



IQWiG Reports – Commission No. A19-48

**Lorlatinib
(NSCLC) –**

**Benefit assessment according to §35a
Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Lorlatinib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 August 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Lorlatinib (NSCLC) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 May 2019

Internal Commission No.:

A19-48

Address of publisher:

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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.

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

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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)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TKI	tyrosine kinase inhibitor

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 lorlatinib. 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 May 2019.

Research question

The aim of the present report is to assess the added benefit of lorlatinib in comparison with the appropriate comparator therapy (ACT) in adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy, or crizotinib and at least one other ALK TKI.

The research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of lorlatinib

Research question	Subindication	ACT ^a
Adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI		
1	Patients who are candidates for further antineoplastic systemic therapy	Individually optimized treatment under consideration of the ALK inhibitors alectinib and ceritinib and of combination or monotherapies
2	Patients who are not candidates for further antineoplastic systemic therapy	Best supportive care
a: Presentation of the respective 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; TKI: tyrosine kinase inhibitor		

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 did not identify any randomized controlled trials (RCTs) on lorlatinib in the present therapeutic indication for either research question and therefore used the results of the single-arm B7461001 study with lorlatinib for the assessment of the added benefit.

In this study, patients were enrolled into 6 cohorts on the basis of driver mutation and pretreatment, of which the company used 3 cohorts for the benefit assessment. Further information on pretreatment was only available for 1 of the 3 cohorts. In this cohort, the majority of patients had been pretreated in compliance with the approval (alectinib or ceritinib in first-line treatment).

The company did not retrieve any information on the ACT because it considered the informative value of the available evidence to be too low to derive an added benefit or a lesser benefit in the absence of dramatic effects.

Since the company did not present any results on the ACT, it is not possible to derive an added benefit of lorlatinib. As a result, there was no hint of an added benefit of lorlatinib versus the ACT for patients who are candidates for further antineoplastic systemic therapy or who are not candidates for further antineoplastic systemic therapy; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Table 3 shows a summary of probability and extent of the added benefit of lorlatinib.

Table 3: Lorlatinib – probability and extent of added benefit

Research question	Subindication	ACT^a	Probability and extent of added benefit
Adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI			
1	Patients who are candidates for further antineoplastic systemic therapy	Individually optimized treatment under consideration of the ALK inhibitors alectinib and ceritinib and of combination or monochemotherapies	Added benefit not proven
2	Patients who are not candidates for further antineoplastic systemic therapy	Best supportive care	Added benefit not proven
a: Presentation of the respective 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; TKI: tyrosine kinase inhibitor			

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 is to assess the added benefit of lorlatinib in comparison with the ACT in adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI.

The research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of lorlatinib

Research question	Subindication	ACT ^a
Adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI		
1	Patients who are candidates for further antineoplastic systemic therapy	Individually optimized treatment under consideration of the ALK inhibitors alectinib and ceritinib and of combination or monochemotherapies
2	Patients who are not candidates for further antineoplastic systemic therapy	Best supportive care
a: Presentation of the respective 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; TKI: tyrosine kinase inhibitor		

The company followed the ACT specified by the G-BA. For the patients of research question 1, the company named concrete combination or monochemotherapies that it considered to be options for chemotherapies without justifying its selection (see Section 2.7.1 of the full dossier assessment).

The assessment was conducted in comparison with the ACT specified by the G-BA and 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

For both research questions, 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 lorlatinib (status: 6 May 2019)
- bibliographical literature search on lorlatinib (last search on 6 May 2019)
- search in trial registries for studies on lorlatinib (last search on 6 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on lorlatinib (last search on 17 June 2019)

Concurring with the company, the check of the completeness of the study pool for both research questions did not produce any RCTs with lorlatinib in comparison with the ACT.

In the absence of comparative studies on lorlatinib in the therapeutic indication, the company presented the data from the ongoing single-arm approval study B7461001 with lorlatinib monotherapy [3] and used them for its benefit assessment.

For both research questions, the company did not retrieve any information on the ACT for a comparison of individual arms from different studies. It justified this with the claim that no dramatic effects for the patient-relevant outcomes were to be expected in the present therapeutic indication of ALK-positive advanced NSCLC.

In the B7461001 study, patients were enrolled into 6 cohorts on the basis of driver mutation and pretreatment, of which the company used 3 cohorts for the present benefit assessment because it considered them to concur with the approved therapeutic indication of lorlatinib. Pretreatment in these cohorts was either 1 ALK TKI other than crizotinib (EXP-3B) or 2 (EXP-4) or 3 ALK TKIs (EXP-5). All 3 cohorts allowed any number of prior chemotherapies.

According to the approved therapeutic indication, lorlatinib is either used after pretreatment with alectinib or ceritinib or after pretreatment with crizotinib and at least one other ALK TKI [4]. The criteria for pretreatment applied to the 3 cohorts used by the company were broader. The extent to which the pretreatments in the 3 cohorts presented by the company nevertheless corresponded to the approval was not addressed by the company in Module 4 A of the dossier. It can be inferred from one publication on the study [3] that pretreatment of most patients in cohort EXP-3B was in compliance with the approval. Of 28 patients, 26 (92.9%) had received alectinib or ceritinib as pretreatment in first-line therapy; only one patient had received brigatinib and one patient entrectinib. The publication contained no separate information on pretreatment for the cohorts EXP-4 and EXP-5.

In accordance with the requirements of the G-BA's rules of procedure, the company arrived at the overall conclusion that the informative value of the available evidence (single-arm study B7461001) was too low to derive an added benefit or a lesser benefit in the absence of dramatic effects. In the summarizing conclusions on the assessment of lorlatinib (Sections 4.4.1 and 4.4.2 of Module 4 A of the dossier), the company nevertheless tried to appraise lorlatinib in the current medical context on the basis of study B7461001.

In line with the company, the present benefit assessment considers the data presented as unsuitable for deriving an added benefit for lorlatinib versus the ACT.

2.4 Results on added benefit

The company presented no suitable data for research questions 1 and 2 for the assessment of the added benefit of lorlatinib versus the ACT for adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI.

For these 2 research questions, this therefore resulted in no hint of an added benefit of lorlatinib versus the ACT; 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 lorlatinib in comparison with the ACT is summarized in Table 5.

Table 5: Lorlatinib – probability and extent of added benefit

Research question	Subindication	ACT ^a	Probability and extent of added benefit
Adult patients with ALK-positive advanced NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI therapy, or crizotinib and at least one other ALK TKI			
1	Patients who are candidates for further antineoplastic systemic therapy	Individually optimized treatment under consideration of the ALK inhibitors alectinib and ceritinib and of combination or monotherapies	Added benefit not proven
2	Patients who are not candidates for further antineoplastic systemic therapy	Best supportive care	Added benefit not proven
a: Presentation of the respective 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; TKI: tyrosine kinase inhibitor			

The assessment of the extent and probability of the added benefit described above concurs with that of the company.

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58.
3. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol* 2018; 19(12): 1654-1667.
4. Pfizer. Lorviqua 25 mg/ 100 mg Filmtabletten: Fachinformation [online]. 05.2019 [Accessed: 05.2019]. URL: <http://www.fachinfo.de>.

The full report (German version) is published under <https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-48-lorlatinib-nsclc-benefit-assessment-according-to-35a-social-code-book-v.12402.html>.