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Brigatinib (NSCLC) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Brigatinib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 2019). 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
ALK	anaplastic lymphoma kinase
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
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 brigatinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 January 2019.

Research question

The aim of the present report was to assess the added benefit of brigatinib in comparison with ceritinib 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.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of brigatinib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Ceritinib
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

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

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

Results

The company identified no randomized controlled trials (RCTs) on the direct comparison or on the adjusted indirect comparison using a common comparator of brigatinib versus the ACT.

The company therefore presented comparisons of individual arms from different studies. It considered the approval-compliant arm of the ALTA study (brigatinib 90 mg/day for 7 days followed by 180 mg/day) and the ceritinib arm of the ASCEND-5 study (750 mg/day fasted). The company conducted a matching-adjusted indirect comparison (MAIC) as main analysis and a simple comparison of both study arms as sensitivity analysis. Both methods were

unsuitable to draw reliable conclusions on the added benefit of brigatinib versus ceritinib because structural equality of the study arms was not guaranteed due to the missing randomization, even despite adjustment for potentially relevant effect modifiers or prognostic factors in the analysis. For none of the investigated outcomes from the categories of overall survival, symptoms, health-related quality of life and side effects were the effects from these comparisons large enough that they could not be caused by systematic bias. Besides, in April 2018, the approved dose of ceritinib was changed from 750 mg/day fasted to 450 mg/day with food. This is another reason against the usability of the results presented by the company in the derivation of an added benefit of brigatinib versus ceritinib.

In support of its assessment, the company considered, without comparison, the results of the approval-compliant brigatinib arms of the ALTA study and of the non-RCT AP26113-11-101 on brigatinib, as well as of the RCT ALTA-1L on the comparison of brigatinib versus crizotinib, which was conducted outside the present therapeutic indication. These results provided no comparison of brigatinib versus ceritinib in the therapeutic indication.

For the reasons stated above, there were no suitable results for the assessment of brigatinib for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. Hence, there was no hint of an added benefit of brigatinib in comparison with the ACT ceritinib. An added benefit is therefore not proven.

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

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

Table 3: Brigatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Ceritinib	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

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, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of brigatinib in comparison with ceritinib as ACT in adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G BA.

Table 4: Research question of the benefit assessment of brigatinib

Research question	**Therapeutic indication**	**ACT[a]**
1	Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Ceritinib
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

The company followed the ACT specified by the G-BA.

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 lists on brigatinib (status: 11 December 2018)
- bibliographical literature search on brigatinib (last search on 22 November 2018)
- search in trial registries for studies on brigatinib (last search on 30 November 2018)
- bibliographical literature search on the ACT (last search on 22 November 2018)
- search in trial registries for studies on the ACT (last search on 5 December 2018)

To check the completeness of the study pool:

- search in trial registries for studies on brigatinib (last search on 24 January 2019)
- search in trial registries for studies on ceritinib (last search on 24 January 2019)

The check of the completeness of the study pool identified no RCTs on the direct comparison or on the adjusted indirect comparison using a common comparator of brigatinib versus the ACT.

The company also identified no RCTs for direct comparisons or adjusted indirect comparisons using a common comparator of brigatinib versus ceritinib. The company presented comparisons of individual arms from different studies for the derivation of the added benefit. It considered the approval-compliant brigatinib arm of the ALTA study [3] and the ceritinib arm of the ASCEND-5 study [4].

In support of its assessment, the company separately considered the results of the approval-compliant brigatinib arms of the ALTA study and of the non-RCT AP26113-11-101 [5] on brigatinib, as well as of the ALTA-1L study [6], which was conducted outside the present therapeutic indication.

The results presented by the company were unsuitable for the derivation of an added benefit of brigatinib versus ceritinib. This is justified below.

Comparison of individual arms from different studies

Studies included by the company

The ALTA study [3] was a 2-arm open-label RCT. The study included patients with ALK-positive, locally advanced or metastatic NSCLC who, according to the inclusion criteria, had to be previously treated with crizotinib. A total of 222 patients were randomly assigned in a 1:1 ratio to their treatments. Treatment was either brigatinib in a dose of 90 mg/day, which is not in compliance with the approval, or to brigatinib in the approval-compliant dose of 90 mg/day for 7 days followed by 180 mg/day. In its comparison, the company considered the 110 patients allocated to the approval-compliant brigatinib arm.

The ASCEND-5 study [4] was a 2-arm open-label RCT. The study included patients with ALK-positive, locally advanced or metastatic NSCLC who, according to the inclusion criteria, had to be previously treated with crizotinib and 1 or 2 chemotherapeutic regimens (thereof ≥ 1 a platinum-based chemotherapy). A total of 231 patients were randomly assigned in a 1:1 ratio to their treatments. Treatment was either ceritinib 750 mg/day fasted or chemotherapy (pemetrexed or docetaxel). In its comparison, the company considered the 115 patients allocated to the ceritinib arm.

Unsuitable approach of the company

In its comparison of individual arms from different studies, the company compared the results of the approval-compliant brigatinib arm of the RCT ALTA with the results of the ceritinib arm of the RCT ASCEND-5. For this purpose, the company conducted a MAIC as main analysis and a simple comparison of both study arms (referred to by the company as “historical comparison”) as sensitivity analysis.

The purpose of the MAIC presented by the company was to draw conclusions on the superiority of brigatinib versus the ACT. The company tried to adjust the patient population of the approval-compliant brigatinib arm of the ALTA study (at the level of individual patient data) to the patient population of the ceritinib arm of the ASCEND-5 study (at the level of aggregate

data) regarding selected patient characteristics. The company used the resulting patient-individual weights to recalculate the results on different outcomes for brigatinib, and compared these results with the results of the ceritinib arm of the ASCEND-5 study.

In the simple comparison of both study arms, the company calculated effects without consideration of structural differences between the arms of both studies.

Both methods were unsuitable to draw reliable conclusions because structural equality of the study arms was not guaranteed due to the missing randomization, even despite adjustment for potentially relevant effect modifiers or prognostic factors in the analysis [7-9]. For none of the investigated outcomes from the categories of overall survival, symptoms, health-related quality of life and side effects were the effects from these comparisons calculated by the company large enough that they could not be caused by systematic bias alone.

Change of approved dose of ceritinib

In April 2018 [10], based on the results of the dose optimization study ASCEND-8 [11], the approved dose of ceritinib was changed from 750 mg/day fasted to 450 mg/day with food. The change in dosing was justified [12] with the fact that fewer gastrointestinal adverse events occurred under 450 mg/day with food than under 750 mg/day fasted. In the ASCEND-5 study considered by the company ceritinib was administered in the dose of 750 mg/day fasted. This is another reason against the usability of the results presented by the company in the derivation of an added benefit of brigatinib versus ceritinib.

Supporting evidence

Studies included by the company

In support of its assessment, the company presented, without comparison, the results for brigatinib of the approval-compliant arm of the ALTA study ([3]; see above for a description of the study design) and of the AP26113-11-101 study [5], as well as of the ALTA-1L study [6], which was conducted outside the present therapeutic indication of brigatinib.

The AP26113-11-101 study was a dose-ranging non-RCT on brigatinib with 137 adult patients with different tumour entities. This study included 25 patients of the present therapeutic indication who received brigatinib in the approval-compliant dose. The company presented the results for these 25 patients as supporting evidence.

The ALTA-1L study was an open-label RCT on the direct comparison of brigatinib versus crizotinib in adult patients with ALK-positive, locally advanced or metastatic NSCLC who, according to the inclusion criteria, were not allowed to be previously treated with a tyrosine kinase inhibitor.

Unsuitable approach of the company

The non-comparative presentation of the respective brigatinib results of the approval-compliant arm of the ALTA study and of the AP26113-11-101 study provided no comparison with the ACT. Hence, no added benefit of brigatinib versus ceritinib can be derived from these results.

Due to the lack of pretreatment with crizotinib, the patients in the ALTA-1L study did not concur with the target population. In addition, the study investigated brigatinib in comparison with crizotinib. Hence, the study allowed no comparison between brigatinib and ceritinib in the therapeutic indication and was therefore not relevant for the present benefit assessment.

Summary

The comparison of individual arms from different studies presented by the company was unsuitable for the derivation of an added benefit because the effects were not large enough that they could not be caused by systematic bias alone. The change of the approved dose of ceritinib is another reason against the usability of the results presented by the company in the derivation of an added benefit of brigatinib versus ceritinib. Finally, the evidence presented by the company to support its assessment contained no comparison of brigatinib versus ceritinib in the therapeutic indication.

2.4 Results on added benefit

There were no suitable results for the assessment of brigatinib for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. Hence, there was no hint of an added benefit of brigatinib in comparison with the ACT ceritinib. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of brigatinib in comparison with the ACT is summarized in Table 5.

Table 5: Brigatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Ceritinib	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit without evaluating the probability of the added benefit.

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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