IQWiG Reports – Commission No. A20-42

Brigatinib (non-small cell lung cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Brigatinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2020). Please note: This translation 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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
EORTC	European Organisation for Research and Treatment of Cancer
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
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

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) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug brigatinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 April 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

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

The ACT specified by the G-BA is shown in Table 2.

Table 2: Research question of the benefit assessment of brigatinib

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

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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 and chose crizotinib from the 2 options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Study pool and study characteristics

The study pool for the present benefit assessment consists of the ALTA-1L study. The 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 one regimen of prior systemic therapy for advanced or metastatic disease was allowed. Excluded from this was any prior tyrosine kinase inhibitor therapy.

275 patients were randomly allocated in a ratio of 1:1 to treatment with brigatinib (N = 137) or crizotinib (N = 138). Treatment in both study arms was conducted without relevant deviation from the requirements of the Summaries of Product Characteristics (SPCs). The patients were treated until disease progression, start of new antineoplastic treatment, withdrawal of consent, intolerable toxicity or end of study. In accordance with the SPC, treatment in the brigatinib arm could be continued beyond disease progression, as determined by the Response Evaluation Criteria in Solid Tumours (RECIST) if, at the investigator's discretion, there was continued clinical benefit. In compliance with the approval, after disease progression, patients in the crizotinib arm could receive brigatinib as subsequent therapy at the investigator's discretion.

The primary outcome of the study was progression-free survival. Patient-relevant secondary outcomes were overall survival, symptom outcomes, as well as health-related quality of life and adverse events (AEs).

The data cut-off on 28 June 2019 presented in the present benefit assessment corresponds to the second interim analysis planned after 149 events (progression or death).

Risk of bias across outcomes and outcome-specific risk of bias

The risk of bias across outcomes was rated as low for the ALTA-1L study. At outcome level, the risk of bias was rated as high for each of the results of all outcomes except for the outcome "overall survival"; the outcome-specific certainty of the results may not be downgraded, however.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". However, there was an effect modification by the characteristic "brain metastases at baseline". For patients with brain metastases at baseline, there was an indication of an added benefit of brigatinib in comparison with crizotinib. For patients without brain metastases at baseline, in contrast, there was no added benefit; an added benefit for these patients is not proven.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] – symptom scales)

- Pain

No statistically significant difference between the treatment groups was shown for the scale "pain". However, there was an effect modification by the characteristic "sex". For women, there

was a hint of an added benefit of brigatinib in comparison with crizotinib. For men, in contrast, no added benefit was shown; an added benefit for men is not proven.

- Nausea and vomiting, constipation

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "nausea and vomiting" and "constipation". This resulted in a hint of an added benefit of brigatinib in comparison with crizotinib for each of the 2 outcomes.

- Fatigue and appetite loss

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "fatigue" and "appetite loss". The difference was no more than marginal for each of these outcomes of the category of non-serious/non-severe symptoms/late complications, however. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for each of these 2 outcomes; an added benefit is therefore not proven.

- Dyspnoea, insomnia and diarrhoea

No statistically significant difference between the treatment groups was shown for each of the scales "dyspnoea", "insomnia" and "diarrhoea". This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for each of these outcomes; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-Lung Cancer 13 [EORTC QLQ-LC13])

No results on symptoms recorded using the EORTC QLQ-LC13 were available in Module 4 B of the dossier. Hence, there was no hint of an added benefit of brigatinib in comparison with crizotinib; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 – functional scales

- Global health status and emotional functioning

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "global health status" and "emotional functioning". This resulted in a hint of an added benefit of brigatinib in comparison with crizotinib for each of these 2 outcomes.

- Role functioning and social functioning

No statistically significant difference between the treatment groups was shown for the scale "role functioning". A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for the scale "social functioning". However, there was an effect modification by the characteristic "sex" for each of the 2 scales. For women, there was a hint of an added benefit of brigatinib in comparison with crizotinib in each case. For men, in contrast, no added benefit was shown in each case; an added benefit for men is not proven.

- Physical functioning and cognitive functioning

No statistically significant difference between the treatment groups was shown for the scales "physical functioning" and "cognitive functioning". This resulted in no hint of an added benefit for each of these outcomes; an added benefit is therefore not proven.

Side effects

Events caused by progression of the underlying disease were recorded as AEs in the ALTA-1L study. The company did not present any analyses in which these events had been deducted from the overall rates of AEs, serious AEs (SAEs), severe AEs and discontinuations due to AEs.

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". However, there was an effect modification by the characteristic "age". This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib for patients < 65 years of age. For patients ≥ 65 years of age, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib; greater or lesser harm for this patient group is therefore not proven.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment arms was shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib for both outcomes; greater or lesser harm is therefore not proven.

Specific AEs

Eye disorders (System Organ Class [SOC], AEs), peripheral oedema (Preferred Term [PT], AEs)

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the outcomes "eye disorders" (SOC, AEs) and "peripheral oedema" (PT, AEs). This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib for each of the 2 outcomes.

In addition, there was an effect modification by the characteristic "sex" for both outcomes. Since for each of the 2 outcomes, there was a hint of lesser harm of the same extent in the subgroups as well as in the total population, hereinafter, the result of the total population is taken into account in the derivation of the added benefit for both outcomes.

Gastrointestinal disorders (SOC, AEs)

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for the outcome "gastrointestinal disorders" (SOC, AEs). This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib.

Skin and subcutaneous tissue disorders (SOC, AEs)

A statistically significant difference between the treatment groups was shown for the outcome "skin and subcutaneous tissue disorders" (SOC, AEs). However, there was an effect modification by the characteristic "age". This resulted in a hint of greater harm of brigatinib in comparison with crizotinib for patients ≥ 65 years of age. For patients < 65 years of age, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib; greater or lesser harm for this patient group is therefore not proven.

Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of brigatinib in comparison with crizotinib was shown for the outcome "creatine phosphokinase increased" (PT, severe AEs [CTCAE grade ≥ 3]). Due to the size of the effect and the early occurrence of the events almost exclusively in the brigatinib arm, a high certainty of results is assumed in these severe AEs despite the high risk of bias at outcome level. This resulted in an indication of greater harm of brigatinib in comparison with crizotinib.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of brigatinib in comparison with crizotinib was shown for the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of brigatinib in comparison with crizotinib.

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

Based on the results presented, probability and extent of the added benefit of the drug brigatinib in comparison with the ACT are assessed as follows:

The overall consideration shows both positive and negative effects of brigatinib in comparison with crizotinib. The positive effect in overall survival was only shown in patients with brain metastases at baseline. For this reason, positive and negative effects are assessed separately for patients with and without brain metastases at baseline below. The effect modifications by the characteristics "age" and "sex" in individual further outcomes had no effects on the overall conclusion on the added benefit, as there were also effects in the same direction in the total population in the respective outcome categories. These effect modifications are therefore not listed separately below.

[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].

Patients with brain metastases at baseline

On the positive side, there was an indication of a minor added benefit of brigatinib in comparison with crizotinib for overall survival for patients with brain metastases at baseline. For these patients, there were also hints of different extent from the outcome categories of non-serious/non-severe symptoms/late complications and health-related quality of life. On the positive side regarding side effects, there were several hints of lesser harm, each with considerable extent, in the category of non-serious/non-severe side effects.

The positive effects were accompanied on the negative side by greater harm in side effects. In the category of serious/severe side effects, greater harm of major extent and different certainty of conclusions (indication and hint) was shown in 2 specific AEs.

Overall, the positive effects outweigh the negative effects, and there is an indication of a minor added benefit of brigatinib in comparison with crizotinib for patients with brain metastases at baseline.

Patients without brain metastases at baseline

No statistically significant difference between the treatment groups was shown for overall survival for patients without brain metastases at baseline. In other respects, the situation was the same as for patients with brain metastases at baseline: Hints of an added benefit in the categories of non-serious/non-severe symptoms/late complications, health-related quality of life and non-serious/non-severe side effects with different extent on the positive side were accompanied on the negative side by one hint and one indication of greater harm, each of major extent, in specific AEs in the category of serious/severe side effects. For the balancing of benefits and harms, it was also taken into account that the point estimation (hazard ratio) for overall survival was markedly above 1 (in the absence of statistical significance of the effect estimation) for patients without brain metastases at baseline. However, the positive effects overall outweighed the negative effects, although the certainty of conclusions was lower in comparison with patients with brain metastases at baseline. For the patient group without brain metastases at baseline, there is therefore a hint of a minor added benefit of brigatinib in comparison with crizotinib.

Table 3 shows a summary of probability and extent of the added benefit of brigatinib.

Table 3: Brigatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **crizotinib**	▪ Patients with brain metastases[b]: indication of a minor added benefit ▪ Patients without brain metastases[b]: hint of a minor added benefit
a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. Referring to the start of treatment. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

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

2.2 Research question

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

The ACT specified by the G-BA is shown in Table 4.

Table 4: Research question of the benefit assessment of brigatinib

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

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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 and chose crizotinib from the 2 options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

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 list on brigatinib (status: 24 March 2020)
- bibliographical literature search on brigatinib (last search on 4 March 2020)
- search in trial registries/trial results databases (last search on 4 March 2020)
- search on the G-BA website for brigatinib (last search on 4 March 2020)

To check the completeness of the study pool:

- search in trial registries for studies on brigatinib (last search on 5 May 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: brigatinib vs. crizotinib

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 (yes/no [citation])
AP26113-13-301 (ALTA-1L[c])	Yes	Yes	No	No[d]	Yes [3-5]	Yes [6]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The study pool for the present benefit assessment consists of the RCT ALTA-1L and concurs with that of the company.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: brigatinib vs. crizotinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ALTA-1L	RCT, open-label, parallel	Adult patients with ALK-positive[b] locally advanced or recurrent (stage IIIB[c]) or metastatic (stage IV) NSCLC who did not previously receive any prior 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[d], start of new antineoplastic treatment, withdrawal of consent, intolerable toxicity or end of study Observation[e]: 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, USA 5/2016–ongoing First data cut-off: 19 Feb 2018[f] Second data cut-off: 28 Jun 2019[g]	Primary: PFS Secondary: overall survival, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Presence of at least one of the following 2 criteria: 1) documentation of a positive result from the Vysis ALK Break-Apart FISH Probe Kit or the Ventana ALK (D5F3) CDx Assay or 2) documented ALK rearrangement 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.
c. And not a candidate for definitive multimodality therapy.
d. Disease progression deemed by the investigator to require alternative therapy, or disease progression assessed by a blinded independent committee; treatment in the brigatinib arm could be continued beyond progression if, at the investigator's discretion, there was continued clinical benefit. At the investigator's discretion, patients in the crizotinib arm could receive brigatinib as subsequent therapy after disease progression.
e. Outcome-specific information is provided in Table 8.
f. First interim analysis planned after 99 events (progression or death).
g. Second interim analysis planned after 149 events (progression or death).

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

Table 7: Characteristics of the intervention – RCT, direct comparison: brigatinib vs. crizotinib

Study	Intervention	Comparison
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 discontinuation possible due to intolerance[a]; stepwise dose reductions to 120 mg, 90 mg and 60 mg daily possible	Dose adjustments, treatment interruptions and discontinuation possible due to intolerance[a]; initial dose reductions to 200 mg twice daily, if required, further reduction to 250 mg once daily
	Pretreatment 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 allowed: ▪ no more than 1 regimen of systemic therapy (except tyrosine kinase inhibitors) for locally advanced or metastatic NSCLC[b] **Concomitant treatment** not allowed: ▪ any other systemic anticancer therapy ▪ drugs associated with the development of torsade de pointes tachycardia ▪ extensive surgery requiring inpatient care to be used with care or be avoided ▪ substances that prolong the QT interval, and drugs that cause bradycardia ▪ in the brigatinib arm: strong CYP inducers and inhibitors ▪ in the crizotinib arm: strong CYP3A inducers, CYP3A inhibitors, CYP3A substrates with narrow therapeutic index and substrates metabolized by PXR and CAR-regulated enzymes **allowed:** ▪ local radiotherapy (e.g. stereotactic radiosurgery) for patients with central nervous system lesions with interruption of the study medication[c] ▪ palliative therapy and supportive care for management of symptoms and underlying medical conditions	

a. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviation from the requirements of the SPCs.
b. Treatment over ≥ 1 cycle with systemic therapy. New maintenance therapy was counted as a new regimen. Neoadjuvant or adjuvant systemic therapy was counted as a prior regimen if this therapy was completed within 12 months prior to randomization.
c. In these patients, central nervous system lesions requiring radiotherapy were considered as disease progression.

ALK: anaplastic lymphoma kinase; CAR: constitutive androstane receptor; CYP: cytochrome P450; NSCLC: non-small cell lung cancer; PXR: pregnane X receptor; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

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 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. Patients with symptomatic brain metastases were excluded. Regarding prior therapy, no more than one regimen of prior systemic therapy for advanced or metastatic disease was allowed. Excluded from this was any prior tyrosine kinase inhibitor therapy.

275 patients were randomly allocated in a ratio of 1:1 to treatment with brigatinib (N = 137) or crizotinib (N = 138). Randomization was stratified by 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 deviation from the requirements of the SPCs [7,8]. The patients were treated until disease progression, start of new antineoplastic treatment, withdrawal of consent, intolerable toxicity or end of study. In accordance with the SPC, treatment in the brigatinib arm could be continued beyond disease progression, as determined by the RECIST criteria if, at the investigator's discretion, there was continued clinical benefit. At the investigator's discretion, and in compliance with the approval, patients in the crizotinib arm could receive brigatinib as subsequent therapy after disease progression.

The primary outcome of the study was progression-free survival. Patient-relevant secondary outcomes were overall survival, symptom outcomes, as well as health-related quality of life and AEs.

Data cut-offs

The ALTA-1L study started in May 2016 and has not yet been completed at the time of the production of this benefit assessment. The data cut-off on 28 June 2019 presented in the present benefit assessment corresponds to the second interim analysis planned after 149 events (progression or death). The final data cut-off is planned after 198 events.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: brigatinib vs. crizotinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ALTA-1L	
Mortality	
Overall survival	Until death, discontinuation 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 category of side effects	Until 30 days after the last dose of the study medication[a]
a. At the investigator's discretion, and in compliance with the approval, patients in the crizotinib arm could 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.	
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; vs.: versus	

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" are systematically shortened, as the observation was conducted only for up to 30 days after the last dose of the study medication. Patients in the crizotinib arm who, at the physician's discretion, received brigatinib upon progression, were observed up to 30 days after the last administration of brigatinib. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary to record the outcomes "morbidity", "health-related quality of life" and "side effects" over the total period of time, as was the case for survival.

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

Table 9: Characteristics of the study population – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Characteristics Category	**Brigatinib N[a] = 137**	**Crizotinib N[a] = 138**
ALTA-1L		
Age [years], mean (SD)	58 (13)	59 (11)
Sex [F/M], %	50/50	59/41
Family origin, n (%)		
White	76 (55.5)	86 (62.3)
Asian	59 (43.1)	49 (35.5)
Other/unknown	2 (1.5)	3 (2.2)
Region, n (%)		
Europe	69 (50.4)	74 (53.6)
Asia-Pacific	58 (42.3)	49 (35.5)
North America	10 (7.3)	15 (10.9)
ECOG PS, n (%)		
0	54 (39.4)	53 (38.4)
1	76 (55.5)	78 (56.5)
2	7 (5.1)	7 (5.1)
Smoking status, n (%)		
Never-smoker	84 (61.3)	75 (54.3)
Former	50 (36.5)	56 (40.6)
Active	3 (2.2)	7 (5.1)
Histology, n (%)		
Adenocarcinoma	126 (92.0)	137 (99.3)
Other/unknown	11 (8.0)[b]	1 (0.7)[b]
Disease stage at baseline, n (%)		
IIIB	8 (5.8)	12 (8.7)
IV	129 (94.2)	126 (91.3)
Time since first diagnosis [months]		
Mean (SD)	10 (23)	13 (28)
Median [min; max]	1.6 [0.1; 145.3]	1.4 [0.3; 189.8]
Brain metastases at baseline, n (%)		
Yes	41 (29.9)	40 (29.0)
No	96 (70.1)	98 (71.0)
Prior antineoplastic treatments, n (%)		
Chemotherapy	36 (26.3)	37 (26.8)
Radiotherapy	33 (24.1)	40 (29.0)
Radiotherapy of the CNS	18 (13.1)	19 (13.8)

Table 9: Characteristics of the study population – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Characteristics Category	Brigatinib N[a] = 137	Crizotinib N[a] = 138
Number of prior antineoplastic treatments, n (%)		
0	99 (72.3)	95 (68.8)
1	34 (24.8)	38 (27.5)
2	3 (2.2)	4 (2.9)
≥ 3	1 (0.7)	1 (0.7)
Treatment discontinuation, n (%)	61 (44.5)	114 (82.6)
Study discontinuation[d], n (%)	47 (34.3)	31 (22.5)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Multiple answers possible.
d. The main reason for study discontinuation in both treatment arms was death of the patient (n [%]: 33 [24.1%] in the brigatinib arm, and 25 [18.1%] in the crizotinib arm).

CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics between both treatment arms of the ALTA-1L study were balanced. The mean age of the patients was about 60 years and the majority were white (approximately 60%). The proportion of women was 50% in the brigatinib arm and 59% in the crizotinib arm. About 5% of the patients included had an ECOG PS of 2. At the start of the study, more than 90% of the patients were in the metastatic stage IV of the disease. The sites most frequently affected by metastases were the lungs (about 90% of patients), the regional lymph nodes (about 70%) and the brain (about 30%). Just under 27% of the patients had already received chemotherapy for the treatment of the advanced or metastatic disease.

A clear difference between the treatment arms was shown in the proportion of patients with treatment discontinuation (44.5% in the brigatinib arm versus 82.6% in the crizotinib arm). The most common reason for treatment discontinuation in both study arms was disease progression.

Table 10 shows the median and mean treatment durations and observation periods of the patients for the individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: brigatinib vs. crizotinib

Study **Duration of the study phase** **Outcome category**	**Brigatinib**	**Crizotinib**
ALTA-1L		
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 (EORTC QLQ-C30)		
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

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration in the ALTA-1L study is almost 3 times longer in the intervention arm than in the comparator arm (median: 24.3 versus 8.4 months). The median observation period for the outcome "overall survival" is comparable between the treatment arms. Since the observation periods for the outcomes of the categories of morbidity, health-related quality of life and side effects are linked to the treatment duration (see also Table 8), the observation periods in the brigatinib arm are also longer than in the crizotinib arm. It is shown here that the observation periods of the outcomes on morbidity, health-related quality of life and side effects differ notably less between the treatment arms than the treatment durations. It should be noted that in the crizotinib arm, the observations for these outcomes were continued when the patients received subsequent treatment with brigatinib (see Table 8 and following section).

Subsequent therapies

The publicly available sources contain only little information on subsequent therapies in the ALTA-1L study. The information in Module 4 B only shows that 61 (44.2%) of the patients in the crizotinib arm received subsequent therapy with brigatinib at the present data cut-off (28 June 2019). This is an approved use of brigatinib [8].

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: brigatinib vs. crizotinib

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			
ALTA-1L	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the ALTA-1L study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 0 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described that the results of the RCT ALTA-1L were transferable to the German health care context due to the intervention and the study population. According to the company, the dosage of the drugs used corresponded to the dosage used in everyday practice in Germany in compliance with the SPCs. Besides, the pretreatment of the study participants was reflected in the German health care context. Here, the company referred to an analysis of the lung cancer registry study CRISP (Clinical Research platform Into molecular testing, treatment and outcome of (non-)Small cell lung carcinoma Patients), according to which some ALK-positive patients also received chemotherapy as first-line therapy [9]. These patients were comprised by the inclusion criteria of the ALTA-1L study. In addition, according to the company, the majority of the study participants were of Caucasian family origin (58.9%) or were included in European study centres (52.0%). In summary, the company noted that the results of the ALTA-1L study were fully transferable to the German health care context.

The company did not provide any 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 considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the EORTC QLQ-C30 and QLQ-LC13
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

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

Outcome category "side effects"

Events caused by progression of the underlying disease were recorded as AEs in the ALTA-1L study. The company did not present any analyses in which these events had been deducted from the overall rates of AEs, SAEs, severe AEs and discontinuations due to AEs. However, the influence of the progression of the underlying disease on the interpretability of the results on side effects is not considered important in the present situation, since the rates of the SOCs that potentially represent events of the progression of the underlying disease (for example, neoplasms benign, malignant and unspecified [incl cysts and polyps]) are comparable between the treatment arms.

Outcome "time to progression in the central nervous system (CNS)"

CNS metastases have a special significance in the present therapeutic indication. In the ALTA-1L study, the outcome "time to progression in the CNS" was defined as the time from randomization until the first radiological evidence of CNS disease progression. The radiological evidence was assessed by a blinded independent committee according to the RECIST criteria. Thus, the assessment was based exclusively on imaging techniques and did not consider any symptoms perceived by the patients. This operationalization of the outcome is therefore not directly patient-relevant. In addition, patient-relevant outcomes on symptoms and health-related

quality of life reported by the patient are available in the ALTA-1L study. The outcome "time to CNS progression" was therefore not used for the derivation of an added benefit.

Regardless of patient relevance, these results can only be interpreted to a limited extent for the following methodological reasons:

- For the outcome "CNS progression", the patients were only observed until the last dose of the study medication, until disease progression or the start of a new systemic anticancer therapy. Thus, the observation period was systematically shortened, as was the case for the outcomes "morbidity", "health-related quality of life" and "side effects".
- This means in particular that patients with prior non-CNS progression were censored for the outcome "CNS progression". Hence, the analyses presented by the company in the dossier only recorded part of the CNS progressions, i.e. only those progressions that had occurred before non-CNS disease progression. It is unclear how many events remained unconsidered due to this analysis.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: brigatinib vs. crizotinib

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs[a]
ALTA-1L	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes

a. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), peripheral oedema (PT, AEs), creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3]), and hypertension (PT, severe AEs [CTCAE grade ≥ 3]).
b. No data available in Module 4 B of the dossier (see below).

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 13; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Symptoms recorded with the EORTC QLQ-LC13

In accordance with the protocol change of 21 September 2016, data on symptoms were also recorded with the EORTC QLQ-LC13 instrument in the ALTA-1L study. However, this recording started only about 4 months after inclusion of the first patient. At this time point, 134 of the total of 275 patients (48.9%) had already been randomized. In Module 4 B of the dossier, the company did not present any results for the EORTC QLQ-LC13 and justified this with the fact that the responses, in relation to the total study population, were markedly below 70% and that therefore a relevant proportion of the study population was not included in the recording. This approach was inadequate. A random and representative subpopulation can be assumed for the patients who were included after the introduction of the EORTC QLQ-LC13. The information in Module 4 B shows that data on study entry were available for all patients in this subpopulation. Thus, the information provided by the company does not mean that the data are not usable.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: brigatinib vs. crizotinib

Study	Study level	Outcomes							
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs[a]
ALTA-1L	L	L	H[b, c, d]	–[e]	H[b, c, d]	H[d, f]	H[d, f]	H[b, d]	H[b, d, f]

a. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), peripheral oedema (PT, AEs), creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3]), and hypertension (PT, severe AEs [CTCAE grade ≥ 3]).
b. Lack of blinding in subjective recording of outcomes (in specific AEs only for the non-severe specific AEs).
c. Strong decrease in response rates to questionnaires in the course of the study that differed between the treatment arms.
d. Selective longer follow-up observation in the crizotinib arm only for patients who received brigatinib as subsequent therapy upon progression.
e. No data available in Module 4 B of the dossier (see Section 2.4.1).
f. Incomplete observations for potentially informative reasons.

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 13; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias of the results on the outcome "overall survival" was rated as low. The company assessed the risk of bias as high due to a change in therapy from the crizotinib arm to the brigatinib arm, since 44.2% of the patients in the crizotinib arm were already receiving brigatinib as subsequent therapy at the time of the present data cut-off. This assessment was inadequate, as the treatment of patients with brigatinib after previous treatment with crizotinib is approved according to the SPC [8] and a therapeutic option according to guidelines [10,11].

The risk of bias of the results on symptoms and health-related quality of life, each recorded with the EORTC QLQ-C30 instrument, was assessed as high. The reasons for this were the lack of blinding in subjective recording of outcomes as well as the strong decrease in response rates to questionnaires in the course of the study that differed between the treatment arms. Furthermore, there was selective follow-up observation of the patients in the control arm. After progression, the patients in the crizotinib arm could receive brigatinib as subsequent therapy at the physician's discretion, and observation was continued also during this treatment. For patients who did not receive crizotinib as subsequent therapy, the observation ended 30 days

after the last dose of the study medication. The company justified its assessment of a high risk of bias for these outcome exclusively with the open-label study design.

The risk of bias of the results on side effect outcomes was rated as high due to the selective follow-up observation in the control arm. Furthermore, for all side effect outcomes except the outcome "discontinuation due to AEs", the possibly high proportion of patients with incomplete observation for potentially informative reasons due to the different observation periods between the treatment arms contributed to the high risk of bias. For the non-serious/non-severe outcomes, the lack of blinding in the recording of outcomes additionally contributed to a high risk of bias. The company assessed the risk of bias of the results on all side effects as high due to the lack of blinding, without differentiating between serious/severe and non-serious/non-severe side effects.

2.4.3 Results

Table 14 summarizes the results of the comparison of brigatinib with crizotinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

Kaplan-Meier curves on the presented event time analyses can be found in Appendix A of the full dossier assessment. The tables with the events on common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs can be found in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Outcome category Outcome	Brigatinib		Crizotinib		Brigatinib vs. crizotinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
ALTA-1L					
Mortality					
Overall survival	137	NA [ND] 33 (24.1)	138	NA [ND] 37 (26.8)	0.91 [0.57; 1.47]; 0.771
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)[b]					
Fatigue	131	15.6 [7.5; NA] 66 (50.4)	131	4.8 [3.3; 8.6] 83 (63.4)	0.67 [0.48; 0.93]; 0.013
Nausea and vomiting	131	12.0 [4.0; NA] 67 (51.1)	131	2.8 [1.9; 5.6] 92 (70.2)	0.55 [0.40; 0.76]; < 0.001
Pain	131	12.1 [6.4; 23.2] 69 (52.7)	131	8.1 [5.7; 11.6] 75 (57.3)	0.82 [0.59; 1.15]; 0.301
Dyspnoea	131	28.6 [10.2; NA] 58 (44.3)	131	16.8 [10.2; NA] 53 (40.5)	0.98 [0.67; 1.43]; 0.839
Insomnia	131	NA [18.6; NA] 52 (39.7)	131	22.1 [12.7; NA] 48 (36.6)	0.91 [0.61; 1.35]; 0.736
Appetite loss	131	NA [17.5; NA] 52 (39.7)	131	9.2 [6.3; 24.9] 63 (48.1)	0.62 [0.43; 0.90]; 0.009
Constipation	131	12.0 [6.5; NA] 65 (49.6)	131	2.8 [1.9; 3.9] 84 (64.1)	0.52 [0.38; 0.73]; < 0.001
Diarrhoea	131	2.1 [1.9; 3.8] 91 (69.5)	131	2.8 [1.9; 3.8] 90 (68.7)	1.00 [0.75; 1.34]; 0.968
Symptoms (EORTC QLQ-LC13 – symptom scales)	No data available[c]				
Health-related quality of life					
EORTC QLQ-C30 – functional scales[b]					
Global health status	131	26.7 [8.3; NA] 57 (43.5)	131	8.3 [5.7; 13.5] 70 (53.4)	0.70 [0.49; 1.00]; 0.049
Physical functioning	131	NA [13.9; NA] 55 (42.0)	131	10.3 [6.5; 17.5] 67 (51.1)	0.67 [0.47; 0.97]; 0.051
Role functioning	131	10.2 [4.3; 21.2] 72 (55.0)	131	6.5 [3.9; 9.5] 77 (58.8)	0.84 [0.61; 1.17]; 0.356
Emotional functioning	131	NA [22.2; NA] 48 (36.6)	131	10.1 [7.6; 14.8] 68 (51.9)	0.56 [0.38; 0.81]; 0.002
Cognitive functioning	131	9.3 [4.7; 16.2] 76 (58.0)	131	4.5 [3.4; 8.3] 83 (63.4)	0.75 [0.54; 1.02]; 0.066
Social functioning	131	27.7 [14.3; NA] 58 (44.3)	131	4.8 [2.9; 12.7] 74 (56.5)	0.59 [0.42; 0.85]; 0.004

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Outcome category Outcome	Brigatinib N	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 (%)	Brigatinib vs. crizotinib HR [95% CI]; p-value[a]
Side effects[d]					
AEs (supplementary information)	136	0.2 [0.1; 0.3] 135 (99.3)	137	0.03 [0.03; 0.07] 137 (100)	–
SAEs	136	NA 45 (33.1)	137	NA [27.6; NA] 51 (37.2)	0.68 [0.44; 1.06]; 0.079
Severe AEs (CTCAE grade ≥ 3)	136	5.1 [2.8; 8.4] 99 (72.8)	137	6.5 [4.0; 12.1] 84 (61.3)	1.25 [0.94; 1.68]; 0.139
Discontinuation due to AEs	136	NA 17 (12.5)	137	NA 12 (8.8)	1.42 [0.68; 2.99]; 0.297
Specific AEs					
Eye disorders (SOC, AEs)	136	NA 22 (16.2)	137	2.8 [0.4; NA] 75 (54.7)	0.19 [0.12; 0.32]; < 0.001
Gastrointestinal disorders (SOC, AEs)	136	1.0 [0.7; 2.0] 104 (76.5)	137	0.1 [0.1; 0.2] 121 (88.3)	0.50 [0.38; 0.66]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	136	8.0 [5.5; 15.4] 73 (53.7)	137	NA 42 (30.7)	2.07 [1.42; 3.05]; < 0.001
Peripheral oedema (PT, AEs)	136	NA 9 (6.6)	137	17.9 [9.7; NA] 61 (44.5)	0.10 [0.05; 0.22]; < 0.001
Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3])	136	NA 33 (24.3)	137	NA 2 (1.5)	18.26 [4.38; 76.13]; < 0.001
Hypertension (PT, severe AEs [CTCAE grade ≥ 3])	136	NA 16 (11.8)	137	NA 4 (2.9)	4.19 [1.40; 12.57]; 0.007

a. HR and 95% CI from a Cox proportional hazards model with stratification parameters as covariates; p-value from a stratified log-rank test. Stratification variables: presence of CNS metastases at baseline and prior chemotherapy for the treatment of the advanced or metastatic disease.
b. Time to first deterioration, defined as an increase in score by ≥ 10 points (for the symptom scales) or a decrease in score by ≥ 10 points (for the functional scales) in comparison with baseline.
c. No data available in Module 4 B of the dossier (see Section 2.4.1).
d. Events caused by progression of the underlying disease are also recorded as AEs.

AE: adverse event; CI: confidence interval; CNS: central nervous system; 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 13; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome “overall survival”. There was a high risk of bias of the results for the outcomes

on morbidity, health-related quality of life and side effects so that at most a hint, e.g. of an added benefit, can be determined. Despite the high risk of bias, an indication, e.g. of lesser or greater harm, can be determined for the outcome "creatine phosphokinase increased" (PT, severe AEs [CTCAE grade ≥ 3]). Further information can be found in the description of the results.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". However, there was an effect modification by the characteristic "brain metastases at baseline". For patients with brain metastases at baseline, there was an indication of an added benefit of brigatinib in comparison with crizotinib. For patients without brain metastases at baseline, in contrast, there was no added benefit; an added benefit for these patients is not proven (see Section 2.4.4).

This deviates from the assessment of the company, which derived an indication of an added benefit for the total population.

Morbidity

Symptoms (EORTC QLQ-C30 – symptom scales)

Pain

No statistically significant difference between the treatment groups was shown for the scale "pain". However, there was an effect modification by the characteristic "sex". For women, there was a hint of an added benefit of brigatinib in comparison with crizotinib. For men, in contrast, no added benefit was shown; an added benefit for men is not proven (see Section 2.4.4).

This deviates from the assessment of the company, which did not derive an added benefit on the basis of the total population without consideration of the effect modification.

Nausea and vomiting, constipation

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "nausea and vomiting" and "constipation". This resulted in a hint of an added benefit of brigatinib in comparison with crizotinib for each of the 2 outcomes.

The assessment deviates from that of the company, which derived an indication of an added benefit for each of the 2 scales.

Fatigue and appetite loss

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "fatigue" and "appetite loss". The difference was no more than marginal for each of these outcomes of the category of non-serious/non-severe symptoms/late

complications, however. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for each of these 2 outcomes; an added benefit is therefore not proven.

The assessment deviates from that of the company, which derived an indication of an added benefit for each of the 2 scales "fatigue" and "appetite loss".

Dyspnoea, insomnia and diarrhoea

No statistically significant difference between the treatment groups was shown for each of the scales "dyspnoea", "insomnia" and "diarrhoea". This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for each of these outcomes; an added benefit is therefore not proven.

The assessment of the added benefit for the outcomes "dyspnoea", "insomnia" and "diarrhoea" concurs with that of the company.

Symptoms (EORTC QLQ-LC13)

No results on symptoms recorded using the EORTC QLQ-LC13 were available in Module 4 B (see Section 2.4.1). Hence, there was no hint of an added benefit of brigatinib in comparison with crizotinib; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 – functional scales

Global health status and emotional functioning

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "global health status" and "emotional functioning". This resulted in a hint of an added benefit of brigatinib in comparison with crizotinib for each of these 2 outcomes.

The assessment of the added benefit deviates from that of the company, which derived no added benefit for the scale "global health status" and an indication of an added benefit for the scale "emotional functioning".

Role functioning and social functioning

No statistically significant difference between the treatment groups was shown for the scale "role functioning". A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for the scale "social functioning". However, there was an effect modification by the characteristic "sex" for each of the 2 scales. For women, there was a hint of an added benefit of brigatinib in comparison with crizotinib in each case. For men, in contrast, no added benefit was shown in each case; an added benefit for men is not proven (see Section 2.4.4).

The assessment of the added benefit deviates from that of the company. The company derived no added benefit for the scale "role functioning" and an indication of an added benefit for the

scale "social functioning", in each case on the basis of the total population without consideration of the effect modification.

Physical functioning and cognitive functioning

No statistically significant difference between the treatment groups was shown for the scales "physical functioning" and "cognitive functioning". This resulted in no hint of an added benefit for each of these outcomes; an added benefit is therefore not proven.

For the scale "physical functioning", the assessment deviates from that of the company, which derived an indication of an added benefit. The assessment of the added benefit for the scale "cognitive functioning" concurs with that of the company.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". However, there was an effect modification by the characteristic "age". This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib for patients < 65 years of age. For patients ≥ 65 years of age, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib; greater or lesser harm for this patient group is therefore not proven (see Section 2.4.4).

The assessment of the added benefit deviates from the assessment of the company, which derived no added benefit for SAEs without consideration of the effect modification on the basis of the total population.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs

No statistically significant difference between the treatment arms was shown for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib for both outcomes; greater or lesser harm is therefore not proven.

For both outcomes, the assessment of the added benefit concurs with that of the company.

Specific AEs

Eye disorders (SOC, AEs), peripheral oedema (PT, AEs)

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the outcomes "eye disorders" (SOC, AEs) and "peripheral oedema" (PT, AEs). This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib for each of the 2 outcomes.

In addition, there was an effect modification by the characteristic "sex" for both outcomes. Since for each of the 2 outcomes, there was a hint of lesser harm of the same extent in the

subgroups as well as in the total population (see Section 2.4.4), hereinafter, the result of the total population is taken into account in the derivation of the added benefit for both outcomes.

Gastrointestinal disorders (SOC, AEs)

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for the outcome "gastrointestinal disorders" (SOC, AEs). This resulted in a hint of lesser harm of brigatinib in comparison with crizotinib.

Skin and subcutaneous tissue disorders (SOC, AEs)

A statistically significant difference between the treatment groups was shown for the outcome "skin and subcutaneous tissue disorders" (SOC, AEs). However, there was an effect modification by the characteristic "age". This resulted in a hint of greater harm of brigatinib in comparison with crizotinib for patients ≥ 65 years of age. For patients < 65 years of age, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib; greater or lesser harm for this patient group is therefore not proven (see Section 2.4.4).

Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of brigatinib in comparison with crizotinib was shown for the outcome "creatine phosphokinase increased" (PT, severe AEs [CTCAE grade ≥ 3]). Due to the size of the effect and the early occurrence of the events almost exclusively in the brigatinib arm (see Figure 39 in the full dossier assessment), a high certainty of results is assumed in these severe AEs despite the high risk of bias at outcome level. This resulted in an indication of greater harm of brigatinib in comparison with crizotinib.

Hypertension (PT, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of brigatinib in comparison with crizotinib was shown for the outcome "hypertension" (PT, severe AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of brigatinib in comparison with crizotinib.

The assessments on the specific harm outcomes deviate from the assessment of the company, which presented specific AEs, but considered them together with the overall rates in the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were used for the present assessment:

- sex (female versus male)
- age (< 65 years versus ≥ 65 years)

Due to the special significance of brain metastases particularly in patients with ALK-positive advanced NSCLC [10], the subgroup characteristic "brain metastases at baseline" (yes versus no) was additionally considered.

No subgroup characteristics were prespecified in the ALTA-1L study. The characteristic “brain metastases at baseline” was a stratification characteristic.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

The subgroup results of brigatinib in comparison with crizotinib are summarized in Table 15.

Table 15: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Outcome Characteristic Subgroup	Brigatinib N	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 (%)	Brigatinib vs. crizotinib HR [95% CI][a]	Brigatinib vs. crizotinib p-value[a]
ALTA-1L						
Overall survival						
Brain metastases at baseline						
Yes	41	NA [28.1; NA] 10 (24.4)	40	NA [18.5; NA] 18 (45.0)	0.45 [0.21; 0.99]	0.046
No	96	NA 23 (24.0)	98	NA 19 (19.4)	1.41 [0.77; 2.60]	0.272
Total					Interaction[b]:	0.024
Pain (EORTC QLQ-C30)						
Sex						
Women	65	18.7 [6.4; NC] 33 (50.8)	76	6.5 [3.7; 8.6] 50 (65.8)	0.56 [0.35; 0.88]	0.019
Men	66	9.3 [3.8; 19.4] 36 (54.5)	55	15.6 [7.5; NC] 25 (45.4)	1.30 [0.77; 2.19]	0.231
Total					Interaction[b]:	0.022
Role functioning (EORTC QLQ-C30)						
Sex						
Women	65	20.3 [4.7; NC] 32 (49.2)	76	3.9 [2.8; 7.7] 49 (64.5)	0.53 [0.34; 0.85]	0.007
Men	66	6.6 [1.9; 15.9] 40 (60.6)	55	8.1 [4.7; NC] 28 (50.9)	1.37 [0.84; 2.25]	0.184
Total					Interaction[b]:	0.012
Social functioning (EORTC QLQ-C30)						
Sex						
Women	65	NA [14.3; NA] 23 (35.4)	76	3.7 [2.0; 8.3] 48 (63.2)	0.40 [0.24; 0.67]	< 0.001
Men	66	16.6 [3.8; 27.7] 35 (53.0)	55	12.7 [3.8; NC] 26 (47.3)	0.95 [0.56; 1.59]	0.974
Total					Interaction[b]:	0.005
SAEs[c]						
Age						
< 65 years	92	NA 20 (21.7)	94	NA [29.5; NA] 32 (34.0)	0.56 [0.32; 0.98]	0.037
≥ 65 years	44	13.7 [1.9; NA] 25 (56.8)	43	16.9 [5.7; NA] 19 (44.2)	1.28 [0.70; 2.35]	0.377
Total					Interaction[b]:	0.039

Table 15: Subgroups (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brigatinib vs. crizotinib (multipage table)

Study Outcome Characteristic Subgroup	Brigatinib N	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 (%)	Brigatinib vs. crizotinib HR [95% CI][a]	Brigatinib vs. crizotinib p-value[a]
Eye disorders (SOC, AEs)						
Sex						
Women	69	NA 10 (14.5)	80	0.3 [0.2; 1.3] 53 (66.3)	0.12 [0.06; 0.24]	< 0.001
Men	67	NA 12 (17.9)	57	NA [9.6; NA] 22 (38.6)	0.33 [0.16; 0.68]	0.002
Total					Interaction[b]:	0.024
Skin and subcutaneous tissue disorders (SOC, AEs)						
Age						
< 65 years	92	10.1 [4.6; 19.2] 49 (53.3)	94	NA [21.3; NA] 35 (37.2)	1.51 [0.98; 2.36]	0.079
≥ 65 years	44	6.5 [2.8; 15.4] 24 (54.4)	43	NA 7 (16.3)	5.66 [2.39; 13.45]	< 0.001
Total					Interaction[b]:	0.027
Peripheral oedema (PT, AEs)						
Sex						
Women	69	NA 2 (2.9)	80	15.4 [3.7; NA] 41 (51.3)	0.04 [0.01; 0.17]	< 0.001
Men	67	NA 7 (10.4)	57	NA [11.8; NA] 20 (35.1)	0.18 [0.07; 0.45]	< 0.001
Total					Interaction[b]:	0.030

a. HR and 95% CI from a Cox proportional hazards model with stratification parameters as covariates; p-value for the individual subgroups from a stratified log-rank test; stratification variables: presence of CNS metastases at baseline and prior chemotherapy for the treatment of the advanced or metastatic disease.
b. p-values for the interaction tests were calculated using a Cox proportional hazards model.
c. Events caused by progression of the underlying disease are also recorded as AEs.

AE: adverse event; CI: confidence interval; CNS: central nervous system; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Mortality

Overall survival

There was an effect modification by the characteristic "brain metastases at baseline" for the outcome "overall survival". A statistically significant difference in favour of brigatinib was shown for patients with brain metastases at baseline. This resulted in a hint of an added benefit

of brigatinib versus crizotinib for patients with brain metastases at baseline. No statistically significant difference between the treatment groups was shown for patients without brain metastases at baseline. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib; an added benefit is therefore not proven for this patient group.

Morbidity

Symptoms (EORTC QLQ-C30 – symptom scales)

Pain

There was an effect modification by the characteristic "sex" for the scale "pain". For women, a statistically significant difference was shown in favour of brigatinib versus crizotinib. This resulted in a hint of an added benefit of brigatinib versus crizotinib for women. For men, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib; an added benefit is therefore not proven for men.

Health-related quality of life

EORTC QLQ-C30 – functional scales

Role functioning and social functioning

There was an effect modification by the characteristic "sex" for each of the scales "role functioning" and "social functioning". For women, a statistically significant difference was shown in favour of brigatinib versus crizotinib for each of the 2 scales. This resulted in a hint of an added benefit of brigatinib versus crizotinib for women for each of the 2 outcomes. For men, there was no statistically significant difference in either of the 2 scales. In each case, there was no hint of an added benefit of brigatinib in comparison with crizotinib for men; an added benefit is therefore not proven for men.

Side effects

SAEs

There was an effect modification by the characteristic "age" for SAEs. For patients < 65 years of age, a statistically significant difference was shown in favour of brigatinib versus crizotinib. This resulted in a hint of lesser harm of brigatinib versus crizotinib for these patients. There was no statistically significant difference for patients ≥ 65 years of age. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for this patient group; greater or lesser harm is therefore not proven for this patient group.

Specific AEs

Eye disorders (SOC, AEs), peripheral oedema (PT, AEs)

An effect modification by the characteristic "sex" was shown for each of the outcomes "eye disorders" (SOC, AEs) and "peripheral oedema" (PT, AEs). A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown both for women and for men. For both sexes, this resulted in a hint of lesser harm of brigatinib in comparison with

crizotinib, with the same extent, for each of the 2 outcomes. Since there was a hint of lesser harm of the same extent in both subgroups as well as in the total population, hereinafter, the result of the total population is taken into account in the derivation of the added benefit for both outcomes.

Skin and subcutaneous tissue disorders (SOC, AEs)

There was an effect modification by the characteristic "age" for the outcome "skin and subcutaneous tissue disorders" (SOC, AEs). For patients ≥ 65 years of age, a statistically significant difference was shown to the disadvantage of brigatinib. This resulted in a hint of greater harm of brigatinib in comparison with crizotinib for patients ≥ 65 years of age. There was no statistically significant difference for patients < 65 years of age. For patients < 65 years of age, there was no hint of greater or lesser harm of brigatinib in comparison with crizotinib; greater or lesser harm for this patient group is therefore not proven.

The derivation of conclusions on individual subgroups deviates from the approach of the company, which only cited the subgroup characteristic "brain metastases at baseline" for the outcome "overall survival" in its derivation of the added benefit.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [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 was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

EORTC QLQ-C30 (symptom scales): fatigue, nausea and vomiting, pain, appetite loss, constipation

Module 4 B of the dossier provided no information to assign the severity grade to the outcomes "fatigue", "nausea and vomiting", "pain", "appetite loss" and "constipation". Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Specific AEs: eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs) and peripheral oedema (PT, AEs)

The outcomes "eye disorders" (SOC, AEs), "gastrointestinal disorders" (SOC, AEs), "skin and subcutaneous tissue disorders" (SOC, AEs) and "peripheral oedema" (PT, AEs) were assigned to the outcome category of non-serious/non-severe side effects, as the proportion of severe or serious events was small.

Table 16: Extent of added benefit at outcome level: brigatinib vs. crizotinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Brigatinib vs. crizotinib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival Brain metastases at baseline Yes	Median: NA vs. NA HR: 0.45 [0.21; 0.99]; p = 0.046 probability: "indication"	Outcome category: mortality $0.95 \leq CIu < 1.00$ added benefit, extent: "minor"
No	Median: NA vs. NA HR: 1.41 [0.77; 2.60]; p = 0.272	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30, symptom scales – deterioration by ≥ 10 points)		
Fatigue	Median: 15.6 vs. 4.8 HR: 0.67 [0.48; 0.93]; p = 0.013	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Nausea and vomiting	Median: 12.0 vs. 2.8 HR: 0.55 [0.40; 0.76]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Pain Sex Women	Median: 18.7 vs. 6.5 HR: 0.56 [0.35; 0.88]; p = 0.019 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Men	Median: 9.3 vs. 15.6 HR: 1.30 [0.77; 2.19]; p = 0.231	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: brigatinib vs. crizotinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Brigatinib vs. crizotinib** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Dyspnoea	Median: 28.6 vs. 16.8 HR: 0.98 [0.67; 1.43]; p = 0.839	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. 22.1 HR: 0.91 [0.61; 1.35]; p = 0.736	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. 9.2 HR: 0.62 [0.43; 0.90]; p = 0.009	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Constipation	Median: 12.0 vs. 2.8 HR: 0.52 [0.38; 0.73]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Diarrhoea	Median: 2.1 vs. 2.8 HR: 1.00 [0.75; 1.34]; p = 0.968	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-LC13 symptom scales)	No data available	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – functional scales (deterioration by ≥ 10 points)		
Global health status	Median: 26.7 vs. 8.3 HR: 0.70 [0.49; 1.00]; p = 0.049 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Physical functioning	Median: NA vs. 10.3 HR: 0.67 [0.47; 0.97]; p = 0.051	Lesser benefit/added benefit not proven
Role functioning Sex Women	Median: 20.3 vs. 3.9 HR: 0.53 [0.34; 0.85]; p = 0.007 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Men	Median: 6.6 vs. 8.1 HR: 1.37 [0.84; 2.25]; p = 0.184	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: brigatinib vs. crizotinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Brigatinib vs. crizotinib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Emotional functioning	Median: NA vs. 10.1 HR: 0.56 [0.38; 0.81]; p = 0.002 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Cognitive functioning	Median: 9.3 vs. 4.5 HR: 0.75 [0.54; 1.02]; p = 0.066	Lesser benefit/added benefit not proven
Social functioning Sex Women	Median: NA vs. 3.7 HR: 0.40 [0.24; 0.67]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$ and risk ≥ 5% added benefit, extent: "major"
Men	Median: 16.6 vs. 12.7 HR: 0.95 [0.56; 1.59]; p = 0.974	Lesser benefit/added benefit not proven
Side effects		
SAEs Age < 65 years	Median: NA vs. NA HR: 0.56 [0.32; 0.98]; p = 0.037 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CIu < 1.00$ lesser harm, extent: "minor"
≥ 65 years	Median: 13.7 vs. 16.9 HR: 1.28 [0.70; 2.35]; p = 0.377	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 5.1 vs. 6.5 HR: 1.25 [0.94; 1.68]; p = 0.139	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 1.42 [0.68; 2.99]; p = 0.297	Greater/lesser harm not proven
Eye disorders (SOC, AEs)	Median: NA vs. 2.8 HR: 0.19 [0.12; 0.32]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Gastrointestinal disorders (SOC, AEs)	Median: 1.0 vs. 0.1 HR: 0.50 [0.38; 0.66]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

Table 16: Extent of added benefit at outcome level: brigatinib vs. crizotinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Brigatinib vs. crizotinib** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Skin and subcutaneous tissue disorders (SOC, AEs)		
Age		
< 65 years	Median: 10.1 vs. NA HR: 1.51 [0.98; 2.36]; p = 0.079	Greater/lesser harm not proven
≥ 65 years	Median: 6.5 vs. NA HR: 5.66 [2.39; 13.45]; HR: 0.18 [0.07; 0.42][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Peripheral oedema (PT, AEs)	Median: NA vs. 17.9 HR: 0.10 [0.05; 0.22]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 18.26 [4.38; 76.13]; HR: 0.05 [0.01; 0.23][d]; p < 0.001 probability: "indication"[e]	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Hypertension (PT, severe AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 4.19 [1.40; 12.57]; HR: 0.24 [0.08; 0.71][d]; p = 0.007 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. Due to the size of the effect and the early occurrence of the events almost exclusively in the brigatinib arm, the certainty of results is not downgraded in these severe specific AEs despite the high risk of bias.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; 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 13; HR: hazard ratio; NA: not achieved; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 17: Positive and negative effects from the assessment of brigatinib in comparison with crizotinib

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ brain metastases at baseline (yes) indication of an added benefit – extent: “minor”	-
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting, constipation: hint of an added benefit – extent: “considerable” ▪ Pain: ▫ sex (women) hint of an added benefit – extent: “minor”	-
Health-related quality of life ▪ Global health status and emotional functioning: hint of an added benefit – extent: “minor” (global health status) and “considerable” (emotional functioning) ▪ Role functioning, social functioning ▫ sex (women) hint of an added benefit – extent: “considerable” (role functioning) and “major” (social functioning)	-
Non-serious/non-severe side effects ▪ Eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), peripheral oedema (PT, AEs): hint of lesser harm – extent: “considerable” Serious/severe side effects ▪ SAEs ▫ age (< 65 years): hint of lesser harm – extent: “minor”	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (SOC, AEs) ▫ age (≥ 65 years): hint of greater harm – extent “considerable” Serious/severe side effects ▪ Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: “major” ▪ Hypertension (PT, severe AEs [CTCAE grade ≥ 3]): hint of greater harm – extent: “major”
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

The overall consideration shows both positive and negative effects of brigatinib in comparison with crizotinib. The positive effect in overall survival was only shown in patients with brain metastases at baseline. For this reason, positive and negative effects are assessed separately for patients with and without brain metastases at baseline below. The effect modifications by the characteristics “age” and “sex” in individual further outcomes had no effects on the overall conclusion on the added benefit, as there were also effects in the same direction in the total population in the respective outcome categories. These effect modifications are therefore not listed separately below.

Patients with brain metastases at baseline

On the positive side, there was an indication of a minor added benefit of brigatinib in comparison with crizotinib for overall survival for patients with brain metastases at baseline. For these patients, there were also hints of different extent from the outcome categories of non-serious/non-severe symptoms/late complications and health-related quality of life. On the positive side regarding side effects, there were several hints of lesser harm, each with considerable extent, in the category of non-serious/non-severe side effects.

The positive effects were accompanied on the negative side by greater harm in side effects. In the category of serious/severe side effects, greater harm of major extent and different certainty of conclusions (indication and hint) was shown in 2 specific AEs.

Overall, the positive effects outweigh the negative effects, and there is an indication of a minor added benefit of brigatinib in comparison with crizotinib for patients with brain metastases at baseline.

Patients without brain metastases at baseline

No statistically significant difference between the treatment groups was shown for overall survival for patients without brain metastases at baseline. In other respects, the situation was the same as for patients with brain metastases at baseline: Hints of an added benefit in the categories of non-serious/non-severe symptoms/late complications, health-related quality of life and non-serious/non-severe side effects with different extent on the positive side were accompanied on the negative side by one hint and one indication of greater harm, each of major extent, in specific AEs in the category of serious/severe side effects. For the balancing of benefits and harms, it was also taken into account that the point estimation (hazard ratio) for overall survival was markedly above 1 (in the absence of statistical significance of the effect estimation) for patients without brain metastases at baseline. However, the positive effects overall outweighed the negative effects, although the certainty of conclusions was lower in comparison with patients with brain metastases at baseline. For the patient group without brain metastases at baseline, there is therefore a hint of a minor added benefit of brigatinib in comparison with crizotinib.

The result of the assessment of the added benefit of brigatinib in comparison with the ACT is summarized in Table 18.

Table 18: Brigatinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **crizotinib**	▪ Patients with brain metastases[b]: indication of a minor added benefit ▪ Patients without brain metastases[b]: hint of a minor added benefit

a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Referring to the start of treatment.

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 of the company, which derived an indication of considerable added benefit for the total population.

The approach for deriving an overall conclusion on the 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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