IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Alectinib (non-small cell lung cancer) – Benefit assessment according to §35a Social Code Book V[1] (new therapeutic indication)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Alectinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V (neues Anwendungsgebiet)* (Version 1.0; Status: 28 March 2018). 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Christoph F. Dietrich, Caritas Hospital, Bad Mergentheim, Germany

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.

IQWiG employees involved in the dossier assessment:

- Vanessa Voelskow
- Christiane Balg
- Gertrud Egger
- Judith Gibbert
- Thomas Kaiser
- Inga Overesch
- Cornelia Rüdig
- Anke Schulz

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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
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
NSCLC	non-small cell lung cancer
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
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) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug alectinib. 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 22 December 2017.

Research question

The aim of the present report was to assess the added benefit of alectinib in comparison with crizotinib as appropriate comparator therapy (ACT) in the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

This resulted in one research question for the benefit assessment, for which the G-BA specified the ACT presented in Table 2.

Table 2: Research question of the benefit assessment of alectinib

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)[b]	Crizotinib
a: Presentation of the ACT specified by the G-BA. b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the International Association for the Study of Lung Cancer [IASLC] and the Union for International Cancer Control [UICC]), without medical indication for curative resection, radiotherapy or radiochemotherapy. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control	

The company followed the G-BA's specification of the ACT.

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

Results

Study pool

The ALEX study was included in the benefit assessment of alectinib in comparison with crizotinib. The ALEX study was an open-label, randomized parallel-group study on the comparison of alectinib versus crizotinib.

Characteristics of the ALEX study

The study included systemic treatment-naive adults with ALK-positive, advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC with or without asymptomatic brain metastases and a general condition concurring with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. The patients were randomly allocated in a ratio of 1:1 to treatment with alectinib (N = 152) or crizotinib (N = 151). More than half of the patients (about 60%) had no brain metastases at the start of the study.

Treatment in both study arms was largely conducted in accordance with the respective Summaries of Product Characteristics (SPCs). The patients were treated until disease progression (systemic progression and/or symptomatic central nervous system [CNS] progression), unacceptable toxicity, withdrawal of consent, or death. At the investigator's discretion, patients with isolated asymptomatic CNS progression could continue treatment with alectinib or crizotinib after local therapy of the metastasis (e.g. stereotactic radiotherapy or surgery) until systemic progression and/or symptomatic CNS progression.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and adverse events (AEs). The ALEX study recorded symptoms, health status, and health-related quality of life until 6 months beyond the end of treatment.

Risk of bias

The risk of bias across outcomes was rated as low for the included ALEX study. At outcome level, the risk of bias of the results was rated as high for all outcomes except for the outcome "overall survival".

Results

Mortality

- Overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

Morbidity

- Symptoms (symptom scales of EORTC QLQ-C30 and EORTC-QLQ-LC13)

Symptoms were recorded with the symptom scales of the disease-specific questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The symptoms and symptom complexes "dyspnoea" and "pain" were recorded with both questionnaires. The time to deterioration by at least 10 points was analysed. Analyses

for the time to first deterioration were available for all outcomes; analyses for the time to confirmed deterioration were additionally available for lung cancer-specific symptoms.

The EORTC QLQ-C30 symptom scales showed statistically significant differences in favour of alectinib in comparison with crizotinib for the time to first deterioration for each of the following symptoms: diarrhoea, nausea and vomiting, and appetite loss. A statistically significant difference in favour of alectinib in comparison with crizotinib was also shown for the time to first deterioration for the symptom "dysphagia" recorded with the EORTC QLQ-LC13. As a result, there was a hint of an added benefit of alectinib in comparison with crizotinib for each of the following symptoms: diarrhoea, nausea and vomiting, appetite loss, and dysphagia.

A statistically significant difference to the disadvantage of alectinib in comparison with crizotinib was shown for the time to first deterioration for the outcome "haemoptysis". This resulted in a hint of lesser benefit of alectinib versus crizotinib.

A statistically significant difference to the disadvantage of alectinib in comparison with crizotinib was shown for the time to confirmed deterioration for the symptom "dyspnoea" recorded with the EORTC QLQ-LC13. This resulted in a hint of lesser benefit of alectinib versus crizotinib.

No statistically significant difference between the treatment groups was shown for the further symptoms recorded with EORTC QLQ-C30 and EORTC QLQ-LC13. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib for these further symptoms; an added benefit is therefore not proven.

- Health status (VAS of the EQ-5D)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

Health-related quality of life

- EORTC QLQ-C30 (global health status and functional scales)

Health-related quality of life was recorded with the global health status scale and with the functional scales of the EORTC QLQ-C30 questionnaire. The time to deterioration by at least 10 points was analysed in each case. Analyses for the time to first deterioration were available for all outcomes; analyses for the time to confirmed deterioration were additionally available for global health status and cognitive functioning. Neither the global health status scale nor the functional scales showed a statistically significant difference between the treatment arms. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

Side effects

- Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcomes "serious AEs (SAEs)", "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from alectinib in comparison with crizotinib; greater or lesser harm is therefore not proven for these outcomes.

- Specific adverse events

A statistically significant difference in favour of alectinib in comparison with crizotinib was shown for each of the following outcomes: gastrointestinal disorders, eye disorders, neoplasms benign, malignant and unspecified (incl cysts and polyps), nervous system disorders, and torsade de pointes/QT prolongation. This resulted in a hint of lesser harm of alectinib in comparison with crizotinib for each of these outcomes.

There was an effect modification by the characteristic "sex" for gastrointestinal disorders with a statistically significant difference in favour of alectinib for women. This resulted in a hint of lesser harm of alectinib versus crizotinib for women. For men, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from alectinib versus crizotinib for men.

A statistically significant difference to the disadvantage of alectinib versus crizotinib was shown for the outcomes "myalgia" and "renal and urinary disorders". There was a hint of greater harm of alectinib in comparison with crizotinib for the outcome "myalgia".

There was an effect modification by the characteristic "age" for the outcome "renal and urinary disorders" with a statistically significant difference to the disadvantage of alectinib for patients < 65 years. This resulted in a hint of greater harm of alectinib versus crizotinib for these patients. For patients ≥ 65 years, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm of alectinib in comparison with crizotinib for these patients.

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

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

[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

In the overall assessment, there are hints of positive and negative effects of different extent, partly for individual subgroups.

In the present assessment, the added benefit was mainly based on a reduction of some side effects. The results of the symptoms “nausea and vomiting”, “diarrhoea”, and “appetite loss” recorded with the EORTC QLQ-C30 pointed in the same direction as the results on gastrointestinal disorders (AEs). It is unclear whether and to what extent these positive effects of alectinib reflect prevention or delay of symptoms associated with CNS metastases or reflect side effects of the comparator therapy.

On the other hand, there are negative effects in other side effects as well as in the disease-specific symptoms “haemoptysis” and “dyspnoea”. No hint of lesser benefit or of an added benefit of alectinib was shown for overall survival.

In summary, there is a hint of a non-quantifiable added benefit of alectinib in comparison with the ACT crizotinib for the first-line treatment of adult patients with ALK-positive advanced NSCLC.

Table 3 presents a summary of the probability and extent of the added benefit of alectinib.

Table 3: Alectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)[b]	Crizotinib	Hint of a non-quantifiable added benefit

a: Presentation of the ACT specified by the G-BA.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the International Association for the Study of Lung Cancer [IASLC] and the Union for International Cancer Control [UICC]), without medical indication for curative resection, radiotherapy or radiochemotherapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

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

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 alectinib in comparison with crizotinib as ACT in the first-line treatment of adult patients with ALK-positive advanced NSCLC.

This resulted in one research question for the benefit assessment, for which the G-BA specified the ACT presented in Table 4.

Table 4: Research question of the benefit assessment of alectinib

Therapeutic indication	**ACT[a]**
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)[b]	Crizotinib
a: Presentation of the ACT specified by the G-BA. b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the International Association for the Study of Lung Cancer [IASLC] and the Union for International Cancer Control [UICC]), without medical indication for curative resection, radiotherapy or radiochemotherapy. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control	

The company followed the G-BA's specification of the ACT.

The assessment was 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 list on alectinib (status: 1 October 2017)
- bibliographical literature search on alectinib (last search on 2 October 2017)
- search in trial registries for studies on alectinib (last search on 4 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on alectinib (last search on 9 January 2018)

The check identified no additional relevant study.

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: alectinib vs. crizotinib

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study BO28984 (ALEX[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

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: alectinib vs. crizotinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ALEX	RCT, open-label, parallel	Systemic treatment-naive[b] adults (≥ 18 years) with ALK-positive, advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC with or without asymptomatic brain metastases, ECOG PS 0–2	Alectinib (N = 152) crizotinib (N = 151)	Screening: ≤ 28 days Treatment: until progression[c], unacceptable toxicity, withdrawal of consent, or death Observation: outcome-specific, at most until death or end of study	98 centres in: Australia, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Costa Rica, Egypt, France, Great Britain, Guatemala, Hong Kong, Israel, Italy, Mexico, New Zealand, Poland, Portugal, Russia, Serbia, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, Ukraine, USA 8/2014–ongoing **First data cut-off:** 9 Feb 2017[d] **Second data cut-off:** 9 May 2017[e]	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 exclusively include information on the relevant available outcomes for this benefit assessment.
b: Whole brain radiation or gamma knife radiosurgery were allowed pretreatments for brain metastases provided that treatment had been completed 14 days before the start of the study and that the patients were clinically stable.
c: At the investigator's discretion, patients with isolated asymptomatic CNS progression could continue treatment with alectinib or crizotinib after local therapy of the metastasis (e.g. stereotactic radiotherapy or surgery) until systemic progression and/or symptomatic CNS progression. After discontinuation of the study medication, further treatment was also at the investigator's discretion and had to be in line with local practice.
d: Primary analysis after 164 progression events.
e: Additional analysis of harm outcomes requested by the FDA.

ALK: anaplastic lymphoma kinase; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; 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: alectinib vs. crizotinib

Study	Intervention	Comparison
ALEX	Alectinib 600 mg twice daily, orally, in the morning and evening with a meal Dose adjustments, treatment interruptions and discontinuation possible due to intolerance[a]; dose reductions in 150 mg steps to a minimum of 300 mg twice daily	Crizotinib 250 mg twice daily, orally, in the morning and evening with a meal or independent of meals 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
	<u>Pretreatment and concomitant treatment:</u> **Non-permitted pretreatment:** ▪ systemic treatments for advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC ▪ strong CYP3A inducers or inhibitors within 2 weeks or 5 half-lives of prior therapy before start of the study medication **Concomitant treatment permitted:** ▪ anticoagulants and antithrombotics (i.e. coumarin derivatives, unfractionated or low molecular weight heparin, acetylsalicylic acid [≤ 325 mg daily] and clopidogrel) ▪ paracetamol (up to 2 g daily) ▪ drugs increasing gastric pH (e.g. proton pump inhibitors, H2 blockers, antacids) ▪ local treatments (e.g. stereotactic radiotherapy or surgery) in isolated asymptomatic CNS progression (e.g. new CNS oligometastases) ▪ palliative radiotherapy for bone lesions or pain control[b] ***Treatments to be used with precaution or avoided*** ▪ substrates of the BCRP or P-gp transporter and those with a narrow therapeutic index (e.g. digoxin, methotrexate) ▪ CYP3A substrates with narrow therapeutic index ▪ P-gp transporter substrates (e.g. digoxin, dabigatran, colchicine, pravastatin) ▪ drugs causing bradycardia (e.g. beta blockers, calcium channel blockers that are not of the dihydropyridine type, clonidine, digoxin) ▪ Substrates metabolized by CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1 **Non-permitted concomitant treatment** ▪ other antitumour treatments ▪ strong CYP3A inducers (e.g. rifampicin, rifabutin, phenobarbital, St. John's Wort) or CYP3A4 inhibitors (e.g. ketoconazole) including grapefruit and grapefruit juice ▪ QT interval prolonging substances for all patients within 2 weeks before the start of the study medication and during the study in the crizotinib arm ▪ systemic immunosuppressants, cytotoxic or chemotherapeutic drugs, ergot derivatives, probenecid, bile acid sequestrants ▪ systemic chemotherapy ▪ radiotherapy/radionuclide therapy ▪ other experimental medication (except during follow-up observation)	

a: Toxicity-related dose adjustments up to treatment discontinuation were performed without relevant deviation from the requirements of the SPC.
b: If palliative radiation due to bone metastases is indicated, radiation should be started within 24 hours after the last dose of alectinib. Resumed alectinib treatment only in case of ≤ grade 1 radiotoxicity.

BCRP: breast cancer resistance protein; CNS: central nervous system; CYP: cytochrome P450; NSCLC: non-small cell lung cancer; P-gp: P-glycoprotein; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; UGT1A1: uridine diphosphate (UPD) glucuronyl transferase 1-A1; vs.: versus

The ALEX study was an open-label, randomized parallel-group study on the comparison of alectinib versus crizotinib. The study included systemic treatment-naive adults with ALK-positive, advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC with or without asymptomatic brain metastases and a general condition concurring with an ECOG PS of 0 to 2. Prior whole brain radiation therapy or gamma knife radiosurgery for brain metastases was allowed.

The patients (N = 303) were randomly allocated in a ratio of 1:1 to treatment with alectinib (N = 152) or crizotinib (N = 151). Randomization was stratified by ethnicity (Asian/non-Asian), general condition according to ECOG PS (0 or 1/2) and CNS metastasis status at the start of the study (yes/no).

Treatment in both study arms was largely conducted in accordance with the respective SPCs [3,4]. The patients were treated until disease progression (systemic progression and/or symptomatic CNS progression), unacceptable toxicity, withdrawal of consent, or death. At the investigator's discretion, patients with isolated asymptomatic CNS progression could continue treatment with alectinib or crizotinib after local therapy of the metastasis (e.g. stereotactic radiotherapy or surgery) until systemic progression and/or symptomatic CNS progression. After discontinuation of the study medication, further treatment was also at the investigator's discretion and had to be in line with local practice.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and AEs.

Data cut-offs

Two data cut-offs were available:

- First data cut-off (9 February 2017): primary analysis after 164 progression events
- Second data cut-off (9 May 2017): additional analysis of harm outcomes

The primary analysis after 164 progression events (first data cut-off) had been planned; the additional analysis of harm outcomes (second data cut-off) was requested by the Food and Drug Administration (FDA). An interim analysis was not planned. For the benefit assessment, data at both data cut-offs were only available for side effects; for all other patient-relevant outcomes only at the first data cut-off. Since the data cut-off dates were only 3 months apart, however, this did not have a relevant influence on the certainty of conclusions. The data of the last data cut-off were used if available; otherwise, those of the first data cut-off were used.

Planned duration of follow-up observation

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: alectinib vs. crizotinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ALEX	
Mortality	
Overall survival	Until death of about 50% of the patients or termination of the study by the sponsor
Morbidity	
Symptoms (EORTC QLQ-LC13 and EORTC QLQ-C30) Health status (EQ-5D VAS)	Initially every 4 weeks until disease progression[a]; then: ▪ in case of treatment discontinuation due to disease progression: at the final study visit 4 weeks after end of treatment; then every 8 weeks until 6 months after end of treatment ▪ in case of treatment discontinuation for other reasons than disease progression: every 4 weeks until disease progression; in case of disease progression within 6 months after end of treatment, every 8 weeks until 6 months after end of treatment
Health-related quality of life (EORTC QLQ-C30)	
Side effects	
All outcomes in the category "side effects"	Until final study visit 4 weeks after the end of treatment

a: In isolated asymptomatic CNS progression and continued study medication after local treatment, the questionnaire was still to be completed every 4 weeks until treatment discontinuation due to systemic progression and/or symptomatic CNS progression.

CNS: central nervous system; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

In the ALEX study, the results on symptoms, health status, and health-related quality of life were recorded beyond the end of treatment. Nonetheless, the observation periods for these outcomes were shortened because they were only recorded for the period of treatment with the study medication plus 6 months. This also applied to the results on side effects (observation period until 4 weeks after the end of treatment). To be able to draw a more reliable conclusion on the total study period or the time until death of the patients, it would be necessary to record all outcomes over the total period of time, as was the case for overall survival.

Patient characteristics

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

Table 9: Characteristics of the study populations – RCT, direct comparison: alectinib vs. crizotinib

Study Characteristics Category	**Alectinib**	**Crizotinib**
Study ALEX	N[a] = 152	N[a] = 151
Age [years], mean (SD)	56 (12)	54 (14)
Sex [F/M], %	55/45	58/42
Ethnicity, n (%)		
White	76 (50.0)	75 (49.7)
Asian	69 (45.4)	69 (45.7)
Other[b]	7 (4.6)	7 (4.6)
Region, n (%)		
Western Europe	30 (19.7)	28 (18.5)
Asia	67 (44.1)	57 (37.7)
USA	11 (7.2)	13 (8.6)
Other	44 (28.9)	53 (35.1)
Smoking status, n (%)		
Current smoker	12 (7.9)	5 (3.3)
Ex-smoker	48 (31.6)	48 (31.8)
Never-smoker	92 (60.5)	98 (64.9)
Time since first diagnosis [months], mean (SD)	7.4 (16.86)	6.6 (17.26)
Histology, n (%)		
Adenocarcinoma	136 (89.5)	142 (94.0)
Other	16 (10.5)	9 (6.0)
Disease stage at start of study, n (%)		
IIIB	4 (2.6)	6 (4.0)
IV	148 (97.4)	145 (96.0)
ECOG PS at start of study, n (%)		
0	43 (28.3)	54 (35.8)
1	99 (65.1)	87 (57.6)
2	10 (6.6)	10 (6.6)
Brain metastases[c] at start of study, n (%)		
Yes	64 (42.1)	58 (38.4)
No	88 (57.9)	93 (61.6)
Prior radiotherapy of the brain[d]		
Yes	26 (17.1)	21 (13.9)
No	126 (82.9)	130 (86.1)
Treatment discontinuations (second data cut-off), n (%)	71 (46.7)	111 (73.5)
Study discontinuation (second data cut-off), n (%)	56 (36.8)	76 (50.3)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: alectinib vs. crizotinib (continued)

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: Comprising: Native Americans or Native Alaskans, black or African American, Native Hawaiians or other Pacific Islanders, unknown.
c: Measurable and non-measurable; recorded by an IRC.
d: Completed at least 14 days before study inclusion with clinically stable condition.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IRC: independent review committee; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the study population were sufficiently comparable between the alectinib and the crizotinib arm. The average time since diagnosis of the ALK-positive advanced NSCLC at the start of the study was about 7 years. Almost all patients had stage IV disease; more than half of them (about 60%) had no brain metastases at the start of the study. About half of the patients were Asian (about 46%); there was no indication of an effect modification by ethnicity.

At the second data cut-off, more patients in the crizotinib arm than in the alectinib arm had discontinued treatment (crizotinib: 74% versus alectinib: 47%) or the study (crizotinib: 50% versus alectinib: 37%).

Mean and median treatment duration

Table 10 shows the mean and median treatment duration of the patients in the ALEX study.

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

Study **Duration of the study phase** **Outcome category**	**Alectinib**	**Crizotinib**
ALEX	N = 152	N = 151
Treatment duration [months] (Second data cut-off)[a]		
Median [min; max]	20.6 [0; 32]	10.8 [0; 30]
Mean (SD)	16.6 (9.9)	12.8 (8.7)
Observation period [months]		
Overall survival	ND	
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	

a: For the first data cut-off, the median [minimum; maximum] treatment duration was 17.9 [0; 29] in the alectinib arm, and 10.7 [0; 27] in the crizotinib arm; the mean and the standard deviations were 15.0 (8.7) in the alectinib arm and 11.8 (7.7) in the crizotinib arm.
max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration in the ALEX study was almost twice as long in the alectinib arm (20.6 months) as in the crizotinib arm (10.8 months). The difference in treatment duration was caused by differences in treatment discontinuation rates, mainly due to disease progression, and, to a lesser extent, due to withdrawal of consent or death.

The dossier contained no information on observation periods of individual outcomes. It was assumed, however, that the difference in the observation period between the arms was similar to the difference in treatment duration (see Table 8 for the planned duration of follow-up observation).

Risk of bias at study level

Table 11 shows the risk of bias at study level.

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ALEX	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 included ALEX study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-LC13

- health status measured with the EQ-5D VAS

- 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 deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

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

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

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30[a] and EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[c]
ALEX	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: EORTC QLQ-C30 symptom scales.
b: EORTC QLQ-C30 functional scales.
c: The following events are considered (MedDRA coding): gastrointestinal disorders (SOC in AEs), eye disorders (SOC in AEs), renal and urinary disorders (SOC in AEs), neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC in AEs), nervous system disorders (SOC in AEs), myalgia (PT in AEs), Torsade de pointes/QT prolongation (SMQ).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: alectinib vs. crizotinib

Study	Study level	Outcomes							
		Overall survival	Symptoms (EORTC QLQ-C30[a] and EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[c]
ALEX	L	L	H[d, e, f]	H[d, e, f]	H[d, e, f]	H[f]	H[e]	H[f]	H[f]

a: EORTC QLQ-C30 symptom scales.
b: EORTC QLQ-C30 functional scales.
c: The following events are considered (MedDRA coding): gastrointestinal disorders (SOC in AEs), eye disorders (SOC in AEs), renal and urinary disorders (SOC in AEs), neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC in AEs), nervous system disorders (SOC in AEs), myalgia (PT in AEs), Torsade de pointes/QT prolongation (SMQ).
d: Large proportion (> 30%) of patients unconsidered in the analyses. There were no indications of a systematic lack of values, however (see Sections 2.7.2.4.3 and 2.7.2.4.2 of the full dossier assessment).
e: Lack of blinding in conjunction with subjective component of the outcome.
f: Potentially informative censoring or shortened observation periods.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias of the result for the outcome “overall survival” was rated as low.

The results for the outcomes “symptoms”, “health status”, “health-related quality of life”, “SAEs” and “severe AEs with CTCAE grade ≥ 3” have a high risk of bias already due to the differences in observation periods between the treatment arms and the associated potentially informative censoring. For the outcomes on discontinuation due to AEs, symptoms, health status and health-related quality of life, the lack of blinding in conjunction with a subjective component of the outcomes resulted in or contributed to the high risk of bias of the results. The results of all outcomes recorded with questionnaires had a high risk of bias particularly due to the large proportion of patients unconsidered in the analyses (> 30%), which principally results in the non-usability of such data (see also Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment). In the present data constellation, however, the results are interpretable nonetheless

as the statistically significant results from the EORTC recordings point to the same direction as the results of related side effect complexes (in the analysis of which, without a large proportion of censorings at the start of the study, all patients were included still under observation). Hence, it was assumed that there was no systematic lack of values at the start of the study and that possible bias for all outcomes with this problem is therefore still acceptable. Due to the resulting uncertainty regarding the position and the width of the confidence interval, the extent of added benefit was non-quantifiable, however.

The result of the rating of the risk of bias only partly concurs with the assessment of the company, which rated the risk of bias for all outcomes on side effects together as low.

2.4.3 Results

Table 14 summarizes the results on the comparison of alectinib with crizotinib in the first-line treatment of patients with ALK-positive advanced NSCLC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves, as far as available, can be found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results – RCT, direct comparison: alectinib vs. crizotinib

Study Outcome category Instrument Outcome	Alectinib N	Alectinib 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 (%)	Alectinib vs. crizotinib HR [95% CI][a]; p-value[b]
ALEX					
Mortality (first data cut-off)					
Overall survival	152	NA [NA; NA][c] 35 (23.0)	151	NA [NA; NA][c] 40 (26.5)	0.76 [0.48; 1.20]; 0.241
Morbidity (first data cut-off)					
Symptoms (EORTC QLQ-C30 symptom scales)					
Time to confirmed deterioration[d, e]					
Dyspnoea	152	NA [NA; NA] 26 (17.1)	151	NA [NA; NA] 15 (9.9)	1.66 [0.88; 3.15]; 0.114
Fatigue	152	NA [NA; NA] 33 (21.7)	151	NA [9.4; NA] 38 (25.2)	0.74 [0.46; 1.19]; 0.208
Time to first deterioration[d]					
Pain	152	11.0 [5.6; 25.8] 54 (35.5)	151	10.0 [5.6; 13.1] 56 (37.1)	0.86 [0.59; 1.25]; 0.418
Insomnia	152	25.8 [25.8; NA] 34 (22.4)	151	21.0 [12.6; NA] 37 (24.5)	0.81 [0.50; 1.30]; 0.379
Diarrhoea	152	21.0 [12.8; NA] 42 (27.6)	151	2.7 [1.6; 3.7] 73 (48.3)	0.28 [0.19; 0.42]; < 0.001
Nausea and vomiting	152	15.7 [9.2; NA] 49 (32.2)	151	1.9 [1.0; 4.4] 68 (45.0)	0.41 [0.28; 0.60]; < 0.001
Appetite loss	152	NA [21.1; NA] 32 (21.1)	151	13.3 [5.4; NA] 48 (31.8)	0.44 [0.28; 0.70]; < 0.001
Constipation	152	1.8 [1.0; 3.6] 70 (46.1)	151	1.7 [1.0; 2.8] 74 (49.0)	0.81 [0.58; 1.12]; 0.181
Symptoms (EORTC QLQ-LC13 symptom scales)					
Time to confirmed deterioration[d, e]					
Dyspnoea	152	22.8 [11.8; NA] 42 (27.6)	151	NA [21.0; NA] 24 (15.9)	1.76 [1.05; 2.92]; 0.029
Cough	152	NA [24.0; NA] 16 (10.5)	151	NA [NA; NA] 17 (11.3)	0.88 [0.44; 1.74]; 0.704
Pain (thorax)	152	NA [NA; NA] 11 (7.2)	151	NA [NA; NA] 17 (11.3)	0.51 [0.24; 1.10]; 0.080
Pain in arm or shoulder	152	NA [NA; NA] 28 (18.4)	151	NA [NA; NA] 18 (11.9)	1.43 [0.79; 2.61]; 0.238

(continued)

Table 14: Results – RCT, direct comparison: alectinib vs. crizotinib (continued)

Study Outcome category Instrument Outcome	Alectinib N	Alectinib 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 (%)	Alectinib vs. crizotinib HR [95% CI][a]; p-value[b]
Time to first deterioration					
Haemoptysis	152	NA [NA; NA] 12 (7.9)	151	NA [NA; NA] 3 (2.0)	3.33 [0.93; 11.83]; 0.049[f]
Pain (other)	152	18.3 [9.4; NA] 45 (29.6)	151	7.6 [5.7; 18.2] 50 (33.1)	0.78 [0.52; 1.17]; 0.220
Sore mouth	152	23.3 [11.8; NA] 42 (27.6)	151	15.2 [7.2; NA] 43 (28.5)	0.77 [0.50; 1.19]; 0.231
Dysphagia	152	NA [22.7; NA] 31 (20.4)	151	10.2 [8.1; NA] 43 (28.5)	0.49 [0.30; 0.79]; 0.003
Neuropathy peripheral	152	8.3 [4.7; 17.2] 54 (35.5)	151	5.3 [2.6; 10.9] 62 (41.1)	0.74 [0.51; 1.06]; 0.101
Alopecia	152	14.8 [11.8; NA] 46 (30.3)	151	18.0 [11.8; NA] 38 (25.2)	1.10 [0.72; 1.70]; 0.654
Health status (EQ-5D VAS[g])					
Time to first deterioration					
7 points	152	9.0 [3.7; 14.8] 59 (38.8)	151	7.9 [2.9; 15.5] 57 (37.7)	0.97 [0.67; 1.40]; 0.861
10 points	152	11.0 [6.2; 21.1] 55 (36.2)	151	10.2 [5.6; 20.0] 52 (34.4)	0.95 [0.65; 1.39]; 0.788
Health-related quality of life (first data cut-off)					
EORTC QLQ-C30 functional scales[h]					
Time to confirmed deterioration[e, h]					
Global health status	152	NA [NA; NA] 17 (11.2)	151	NA [NA; NA] 20 (13.2)	0.72 [0.38; 1.39]; 0.326
Cognitive functioning	152	NA [14.5; NA] 40 (26.3)	151	20.0 [9.5; NA] 39 (25.8)	0.85 [0.55; 1.33]; 0.490
Time to first deterioration[h]					
Physical functioning	152	10.1 [5.1; NA] 51 (33.6)	151	17.3 [6.5; NA] 47 (31.1)	1.07 [0.72; 1.60]; 0.736
Role functioning	152	5.6 [3.4; 9.5] 61 (40.1)	151	10.2 [4.9; 14.6] 54 (35.8)	1.16 [0.80; 1.68]; 0.431
Emotional functioning	152	NA [11.8; NA] 40 (26.3)	151	17.3 [9.9; NA] 41 (27.2)	0.80 [0.52; 1.24]; 0.324
Social functioning	152	8.6 [5.1; 14.3] 56 (36.8)	151	7.6 [2.9; 17.6] 53 (35.1)	0.90 [0.62; 1.31]; 0.577

(continued)

Table 14: Results – RCT, direct comparison: alectinib vs. crizotinib (continued)

Study Outcome category Instrument Outcome	Alectinib N	Alectinib 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 (%)	Alectinib vs. crizotinib HR [95% CI][a]; p-value[b]
Side effects (second data cut-off)					
AEs (supplementary information)	152	ND 147 (96.7)	151	ND 147 (97.4)	–
SAEs	152	ND 46 (30.3)	151	ND 45 (29.8)	0.98 [0.65; 1.48][i]; 0.917[j]
Severe AEs (CTCAE grade ≥ 3)	152	ND 68 (44.7)	151	ND 77 (51.0)	0.80 [0.58; 1.12][i]; 0.187[j]
Discontinuation due to AEs	152	ND 18 (11.8)	151	ND 19 (12.6)	RR[k]: 0.94 [0.51; 1.72]; 0.897
Specific adverse events					
Gastrointestinal disorders	152	ND 87 (57.2)	151	ND 121 (80.1)	0.44 [0.34; 0.58][i]; < 0.001[j]
Eye disorders	152	ND 13 (8.6)	151	ND 52 (34.4)	0.20 [0.11; 0.37][i]; < 0.001[j]
Renal and urinary disorders	152	ND 17 (11.2)	151	ND 6 (4.0)	2.86 [1.13; 7.24][i]; 0.021[j]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	152	ND 0 (0.0)	151	ND 3 (2.0)	-[l]; 0.047[j]
Nervous system disorders	152	ND 44 (28.9)	151	ND 69 (45.7)	0.52 [0.35; 0.75][i]; < 0.001[j]
Myalgia	152	ND 24 (15.8)	151	ND 3 (2.0)	8.39 [2.53; 27.88][i]; < 0.001[j]
Torsade de pointes/QT prolongation	152	ND 0 (0.0)	151	ND 8 (5.3)	-[l]; 0.004[j]

(continued)

Table 14: Results – RCT, direct comparison: alectinib vs. crizotinib (continued)

a: Stratified Cox model with the following stratification factors: ethnicity (Asian/non-Asian) and CNS metastases at the start of the study according to the IRC (yes/no).
b: Stratified log-rank test with the following stratification factors: ethnicity (Asian/non-Asian) and CNS metastases at the start of the study according to the IRC (yes/no).
c: Median [Q1; Q3] of time to event in months: NA [19.9; NA] (alectinib) and NA [17.1; NA] (crizotinib).
d: Deterioration defined as increase in score by at least 10 points versus the baseline value.
e: Confirmed defined as deterioration for at least 2 consecutive measurements or death within 5 weeks after initial deterioration.
f: Discrepancy between p-value (log-rank test, primary method) and 95% CI (Cox model, non-primary method) due to different calculation methods.
g: Deterioration defined as decrease in score by 7 or 10 points.
h: Deterioration defined as decrease in score by at least 10 points versus the baseline value.
i: Unstratified Cox model.
j: Unstratified log-rank test.
k: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test: CSZ method according to [5]).
l: No presentation of effect estimation and CI as these are not informative.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IRC: independent review committee; n: number of patients with at least one event; N: number of analysed patients; NA: not achieved; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome “all-cause mortality”. Due to the high risk of bias, at most hints can be determined for the following outcomes: symptoms, health status, health-related quality of life, SAEs, discontinuation due to AEs, severe AEs (CTCAE grade ≥ 3) and specific AEs (see Section 2.4.2).

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome “overall survival”. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived a non-quantifiable added benefit based on a numerically positive trend for alectinib.

Morbidity

Symptoms (symptom scales of EORTC QLQ-C30 and EORTC-QLQ-LC13)

Symptoms were recorded with the symptom scales of the disease-specific questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13. The symptoms and symptom complexes “dyspnoea” and “pain” were recorded with both questionnaires. The time to deterioration by at least 10 points was analysed. Analyses for the time to first deterioration were available for all

outcomes; analyses for the time to confirmed deterioration were additionally available for lung cancer-specific symptoms.

The symptoms with statistically significant group differences are initially described.

Diarrhoea, nausea and vomiting, appetite loss (each EORTC QLQ-C30), dysphagia (EORTC QLQ-LC13)

The EORTC QLQ-C30 symptom scales showed statistically significant differences in favour of alectinib in comparison with crizotinib for the time to first deterioration for each of the following symptoms: diarrhoea, nausea and vomiting, and appetite loss. A statistically significant difference in favour of alectinib in comparison with crizotinib was also shown for the time to first deterioration for the symptom "dysphagia" recorded with the EORTC QLQ-LC13. As a result, there was a hint of an added benefit of alectinib in comparison with crizotinib for each of the following symptoms: diarrhoea, nausea and vomiting, appetite loss, and dysphagia.

This concurs with the company's assessment.

Haemoptysis (EORTC QLQ-LC13)

For the symptom "haemoptysis", there was a discrepancy between p-value and 95% confidence interval (CI) because of different calculation methods. The statistical analysis plan predefined the log-rank test for the calculation of the p-value as primary method; hence, the conclusion on the added benefit was based on the p-value. A statistically significant difference to the disadvantage of alectinib in comparison with crizotinib was shown for the time to first deterioration for the symptom "haemoptysis". This resulted in a hint of lesser benefit of alectinib versus crizotinib.

This deviates from the assessment of the company, which did not consider the difference between the treatment groups to be significantly different for the symptom "haemoptysis".

Dyspnoea (EORTC QLQ-C30 and EORTC QLQ-LC13)

Both questionnaires used record the symptom "dyspnoea". No statistically significant difference between the treatment groups for the time to confirmed deterioration was shown for dyspnoea recorded with one single question of the EORTC QLQ-C30; an added benefit for this outcome is therefore not proven. The EORTC QLQ-LC13, in contrast, has 3 different questions to record dyspnoea, making the recording more differentiated and more specific for the underlying condition NSCLC. A statistically significant difference to the disadvantage of alectinib in comparison with crizotinib was shown for the time to confirmed deterioration for the symptom "dyspnoea" recorded with the EORTC QLQ-LC13. This resulted in a hint of lesser benefit of alectinib versus crizotinib.

In the result, this also concurs with the company's assessment.

Further symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)

There was no statistically significant difference between the treatment groups for further symptoms. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib for these further symptoms; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (VAS of the EQ-5D)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

EORTC QLQ-C30 (global health status and functional scales)

Health-related quality of life was recorded with the global health status scale and with the functional scales of the EORTC QLQ-C30 questionnaire. The time to deterioration by at least 10 points was analysed in each case. Analyses for the time to first deterioration were available for all outcomes; analyses for the time to confirmed deterioration were additionally available for global health status and cognitive functioning. Neither the global health status scale nor the functional scales showed a statistically significant difference between the treatment arms. Hence, there was no hint of an added benefit of alectinib in comparison with crizotinib; an added benefit is therefore not proven.

In the result, this also concurs with the company's assessment.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

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

This concurs with the company's assessment.

Specific adverse events

Gastrointestinal disorders, eye disorders, neoplasms benign, malignant and unspecified (incl cysts and polyps), nervous system disorders and torsade de pointes/QT prolongation

A statistically significant difference in favour of alectinib in comparison with crizotinib was shown for each of the following outcomes: gastrointestinal disorders, eye disorders, neoplasms

benign, malignant and unspecified (incl cysts and polyps), nervous system disorders, and torsade de pointes/QT prolongation. This resulted in a hint of lesser harm of alectinib in comparison with crizotinib for each of these outcomes.

There was an effect modification by the characteristic "sex" for gastrointestinal disorders with a statistically significant difference in favour of alectinib for women. This resulted in a hint of lesser harm of alectinib versus crizotinib for women. For men, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from alectinib versus crizotinib for men.

Renal and urinary disorders and myalgia

A statistically significant difference to the disadvantage of alectinib versus crizotinib was shown for the outcomes "myalgia" and "renal and urinary disorders". There was a hint of greater harm of alectinib in comparison with crizotinib for the outcome "myalgia".

There was an effect modification by the characteristic "age" for the outcome "renal and urinary disorders" with a statistically significant difference to the disadvantage of alectinib for patients < 65 years. This resulted in a hint of greater harm of alectinib versus crizotinib for these patients. For patients ≥ 65 years, in contrast, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm of alectinib in comparison with crizotinib for these patients.

This partly concurs with the assessment of the company, which, on the basis of some AEs, derived considerable added benefit for these AEs jointly. In line with the benefit assessment, it considered the AEs "myalgia", which, referring to the severity grade of the events, it considered to be not clinically relevant, and "prolongation of QT interval".

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 65, ≥ 65)
- sex (male, female)
- geographical region (Western Europe, USA, Asia, other)
- ECOG PS (0 or 1, 2)
- CNS metastases at the start of the study according to the Response Evaluation Criteria in Solid Tumours (RECIST) and an independent review committee (IRC) (yes, no)
- prior radiotherapy of the brain (yes, no)

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.

Only subgroup analyses on the characteristics of sex, age, region, and ECOG PS were available for side effect outcomes.

The subgroup analyses for the outcomes recorded with questionnaires were incomplete; they were only available for time to first deterioration. Furthermore, a large proportion (> 30%) of patients was unconsidered in the analyses of the outcomes recorded with questionnaires. The corresponding subgroup analyses were therefore not considered.

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

Table 15: Subgroups – RCT, direct comparison: alectinib vs. crizotinib

Study Outcome Characteristic Subgroup	Alectinib N	Alectinib 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 (%)	Alectinib vs. crizotinib HR [95% CI][a]	Alectinib vs. crizotinib p-value[b]
ALEX						
Gastrointestinal disorders						
Sex						
Men	68	ND 40 (58.8)	64	ND 44 (68.8)	0.66 [0.43; 1.01]	0.062
Women	84	ND 47 (56.0)	87	ND 77 (88.5)	0.32 [0.22; 0.47]	< 0.001
					Interaction:	0.016[c]
Renal and urinary disorders						
Age						
< 65 years	115	ND 14 (12.2)	118	ND 2 (1.7)	7.39 [1.68; 32.51]	0.002
≥ 65 years	37	ND 3 (8.1)	33	ND 4 (12.1)	0.65 [0.15; 2.90]	0.568
					Interaction:	0.018[c]
Nervous system disorders						
Age						
< 65 years	115	ND 39 (33.9)	118	ND 47 (39.8)	0.75 [0.49; 1.15]	0.195
≥ 65 years	37	ND 5 (13.5)	33	ND 22 (66.7)	0.12 [0.04; 0.32]	< 0.001
					Interaction:	< 0.001[c]
ECOG PS						
0/1	142	ND 39 (27.5)	141	ND 66 (46.8)	0.47 [0.31; 0.69]	< 0.001
2	10	ND 5 (50.0)	10	ND 3 (30.0)	2.84 [0.66; 12.17]	0.144
					Interaction:	0.031[c]

a: Unstratified Cox model.
b: Unstratified log-rank test.
c: p-value from likelihood ratio test.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; n: number of patients with at least one event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

Side effects

Gastrointestinal disorders

There was an effect modification by the characteristic "sex" for the outcome "gastrointestinal disorders". A statistically significant difference in favour of alectinib in comparison with crizotinib was shown for women, whereas there was no statistically significant difference between the treatment groups for men. This resulted in a hint of lesser harm from alectinib for women. For men, in contrast, there was no hint of greater or lesser harm from alectinib in comparison with crizotinib; greater or lesser harm for men is therefore not proven.

Renal and urinary disorders

There was an effect modification by the characteristic "age" for the outcome "renal and urinary disorders". A statistically significant difference to the disadvantage of alectinib was shown for patients < 65 years, whereas there was no statistically significant difference between the treatment groups for patients ≥ 65 years. This resulted in a hint of greater harm from alectinib versus crizotinib for patients < 65 years. For patients ≥ 65 years, in contrast, there was no hint of greater or lesser harm from alectinib in comparison with crizotinib; greater or lesser harm for these patients is therefore not proven.

Nervous system disorders

There were effect modifications by the characteristics "age" and "ECOG PS" for the outcome "nervous system disorders". A statistically significant difference in favour of alectinib was shown for patients ≥ 65 years, whereas there was no statistically significant difference between the treatment groups for patients < 65 years. A statistically significant difference in favour of alectinib versus crizotinib was also shown for patients with an ECOG PS of 0 or 1, whereas there was no statistically significant difference between the treatment groups for patients with an ECOG PS of 2.

However, since no data were available for investigating the dependencies between the subgroup characteristics "age" and "ECOG PS", the results of the total population were used for the derivation of an added benefit.

The derivation of conclusions for individual subgroups deviates from the approach of the company, which did not use the specific AEs for the derivation of the added benefit and hence drew no conclusion on the presence of effect modifications.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, 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 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 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 AEs

It was not clear from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification is therefore justified below.

It could not be inferred from the dossier that the outcomes on symptoms of the EORTC QLQ-C30 and QLQ-LC13 were severe or serious symptoms. These outcomes were therefore rated as non-severe or non-serious. The specific AEs, except for Torsade de pointes/QT prolongation, were also allocated to the category of non-serious/non-severe side effects, as these AEs – or the AEs included in these outcomes – were mostly non-serious/non-severe. The outcome "Torsade de pointes/QT prolongation", in contrast, was allocated to the category of serious/severe side effects because most of them were severe events (CTCAE grade 3).

Table 16: Extent of added benefit at outcome level: alectinib vs. crizotinib

Outcome category **Outcome**	**Alectinib vs. crizotinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. NA HR 0.76 [0.48; 1.20]; p = 0.241	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales)		
Time to confirmed deterioration		
Dyspnoea	Median: NA vs. NA HR 1.66 [0.88; 3.15]; p = 0.114	Lesser benefit/added benefit not proven
Fatigue	Median: NA vs. NA HR 0.74 [0.46; 1.19]; p = 0.208	Lesser benefit/added benefit not proven
Time to first deterioration		
Pain	Median: 11.0 vs. 10.0 HR 0.86 [0.59; 1.25]; p = 0.418	Lesser benefit/added benefit not proven
Insomnia	Median: 25.8 vs. 21.0 HR 0.81 [0.50; 1.30]; p = 0.379	Lesser benefit/added benefit not proven
Diarrhoea	Median: 21.0 vs. 2.7 HR 0.28 [0.19; 0.42]; p = < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
Nausea and vomiting	Median: 15.7 vs. 1.9 HR 0.41 [0.28; 0.60]; p = < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
Appetite loss	Median: NA vs. 13.3 HR 0.44 [0.28; 0.70]; p = < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
Constipation	Median: 1.8 vs. 1.7 HR 0.81 [0.58; 1.12]; p = 0.181	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: alectinib vs. crizotinib (continued)

Outcome category **Outcome**	**Alectinib vs. crizotinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Symptoms (EORTC QLQ-LC13 symptom scales)		
Time to confirmed deterioration		
Dyspnoea	Median: 22.8 vs. NA HR: 1.76 [1.05; 2.92] HR: 0.57 [0.34; 0.95][d] p = 0.029 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications Lesser benefit, extent: "non-quantifiable"[c]
Cough	Median: NA vs. NA HR 0.88 [0.44; 1.74]; p = 0.704	Lesser benefit/added benefit not proven
Pain (thorax)	Median: NA vs. NA HR 0.51 [0.24; 1.10]; p = 0.080	Lesser benefit/added benefit not proven
Pain in arm or shoulder	Median: NA vs. NA HR 1.43 [0.79; 2.61]; p = 0.238	Lesser benefit/added benefit not proven
Time to first deterioration		
Haemoptysis	Median: NA vs. NA HR: 3.33 [0.93; 11.83][f]; p = 0.049 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications Lesser benefit, extent: "non-quantifiable"[c]
Pain (other)	Median: 18.3 vs. 7.6 HR 0.78 [0.52; 1.17]; p = 0.220	Lesser benefit/added benefit not proven
Sore mouth	Median: 23.3 vs. 15.2 HR 0.77 [0.50; 1.19]; p = 0.231	Lesser benefit/added benefit not proven
Dysphagia	Median: NA vs. 10.2 HR 0.49 [0.30; 0.79]; p = 0.003 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[c]
Neuropathy peripheral	Median: 8.3 vs. 5.3 HR 0.74 [0.51; 1.06]; p = 0.101	Lesser benefit/added benefit not proven
Alopecia	Median: 14.8 vs. 18.0 HR 1.10 [0.72; 1.70]; p = 0.654	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: alectinib vs. crizotinib (continued)

Outcome category **Outcome**	**Alectinib vs. crizotinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health status (EQ-5D VAS)		
Time to first deterioration		
7 points	Median: 9.0 vs. 7.9 HR 0.97 [0.67; 1.40]; p = 0.861	Lesser benefit/added benefit not proven
10 points	Median: 11.0 vs. 10.2 HR 0.95 [0.65; 1.39]; p = 0.788	
Health-related quality of life		
EORTC QLQ-C30 functional scales		
Time to confirmed deterioration		
Global health status	Median: NA vs. NA HR 0.72 [0.38; 1.39]; p = 0.326	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NA vs. 20.0 HR 0.85 [0.55; 1.33]; p = 0.490	Lesser benefit/added benefit not proven
Time to first deterioration		
Physical functioning	Median: 10.1 vs. 17.3 HR 1.07 [0.72; 1.60]; p = 0.736	Lesser benefit/added benefit not proven
Role functioning	Median: 5.6 vs. 10.2 HR 1.16 [0.80; 1.68]; p = 0.431	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA vs. 17.3 HR 0.80 [0.52; 1.24]; p = 0.324	Lesser benefit/added benefit not proven
Social functioning	Median: 8.6 vs. 7.6 HR 0.90 [0.62; 1.31]; p = 0.577	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: alectinib vs. crizotinib (continued)

Outcome category **Outcome**		**Alectinib vs. crizotinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects			
SAEs		Median: ND HR 0.98 [0.65; 1.48]; p = 0.917	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)		Median: ND HR 0.80 [0.58; 1.12]; p = 0.187	Greater/lesser harm not proven
Discontinuation due to adverse events		Proportion of events: 11.8 vs. 12.6 RR: 0.94 [0.51; 1.72]; p = 0.897	Greater/lesser harm not proven
Specific adverse events			
Gastrointestinal disorders			
Sex	Men	Median: ND HR: 0.66 [0.43; 1.01] p = 0.062	Greater/lesser harm not proven
	Women	Median: ND HR: 0.32 [0.22; 0.47] p = < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Eye disorders		Median: ND HR: 0.20 [0.11; 0.37] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Renal and urinary disorders			
Age	< 65 years	Median: ND HR: 7.39 [1.68; 32.51] HR: 0.14 [0.03; 0.60][d] p = 0.002 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”
	≥ 65 years	Median: ND HR: 0.65 [0.15; 2.90] p = 0.568	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: alectinib vs. crizotinib (continued)

Outcome category **Outcome**	**Alectinib vs. crizotinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Median: ND HR: -[g] p = 0.047 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications lesser harm, extent: "non-quantifiable"
Nervous system disorders	Median: ND HR: 0.52 [0.35; 0.75] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Myalgia	Median: ND HR: 8.39 [2.53; 27.88] HR: 0.12 [0.04; 0.40][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: "considerable"
Torsade de pointes/QT prolongation	Median: ND HR: -[g] p = 0.004 Probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Due to the large proportion of missing patients in the analysis (> 30%), the extent of the added benefit is non-quantifiable (see Section 2.4.2).
d: Institute's calculation; inverse direction of effect.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f: Discrepancy between p-value (log-rank test, primary method) and 95% CI (Cox model, non-primary method) due to different calculation methods.
g: No presentation of effect estimation and CI as these are not informative.
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; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Symptoms (diarrhoea, nausea and vomiting, appetite loss, dysphagia): hint of an added benefit – extent "non-quantifiable"	Non-serious/non-severe symptoms/late complications ▪ Symptoms (dyspnoea, haemoptysis): hint of lesser benefit – extent "non-quantifiable"
Non-serious/non-severe side effects ▪ Gastrointestinal disorders: ▫ sex (women): hint of lesser harm – extent "considerable" ▪ Eye disorders: hint of lesser harm – extent "considerable" ▪ Neoplasms benign, malignant and unspecified (incl cysts and polyps): hint of lesser harm – extent "non-quantifiable" ▪ Nervous system disorders: hint of lesser harm – extent "considerable"	Non-serious/non-severe side effects ▪ Renal and urinary disorders: ▫ age (< 65 years): hint of greater harm – extent "considerable" ▪ Myalgia: hint of greater harm – extent "considerable"
Serious/severe side effects ▪ Torsade de pointes/QT prolongation: hint of lesser harm – extent "non-quantifiable"	-

In the overall assessment, there are hints of positive and negative effects of different extent, partly for individual subgroups.

In the present assessment, the added benefit was mainly based on a reduction of some side effects. The results of the symptoms "nausea and vomiting", "diarrhoea", and "appetite loss" recorded with the EORTC QLQ-C30 pointed in the same direction as the results on gastrointestinal disorders (AEs). It is unclear whether and to what extent these positive effects of alectinib reflect prevention or delay of symptoms associated with CNS metastases or reflect side effects of the comparator therapy.

On the other hand, there are negative effects in other side effects as well as in the disease-specific symptoms "haemoptysis" and "dyspnoea". No hint of lesser benefit or of an added benefit of alectinib was shown for overall survival.

In summary, there is a hint of a non-quantifiable added benefit of alectinib in comparison with the ACT crizotinib for the first-line treatment of adult patients with ALK-positive advanced NSCLC.

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

Table 18: Alectinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)[b]	Crizotinib	Hint of a non-quantifiable added benefit

a: Presentation of the ACT specified by the G-BA.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the International Association for the Study of Lung Cancer [IASLC] and the Union for International Cancer Control [UICC]), without medical indication for curative resection, radiotherapy or radiochemotherapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

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

2.6 List of included studies

ALEX

F. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer: study BO28984; clinical study protocol [unpublished]. 2016.

F. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer: study BO28984; primary clinical study report [unpublished]. 2017.

F. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer: study BO28984; Zusatzanalysen [unpublished]. 2017.

F. Hoffmann-La Roche. Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer: study BO28984; statistical analysis plan [unpublished]. 2017.

Roche. 90-day safety update report for alectinib (RO5424802) [unpublished]. 2017.

Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017; 377(9): 829-838.

Hoffmann-La Roche. A study comparing alectinib with crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer participants (ALEX): study details [online]. In: ClinicalTrials.gov. 28.11.2017 [Accessed: 11.01.2018]. URL: https://ClinicalTrials.gov/show/NCT02075840.

F. Hoffmann-La Roche. Randomized, multicenter, phase III, open label study of alectinib versus crizotinib in treatment naïve anaplastic lymphoma kinase-positive advanced non-small cell lung cancer [online]. In: EU Clinical Trials Register. [Accessed: 11.01.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004133-33.

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Pfizer. Xalkori 200/250 mg Hartkapseln: Fachinformation [online]. 07.2017 [Accessed: 11.09.2017]. URL: http://www.fachinfo.de.

4. Roche. Alecensa: Fachinformation [online]. 12.2017. URL: https://www.fachinfo.de/.

5. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-67-alectinib-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.8474.html.