IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ceritinib (non-small cell lung cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ceritinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 October 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse Events
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
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 20 July 2017.

Research question

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

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA for the research question presented in Table 2.

Table 2: Research question of the benefit assessment of ceritinib

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

The G-BA specified crizotinib as ACT in the present therapeutic indication. In its dossier, the company partly referred to an earlier G-BA specification of the ACT from 7 February 2017, which comprised further alternatives besides crizotinib, e.g. platinum-based combination chemotherapies. This approach was inadequate. The present assessment was conducted in comparison with the current ACT specified by the G-BA, i.e. crizotinib.

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

Results

The company identified no study of direct comparison of ceritinib versus crizotinib. However, it identified 3 studies that are potentially relevant for an indirect comparison of ceritinib with

crizotinib (study ASCEND-4 on ceritinib as well as the studies PROFILE 1014 and PROFILE 1029 on crizotinib).

An indirect comparison based on these 3 studies would be largely unsuitable for the benefit assessment. The company itself also did not conduct an indirect comparison based on these studies because it also considered these 3 studies unsuitable for such an indirect comparison.

Study ASCEND-4 on ceritinib

Study ASCEND-4 was a randomized, active-controlled, unblinded approval study sponsored by the company. Treatment-naive adult patients with ALK-positive NSCLC in the locally advanced or metastatic stage (stage IIIB or IV) were enrolled in the study. Patients in the study received either treatment with ceritinib or with platinum-based chemotherapy consisting of cisplatin in combination with pemetrexed (cisplatin + pemetrexed) or of carboplatin in combination with pemetrexed (carboplatin + pemetrexed).

Studies PROFILE 1014 and PROFILE 1029 on crizotinib

Since the ASCEND-4 study was the only randomized controlled trial (RCT) with ceritinib in the therapeutic indication and a combination chemotherapy of cisplatin and pemetrexed or of carboplatin and pemetrexed was used as comparator therapy in this study, platinum-based combination chemotherapy constituted the only possible common comparator for an indirect comparison.

The company identified 2 studies on the comparison of crizotinib with this common comparator, namely the studies PROFILE 1014 and PROFILE 1029. Both studies were randomized, active-controlled, unblinded studies. Treatment-naive adult patients with ALK-positive NSCLC in the locally advanced or metastatic stage were enrolled in the studies.

Indirect comparison based on the studies ASCEND-4, PROFILE 1014 and PROFILE 1029

There were differences in the common comparator between the studies ASCEND-4, PROFILE 1014 and PROFILE 1029:

- In the ASCEND-4 study, patients in the control arm received initial platinum-based combination chemotherapy for a maximum of 4 21-day cycles. Patients without interim progression received subsequent therapy with continued maintenance treatment with pemetrexed.
- In the studies PROFILE 1014 and PROFILE 1029, platinum-based combination chemotherapy in the control arm was limited to a maximum of 6 21-day cycles. Maintenance treatment with pemetrexed was not allowed.

However, the treatment regimens used in the respective comparator arm only differed after the initial 4 cycles of the platinum-based combination chemotherapy. The differences therefore mostly affected those considerations that are based on the total course of the study, e.g. overall survival. An indirect comparison would therefore be not usable for this kind of outcomes.

Greater risk of harm from ceritinib in comparison with crizotinib in severe adverse events (AEs).

It can be inferred from the Kaplan-Meier curves available for the studies ASCEND-4 and PROFILE 1014 that the risk of a severe AE (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4) within the first 3 months of treatment was similar in both studies under the control treatment with identical treatment regimens. In addition, it was shown in both studies that the majority of severe AEs (CTCAE grade 3 or 4) under the control treatment were observed during the first 3 months of treatment.

The Kaplan-Meier curves from the studies ASCEND-4 and PROFILE 1014 additionally showed that the majority of severe AEs were already observed during the first 3 months of treatment also under the respective experimental intervention (ceritinib in the ASCEND-4 study and crizotinib in the PROFILE 1014 study). Within this period, severe AEs were notably more common under ceritinib than under the combination chemotherapy (study ASCEND-4), whereas such events were notably less common under crizotinib (study PROFILE 1014).

In summary, this results in a greater risk of harm from ceritinib in comparison with crizotinib regarding the outcome "severe AEs (CTCAE grade 3 or 4)". The company entirely disregarded this in its dossier.

Regarding reliable conclusions, it would also be meaningful and necessary to investigate ceritinib in comparison with crizotinib in a study of direct comparison.

Analyses on patient-reported outcomes not usable for indirect comparison

Since different methods of measuring patient-reported outcomes were used in the studies, the corresponding results from an indirect comparison were not usable.

Summary

Due to the lack of similarity, the studies ASCEND-4, PROFILE 1014 and PROFILE 1029 identified by the company were unsuitable for an indirect comparison for long-term outcomes (overall survival) and for patient-reported outcomes. The available information on the initial treatment period of 3 months resulted in a greater risk of harm from ceritinib than from crizotinib; the company did not present the corresponding analyses, however.

Overall, the company presented no usable data for the benefit assessment of ceritinib versus the ACT crizotinib.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug ceritinib compared with the ACT is assessed as shown in Table 3.

Table 3: Ceritinib – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	Crizotinib	Added benefit not proven

a: It was assumed for the present therapeutic indication that the NSCLC patients have stage IIIB or IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
b: Presentation of the ACT specified by the G-BA.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of this report was to assess the added benefit of ceritinib in comparison with crizotinib as ACT in the first-line treatment of adult patients with ALK-positive advanced NSCLC.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA for the research question presented in Table 4.

Table 4: Research question of the benefit assessment of ceritinib

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

The G-BA specified crizotinib as ACT in the present therapeutic indication. In its dossier, the company partly referred to an earlier G-BA specification of the ACT from 7 February 2017, which comprised further alternatives besides crizotinib, e.g. platinum-based combination chemotherapies. This approach was inadequate (see Section 2.7.1 of the full dossier assessment). The present assessment was conducted in comparison with the current ACT specified by the G-BA, i.e. crizotinib.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ceritinib (status: 17 July 2017)
- bibliographical literature search on ceritinib (last search on 29 May 2017)
- search in trial registries for studies on ceritinib (last search on 29 May 2017)
- bibliographical literature search on the ACT (last search on 29 May 2017)
- search in trial registries for studies on the ACT (last search on 29 May 2017)

To check the completeness of the study pool:

- search in trial registries for studies on ceritinib (last search on 14 August 2017)
- search in trial registries for studies on crizotinib (last search on 14 August 2017)

No studies other than the ones cited by the company in the dossier were identified from this check.

The company did not identify any study of direct comparison of ceritinib with crizotinib from the steps of information retrieval mentioned. However, it identified 3 studies that are potentially relevant for an indirect comparison of ceritinib with crizotinib (study ASCEND-4 on ceritinib [3-5] as well as the studies PROFILE 1014 [6-8] and PROFILE 1029 [9,10] on crizotinib).

An indirect comparison based on these 3 studies would be largely unsuitable for the benefit assessment. The company itself also did not conduct an indirect comparison based on these studies because it also considered these 3 studies unsuitable for such an indirect comparison.

The study pool of the company is described below and the reasons are explained why an indirect comparison based on this study pool was largely unsuitable for the benefit assessment.

Study ASCEND-4 on ceritinib

Study ASCEND-4 was a randomized, active-controlled, unblinded approval study sponsored by the company. Treatment-naive adult patients with ALK-positive NSCLC in the locally advanced or metastatic stage (stage IIIB or IV) were enrolled in the study. Patients in the study received either treatment with ceritinib or with platinum-based chemotherapy consisting of cisplatin in combination with pemetrexed (cisplatin + pemetrexed) or of carboplatin in combination with pemetrexed (carboplatin + pemetrexed). The platinum-based chemotherapy was initially administered over 4 cycles. Following this initial phase, patients without interim progression switched to maintenance treatment with pemetrexed, which was continued until progression, unacceptable toxicity, treatment discontinuation or death. Further information on the design of the ASCEND-4 study can be found in Table 9 and Table 10 in Appendix A.1 of the full dossier assessment.

Studies PROFILE 1014 and PROFILE 1029 on crizotinib

Since the ASCEND-4 study was the only RCT with ceritinib in the therapeutic indication and a combination chemotherapy of cisplatin and pemetrexed or of carboplatin and pemetrexed was used as comparator therapy in this study, platinum-based combination chemotherapy constituted the only possible common comparator for an indirect comparison.

The company identified 2 studies on the comparison of crizotinib with this common comparator, namely the studies PROFILE 1014 and PROFILE 1029. Both studies were

randomized, active-controlled, unblinded studies. Treatment-naive adult patients with ALK-positive NSCLC in the locally advanced or metastatic stage were enrolled in the studies. In both studies, the platinum-based combination chemotherapy was administered for a maximum of 6 cycles; maintenance treatment with pemetrexed was not mandated. Further information on the design of the studies PROFILE 1014 and PROFILE 1029 can be found in Table 11 and Table 12 in Appendix A.1 of the full dossier assessment.

Indirect comparison based on the studies ASCEND-4, PROFILE 1014 and PROFILE 1029

The company considered the studies to be not sufficiently similar and did not conduct an indirect comparison

The company described in its dossier that it considered the studies it had identified – ASCEND-4, PROFILE 1014 and PROFILE 1029 – to be not sufficiently similar and that it had therefore not conducted an adjusted indirect comparison with them.

The company justified this assessment mainly with the lack of comparability of the common comparator:

- In the ASCEND-4 study, patients in the control arm received initial platinum-based combination chemotherapy for a maximum of 4 21-day cycles. Patients without interim progression received subsequent therapy with continued maintenance treatment with pemetrexed (see Table 10 of the full dossier assessment).
- In the studies PROFILE 1014 and PROFILE 1029, platinum-based combination chemotherapy in the control arm was limited to a maximum of 6 21-day cycles. Maintenance treatment with pemetrexed was not allowed (see Table 12 of the full dossier assessment).

The company argued that the different therapeutic strategies resulted in demonstrable important differences between the studies regarding the treatment duration with the chemotherapy. In addition, the company added, differences in outcomes such as progression-free survival and overall survival could not be excluded due to the different therapeutic strategies. To support this, the company cited results from a randomized study [11,12], which compared maintenance treatment with pemetrexed versus placebo after previous platinum-based combination chemotherapy and showed longer overall survival and longer progression-free survival under the maintenance treatment. According to the company, progression-free survival was also longer in the control arm of the ASCEND-4 study than in the control arms of both crizotinib studies and time to deterioration of various symptoms and quality of life scales was also longer in the control arm of the ASCEND-4 study than in the control arm of the PROFILE 1014 study.

The company considered the patient populations in the studies ASCEND-4 and PROFILE 1014 to be sufficiently similar, but claimed that the population of the

PROFILE 1029 study differed from the 2 other studies regarding the origin of the patients (Asia) and regarding individual prognostic factors such as presence of brain metastases and stage of disease. In the company's opinion, better prognosis cannot be excluded particularly for patients in the crizotinib arm of the PROFILE 1029 study than for the populations in the other studies.

Differences in common comparator allowed no conclusions on long-term outcomes

In principle, the company's view was shared that there were no indications that the patient populations at least of the studies ASCEND-4 and PROFILE 1014 were not sufficiently similar, but that the common comparator differed notably between the ASCEND-4 study on the one hand and the studies PROFILE 1014 and PROFILE 1029 on the other. However, the treatment regimens used in the respective comparator arm only differed after the initial 4 cycles of the platinum-based combination chemotherapy (see Table 10 and Table 12 in Appendix A.2 of the full dossier assessment). The differences therefore mostly affected those considerations that are based on the total course of the study, e.g. overall survival. An indirect comparison would therefore be not usable for this kind of outcomes.

However, conclusions might be possible on outcomes in which most events occurred within an observation period during which the platinum-based chemotherapy administered in all control arms, and hence the common comparator, was sufficiently comparable (initial 4 cycles). To provide an example, this is explained below based on results on the outcome "severe AEs (CTCAE grade 3 or 4)".

Greater risk of harm from ceritinib in comparison with crizotinib in severe AEs

Analyses on severe AEs (CTCAE grade 3 or 4) in form of Kaplan-Meier curves were available for the studies ASCEND-4 (see Figure 1 in Appendix B.1 of the full dossier assessment) and PROFILE 1014 (see Figure 2 in Appendix B.2 of the full dossier assessment). The documents identified contained no analyses on severe AEs for the PROFILE 1029 study.

It can be inferred from the available Kaplan-Meier curves that the risk of a severe AE (CTCAE grade 3 or 4) within the first 3 months of treatment was similar in both studies under the control treatment with identical treatment regimens (about 50% in the ASCEND-4 study and about 45% in the PROFILE 1014 study). In addition, it was shown in both studies that the majority of severe AEs (CTCAE grade 3 or 4) under the control treatment were observed during the first 3 months of treatment.

The Kaplan-Meier curves from the studies ASCEND-4 and PROFILE 1014 additionally showed that the majority of severe AEs were already observed during the first 3 months of treatment also under the respective experimental intervention (ceritinib in the ASCEND-4 study and crizotinib in the PROFILE 1014 study). Within this period, severe AEs were notably more common under ceritinib than under the combination chemotherapy (study ASCEND-4, see Figure 1 of the full dossier assessment), whereas such events were notably

less common under crizotinib (study PROFILE 1014, see Figure 2 of the full dossier assessment).

In summary, this results in a greater risk of harm from ceritinib in comparison with crizotinib regarding the outcome "severe AEs (CTCAE grade 3 or 4)". The company entirely disregarded this in its dossier.

Regarding reliable conclusions, it would also be meaningful and necessary to investigate ceritinib in comparison with crizotinib in a study of direct comparison.

Analyses on patient-reported outcomes not usable for indirect comparison

The company described that the studies used different methods for the recording of patient-relevant outcomes. The intervals of recording were considerably shorter in the PROFILE 1014 study than in the ASCEND-4 study (see Table 13 of the full dossier assessment), for instance. According to the company, comparability of the studies for these outcomes could therefore not be assumed. This view was shared.

Summary

Due to the lack of similarity, the studies ASCEND-4, PROFILE 1014 and PROFILE 1029 identified by the company were unsuitable for an indirect comparison for long-term outcomes (overall survival) and for patient-reported outcomes. The available information on the initial treatment period of 3 months resulted in a greater risk of harm from ceritinib than from crizotinib; the company did not present the corresponding analyses, however.

Overall, the company presented no usable data for the benefit assessment of ceritinib versus the ACT crizotinib.

2.4 Results

In the dossier, the company presented no suitable data for the assessment of the added benefit of ceritinib versus the ACT. This resulted in no hint of an added benefit of ceritinib in comparison with the ACT; an added benefit of ceritinib versus the ACT is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of ceritinib in comparison with the ACT is shown in Table 5.

Table 5: Ceritinib – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	Crizotinib	Added benefit not proven
a: It was assumed for the present therapeutic indication that the NSCLC patients have stage IIIB or IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy. b: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control		

This deviates from the approach of the company, which derived a considerable added benefit of ceritinib, without providing information on probability, on the basis of the company's data from the comparison of ceritinib versus combination chemotherapy of cisplatin and pemetrexed or carboplatin and pemetrexed.

The G-BA decides on the added benefit.

2.6 List of included studies

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

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-32-ceritinib-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.7920.html.