IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-62

Ceritinib (non-small cell lung cancer) – Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ceritinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2016). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ceritinib (non-small cell lung cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 September 2016

Internal Commission No.:

A16-62

Address of publisher:

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:

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, 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[2]:

- Gregor Moritz
- Lars Beckmann
- Katharina Biester
- Thomas Kaiser
- Marco Knelangen
- Petra Kohlepp
- Martina Markes
- Corinna ten Thoren

Keywords: ceritinib, carcinoma – non-small-cell lung, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] 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
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCSS	Lung Cancer Symptom Scale
MMRM	mixed-effects model repeated measures
NSCLC	non-small cell lung cancer
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 ceritinib. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier of the drug to be evaluated on 30 June 2015 for the early benefit assessment. This dossier was assessed in dossier assessment A15-24. In this procedure, by decision of 17 December 2015, the G-BA limited its decision until 1 October 2016. 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 September 2016.

Research question

The aim of the present report was to assess the added benefit of ceritinib in comparison with docetaxel or pemetrexed as appropriate comparator therapy (ACT) in adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

According to the approved therapeutic indication, ceritinib is used in patients previously treated with crizotinib. When the first procedure was initiated, crizotinib was not approved before the second line of treatment, and, consequently, ceritinib not before the third line of treatment. In the meantime, following an extension of approval of crizotinib on 23 November 2015 to first-line treatment, the therapeutic indication of ceritinib was also extended, i.e. to use from the second line of treatment. According to the G-BA commission, however, the present benefit assessment of ceritinib only refers to the treatment situation in which patients had already been treated with at least one further therapy before treatment with crizotinib. This concurs with the subject of the first benefit assessment of ceritinib.

In its specification of the ACT, the G-BA differentiated between patients for whom treatment with docetaxel or pemetrexed is an option and those patients for whom such treatment is not an option. This differentiation of the patient groups resulted in 2 research questions for the assessment. Table 2 shows an overview of the research questions.

Table 2: Research questions of the benefit assessment of ceritinib

Research question	Therapeutic indication[a]	ACT[b]
1	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option[c]	**Docetaxel** or **pemetrexed**
2	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option[d]	BSC[e]

a: It is assumed for the present therapeutic indication that the patients had received platinum-based chemotherapy in their first-line treatment and were then treated with crizotinib.
b: Presentation of the respective 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.
c: Operationalized in the present benefit assessment as patients with ECOG PS 0, 1 and possibly 2.
d: Operationalized in the present benefit assessment as patients with ECOG PS 4, 3 and possibly 2.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

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.

Results for research question 1: patients for whom treatment with docetaxel or pemetrexed is an option

Study pool and study characteristics

The study ASCEND-5 was included in the benefit assessment. The study was an open-label, randomized controlled, multicentre study on the comparison of ceritinib with docetaxel or pemetrexed. It included adult patients with ALK-positive advanced NSCLC previously treated both with platinum-based chemotherapy and crizotinib. 231 patients were randomized, of which 115 patients were allocated to the ceritinib arm and 116 patients to the chemotherapy arm. The physician decided whether the patients in the chemotherapy arm received docetaxel or pemetrexed. Patients in the ceritinib arm received a daily dose of 750 mg ceritinib orally. Patients in the chemotherapy arm received either 75 mg/m^2 body surface area docetaxel or 500 mg/m^2 body surface area pemetrexed, each as an infusion, every 3 weeks. Treatments were administered in accordance with the approval. Treatment with the randomized study medication was continued until a criterion for discontinuation occurred, e.g. progression. The patients in both treatment arms could receive the randomized study medication beyond progression. In the chemotherapy arm, the patients could switch to ceritinib when progression occurred.

Primary outcome of the study was progression-free survival. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and adverse events (AEs).

The median treatment duration in the ASCEND-5 study was notably longer in the ceritinib arm (30.3 weeks) than in the chemotherapy arm (6.3 weeks). The difference in treatment durations was caused by differences in the rates of treatment discontinuation particularly due to progression. 64.7% of the patients in the chemotherapy arm switched to subsequent treatment with ceritinib.

Risk of bias

The risk of bias at study level was rated as low for the ASCEND-5 study. The risk of bias was rated as high for the following outcomes: overall survival, serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4) and discontinuation due to AEs. The risk of bias for the outcome "overall survival" was rated as high because of the large proportion of patients who switched treatment from the chemotherapy to the ceritinib arm (64.7%); for the outcomes "SAEs", "severe AEs" (CTCAE grade 3 or 4) and "discontinuation due to AEs" additionally due to potentially informative censoring.

The company presented responder analyses for the outcomes on morbidity and health-related quality of life. The time to definitive deterioration by a validated threshold value versus the baseline value was considered as response criterion. Deterioration was only considered to be definitive, and therefore as event, if this also applied to all subsequent values or if the deterioration (response) was present at the time point of the last measurement in the observation period. The outcomes were recorded with different questionnaires. Due to the design of the ASCEND-5 study, these data are not meaningfully interpretable, however.

Between the treatment arms, the number of patients with completed questionnaires was notably lower in the chemotherapy arm than in the ceritinib arm already at early documentation times. Due to the design, no subsequent documentation was conducted in a notable proportion of the patients in the chemotherapy arm because the observation period of the patients was not long enough because of the early progression. For the Lung Cancer Symptom Scale (LCSS), for example, data were only available for 76.7% of the patients at the second documentation time, for fewer than half of the patients at the third documentation time and for only about one quarter of the patients at the fourth documentation time. In the ceritinib arm, in contrast, about 90% (second and third time points of documentation) and about three quarters at the fourth time point of documentation were available. The fact that data were available for only few patients already at an early time point, particularly in the chemotherapy arm, can lead to the erroneous recording of a single or temporary deterioration by the corresponding threshold value as definitive deterioration in the ASCEND-5 study. This can eventually lead to a comparison not of the time to definitive deterioration, which was the

comparison aimed at, but rather to a comparison between the time to definitive deterioration (ceritinib arm) and the time to a single or temporary deterioration (chemotherapy arm).

Concerning the other questionnaires used in the ASCEND-5 study to record symptoms, health status and health-related quality of life, the patients considered in the survival time analysis (with information provided at the start of the study and at least one further time point) differed by about 15 to 21 percentage points between the treatment arms. Even if the patients for whom no completed questionnaire from the start of the study or no value at a later documentation time was available were included in the corresponding survival time analyses, this effectively added no information to the analyses.

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 ceritinib in comparison with docetaxel or pemetrexed; an added benefit is therefore not proven.

Morbidity

- Symptoms, health status

The dossier contained no usable data for the outcomes "symptoms" and "health status". Hence there was no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for these outcomes; an added benefit is therefore not proven.

Health-related quality of life

The dossier contained no usable data for health-related quality of life. Hence there was no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for this outcome; an added benefit is therefore not proven.

Side effects

- Serious adverse events, severe adverse events (CTCAE grade 3 or 4), discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs" (CTCAE grade 3 or 4)" and "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from ceritinib in comparison with docetaxel or pemetrexed; greater or lesser harm is therefore not proven.

- Specific adverse events

No analyses on specific AEs were used for the present benefit assessment because the company only presented selective analyses on this.

Results for research question 2: patients for whom treatment with docetaxel or pemetrexed is not an option

No data were available for the assessment of the added benefit of ceritinib in crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option. Hence there was no hint of an added benefit of ceritinib in comparison with best supportive care (BSC). An added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Research question 1: patients for whom treatment with docetaxel or pemetrexed is an option

Overall, there are neither positive nor negative effects.

In summary, there is no proof of an added benefit of ceritinib versus the ACT docetaxel or pemetrexed for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option.

Research question 2: patients for whom treatment with docetaxel or pemetrexed is not an option

There is no proof of an added benefit of ceritinib versus the ACT BSC for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option.

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

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Ceritinib – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
1	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option[b]	**Docetaxel** or **pemetrexed**	Added benefit not proven
2	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option[c]	BSC[d]	Added benefit not proven

a: Presentation of the respective 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: Operationalized in the present benefit assessment as patients with ECOG PS 0, 1 and possibly 2.
c: Operationalized in the present benefit assessment as patients with ECOG PS 4, 3 and possibly 2.
d: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The approach for deriving an overall conclusion on 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 ceritinib in comparison with docetaxel or pemetrexed as ACT in adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

According to the approved therapeutic indication, ceritinib is used in patients previously treated with crizotinib [3]. When the first procedure was initiated, crizotinib was not approved before the second line of treatment, and, consequently, ceritinib not before the third line of treatment. In the meantime, following an extension of approval of crizotinib on 23 November 2015 to first-line treatment, the therapeutic indication of ceritinib was also extended [4], i.e. to use from the second line of treatment. According to the G-BA commission, however, the present benefit assessment of ceritinib only refers to the treatment situation in which patients had already been treated with at least one further therapy before treatment with crizotinib. This concurs with the subject of the first benefit assessment of ceritinib [4,5].

In its specification of the ACT, the G-BA differentiated between patients for whom treatment with docetaxel or pemetrexed is an option and those patients for whom such treatment is not an option. This differentiation of the patient groups resulted in 2 research questions for the assessment. Table 4 shows an overview of the research questions.

Table 4: Research questions of the benefit assessment of ceritinib

Research question	**Therapeutic indication**[a]	**ACT**[b]
1	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option[c]	**Docetaxel** or **pemetrexed**
2	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option[d]	BSC[e]

a: It is assumed for the present therapeutic indication that the patients had received platinum-based chemotherapy in their first-line treatment and were then treated with crizotinib.
b: Presentation of the respective 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.
c: Operationalized in the present benefit assessment as patients with ECOG PS 0, 1 and possibly 2.
d: Operationalized in the present benefit assessment as patients with ECOG PS 4, 3 and possibly 2.
e: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The formulation of 2 research questions generally concurs with the company. However, the company did not investigate research question 2 because it considered the added benefit of ceritinib in comparison with BSC to implicitly result from the added benefit of ceritinib versus docetaxel or pemetrexed.

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. This concurs with the company's inclusion criteria.

2.3 Research question 1: patients for whom treatment with docetaxel or pemetrexed is an option

2.3.1 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 ceritinib (status: 26 September 2016)
- bibliographical literature search on ceritinib (last search on 2 September 2016)
- search in trial registries for studies on ceritinib (last search on 2 September 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ceritinib (last search on 21 October 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ASCEND-5	No	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of ceritinib in comparison with treatment with docetaxel or pemetrexed (referred to as "chemotherapy" in the present report) consisted of the ASCEND-5 study. The company also included this study.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 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: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ASCEND-5	RCT, open-label, parallel	Adult patients with ALK-positive advanced NSCLC (stage IIIB or IV) pretreated with 1 or 2 chemotherapeutic regimens (at least 1 platinum-based regimen) and crizotinib with an ECOG PS ≤ 2[b]	▪ Ceritinib (N = 115) ▪ chemotherapy (N = 116) Of which: pemetrexed (N = 40)[c] docetaxel (N = 73)[c]	▪ Screening: 28 days ▪ Treatment: until tumour progression[d], unacceptable toxicity, pregnancy, initiation of a new antineoplastic treatment, treatment discontinuation by investigator/patient or death ▪ Observation[e]: outcome-specific, at most until the final analysis of overall survival after about 196 deaths or evidence of a significant difference for overall survival	99 centres in: Belgium, Canada, France, Germany, Hong Kong; Ireland, Israel, Italy, Japan, Republic of Korea, Lebanon, Netherlands, Portugal, Russia, Singapore, Spain Switzerland, Turkey, United Kingdom, USA 6/2013–ongoing (data cut-off of the primary analysis on 26 Jan 2016; after 172 PFS events + 12-week follow-up)	Primary: PFS Secondary: overall survival, symptoms, health-related quality of life, health status, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The designation "WHO PS" is used as a synonym for the ECOG PS in the inclusion criteria of the study. The definitions provided on the allocation to classes concur exactly with the ECOG criteria.
c: 3 patients with randomization to chemotherapy received no dose of the allocated study medication.
d: Patients in both study arms could continue treatment with the respective study medication also after progression if this treatment was considered beneficial by the investigator. On determination of tumour progression, patients in the chemotherapy arm also had the option to switch to treatment with ceritinib.
e: Outcome-specific information is provided in Table 8.

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

Table 7: Characteristics of the interventions – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study	Intervention	Comparison
ASCEND-5	Ceritinib 750 mg/day, orally, at least 1–2 hours after a meal, continuous treatment Dose adjustments or temporary treatment discontinuations due to intolerance allowed; dose reduction below 300 mg/day not allowed	Chemotherapy[a] at the investigator's choice, each on day 1 of each 21-day cycle: ▪ pemetrexed (500 mg/m^2 IV) or ▪ docetaxel (75 mg/m^2 IV) Application, dose adjustments and temporary treatment discontinuations in compliance with the approval Additional medication in the pemetrexed arm: ▪ folic acid (0.4 to 1 mg, orally), daily for 7 days before the first dose of pemetrexed until 3 weeks after the last dose of pemetrexed ▪ vitamin B12 (1 mg, IM), first dose 7 days after the first dose of pemetrexed, then repeated every 9 weeks until the end of the chemotherapy ▪ dexamethasone (4 mg twice/day, orally), on the day of treatment, one day before and one day after Additional medication in the docetaxel arm: ▪ corticosteroids (orally), equivalent to twice/day 8 mg oral dexamethasone on the day of treatment, one day before and one day after
	Pretreatment and concomitant treatment	
	Pretreatment ▪ previous treatment of the advanced disease with crizotinib and 1 or 2 chemotherapeutic regimens, including 1 platinum-based chemotherapy **Non-permitted pretreatment** ▪ treatment with an ALK-inhibitor except crizotinib ▪ systemic antineoplastic therapies for the treatment of the advanced NSCLC except crizotinib and 1 or 2 chemotherapeutic regimens **Concomitant treatment** ▪ drugs that were necessary for the best possible supportive treatment of the patient could be used at the physician's discretion (e.g. antiemetics or antidiarrhoeal drugs) ▪ palliative radiotherapy if considered necessary by the investigator ▪ bisphosphonates **Non-permitted concomitant treatment** ▪ drugs with narrow therapeutic indices that are mostly metabolized by cytochrome 3A4/5 and/or cytochrome 2C9 ▪ strong cytochrome 3A4/5 inhibitors or inducers ▪ other antineoplastic treatments ▪ drugs associated with a high risk of QTc time prolongation	

a: Switching between pemetrexed and docetaxel was not possible after initiation of the treatment.

ALK: anaplastic lymphoma kinase; IM: intramuscular; IV: intravenous; NSCLC: non-small cell lung cancer; QTc: time interval between the start of the Q wave and the end of the T wave (corrected for heart rate); RCT: randomized controlled trial; vs.: versus

The ASCEND-5 study was an open-label, randomized controlled, multicentre study on the comparison of ceritinib with docetaxel or pemetrexed. It included adult patients with ALK-positive advanced NSCLC previously treated both with platinum-based chemotherapy and crizotinib.

Randomization was stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1/2) and brain metastases at the start of the study (present versus not present). A total of 231 patients were randomized, 115 patients to the ceritinib arm and 116 patients to the chemotherapy arm. The physician decided whether the patients in the chemotherapy arm received docetaxel or pemetrexed. Patients with progression as best response under a previous docetaxel-based chemotherapy were to receive pemetrexed and vice versa.

Patients in the ceritinib arm received a daily dose of 750 mg ceritinib orally. Patients in the chemotherapy arm received either 75 mg/m^2 body surface area docetaxel or 500 mg/m^2 body surface area pemetrexed, each as an infusion, every 3 weeks. Treatments were administered in accordance with the approval [6-8].

Primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and AEs.

Treatment with the randomized study medication was continued until a criterion for discontinuation occurred, e.g. progression. Occurrence of progression was determined with an independent review according to the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 [9]. The patients in both treatment arms could continue to receive the randomized study medication beyond progression if the investigator considered the treatment to be beneficial to them. In the chemotherapy arm, the patients could switch to ceritinib when progression occurred.

Planned duration of follow-up

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

Table 8: Planned duration of follow up – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study **Outcome category** **Outcome**	**Planned follow-up**
ASCEND-5	
Mortality	
Overall survival	▪ All patients with progression (according to BIRC) and/or discontinuation of the further study investigations are followed-up every 12 weeks until withdrawal of consent or loss to follow-up or until death. ▪ At most until final analysis of overall survival
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, LCSS), health status (EQ-5D VAS)	▪ Screening, cycle[a] 2, 3, then every 6 weeks until month 18, then every 9 weeks until progression (according to BIRC), withdrawal of consent, pregnancy, loss to follow-up or death ▪ On treatment discontinuation during the treatment phase without progression (according to BIRC): continued follow-up until progression (according to BIRC), withdrawal of consent, pregnancy, loss to follow-up or death
Health-related quality of life	
EORTC QLQ-C30	▪ Screening, cycle[a] 2, 3, then every 6 weeks until month 18, then every 9 weeks until progression (according to BIRC), withdrawal of consent, pregnancy, loss to follow-up or death ▪ On treatment discontinuation during the treatment phase without progression (according to BIRC): continued follow-up until progression (according to BIRC), withdrawal of consent, pregnancy, loss to follow-up or death
Side effects	
All outcomes in the category "side effects"	▪ Continuously until 30 days after the last administration of the study medication at the end of the treatment phase ▪ Patients with permanent treatment discontinuation due to an AE are followed up until symptom relief or improvement of the event.

a: One cycle lasted 21 days.

AE: adverse event; BIRC: blinded independent review committee; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

In the ASCEND-5 study, data recorded after the end of the randomized study medication and, if applicable, after treatment switching from chemotherapy to ceritinib were also used for the analysis of overall survival.

For all outcomes except overall survival, the duration of follow-up in the ASCEND-5 study was attached either to the diagnosis of progression or to the end of the randomized study treatment. The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period until progression or for the time period of the treatment with the study medication (plus 30 days). 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, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

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

Table 9: Characteristics of the study populations – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study **Characteristics** **Category**	**Ceritinib**	**Chemotherapy**
ASCEND-5	**N = 115**	**N = 116**
Age [years], mean (SD)	53 (12)	54 (12)
Sex [F/M], %	59/41	53/47
Geographical region: n (%)		
Europe	80 (69.6[a])	71 (61.2[a])
North America	9 (7.8[a])	11 (9.5[a])
Asia/Pacific	26 (22.6[a])	34 (29.3[a])
Ethnicity, n (%)		
White	81 (70.4)	68 (58.6)
Asian	30 (26.1)	38 (32.8)
Other	4 (3.5[a])	10 (8.6[a])
Disease stage, n (%)		
IIIB	1 (0.9)	1 (0.9)
IV	114 (99.1)	115 (99.1)
Disease duration [months]		
Median [min; max]	19.4 [5.5; 153.3]	19.8 [6.5; 94.6]
Mean (SD)	24.1 (20.4)	24.9 (18.8)
ECOG PS, n (%)		
0	56 (48.7)	51 (44.0)
1	50 (43.5)	60 (51.7)
2	9 (7.8)	5 (4.3)
Histology, n (%)		
Adenocarcinoma	111 (96.5)	113 (97.4)
Squamous cell carcinoma	0 (0)	2 (1.7)
Other	4 (3.5)	1 (0.9)
Smoking status, n (%)		
Never smoker	71 (61.7)	61 (52.6)
Ex-smoker	39 (33.9)	51 (44.0)
Smoker	4 (3.5)	1 (0.9)
Unknown	1 (0.9)	3 (2.6)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Study Characteristics Category	Ceritinib	Chemotherapy
ASCEND-5	**N = 115**	**N = 116**
Number of prior antineoplastic treatments, n (%)[b]		
1	1 (0.9)	0 (0)
2	98 (85.2)	95 (81.9)
3	15 (13.0)	18 (15.5)
> 3	1 (0.9)	3 (2.6)
Type of prior antineoplastic treatment, n (%)[b, c]		
Carboplatin	48 (41.7)	50 (43.1)
Cisplatin	76 (66.1)	71 (61.2)
Crizotinib	115 (100)	116 (100)
Brain metastases at the start of the study, n (%)	65 (56.5)	69 (59.5)
Treatment discontinuation, n (%)[d]	82 (71.3)	108 (93.1)
Study discontinuation, n (%)	14 (12.2)	10 (8.6)

a: Institute's calculation.
b: It is assumed for the present therapeutic indication that the patients had received platinum-based chemotherapy in their first-line treatment and were then treated with crizotinib.
c: Multiple answers of the treatments provided are possible. Overall, the treatments listed only represent a choice of the prior antineoplastic treatments actually administered.
d: The most common reason for treatment discontinuation in both treatment arms was progression (ceritinib: n = 56; chemotherapy: n = 82).
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 patients included in the ASCEND-5 study had a mean age of 53 years and almost exclusively were in disease stage IV. Slightly more than half of the patients had already developed brain metastases. The proportion of patients with treatment discontinuation was lower in the ceritinib arm than in the chemotherapy arm. The most common reason for treatment discontinuation was progression.

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study **Duration of the study phase** **Outcome category**	**Ceritinib**	**Chemotherapy**
ASCEND-5	**N = 115**	**N = 113**
Treatment duration [weeks]		
Median [min; max]	30.3 [0.3; 122.9]	6.3 [3.0; 69.1]
Mean (SD)	36.4 (27.3)	13.4 (13.8)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	10.9 [5.0; 15.9]	9.3 [4.4; 16.1]
Mean (SD)	11.0 (6.7)	10.6 (7.1)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration in the ASCEND-5 study was notably longer in the ceritinib arm (30.3 weeks) than in the chemotherapy arm (6.3 weeks). The difference in treatment durations was caused by differences in the rates of treatment discontinuation particularly due to progression. At the time point of the primary analysis, progression was diagnosed in 82 of the 116 patients (70.7%) in the chemotherapy arm. 75 of these 82 patients (64.7% of 116 patients) switched to subsequent treatment with ceritinib.

The company's dossier contained information on the observation period only for the outcome "overall survival". For the outcomes on morbidity, health-related quality of life and side effects, the differences in treatment duration resulted in notable differences of the respective observation period because this was only mandated until diagnosis of progression or until 30 days after the last administration of the randomized study treatment (see Table 8).

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

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			
ASCEND-5	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the ASCEND-5 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), Quality of Life Questionnaire-Lung Cancer (QLQ-LC13) and LCSS
  - health status measured with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3 or 4)
  - discontinuation due to 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 2.6.2.4.3 of the full dossier assessment).

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

Table 12: Matrix of outcomes – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study	Outcomes						
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, LCSS)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	SAEs	Severe AEs (CTCAE grade 3 or 4)	Discontinuation due to AEs
ASCEND-5	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes

a: Measured with the symptom scales.
b: Measured with the global scale and the functional scales.
c: No usable data available; for reasons, see Section 2.3.2.2.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study	Study level	Outcomes						
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, LCSS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade 3 or 4)	Discontinuation due to AEs
ASCEND-5	L	H[a]	-[b]	-[b]	-[b]	H[c]	H[c]	H[c]

a: Large proportion of patients who switched treatment from the chemotherapy arm to ceritinib (64.7%).
b: No usable data available.
c: Due to potentially informative censoring and large proportion of patients who switched treatment from the chemotherapy arm to ceritinib (64.7%).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Overall survival, side effects

The risk of bias for the outcomes "overall survival", "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade 3 or 4) was classed as high. The risk of bias for the outcome "overall survival" was rated as high because of the large proportion of patients who switched treatment from the chemotherapy to the ceritinib arm (64.7%); for the outcomes "SAEs", "severe AEs" (CTCAE grade 3 or 4) and "discontinuation due to AEs" additionally due to potentially informative censoring.

Symptoms, health status and health-related quality of life

In Module 4 A of the dossier, the company presented responder analyses for the outcomes on morbidity and health-related quality of life. The time to deterioration by a validated threshold value versus the baseline value was considered as response criterion. Deterioration was only considered to be definitive, and therefore as event, if this also applied to all subsequent values or if the deterioration (response) was present at the time point of the last measurement in the observation period. As shown in Table 8, the outcomes were only recorded until progression.

The observation periods therefore differed notably between the treatment arms (see Table 10). Since an association between progression and the outcomes is possible, informative censorings can be assumed. With a ratio of the observation period of the chemotherapy arm versus the ceritinib arm of about 21%, informative censoring to an important degree is possible. The assumption of the Cox proportional hazards model that the censorings were non-informative censorings is potentially violated to an important degree.

In principle, the recording of the time to definitive change is clinically meaningful. However, the responder analyses on the time to definitive change presented by the company cannot be meaningfully interpreted because of the study design and are therefore not usable for the present benefit assessment. This is further explained below.

The instruments on symptoms, health status and health-related quality of life were recorded on the first day of cycle 1 (screening), at the beginning of the second and the third cycle, then at the beginning of every second cycle (i.e. every 6 weeks) until month 18 and then every 9 weeks (see Table 8). There was no further recording after progression.

The notable difference in the time to progression between the treatment arms resulted in a large difference between the treatment arms in the number of patients who had completed the respective questionnaire, already at early documentation times. This is explained below using the example of the response rates for the LCSS questionnaire (see Table 20 of the full dossier assessment). For the LCSS questionnaire, information at the second documentation time (first day of cycle 2) was available for 91.3% of the patients at risk (i.e. patients who had not had disease progression yet) in the ceritinib arm, whereas this was the case for 76.7% of the patients in the chemotherapy arm. At the third time point, i.e. 6 weeks after the start of the treatment (first day of cycle 3), information was available for about 90% of the patients in the ceritinib arm and for fewer than half (about 44%) of the patients in the chemotherapy arm. At the fourth documentation time, i.e. 9 weeks after the start of the treatment (first day of cycle 5), only data of about 1 quarter of the patients at risk were available in the chemotherapy arm, whereas in the ceritinib arm, information was available for about 3 quarters of the patients at risk.

The data on the response rate show that, particularly in the chemotherapy arm, no definitive deterioration could be measured in a notable proportion of the patients because the observation period of the patients was not long enough due to the early progression. Hence, in contrast to the ceritinib arm, no subsequent recordings could be conducted in the chemotherapy arm already at an early time point of the study. This can lead to the erroneous recording of a single or temporary deterioration by the corresponding threshold value as definitive deterioration in the ASCEND-5 study. This can eventually lead to a comparison not of the time to definitive deterioration, which was the comparison aimed at, but rather to a comparison between the time to definitive deterioration (ceritinib arm) and the time to a single or temporary deterioration (chemotherapy arm).

The different response rates not only resulted in an actually different operationalization of the response criterion, but also in a different information content between the treatment arms. Across all questionnaires, information for the start of the treatment and for at least one further time point was available for about 90% to 93% of the patients in the ceritinib arm. In the chemotherapy arm, this was about 71% to 76%; as described above, this proportion was even notably lower in the further course. Hence the patients considered in the survival time analysis (with information provided at the start of the study and at least one further time point) differed by about 15 to 21 percentage points between the treatment arms. Even if the patients for whom no completed questionnaire from the start of the study or no value at a later documentation time was available were included in the corresponding survival time analyses, this effectively added no information to the analyses.

The assessment that the responder analyses presented by the company for the recording of definitive deterioration are not usable deviates from that of the company. It included the analyses in its benefit assessment and assessed the risk of bias for the outcomes on morbidity and health-related quality of life as high. It justified this exclusively with the open-label study design and potentially informative censoring due to progression.

Further analyses

For the outcomes on morbidity and health-related quality of life, the study documents also contained analyses on the mean deterioration in comparison with baseline in the form of mixed-effects model repeated measures (MMRM) analyses. As for the responder analyses on the time to definitive deterioration, the problem of large differential proportions of patients who were not considered in the analysis described above also exists for these analyses. The MMRM analyses were therefore not usable. The company did not use these analyses in its assessment.

2.3.2.3 Results

The results on the comparison of ceritinib with chemotherapy (docetaxel or pemetrexed) for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option are summarized in Table 14.

Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. Kaplan-Meier curves on the outcomes with usable data included are presented in Appendix A of the full dossier assessment.

Table 14: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study Outcome category Outcome	Ceritinib N	Ceritinib Median survival time in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median survival time in months [95% CI] Patients with event n (%)	Ceritinib vs. chemotherapy HR [95% CI]; p-value
ASCEND-5					
Mortality					
Overall survival	115	18.1 [13.4; 23.9] 48 (41.7)	116	20.1 [11.9; 25.1] 50 (43.1)	1.00 [0.67; 1.49] 0.496
Morbidity – time to deterioration					
Symptoms					
EORTC QLQ-C30 – symptom scales[a]	No usable data				
EORTC QLQ-LC13 – symptom scales[a]	No usable data				
LCSS – ASBI[b]	No usable data				
Health status (EQ-5D VAS)[a]	No usable data				
Health-related quality of life – time to deterioration[a]					
EORTC QLQ-C30 – functional scales	No usable data				
Side effects – time to event[c]					
AEs (supplementary information)	115	0.1 [0.0; 0.1] 115 (100)	113	0.1 [0.1; 0.2] 112 (99.1)	–
SAEs	115	11.9 [9.4; 18.0] 49 (42.6)	113	10.1 [3.5; NA] 36 (31.9)	0.69 [0.43; 1.08] 0.104
Severe AEs (CTCAE grade 3 or 4)[d]	115	2.1 [1.4; 3.4] 89 (77.4)	113	1.1 [0.5; 1.6] 72 (63.7)	0.79 [0.57; 1.08] 0.133
Discontinuation due to AEs	115	NA 18 (15.7)	113	NA 11 (9.7)	0.89 [0.41; 1.94] 0.763

(continued)

Table 14: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

a: Time to deterioration by at least 10 points versus the baseline value. Deterioration by the defined threshold value was only recorded as event if this also applied to all subsequent values or if the response was present at the time point of the last measurement in the observation period.
b: Time to deterioration by at least 15 points versus the baseline value. Deterioration by the defined threshold value was only recorded as event if this also applied to all subsequent values or if the response was present at the time point of the last measurement in the observation period.
c: AEs that occurred until 30 days after the last administration of the study medication at the end of the treatment phase are considered.
d: In the study, severe AEs with fatal outcome were not recorded as CTCAE grade 5 AEs but only as deaths. The study report presents n = 1 vs. n = 0 events for the MedDRA SOC "nervous system disorders" and n = 1 vs. n = 0 events for the MedDRA SOC "respiratory, thoracic and mediastinal disorders".
AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; VAS: visual analogue scale; vs.: versus

Due to the high risk of bias, no more than "hints" of an added benefit can be derived for all outcomes.

Mortality

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 ceritinib in comparison with docetaxel or pemetrexed; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Morbidity

Symptoms, health status

The dossier contained no usable data for the outcomes "symptoms" and "health status" (see Section 2.3.2.2). Hence there was no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for these outcomes; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived an added benefit of ceritinib for the outcomes on morbidity.

Health-related quality of life

The dossier contained no usable data for health-related quality of life (see Section 2.3.2.2). Hence there was no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for this outcome; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived an added benefit of ceritinib for the outcome “health-related quality of life”.

Side effects

Serious adverse events, severe adverse events (CTCAE grade 3 or 4), discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcomes “SAEs”, “severe AEs” (CTCAE grade 3 or 4)” and “discontinuation due to AEs”. Hence there was no hint of greater or lesser harm from ceritinib in comparison with docetaxel or pemetrexed; greater or lesser harm from ceritinib is therefore not proven.

The assessment concurs with that of the company.

Specific adverse events

No analyses on specific AEs were used for the present benefit assessment because the company only presented selective analyses on this (see Section 2.6.2.4.3 of the full dossier assessment). This approach deviates from that of the company, which included the specific AEs selectively chosen by the company in the benefit assessment.

2.3.2.4 Subgroups and other effect modifiers

Mainly due to informative censoring and the large proportion of patients who switched treatment from the chemotherapy arm to subsequent treatment with ceritinib, the subgroup analyses of the ASCEND-5 study presented are not meaningfully interpretable. They were therefore not considered in this benefit assessment.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of 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.

2.3.3.1 Assessment of added benefit at outcome level

For crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option, the data presented in Section 2.3.2 resulted in no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for any of the outcomes considered. The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 18.1 vs. 20.1 months HR: 1.00 [0.67; 1.49] p = 0.496	Lesser benefit/added benefit not proven
Morbidity		
Symptoms – time to deterioration		
EORTC QLQ-C30 – symptom scales	No usable data	Lesser benefit/added benefit not proven
EORTC QLQ-LC13 – symptom scales	No usable data	Lesser benefit/added benefit not proven
LCSS – ASBI	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life – time to deterioration		
EORTC QLQ-C30 – functional scales	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 11.9 vs. 10.1 months HR: 0.69 [0.43; 1.08] p = 0.104	Lesser benefit/added benefit not proven
Severe AEs (CTCAE grade 3 or 4)	Median: 2.1 vs. 1.1 months HR: 0.79 [0.57; 1.08] p = 0.133	Lesser benefit/added benefit not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 0.89 [0.41; 1.94] p = 0.763	Lesser benefit/added benefit not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORT QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer-13;; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Overall, there are neither positive nor negative effects.

In summary, there is no proof of an added benefit of ceritinib versus the ACT docetaxel or pemetrexed for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option.

2.3.4 List of included studies

Novartis (2016). A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib: study CLDK378A2303; Zusatzanalysen [unpublished].

Novartis (2016). A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib: study CLDK378A2303; clinical study report [unpublished].

Novartis Pharma Services. "A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib." Retrieved 25.07.2016, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005637-36.

Novartis Pharmaceuticals (25.04.2016). "LDK378 versus chemotherapy in ALK rearranged (ALK positive) patients previously treated with chemotherapy (platinum doublet) and crizotinib: full text view." Retrieved 25.07.2016, from https://clinicaltrials.gov/ct2/show/NCT01828112.

2.4 Research question 2: patients for whom treatment with docetaxel or pemetrexed is not an option

2.4.1 Information retrieval and study pool

As in its first dossier on ceritinib [10], the company did not investigate research question 2. Hence it conducted no information retrieval for this research question and presented no data. The company argued that an added benefit of ceritinib in comparison with BSC implicitly results from the added benefit of ceritinib versus docetaxel or pemetrexed and that it therefore only investigated the comparison of ceritinib for patients for whom pemetrexed and docetaxel are an option. The company's rationale was not followed (see dossier assessment A15-24 [5]).

The Institute's check of completeness on the basis of the company's study list on ceritinib (status: 26 September 2016) and the search in trial registries on ceritinib (last search on 21 October 2016) identified no studies relevant for research question 2.

Overall, there were no data for the assessment of ceritinib for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option.

2.4.2 Results on added benefit

No data were available for the assessment of the added benefit of ceritinib in crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option. Hence there was no hint of an added benefit of ceritinib in comparison with BSC. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of ceritinib for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option, there is no proof of an added benefit of ceritinib versus the ACT BSC.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of ceritinib in comparison with the ACT is summarized in Table 16.

Table 16: Ceritinib – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
1	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option[b]	**Docetaxel** or **pemetrexed**	Added benefit not proven
2	Crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option[c]	BSC[d]	Added benefit not proven

a: Presentation of the respective 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: Operationalized in the present benefit assessment as patients with ECOG PS 0, 1 and possibly 2.
c: Operationalized in the present benefit assessment as patients with ECOG PS 4, 3 and possibly 2.
d: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The added benefit of ceritinib in comparison with the respective ACT is not proven for patients for whom treatment with docetaxel or pemetrexed is an option (research question 1: patients with ECOG PS 0, 1 and possibly 2) or for patients for whom such treatment is not an option (research question 2: patients with ECOG PS 4, 3 and possibly 2).

This deviates from the company's approach, which derived considerable added benefit of ceritinib for the overall population of patients with crizotinib-pretreated advanced ALK-positive NSCLC without providing information on probability.

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

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.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]. 08.2016 [Accessed: 22.11.2016]. URL: http://www.fachinfo.de.

4. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Ceritinib [online]. 17.12.2015 [Accessed: 29.11.2016]. URL: https://www.g-ba.de/downloads/40-268-3496/2015-12-17_AM-RL-XII_Ceritinib_2015-07-01-D-171_TrG.pdf.

5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ceritinib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-24 [online]. 29.09.2015 [Accessed: 08.10.2015]. (IQWiG-Berichte; Volume 329). URL: https://www.iqwig.de/download/A15-24_Ceritinib_Nutzenbewertung_35a_SGB-V.pdf.

6. Lilly. Alimta: Fachinformation [online]. 02.2016 [Accessed: 25.11.2016]. URL: http://www.fachinfo.de.

7. Novartis Pharma. Zykadia 150 mg Hartkapseln: Fachinformation [online]. 08.2015 [Accessed: 21.11.2016]. URL: http://www.fachinfo.de.

8. Sanofi. Taxotere 20 mg/1 ml, Taxotere 80 mg/4 ml, Taxotere 160 mg/8 ml: Fachinformation [online]. 05.2016 [Accessed: 25.11.2016]. URL: http://www.fachinfo.de.

9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247.

10. Novartis Pharma. Ceritinib (Zykadia): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Behandlung des Crizotinib-vorbehandelten, ALK-positiven, fortgeschrittenen, nicht-kleinzelligen Lungenkarzinoms (NSCLC); medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 29.06.2015 [Accessed: 22.11.2016]. URL: https://www.g-ba.de/downloads/92-975-879/2015-06-24_Modul4A_Ceritinib.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-62-ceritinib-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.7684.html.