IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ceritinib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2015). 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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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)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
- Katharina Biester
- Andreas Gerber-Grote
- Charlotte Guddat
- Thomas Kaiser
- Marco Knelangen
- Petra Kohlepp
- Sarah Mostardt

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

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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 assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 30 June 2015.

Research question

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

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.

Two research questions resulted for the assessment, which are derived from the ACT. Table 2 shows the research questions relevant for the present benefit assessment and the ACTs.

Table 2: Research questions and ACTs for the benefit assessment of ceritinib

Research question	**Subindication**[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 is understood as the therapy that ensures 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 company followed the G-BA's specification, but deviated from the G-BA's specification regarding the differentiation of the 2 patient groups (based on the Eastern Cooperative Oncology Group Performance Status [ECOG PS]), which was determined in the consultation.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

Study pool of the company

The company presented no relevant data for research questions 2.

For research question 1, the company identified no randomized or non-randomized study of direct comparison on the comparison of ceritinib with the ACT. The company therefore searched for studies for a historical comparison of ceritinib with the ACT. Since it identified hardly any data on docetaxel and pemetrexed for crizotinib-pretreated patients, it also included studies that investigated pemetrexed with docetaxel in second-line treatment (or subsequent lines of treatment) in crizotinib-naive patients with ALK-positive NSCLC in its investigations.

The company identified 3 prospective studies on ceritinib, one of which in patients in the therapeutic indication under assessment (crizotinib-pretreated patients, study A2201), one outside the present therapeutic indication (crizotinib-naive patients, study A2203), and one that was conducted both within and outside the present therapeutic indication (study X2101).

The company identified no prospective study on the ACT that was conducted within the therapeutic indication, but 2 retrospective analyses (Berge 2013 and Ou 2014). The prospective study on the ACT (PROFILE 1007) identified by the company and 3 further retrospective analyses (Lee 2011, Lee 2013, Shaw 2013) were conducted outside the therapeutic indication under assessment.

Unadjusted historical comparisons of the company on research question 1

The company conducted different unadjusted historical comparisons on patient-relevant outcomes based on the studies and analyses A2201, X2101, Ou 2014 as well as PROFILE 1007.

All of the unadjusted historical comparisons presented by the company are not interpretable for the present benefit assessment.

Unadjusted historical comparison on symptoms and health-related quality of life

For the outcomes on symptoms and health-related quality of life, the company compared results from the ceritinib study A2201, which was conducted within the therapeutic indication under assessment, with results for the ACT from the chemotherapy arm of the PROFILE 1007 study, which was conducted outside the therapeutic indication under assessment.

The comparison of data on crizotinib-pretreated patients with data on crizotinib-naive patients is not interpretable. The company argued that the results from such a historical comparison per se are biased to the disadvantage of ceritinib because, according to the company, crizotinib-pretreated patients as a group have a worse prognosis than crizotinib-naive patients due to their more progressive stage of disease. Even though a more advanced stage of disease may be a cause of bias, there are other possible causes of bias. The company did not consider them in its rationale, however.

Furthermore due to the low certainty of results of a historical comparison, the observed differences have to be of a magnitude that suggests the reversal of a more or less deterministic course of the disease so that conclusions on the added benefit can be derived from data from such a comparison. This applies all the more to subjective outcomes, which per se have a high risk of bias if the treatment administered is known, as was the case here. The differences of the results presented by the company on these outcomes in the magnitude of a standardized mean difference of up to a maximum of 0.5 standard deviations are far from reaching such a magnitude and may therefore be caused by systematic bias alone.

Unadjusted historical comparison for the outcome "overall survival"

For the outcome "overall survival", the company used only data within the therapeutic indication under assessment (the A2201 study and a subpopulation of the X2101 study on ceritinib; the retrospective analysis Ou 2014 on the ACT).

The data from the retrospective analysis Ou 2014 are not evaluable for an unadjusted historical comparison to derive an added benefit of ceritinib for the following reasons:

- It was not reported which type of systemic treatment the patients had received. Hence it was unclear whether the ACT (pemetrexed or docetaxel) was used at all.
- No information on patient characteristics was available for the group of patients with systemic treatment considered by the company. The similarity of the populations considered in the ceritinib studies and in Ou 2014 cannot be assessed.
- The basis of decision for or against continuation of crizotinib treatment remained unclear. Patients could continue their crizotinib treatment (although the patients had progressed under this treatment), switch to a different systemic treatment, or no further systemic treatment was administered. It can be assumed that the decision to continue crizotinib treatment, to switch to a different systemic treatment or to not have any systemic treatment was made based on individual patient characteristics, which may have an influence on the prognosis. The low median survival time of the patients who did not receive continued treatment with crizotinib reported by Ou 2014 and the historical comparison of the company derived from this are therefore not interpretable.

Moreover, the results on overall survival determined by the company were not so large that they could not be caused by bias due to the historical comparison alone. In particular, no reversal of a more or less deterministic course of disease can be derived from the results.

Unadjusted historical comparison for the outcome "adverse events"

The company used data from the studies A2201, X2101 and PROFILE 1007 to investigate adverse events (AEs). However, it did not separate the results from the X2101 study into crizotinib-pretreated and crizotinib-naive patients. A comparison of data on crizotinib-pretreated patients with data on crizotinib-naive patients is not interpretable for AEs either. It should be noted as additional information that the "good tolerability" of ceritinib postulated by the company is not supported by the available data because high rates of serious AEs (SAEs) and severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 were observed.

Ongoing RCT A2303

It should also be mentioned that there is an ongoing randomized controlled trial (RCT) on the direct comparison of ceritinib in comparison with docetaxel or pemetrexed in crizotinib-pretreated patients. Study A2303 would therefore be potentially relevant for research question 1 of the present assessment. According to information from the European Public Assessment Report (EPAR) on ceritinib (status: 26 February 2015), 177 patients have been enrolled into the study so far; the target sample size is 236 patients in total. The final clinical study report (CSR) is expected in the third quarter of 2018.

Summary

In summary, the company presented no suitable data for research question 1 (patients for whom treatment with docetaxel or pemetrexed is an option) or for research question 2 (patients for whom such treatment is not an option). Hence there was no hint of an added benefit for both research questions; the added benefit is therefore not proven.

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

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	Subindication	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 is understood as the therapy that ensures 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 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 the ACT in adult patients for the treatment of ALK-positive advanced NSCLC previously treated with crizotinib.

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.

Two research questions resulted for the assessment, which are derived from the ACT. Table 4 shows an overview of the research questions.

Table 4: ACTs specified by the G-BA

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

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: BSC is understood as the therapy that ensures 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; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

The company followed the G-BA's ACTs, but deviated from the G-BA's specification regarding the differentiation of the 2 patient groups, which was determined in the consultation. From the company's point of view, besides patients with ECOG PS 0 or 1, all patients with ECOG PS 2 are also candidates for treatment with docetaxel or pemetrexed. From the G-BA's point of view, however, both chemotherapy and best supportive care (BSC) are a suitable treatment for patients with ECOG PS 2. The company's rationale was not followed (see Section 2.6.1 of the full dossier assessment). The assessment was therefore conducted in comparison with the ACT specified by the G-BA, with research question 1 comprising patients with ECOG PS 0, 1 and possibly 2, and research question 2 comprising patients with ECOG 4, 3 and possibly 2.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

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 lists on ceritinib (status: 2 May 2015)
- bibliographical literature search on ceritinib (last search on 4 May 2015)
- search in trial registries for studies on ceritinib (last search on 4 May 2015)
- bibliographical literature search on the ACT (last search on 29 April 2015)
- search in trial registries for studies on the ACT (last search on 4 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ceritinib (last search on 16 July 2015)

From its information retrieval, the company identified no randomized or non-randomized study of direct comparison on the comparison of ceritinib with the ACT. The check of completeness also produced no studies of direct comparisons.

The company therefore searched for studies for a historical comparison of ceritinib with the ACT. Since, according to the company, it identified hardly any data on docetaxel and pemetrexed for crizotinib-pretreated patients, it also included studies that investigated pemetrexed with docetaxel in second-line treatment (or subsequent lines of treatment) in crizotinib-naive patients with ALK-positive NSCLC.

Table 5 shows the prospective studies and retrospective analyses included by the company.

Table 5: Study pool of the company – further investigations

Population Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Crizotinib-pretreated patients			
Studies with ceritinib			
A2201 [3]	Yes	Yes	No
X2101 (subpopulation) [4]	Yes	Yes	No
Retrospective analyses with ACT			
Berge 2013 [5]	No	No	Yes
Ou 2014 [6]	No	No	Yes
Crizotinib-naive patients			
Studies with ceritinib			
A2203 [7]	Yes	Yes	No
X2101 (subpopulation) [4]	Yes	Yes	No
Study with ACT			
PROFILE 1007 [8]	No	No	Yes
Retrospective analyses with ACT			
Lee 2011 [9]	No	No	Yes
Lee 2013 [10]	No	No	Yes
Shaw 2013 [11]	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
ACT: appropriate comparator therapy

The company identified 3 prospective studies on ceritinib, one of which in patients in the therapeutic indication under assessment (crizotinib-pretreated patients, study A2201), one outside the present therapeutic indication (crizotinib-naive patients, study A2203), and one that was conducted both within and outside the present therapeutic indication (study X2101).

The company identified no prospective study on the ACT that was conducted within the therapeutic indication, but 2 retrospective analyses (Berge 2013 and Ou 2014). The prospective study on the ACT (PROFILE 1007) identified by the company and 3 further retrospective analyses (Lee 2011, Lee 2013, Shaw 2013) were conducted outside the therapeutic indication under assessment.

The company conducted different unadjusted historical comparisons on patient-relevant outcomes based on the studies and analyses A2201, X2101, Ou 2014 as well as PROFILE 1007:

- For the outcomes on symptoms and health-related quality of life, the company compared results from the ceritinib study A2201, which was conducted within the therapeutic

indication under assessment, with results for the ACT from the chemotherapy arm of the PROFILE 1007 study, which was conducted outside the therapeutic indication under assessment. The company did not use the subpopulation of the X2101 study with ceritinib and the retrospective analyses Lee 2011, Lee 2013 and Shaw 2013 because no data on symptoms and health-related quality of life had been recorded there.

- For the outcome "overall survival", the company used only data within the therapeutic indication under assessment (the A2201 study and a subpopulation of the X2101 study on ceritinib; the retrospective analysis Ou 2014 on the ACT). The company did not use the analysis Berge 2013 because it contained no interpretable data on the outcome "overall survival".
- The company used data from the studies A2201, X2101 and PROFILE 1007 to investigate AEs. However, it did not separate the results from the X2101 study into crizotinib-pretreated and crizotinib-naive patients. The company did not use the retrospective analyses Lee 2011, Lee 2013 and Shaw 2013 on the ACT because no data on AEs had been recorded there.

All of the unadjusted historical comparisons presented by the company are unsuitable for the present benefit assessment. This is described in detail below. A comprehensive description of the studies and analyses A2201, X2101, Ou 2014 and PROFILE 1007 underlying the historical comparisons can be found in Appendix A of the full dossier assessment.

2.3.1.1.1 Unadjusted historical comparison on symptoms and health-related quality of life

In its dossier, the company presented an unadjusted historical comparison on the outcomes on symptoms and health-related quality of life. For this purpose, it compared the results on crizotinib-pretreated patients in the A2201 ceritinib study with results of crizotinib-naive patients in the chemotherapy arm of the PROFILE 1007 study. This historical comparison is not evaluable for the benefit assessment because the comparison of data on crizotinib-pretreated patients (within the therapeutic indication under assessment) with those on crizotinib-naive patients (outside the therapeutic indication under assessment) is not interpretable. Even regardless of this aspect, no advantages of ceritinib in comparison with the ACT can be derived from the historical comparison on symptoms and health-related quality of life presented by the company. Both aspects are described in detail below.

Historical comparison presented not interpretable

Ceritinib was only approved for patients previously treated with crizotinib [12]. Based on the non-comparative data available for the approval, the European Medicines Agency (EMA) initially granted conditional approval for crizotinib-pretreated patients and referred to the ongoing randomized controlled trial (RCT) A2303 (see also Section 2.3.1.2).

The company argued that the results from such a historical comparison per se are biased to the disadvantage of ceritinib. According to the company, the reason for this is that crizotinib-

pretreated patients as a group have a worse prognosis than crizotinib-naive patients because they have a more progressive stage of disease. According to the company, this is shown clearly in a more unfavourable distribution of the patients' ECOG PS in the 2 ceritinib studies A2201 and X2101 in comparison with the patients in the chemotherapy arm of the PROFILE 1007 study. The company assumed that, with known direction of the bias in a comparison of different populations as the one presented by the company, differences observed in favour of ceritinib are to be considered a clear advantage of ceritinib. This rationale is not adequate.

Firstly, the company's argument that the ECOG PS in patients in the studies A2201 and X2101 differed considerably from the one in PROFILE 1007 is not true. The distribution of patients to the ECOG PS 0 to 2 was similar in these 3 studies (see Table 16 in Appendix A of the full dossier assessment). There is principle agreement with the company in so far as a more advanced stage of disease may be a cause of bias. However, the stage of disease is not only represented by pretreatment status or ECOG PS, and there are additional possible causes of bias. However, the company did not address these causes of bias in its dossier. Possible causes of bias could include the influence of different treatment variations or different pretreatments on the course of disease, the metastatic pattern as well as the period between the individual lines of treatment and the patients' disease duration. The dossier contained hardly any information on this. Information on the disease duration was exclusively available for the ceritinib studies (see Table 16 in Appendix A of the full dossier assessment).

Results from Ou 2014 on overall survival

Such further causes of bias and unknown factors are discussed below using the example of Ou 2014 (outcome "overall survival). Table 6 shows the results on overall survival from the retrospective analysis Ou 2014.

Table 6: Results overall survival – further investigations (Ou 2014): ACT (crizotinib-pretreated patients)

Outcome **Retrospective analysis** **Cohort**	**N**	**Median survival time in months [95% CI]**
Overall survival		
Ou 2014		
Crizotinib not continued	74	3.9 [2.7; 5.1]
Unspecified systemic treatment	37	5.4 [3.8; 12.3]
No systemic treatment	37	2.2 [1.1; 3.8]
Crizotinib continued	120	16.4 [14.5; NC]

ACT: appropriate comparator therapy; CI: confidence interval; N: number of analysed patients; NC: not calculable

Notably shorter median overall survival (4 months) was observed in patients who had not continued crizotinib treatment after progression, but had received either a different systemic or no further systemic treatment than in patients who had continued crizotinib treatment after progression (16.4 months). Different results on overall survival were also observed within the cohort of patients who had not continued treatment with crizotinib. The median survival observed in patients who had received further systemic treatment was 5.4 months, whereas it was 2.2 months in patients without further systemic treatment.

The results on overall survival in Ou 2014 show that factors (e.g. patient characteristics or subsequent treatments) leading to notably different results in the observed overall survival have to be present also in patients with crizotinib pretreatment. The authors of Ou 2014 found that ECOG PS was a prognostic factor for overall survival. Overall it was shown for all cohorts, however, that the vast majority of the patients had an ECOG PS of 0 or 1 (see Table 16 in Appendix A of the full dossier assessment). This proportion was 82% in patients who had not continued crizotinib treatment, and 96% in patients with continued crizotinib treatment. In association with the results on overall survival, this finding leads to the conclusion that besides ECOG PS (and besides pretreatment status) further factors that influence the patients' prognosis, e.g. treatment itself or the pattern of new metastases, have to be present.

Table 7 provides an overview of the sites and the distribution of new metastases on which diagnosed progression in Ou 2014 was based [13].

Table 7: Sites of disease progression under crizotinib – further investigations (Ou 2014): ACT (crizotinib-pretreated patients)

Retrospective analysis Cohort	**N[a]**	**Sites of disease progression n (%[b])**						
		Brain	**Liver**	**Lung**	**Bone**	**Pleural effusion/ cavity**	**Lymph node (distant and regional)**	**Other**
Ou 2014								
Crizotinib not continued	60	17 (28)	22 (37)	12 (20)	5 (8)	8 (13)	5 (8)	20 (33)
Crizotinib continued	78	40 (51)	12 (15)	10 (13)	8 (10)	3 (4)	2 (3)	10 (13)

a: The data refer to a subset of the 74 and 120 analysed patients whose disease progression under crizotinib pretreatment was caused by the development of new lesions and/or new target lesions, irrespective of progression in target lesions. 48 patients whose disease progression was exclusively caused by target lesions, and 8 patients with missing data were not included in the analysis.
b: Percentages may total over 100% because disease progression could be caused by more than one site of new lesion and/or new target lesion.
ACT: appropriate comparator therapy; N: number of analysed patients; n: number of patients with event

Notable differences in the metastatic pattern were shown in Ou 2014 for new metastases between patients who had not continued crizotinib and patients who had continued crizotinib.

Diagnosed progression was caused by the development of new metastases in 78 patients (65%) of the 120 patients who had continued crizotinib treatment. Progression was caused by the development of new metastases in 60 patients (76.9%) of the 74 patients who had not continued crizotinib treatment. In addition, the metastatic pattern was notably more multiple than in the cohort of patients who had continued crizotinib treatment. Patients who continued crizotinib treatment had brain metastases more often, but at the same time developed additional new liver and lung metastases considerably less frequently than patients who did not continue crizotinib treatment. The different metastatic pattern in the patients analysed in Ou 2014 might be a decisive prognostic factor, which also affects the patients' overall survival.

In their conclusion, the authors of Ou 2014 also discussed an influence of further, so far unknown causes of bias on their observed results on overall survival. They noted that the following data had not been recorded: use of ALK inhibitors other than crizotinib, further progression after continuation of crizotinib treatment, type of continued systemic treatment after progression, and concomitant radiotherapy.

In summary, further known and unknown causes of bias may be present irrespective of pretreatment in a magnitude that they alone can explain the differences in the historical comparison described by the company.

No advantage of ceritinib can be derived from the magnitude of the difference

Due to the low certainty of results of a historical comparison, the observed differences have to be of a magnitude that suggests the reversal of a more or less deterministic course of the disease so that conclusions on the added benefit can be derived from data from such a comparison. This applies all the more to subjective outcomes such as the results on symptoms and health-related quality of life presented by the company if these were recorded in open-label studies (as was the case here). Such data per se have a high risk of bias if the treatment administered is known. The differences of the results presented by the company on these outcomes in the magnitude of a standardized mean difference of up to a maximum of 0.5 standard deviations are far from reaching such a magnitude. The differences reported by the company may therefore be caused by systematic bias alone.

2.3.1.1.2 Unadjusted historical comparison for the outcome "overall survival"

In its dossier, the company presented an unadjusted historical comparison on the outcome "overall survival" for crizotinib-pretreated patients. For this purpose, it used the ceritinib studies A2201 and X2101 (subpopulation) as well as the retrospective analysis Ou 2014 for the ACT.

The data from the retrospective analysis Ou 2014 are not evaluable for an unadjusted historical comparison to derive an added benefit of ceritinib, particularly for the following reasons:

- It was not reported which type of systemic treatment the patients had received. Hence it was unclear whether the ACT (pemetrexed or docetaxel) was used at all.
- No information on patient characteristics was available for the group of patients with systemic treatment considered by the company. The similarity of the populations considered in the ceritinib studies and in Ou 2014 cannot be assessed.
- The basis of decision for or against continuation of crizotinib treatment remained unclear. Patients could continue their crizotinib treatment (although the patients had progressed under this treatment), switch to a different systemic treatment, or no further systemic treatment was administered. It can be assumed that the decision to continue crizotinib treatment, to switch to a different systemic treatment or to not have any systemic treatment was made based on individual patient characteristics, which may have an influence on the prognosis. Patients who did not continue crizotinib treatment had a notably more multiple metastatic pattern than patients who continued crizotinib treatment, for example (see Table 7 in Section 2.3.1.1.1). The low median survival time of the patients who did not receive continued treatment with crizotinib reported by Ou 2014 (see Table 6 in Section 2.3.1.1.1) and the historical comparison of the company derived from this are therefore not interpretable. In addition, the literature describes median survival times in NSCLC patients after third-line treatment that are notably higher than the observed median survival times in patients with systemic treatment in Ou 2014. The retrospective analysis Chen 2011 of NSCLC patients with ECOG PS 0 to 2 who received either pemetrexed or docetaxel as third- or fourth-line treatment determined a median survival time of about 12 to 13 months, for example [14]. Further publications found median survival times in NSCLC patients under different third-line treatments that were in a range of about 10 to 12 months [15-17]. However, it should be pointed out that the publications cited did not refer to patients with ALK-positive NSCLC after crizotinib pretreatment.

Moreover, the results on overall survival determined by the company did not appear so large that they could not be caused solely by bias due to the historical comparison. In particular, no reversal of a more or less deterministic course of disease can be derived from the results.

Overall, neither the data on overall survival from Ou 2014 used by the company for the ACT were interpretable, nor did the historical comparison itself produce a result that could be interpreted as advantage of ceritinib in comparison with the ACT with sufficient certainty.

The company itself assessed the results on overall survival from its ceritinib studies A2201 and X2101 as preliminary because a large proportion of patients without event were still participating in the study at the time of analysis (A2201: 71.4%, X2101: 44.8%). Nonetheless, the company derived a “clear advantage” of ceritinib in comparison with the ACT on the basis of its historical comparison.

2.3.1.1.3 Unadjusted historical comparison for the outcome "adverse events"

The company used data from the studies A2201, X2101 (total population) and PROFILE 1007 to investigate AEs.

As described in Section 2.3.1.1.1, such a historical comparison is not evaluable for the benefit assessment because the comparison of data on crizotinib-pretreated patients (within the therapeutic indication under assessment) with those on crizotinib-naive patients (outside the therapeutic indication under assessment) is not interpretable. This also applies to AEs. Firstly, the company provided no proof for the assumption that pattern and frequency of AEs, both under ceritinib and under the ACT, do not depend on the disease stage (referring to pretreatment with crizotinib). But even under this assumption, the historical comparison presented would not be interpretable because not only AEs of the treatment, but also, for example, disease-related harm depending on the disease stage were recorded in the framework of the recording of AEs.

In addition, the "good tolerability" of ceritinib postulated by the company is not supported by the available data because high rates of SAEs and of severe AEs (CTCAE grade ≥ 3) were observed in the ceritinib studies A2201 and X2101. The corresponding results are shown in Table 8.

Table 8: Results SAEs and severe AEs of the studies A2201, X2101 – further analyses: ceritinib (crizotinib-pretreated and crizotinib-naive patients)

Outcome category Outcome Study	N	Patients with event n (%)
Adverse events		
SAEs		
A2201	140	51 (36.4)[a]
X2101[b]	255	121 (47.5)
Severe AEs CTCAE ≥ 3		
A2201	140	94 (67.1)[a]
X2101[b]	255	206 (80.8)

a: Discrepant information between the CSR and Module 4 A of the dossier.
b: No differentiated analysis in dependence on pretreatment with crizotinib in study X2101.
AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with (at least one) event; SAE: serious adverse event; vs.: versus

2.3.1.2 Ongoing RCT A2303

There is an ongoing RCT on the direct comparison of ceritinib in comparison with docetaxel or pemetrexed in crizotinib-pretreated patients [18]. According to information from the EPAR on ceritinib (status: 26 February 2015), 177 patients have been enrolled into the study so far;

the target sample size is 236 patients in total. The final CSR is expected in the third quarter of 2018.

2.3.2 Results on added benefit

No suitable 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 an option. Hence there was no hint of an added benefit of ceritinib in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no suitable data for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option, an added benefit of ceritinib is not proven for these patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

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.

2.3.4 List of included studies

Not applicable because the company presented no relevant data for the assessment of the added benefit of ceritinib.

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

For the present benefit assessment, the research question on the added benefit of ceritinib in comparison with BSC in crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option (patients with ECOG PS 4, 3 and possibly 2) resulted from the G-BA's specification of the ACT.

The company presented no specific data for this research question. Instead it argued that an advantage of ceritinib observed in research question 1 applies all the more to research question 2. The company's rationale was not accepted (see Section 2.6.2.1 of the full dossier assessment). Overall, no relevant data on the assessment of ceritinib in patients for whom treatment with docetaxel or pemetrexed is not an option were available.

2.4.2 Results on added benefit

No suitable 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 (patients with ECOG PS 4, 3 and possibly 2).

Hence there was no hint of an added benefit of ceritinib in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no suitable data for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is not an option, an added benefit of ceritinib is not proven for these patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company did not investigate this research question.

2.4.4 List of included studies

Not applicable because the company presented no relevant data for the assessment of the added benefit of ceritinib.

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 9.

Table 9: Ceritinib – extent and probability of added benefit

Research question	Subindication	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 is understood as the therapy that ensures 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 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 G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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