervention / comparator therapy	Common comparator
Lorlatinib vs. crizotinib		
CROWN	Lorlatinib: 100 mg once daily, orally	Crizotinib: 250 mg twice daily, orally
	Dose adjustments, treatment interruptions and discontinuation allowed due to intolerance[a]; stepwise dose reductions allowed to 75 mg and 50 mg once daily	Dose adjustments, treatment interruptions and discontinuation allowed due to intolerance[a]; initial dose reductions allowed to 200 mg twice daily, further reduction to 250 mg once daily if necessary
	Pretreatment Allowed: ▪ Prior systemic therapies for earlier stages of disease[b] Not allowed: ▪ Systemic NSCLC treatment of locally advanced (stage IIIB, not candidate for multimodal treatment) or metastatic (stage IV) disease, including angiogenesis inhibitors, immunotherapy, chemotherapy, or molecular targeted drugs (e.g. ALK tyrosine kinase inhibitor) ▪ Major surgery within 4 weeks before randomization ▪ Radiotherapy 2 weeks prior to randomization (e.g. stereotactic or partial-brain radiotherapy) ▪ Palliative radiotherapy outside the CNS within 48 hours prior to randomization ▪ Whole-brain radiotherapy 4 weeks prior to randomization ▪ Known strong CYP3A inhibitors[c], CYP3A and P-gp substrates with narrow therapeutic index, and strong CYP3A inducers within 12 days prior to the first dose of the study drug ▪ Experimental drugs within 2 weeks prior to study inclusion **Concomitant treatment** Allowed: ▪ Steady or decreasing dose of ≤ 10 mg prednisone daily or an equivalent for treatment of CNS metastases ▪ Medications for supportive treatment (e.g. antiemetics, analgesics, megestrol acetate in anorexia, bisphosphonates, or RANK ligands in osteoporosis and bone metastases) ▪ Palliative radiotherapy in certain foci of disease if medically necessary Disallowed: ▪ Other experimental medications ▪ Other systemic anticancer therapies, chemotherapy, and biologics ▪ Radiotherapy (except palliative therapy[d]) ▪ Select vitamins and herbal preparations ▪ Herbal drugs potentially influencing organ functions or the metabolism of the study drug or those with anticancer properties	

Table 7: Characteristics of the interventions – RCT, indirect comparison: lenvatinib versus brigatinib (multipage table)

Study	Intervention / comparator therapy	Common comparator
Brigatinib vs. crizotinib		
ALTA-1L	Brigatinib ▪ Days 1–7: 90 mg once daily, orally ▪ From Day 8: 180 mg once daily, orally	Crizotinib 250 mg twice daily, orally
	Dose adjustments, treatment interruptions, and treatment discontinuation allowed due to intolerance[a]; stepwise dose reductions to 120 mg, 90 mg, and 60 mg daily allowed	Dose adjustments, treatment interruptions, and treatment discontinuation allowed due to intolerance[a]; initial dose reductions to 200 mg twice daily, further reduction to 250 mg once daily if necessary
	Pretreatment Allowed: ▪ Maximum of 1 regimen of systemic therapy (except tyrosine kinase inhibitors) for locally advanced or metastatic NSCLC[e] Not allowed: ▪ Tyrosine kinase inhibitors, including ALK inhibitors ▪ Chemotherapy or radiotherapy (except stereotactic radiosurgery or radiation) within 14 days of the first dose of study medication ▪ Antineoplastic monoclonal antibodies within 30 days of the first dose of study medication **Concomitant treatment** Allowed: ▪ Local radiotherapy (e.g. stereotactic radiosurgery) for patients with central nervous system lesions with interruption of the study medication[f] ▪ Palliative therapy and supportive care for management of symptoms and underlying medical conditions Not allowed: ▪ Any other systemic anticancer therapy ▪ Drugs associated with the development of torsade de pointes tachycardia ▪ Extensive surgery requiring inpatient care	

a. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviation from the requirements of the SPC.
b. Allowed if completed more than 12 months prior to randomization.
c. Topical use of these medications (if applicable), e.g. ketoconazole cream, was allowed.
d. Palliative radiotherapy for the treatment of bone pain in bone lesions not localized at baseline was interpreted as disease progression.
e. Systemic therapy for ≥ 1 cycle. New maintenance therapy was counted as a new regimen. Neoadjuvant or adjuvant systemic therapy was counted as a prior therapy if this therapy was completed within 12 months prior to randomization.
f. In these patients, central nervous system lesions requiring radiotherapy were deemed disease progression.

ALK: anaplastic lymphoma kinase; CAR: constitutive androstane receptor; CNS: central nervous system; CYP: cytochrome P450; NSCLC: non-small cell lung cancer; P-gp: p-glycoprotein; PXR: pregnane X receptor; RCT: randomized controlled trial

CROWN study (with lorlatinib)

The CROWN study is an open-label RCT comparing lorlatinib versus crizotinib. The study included adult patients with previously untreated locally advanced or metastatic ALK-positive

NSCLC. Patients had to have a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 to 2. Patients with asymptomatic brain metastases were allowed to participate in the study. Systemic prior therapies, including therapy of the advanced or metastatic disease with a tyrosine kinase inhibitor, were disallowed. Only systemic prior therapies for the treatment of prior stages were allowed, provided they had been completed 12 months prior to study inclusion.

A total of 296 patients were randomly allocated in a 1:1 ratio to treatment with lorlatinib (N = 149) or crizotinib (N = 147). Randomization was stratified by the presence of brain metastases at baseline (yes/no) and ancestry (Asian/non-Asian).

Treatment in both study arms was largely in compliance with the respective SPC [17,18]. Patients were treated until disease progression, withdrawal of consent, unacceptable toxicity, lost to follow-up, or study end. However, both study arms allowed continuing treatment beyond disease progression as determined via RECIST, provided that the investigator deemed the treatment to still be of clinical benefit to the patient. The crizotinib SPC does not specify whether treatment beyond progression is allowed under certain conditions [17]. According to the lorlatinib SPC, treatment is to continue only until disease progression or unacceptable toxicity [18]. No information is available on the number of patients who were treated with the study medication beyond disease progression.

The study's primary outcome was PFS. Patient-relevant secondary outcomes were mortality, morbidity, health-related quality of life, and side effects outcomes.

ALTA-1L study (with brigatinib)

As described in dossier assessment A20-42 [13], the ALTA-1L study is an open-label RCT comparing brigatinib with crizotinib. The study included adult patients with ALK-positive, locally advanced, recurrent, or metastatic NSCLC. Patients' general condition had to correspond to an ECOG-PS of 0 to 2. Patients with asymptomatic brain metastases were allowed to participate in the study. Regarding prior therapy, no more than 1 regimen of prior systemic therapy for advanced or metastatic disease was allowed. This count did not include any prior tyrosine kinase inhibitor therapy.

A total of 275 patients were randomly allocated in a 1:1 ratio to treatment with brigatinib (N = 137) or crizotinib (N = 138). Randomization was stratified by the presence of brain metastases at baseline (yes/no) and prior chemotherapy for the treatment of advanced or metastatic disease (yes/no).

Treatment in both study arms was conducted without relevant deviations from the requirements of the SPCs [17,19]. Patients were treated until disease progression, start of new antineoplastic treatment, withdrawal of consent, unacceptable toxicity, or end of study. In line with the SPC; the brigatinib arm allowed continuing treatment beyond disease progression as determined by RECIST, provided that the investigator deemed the treatment to still be of clinical benefit to

the patient. At the investigator's discretion and in compliance with approval, patients in the crizotinib arm were allowed to receive brigatinib as subsequent therapy after disease progression.

The study's primary outcome was PFS. Patient-relevant secondary outcomes were mortality, morbidity, health-related quality of life, and side effects outcomes.

2.3.2.2 Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, indirect comparison: lorlatinib versus brigatinib

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Lorlatinib vs. crizotinib	
CROWN	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13) and health status (EQ-5D VAS)	Until 28 days after the last dose of the study medication or until initiation of a subsequent therapy (whichever occurred first)
Health-related quality of life (EORTC QLQ-C30)	Until 28 days after the last dose of the study medication or until initiation of a subsequent therapy (whichever occurred first)
Side effects	
AEs	Until 28 days after the last dose of the study medication or until initiation of a subsequent therapy (whichever occurred first)
SAEs	Until 28 days after the last dose of the study medication
Brigatinib vs. crizotinib	
ALTA-1L	
Mortality	
Overall survival	Until death, loss of patient contact, or withdrawal of consent
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Until 30 days after the last dose of the study medication[a]
Health-related quality of life (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication[a]
Side effects	
All outcomes in the side effects category	Until 30 days after the last dose of the study medication[a]

a. At the investigator's discretion and in compliance with approval, patients in the crizotinib arm were allowed to receive brigatinib as subsequent therapy after disease progression. For these patients, the date of the last dose of the study medication corresponds to the date of the last dose of brigatinib.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In both studies, the observation durations for the morbidity, health-related quality of life, and side effects outcomes are systematically shortened because they were surveyed only for the period of treatment with the study drug (plus 28 days in the CROWN study or 30 days in the ALTA-1L study). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

2.3.2.3 Data cut-offs

CROWN study

The CROWN study started in April 2017 and is still ongoing. The company has presented analyses on the 20 March 2020 data cut-off. This is the 1st interim analysis, which was planned to occur after 133 PFS events. This data cut-off was used for the benefit assessment.

Study ALTA-1L

The ALTA-1L study started in May 2016 and has already been completed. A total of 3 data cut-offs were implemented:

- The 1st data cut-off (19 February 2018) is a predefined interim analysis conducted after about 99 events (progression or death).
- The 2nd data cut-off (28 June 2019) is a predefined interim analysis conducted after about 149 events (progression or death).
- The 3rd data cut-off (29 January 2021) represents the predefined final analysis at study end, about 3 years after inclusion of the last patient.

The company's dossier presents analyses of the 2nd data cut-off, which it used for the adjusted indirect comparison. For the outcomes of overall survival and PFS, the company presented additional analyses on the 3rd data cut-off. The company justifies its use of the 2nd data cut-off for the adjusted indirect comparison with a substantially longer duration of follow-up observation and consequently substantially increased informative value.

The company's reasoning is not plausible because, as reported by the company, a data cut-off at study end exists and is associated with a longer follow-up duration.

In the present situation, comprehensive analyses of the 2nd data cut-off are available for all relevant outcomes from brigatinib dossier assessment procedure [12-14]. For the 3rd data cut-off, in contrast, only limited data are available from a publication [11]; these data lack, e.g. adequate analyses of adverse events (AEs). However, where results are available from the 3rd data cut-off, the data suggest that the results from the 2nd and 3rd data cut-offs do not differ to a relevant extent for patient-reported outcomes or for AE outcomes. Further, the observation duration of the ALTA-1L study's 2nd data cut-off is already longer than that of the entire CROWN study. Given the specific available evidence, the 2nd data cut-off of the ALTA-1L study is therefore suitable for assessing these outcomes.

In the present benefit assessment, the final 3rd data cut-off was used for the outcome of overall survival. For the above reasons, the 2nd data cut-off was used for the remaining outcomes. Irrespective of the data cut-off, however, no indirect comparison is possible for these outcomes due to insufficient similarity of operationalizations (see Section 2.3.3 for the planned duration of follow-up observation).

2.3.2.4 Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: lorlatinib versus brigatinib (multipage table)

Study	CROWN		ALTA-1L	
Characteristic Category	Lorlatinib	Crizotinib	Brigatinib	Crizotinib
	N[a] = 149	N[a] = 147	N[a] = 137	N[a] = 138
Age [years], mean (SD)	59 (13)	56 (14)	58 (13)	59 (11)
Sex [f/m], %	56/44	62/38	50/50	59/41
Ancestry, n (%)				
White	72 (48)	72 (49)	76 (55)	86 (62)
Asian	65 (44)	65 (44)	59 (43)	49 (36)
Other/unknown	12 (8)	10 (7)[b]	2 (1)	3 (2)
Region, n (%)				
Europe	72 (48)	70 (48)	69 (50)	74 (54)
Asia-Pacific	ND	ND	58 (42)	49 (36)
North America	ND	ND	10 (7)	15 (11)
ECOG-PS, n (%)				
0	67 (45)	57 (39)	54 (39)	53 (38)
1	79 (53)	81 (55)	76 (55)	78 (57)
2	3 (2)	9 (6)	7 (5)	7 (5)
Smoking status, n (%)				
Never-smoker	81 (54)	94 (64)	84 (61)	75 (54)
Former	55 (37)	43 (29)	50 (36)	56 (41)
Active	13 (9)	9 (6)	3 (2)	7 (5)
Histology, n (%)				
Adenocarcinoma	140 (94)	140 (95)	126 (92)	137 (99)
Other/unknown	9 (6)	7 (5)	11 (8)	1 (1)
Disease stage at baseline, n (%)				
Locally advanced	14 (9)	8 (5)	8 (6)	12 (9)
Metastatic	135 (91)	139 (95)	129 (94)	126 (91)
Time since first diagnosis [months]				
Mean (SD)	ND	ND	10 (23)	13 (28)
Median [min; max]	ND	ND	1.6 [0.1; 145.3]	1.4 [0.3; 189.8]
Brain metastases at baseline, n (%)[c]				
Yes	38 (26)	40 (27)	41 (30)	40 (29)
No	107 (72)[b]	104 (71)[b]	96 (70)	98 (71)

Table 9: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: lorlatinib versus brigatinib (multipage table)

Study	CROWN		ALTA-1L	
Characteristic Category	Lorlatinib	Crizotinib	Brigatinib	Crizotinib
	N[a] = 149	N[a] = 147	N[a] = 137	N[a] = 138
Prior antineoplastic treatments, n (%)[d]				
Systemic therapy[e,f]	12 (8)	9 (6)	36 (26)	37 (27)
Radiotherapy	20 (13)	20 (14)	33 (24)	40 (29)
Radiotherapy of the CNS	ND	ND	18 (13)	19 (14)
Treatment discontinuation, n (%)	46 (31)[g]	111 (78)[g]	61 (45)[h, i]	114 (83)[h, i]
Study discontinuation, n (%)	ND	ND	47 (34)[j]	31 (22)[j]

a. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding row if the deviation is relevant.
b. Institute's calculation.
c. The information on the CROWN study is based on the evaluation at baseline by a blinded independent review committee; the information on the ALTA-1L study are based on the investigator-assessed status at baseline.
d. Multiple responses allowed.
e. The information on the ALTA-1L study concerns chemotherapies; for the CROWN study, the types of systemic therapies are unclear.
f. In the CROWN study, 1 patient had received systemic therapy for the treatment of advanced or metastatic disease, while in the ALTA-1L study, nearly 27% of patients had received chemotherapy for the treatment of advanced or metastatic disease.
g. Common reasons for treatment discontinuation in the lorlatinib versus crizotinib arm: disease progression (17% vs. 56%), AEs (7% vs. 8%), patient decision (3% vs. 6%).
h. Data are based on the 2nd data cut-off (28 June 2019): common reasons for treatment discontinuation in the brigatinib versus crizotinib arms: disease progression (26% vs. 68%), AEs (9% vs. 7%), patient decision (3% vs. 4%).
i. At the time of the 3rd data cut-off (29 January 2021), 78 patients (57%) in the brigatinib arm and 212 patients (88%) in the crizotinib arm had discontinued therapy. Common reasons for treatment discontinuation in the brigatinib arm versus crizotinib arm were: disease progression (35% vs. 73%), AEs (12% vs. 7%), patient decision (3% vs. 5%).
j. Data are based on the 2nd data cut-off (28 June 2019); main reason for study discontinuation in the brigatinib arm versus crizotinib arm: patient death (24% vs. 18%); no information available on the 3rd data cut-off (29 January 2021).

CNS: central nervous system; ECOG–PS: Eastern Cooperative Oncology Group – Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

CROWN

Patient characteristics are balanced between the study arms. The patients' mean age was approximately 58 years, and the majority were White (approximately 44%) or Asian (44%). Women made up 56% of lorlatinib arm and 62% of crizotinib arm participants. At baseline, 2% of patients in the lorlatinib arm and 6% in the crizotinib arm had an ECOG-PS of 2, and almost all of them were in the metastatic disease stage (> 90%). Approximately 26% of patients had brain metastases. Almost 10% of patients had received prior systemic therapy, and all except 1 patient received it exclusively for (neo)adjuvant treatment, as specified in the inclusion criteria.

A marked difference was found in the proportion of patients with treatment discontinuation. Treatment was discontinued by 31% of patients in the lorlatinib arm and 78% of the crizotinib arm. The most common reason for treatment discontinuation in both study arms was disease progression. No data about study discontinuation are available for the CROWN study.

ALTA-1L

Patient characteristics between the 2 treatment arms of the ALTA-1L study were balanced. The mean age of the patients was about 59 years, and the majority (approximately 59%) were White. Women made up 50% of brigatinib arm and 59% of crizotinib arm participants. A total of 5% of included patients had an ECOG-PS of 2. Over 90% of patients were in the metastatic stage of disease at baseline. Approximately 30% of patient had brain metastases. Just under 27% of patients had already received chemotherapy for the treatment of the advanced or metastatic disease.

At the time of the 2nd data cut-off (28 June 2019), there was a substantial difference between treatment arms in the proportion of patients with treatment discontinuation (45% in the brigatinib arm versus 83% in the crizotinib arm). At the final data cut-off (29 January 2021), 57% of patients in the brigatinib arm and 88% of patients in the crizotinib arm had discontinued therapy. In both study arms, the most common reason for treatment discontinuation was disease progression.

2.3.2.5 Treatment duration and observation period

Table 10 shows patients' mean and median treatment durations and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: lorlatinib versus brigatinib (multipage table)

Comparison **Study** **Duration of the study phase** **Outcome category**	**Lorlatinib/brigatinib**	**Crizotinib**
Lorlatinib vs. crizotinib		
CROWN		
Treatment duration [months]	N = 149	N = 142
Median [Q1; Q3]	16.7 [12.9; 22.4]	9.6 [4.7; 14.5]
Mean (SD)	ND	ND
Observation period [months]	N = 149	N = 147
Overall survival		
Median [Q1; Q3]	20.0 [16.4; 24.9]	19.8 [15.0; 24.2]
Mean (SD)	ND	ND
Morbidity, health-related quality of life, side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Brigatinib vs. crizotinib		
ALTA-1L (2nd data cut-off 28 June 2019)		
Treatment duration [months]	N = 136	N = 137
Median [min; max]	24.3 [0.1; 34.6]	8.4 [0.1; 36.0]
Mean (SD)	19.0 (11.2)	12.0 (9.6)
Observation period [months]	N = 137	N = 138
Overall survival		
Median [min; max]	27.0 [ND]	27.3 [ND]
Mean (SD)	ND	ND
Morbidity, health-related quality of life		
Median [min; max]	24.0 [ND]	21.3 [ND]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	25.1 [ND]	20.4 [ND]
Mean (SD)	ND	ND
ALTA-1L (3rd data cut-off 29 January 2021)		
Treatment duration [months]	N = 137	N = 138
Median [min; max]	34.9 [0.1; 52.4]	9.3 [0.1; 51.5]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, indirect comparison: lorlatinib versus brigatinib (multipage table)

Comparison	**Lorlatinib/brigatinib**	**Crizotinib**
Study		
Duration of the study phase		
Outcome category		

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC30: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SD: standard deviation

In the CROWN study, the median treatment duration was about twice as long in the intervention arm as in the comparator arm (median: 16.7 vs. 9.6 months). The median observation duration for the outcome of overall survival is comparable between the treatment arms. No information on the observation duration was available for the outcomes of the morbidity, health-related quality of life, and side effects categories. The observation duration for these categories is linked to treatment duration (plus 28 days, see Table 8). For these outcomes, therefore, the observation duration, like treatment duration, is presumably almost twice as long in the lorlatinib arm as in the crizotinib arm.

In the ALTA-1L study, the median treatment duration at the 2nd data cut-off (28 June 2019) was about 3 times as long in the comparator arm as in the intervention arm (median: 24.3 versus 8.4 months). The median observation duration for the outcome of overall survival is comparable between the treatment arms. Since the observation duration for the morbidity, health-related quality of life, and side effects outcome categories are linked to treatment duration (see Table 8), the observation durations are also longer in the brigatinib arm than in the crizotinib arm. However, it has been found that the treatment arms differ notably less in observation durations regarding the outcomes of the morbidity, health-related quality of life, and side effects than they do in treatment durations. This is due to the fact that, in the crizotinib arm, the observation of these outcomes was continued if patients received subsequent therapy in the context of the allowed treatment switching with brigatinib (see Table 8). At the time of the 3rd data cut-off (29 January 2021), the ALTA-1L study's median treatment duration was almost 4 times longer in the intervention arm than in the comparator arm (median: 34.9 versus 9.3 months). For this data cut-off, no data are available on the observation duration for the outcome of overall survival.

At the ALTA-1L study's 2nd data cut-off, the individual studies already differ in observation durations. However, this is of no consequence for the indirect comparison of the 2 studies. Assuming proportional hazards, the observation duration does not affect the point estimation of the effect given the analysis method chosen here for the indirect comparison (Cox proportional hazards model). Since hypothesizing such model seems plausible, the adjusted indirect comparison can be carried out and assessed despite the between-study differences in observation durations.

2.3.2.6 Subsequent therapies

Table 11 and Table 12 show the subsequent therapies patients received after discontinuation of the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: brigatinib versus crizotinib (CROWN)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)** **Lorlatinib** **N = 149**	 **Crizotinib** **N = 147**
CROWN		
Total, n (%)	26 (17.4)	86 (58.5)
ALK inhibitor, n (%)[a]	17 (11.4[b])	79 (53.7[b])
Alectinib	9 (6.0[b])	53 (36.1[b])
Brigatinib	1 (0.7[b])	17 (11.6[b])
Crizotinib	4 (2.7[b])	4 (2.7[b])
Ceritinib	2 (1.3[b])	2 (1.4[b])
Lorlatinib	1 (0.7[b])	3 (2.0[b])
Chemotherapy ± antiangiogenesis therapy, n (%)[a]	8 (5.4[b])	3 (2.0[b])
Immunotherapy, n (%)[a]	1 (0.7[b])	0 (0)
Other therapy, n (%)[a]	0 (0)	4 (2.7[b])

a. Data refer to the 1st subsequent therapy.
b. Institute's calculation.

ALK: anaplastic lymphoma kinase; n: number of patients with at least 1 subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: brigatinib versus crizotinib (ALTA-1L)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Brigatinib **N = 136**	**Crizotinib** **N = 137**
ALTA-1L (2nd data cut-off dated 28 June 2019)		
Total	ND	ND
Surgery	0 (0)	2 (1.5)
Radiotherapy	1 (0.7)	10 (7.3)
Systemic therapy	35 (25.7)	97 (70.8)
ALK inhibitor	31 (22.8)	93 (67.9)
Alectinib	10 (7.4)	24 (17.5)
Brigatinib	1 (0.7)	73 (53.3)[a]
Ceritinib	4 (2.9)	5 (3.6)
Crizotinib	11 (8.1)	5 (3.6)
Lorlatinib	14 (10.3)	12 (8.8)
Chemotherapy	15 (11.0)	16 (11.7)
Carboplatin	7 (5.1)	10 (7.3)
Cisplatin	6 (4.4)	4 (2.9)
Docetaxel	3 (2.2)	0 (0)
Erlotinib	1 (0.7)	0 (0)
Etoposide	1 (0.7)	0 (0)
Gemcitabine	2 (1.5)	4 (2.9)
Paclitaxel	1 (0.7)	1 (0.7)
Pemetrexed	11 (8.1)	11 (8.0)
Vinorelbine	0 (0)	1 (0.7)

a. According to the study protocol, switching from the crizotinib arm to intervention arm treatment with brigatinib was allowed in case of disease progression. By the 2nd data cut-off, this option had been taken by 61 patients (44.2%). The remaining 12 patients with brigatinib subsequent therapy presumably received it outside the context of the described treatment switching.

ALK: anaplastic lymphoma kinase; n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

The subsequent therapy received by most patients of both study arms was ALK inhibitors. In the CROWN study, most patients in the crizotinib arm received alectinib (36.1%), followed by brigatinib (11.6%); in the lorlatinib arm, most received alectinib (6.0%) followed by crizotinib (2.7%). In the ALTA-1L study, the majority of crizotinib arm participants received brigatinib (53.3%) followed by alectinib (17.5%); in the brigatinib arm, most received lorlatinib (10.3%) followed by crizotinib (8.1%) and alectinib (7.4%).

2.3.3 Similarity of the studies for the indirect comparison

Similarity of study conduct

Study design

Both included studies are multicentre, open-label RCTs which included adults with ALK-positive, locally advanced or metastatic NSCLC who were not previously treated with an ALK inhibitor.

The periods during which the studies were conducted are comparable as well. The ALTA-1L study started in May 2016 and ended in January 2021, whereas the CROWN study began in April 2017 and is currently ongoing.

Planned duration of follow-up observation – majority of outcomes exhibiting dissimilar operationalizations

Information on the planned duration of follow-up observation in the 2 studies is found in Section 2.3.2.2.

In both studies, the morbidity, health-related quality of life, and side effects outcomes were to be surveyed until 28 or 30 days after the last administration of the study medication. According to the ALTA-1L study protocol, patients in the crizotinib arm were allowed to switch to the intervention arm treatment with brigatinib in case of disease progression, and if they did, they were followed up for said outcomes for up to 30 days after the last brigatinib administration. At the time of the 2nd data cut-off, 61 patients (44.2%) of the ALTA-1L study's crizotinib arm had switched to brigatinib treatment, thereby taking advantage of the treatment switching option. Hence, even beyond the crizotinib treatment, a relevant percentage of patients in the ALTA-1L study's crizotinib arm continued to be observed under subsequent therapy with brigatinib for the outcomes regarding morbidity, health-related quality of life, and side effects. In the CROWN study, by contrast, the observation of these outcomes ended with the discontinuation of crizotinib treatment. Due to the described difference in follow-up observation, the affected outcomes' operationalizations are insufficiently similar, thereby precluding the interpretation of results. This applies to all patient-relevant outcomes of the morbidity, health-related quality of life, and side effects categories. The data available on said outcomes are therefore unusable, and a indirect comparison was foregone.

Irrespective of the dissimilar operationalizations, the risk of bias would be high for the results of all identified outcomes in the ALTA-1L study, in part due to the above-mentioned selective follow-up observation in the crizotinib arm. Likewise, lack of blinding in the presence of subjective recording of outcomes regarding the morbidity, health-related quality of life, and discontinuation due to AEs as well as incomplete observation for potentially informative reasons regarding the serious AEs (SAEs) and severe AEs outcomes would lead to a high risk of bias for the results of both the ALTA-1L and CROWN studies. For the results of all outcomes except overall survival, the risk of bias is therefore high in both studies. Irrespective of the

operationalizations' insufficient similarity, the certainty of results criterion for adjusted indirect comparisons would therefore not be met.

Similarity of the patient population

Patient characteristics

Section 2.3.2.4 provides information on patient characteristics.

The demographic and clinical characteristics of the included patients are sufficiently comparable between the CROWN and ALTA-1L studies.

Prior treatment

The 2 studies differ in prior treatment. While the CROWN study did not allow any systemic prior treatment in the advanced stage, the ALTA-1L study permitted up to 1 systemic therapy in the advanced stage. Nearly 27% of patients in the ALTA-1L study had received prior chemotherapy in the advanced stage. While this difference does not generally call into question the studies' similarity, it is accounted for in the interpretation of results.

Subsequent therapies

Section 2.3.2.6 provides information on subsequent therapies.

In the CROWN study, most crizotinib arm participants received subsequent therapy with alectinib (36.1%) and brigatinib (11.6%), while the ALTA-1L study, they received brigatinib (11.6%) and alectinib (17.5%). The discrepancy in the frequency of use of the drugs between the 2 studies' crizotinib arms can be explained by the fact that patients in the ALTA-1L study's crizotinib arm were allowed to switch to brigatinib within the study after disease progression. Both brigatinib and alectinib are 2nd generation ALK inhibitors and are equally recommended by the S3 guideline [20] as subsequent therapies after initial ALK inhibitor therapy. Overall, a slightly higher percentage of ALTA-1L participants than CROWN participants received subsequent therapy. Taking into account the ALTA-1L study's longer observation duration already at the 2nd data cut-off and the correspondingly higher percentage of patients with treatment discontinuation, this difference appears plausible and does not call into question the studies' similarity.

Similarity of the common comparator

With regard to dosage and possible dose reduction or interruption, the common comparator crizotinib was administered in a comparable way in both studies, without relevant deviations from the SPC (see Table 7). For the common comparator of crizotinib, the similarity between the CROWN study and the ALTA-1L study was therefore generally sufficient.

Summary of the comparability of studies

In all, the CROWN and ALTA-1L studies exhibit differences in both the planned duration of follow-up observation and in patients' prior treatment. These differences do not fundamentally call into question a similarity sufficient for conducting an adjusted indirect comparison via the

common comparator of crizotinib. However, the differences in the planned duration of follow-up observation leads to insufficient similarity in the operationalizations of the morbidity, health-related quality of life, and side effects outcomes, whose observation is linked to treatment duration. Hence, no indirect comparison is conducted for said outcomes.

This concurs with the company's assessment to the extent that the company deems the CROWN and ALTA-1L studies to be sufficiently similar for conducting an adjusted indirect comparison. The company did not address the aspect of different durations of planned follow-up observation. With regard to differences in prior treatment, the company submitted sensitivity analyses on individual outcomes for which analyses of ALTA-1L participants without prior treatment are available from subgroup analyses in the brigatinib dossier assessment. No such analyses are available for the outcome of overall survival.

2.3.4 Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, indirect comparison: lorlatinib versus brigatinib

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Lorlatinib vs. crizotinib							
CROWN	Yes	Yes	No	No	Yes	Yes	Low
Brigatinib vs. crizotinib							
ALTA-1L	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

2.3.5 Transferability of the study results to the German health care context

For both studies, the company presumes good transferability of the individual study results to the German health care context. To substantiate this view, the company cites (a) the sex distribution of study participants being similar to data from the German healthcare context, (b) a younger patient age being expected for ALK-positive NSCLC when compared to the mean age at onset for NSCLC in general, and (c) the dosages of each of the drugs being line with the SPC, which corresponds to routine practice in Germany. In addition, nearly half of the CROWN participants and the majority of ALTA-1L participants were of White ancestry, and many patients were enrolled in European study centres.

The company has provided no further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the EORTC QLQ-C30 and QLQ-LC13
  - health status (EQ-5D VAS)
- Health-related quality of life
  - surveyed with the EORTC QLQ-HCC18 functioning scales
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 14 shows the outcomes for which data are available in the included studies and states whether an indirect comparison is possible based on the available data.

Table 14: Matrix of outcomes – RCT, indirect comparison: lorlatinib versus crizotinib

Comparison / Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Lorlatinib vs. crizotinib									
CROWN	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	No[c]
Brigatinib vs. crizotinib									
ALTA-1L	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	No[c]
Indirect comparison possible	Yes	No[e]	No[e]	No	No[e]	No[e]	No[e]	No[e]	No[c]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The outcome was recorded in the CROWN study, but no adequate analyses are available for it.
c. No specific AEs were selected because no indirect comparison is conducted for the side effects outcomes due to insufficient similarity.
d. Outcome not recorded.
e. Due to insufficient similarity, the present assessment does not include an indirect comparison regarding this outcome (see Section 2.3.3 on planned duration of follow-up observation).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer Module 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No indirect comparison is possible for the outcome of health status because it was not recorded in the ALTA-1L study.

For the symptoms, health-related quality of life, and side effects outcomes, no indirect comparison is possible due to insufficient similarity (see Section 2.3.3 on the planned duration of follow-up observation). For this reason, a selection of specific AEs was foregone as well.

Outcome of time to central nervous system (CNS) progression

In the present therapeutic indication, CNS metastases are of particular significance. In both studies, the outcome of time to CNS progression was defined as the time from randomization until the first radiological evidence of CNS disease progression (progression of brain metastases already existing at baseline and/or development of new brain metastases). Radiological evidence was assessed by a blinded independent committee based on (modified) RECIST criteria. Thus, the assessment was based exclusively on imaging technology and did not take

into account any symptoms noticeable by patients. This operationalization of the outcome is therefore not directly patient-relevant.

Irrespective of patient relevance, these results can be interpreted only to a limited extent or not at all for the adjusted indirect comparison due to the following methodological reasons:

- For the outcome of CNS progression, ALTA-1L participants were observed only until the last dose of the study medication, disease progression, or the start of a new systemic anticancer therapy. CROWN participants were observed for the outcome of CNS progression only until disease progression. Hence, the 2 studies surveyed the outcome (a) for different periods and (b) only for a systematically shortened observation period. This also means that patients with prior non-CNS progression were censored for the outcome of CNS progression. Hence, only some of the CNS progressions were recorded, i.e. only those which occurred before non-CNS disease progression.
- As was the case for the symptoms, health-related quality of life, and side effects outcomes, no indirect comparison is possible for the analyses submitted by the company on the outcome of time to CNS progression because of insufficient similarity (see Section 2.3.3 on the planned duration of follow-up observation).

2.4.2 Risk of bias

Table 15 presents the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: lorlatinib versus brigatinib

Comparison Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
Lorlatinib vs. crizotinib										
CROWN	L	L	_[b]	_[b]	_[c]	_[b]	_[b]	_[b]	_[b]	_[d]
Brigatinib vs. crizotinib										
ALTA-1L	L	L	_[b]	_[b]	_[c]	_[b]	_[b]	_[b]	_[b]	_[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Due to insufficient similarity, the present assessment does not include an indirect comparison regarding this outcome (see Section 2.3.3 on the planned duration of follow-up observation).
c. No indirect comparison is possible because the outcome was not recorded in the ALTA-1L study.
d. No specific AEs were selected because for the side effects outcomes, no indirect comparison is carried out due to insufficient similarity.

ACT: appropriate comparator therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; H: high; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No indirect comparison can be conducted for outcomes which do not exhibit sufficient similarity or which were not recorded in at least 1 of the 2 studies of the indirect comparison. Hence, the risk of bias was not assessed for these outcomes. Irrespective of this, Section 2.3.3 on the planned duration of follow-up observation described potential aspects of bias for the results of the outcomes which do not exhibit sufficient similarity.

In the present scenario, an indirect comparison can be conducted only for the outcome of overall survival. For both studies, this results in a low risk of bias for the results on overall survival.

2.4.3 Results

Table 16 summarizes the results of the comparison of lorlatinib with brigatinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: lorlatinib versus brigatinib

Outcome category Outcome Comparison Study	Lorlatinib or brigatinib N	Lorlatinib or brigatinib Median time to event in months [95% CI] Patients with event n (%)	Crizotinib N	Crizotinib Median time to event in months [95% CI] Patients with event n (%)	Group difference HR [95% CI]; p-value
Mortality					
Overall survival					
Lorlatinib vs. crizotinib					
CROWN	149	NR 23 (15.4)	147	NR 28 (19.0)	0.72 [0.41; 1.25]; 0.240[a]
Brigatinib vs. crizotinib					
ALTA-1L (3rd data cut-off, 29 January 2021)	137	ND[b] 41 (30.0)	138	ND[b] 51 (37.0)	0.81 [0.53; 1.22]; 0.305[c]
Indirect comparison using common comparators[d]:					
Lorlatinib or brigatinib					0.89 [0.44; 1.77]; 0.736[e, f]
Morbidity					
Symptoms (EORTC QLQ-C30)	No indirect comparison due to insufficient similarity				
Symptoms (EORTC QLQ-LC13)	No indirect comparison due to insufficient similarity				
Health status (EQ-5D VAS)	No data for the indirect comparison[g]				
Health-related quality of life	No indirect comparison due to insufficient similarity				
Side effects	No indirect comparison due to insufficient similarity				

a. Cox proportional hazards model adjusted and log rank test stratified concerning the presence of CNS metastases at baseline (yes/no) and ancestry (Asian/non-Asian).
b. The information available in Module 4 A indicates the probability of survival after 3 years (see [11]), but not median time to event).
c. Cox proportional hazards model and log rank test stratified by the presence of CNS metastases at baseline (yes/no) and prior chemotherapy for the treatment of advanced or metastatic disease (yes/no).
d. Indirect comparison according to Bucher [3].
e. Institute's calculation.
f. The analysis of the ALTA-1L study's 2nd data cut-off (28 June 2019) shows a consistent result for the indirect comparison: HR: 0.79; 95% CI: [0.38; 1.64].
g. The outcome was recorded only in the CROWN study.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; ND: no data; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13

One RCT was found on each side of the available adjusted indirect comparison. Hence, homogeneity was not checked. As there is no directly comparative study for the comparison of lorlatinib versus the ACT, it is impossible to check the consistency of results. Therefore, the adjusted indirect comparison has at most a low certainty of results. Consequently, at most hints, e.g. of an added benefit, can be derived on the basis of the data available from the adjusted indirect comparison.

Mortality

Overall survival

For the outcome of overall survival, the adjusted indirect comparison shows no statistically significant difference between lorlatinib and brigatinib. This results in no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)

Due to the insufficient similarity of operationalization of outcomes in the 2 studies, no data usable for an adjusted indirect comparison are available for the symptoms outcomes (see Section 2.3.3 on the planned duration of follow-up observation). For each of the symptoms outcomes, this results in no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven for any of them.

Health status (EQ-5D VAS)

The outcome of health status was recorded only in the CROWN study. Therefore, an adjusted indirect comparison is not possible for this outcome. This results in no hint of an added benefit of lorlatinib in comparison with brigatinib; an added benefit is therefore not proven.

Health-related quality of life, side effects

Due to the insufficient similarity of the 2 studies with regard to the operationalization of outcomes, no data usable for an adjusted indirect comparison are available for the health-related quality of life and side effects outcomes (see Section 2.3.3 on the planned duration of follow-up observation). This results in no hint of an added benefit of lorlatinib in comparison with brigatinib for either of these outcomes; an added benefit is therefore not proven for either of them.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present assessment:

- age (< 65 versus ≥ 65 years)
- sex (female versus male)
- brain metastases at baseline (yes versus no)

In the CROWN study, all listed subgroup characteristics and cutoffs for the outcome of overall survival were predefined. The ALTA-1L study did not specifically predefine any subgroup characteristics. Nevertheless, subgroup analyses of sensitivity were to be conducted for all potential prognostic factors at baseline, including the above-mentioned subgroup characteristics.

This benefit assessment takes into account only subgroup analyses on the outcome of overall survival because it is the only outcome for which an adjusted indirect comparison can be carried out. For the indirect comparison, the results on the final 3rd data cut-off are used for the ALTA-1L study, whereas the company analysed the 2nd data cut-off (see Section 2.3.2.3). The company's Module 4 A therefore presents exclusively subgroup analyses, taking into account the ALTA-1L study's 2nd data cut-off. With regard to the above-mentioned effect modifiers, the publication for the ALTA-1L study's 3rd data cut-off [11] presents results for the individual subgroups only regarding the characteristic of brain metastases at baseline. For this characteristic, the subgroup analysis was calculated by the Institute, taking into account the ALTA-1L study's final data cut-off.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if a statistically significant and relevant effect is in place in at least 1 subgroup.

The Institute's calculation showed no relevant effect modification with regard to the characteristic of brain metastases at baseline for the outcome of overall survival.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4 (see Table 17).

Table 17: Extent of added benefit at outcome level: lorlatinib versus brigatinib

Outcome category **Outcome**	**Lorlatinib vs. brigatinib** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Total observation period		
Mortality		
Overall survival	NR vs. ND HR: 0.89 [0.44; 1.77]; p = 0.736	Lesser/added benefit not proven
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No indirect comparison due to insufficient similarity	Lesser/added benefit not proven
Symptoms (EORTC QLQ-LC13)	No indirect comparison due to insufficient similarity	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No indirect comparison due to insufficient similarity	Lesser/added benefit not proven
Side effects		
SAEs	No indirect comparison due to insufficient similarity	Greater/lesser harm not proven
Severe AEs	No indirect comparison due to insufficient similarity	Greater/lesser harm not proven
Discontinuation due to AEs	No indirect comparison due to insufficient similarity	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The outcome was recorded only in the CROWN study.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of lorlatinib in comparison with brigatinib

Favourable effects	**Unfavourable effects**
–	–
For the outcomes of the morbidity, health-related quality of life, and side effects categories, no usable data are available for the indirect comparison.	

Overall, based on the adjusted indirect comparison using the common comparator of crizotinib, there are neither favourable nor unfavourable effects of lorlatinib in comparison with brigatinib.

However, it should be noted that results usable for an indirect comparison are available only for the outcome of overall survival. For this outcome, there is no hint of an added benefit of lorlatinib because the indirect comparison shows no statistically significant difference. For the outcomes of the morbidity, health-related quality of life, and side effects categories, no usable data are available for the indirect comparison. An adequate weighing of benefit and harm is made impossible by the lack of usable results on these outcome categories.

In summary, for adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor, there is no hint of added benefit of lorlatinib in comparison with brigatinib.

Table 19 summarizes the result of the assessment of added benefit of lorlatinib in comparison with the ACT.

Table 19: Lorlatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **brigatinib**	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

The assessment described above deviates from that by the company, which derived a hint of considerable added benefit.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-31.html.