IQWiG Reports – Commission No. A18-45

Osimertinib (non-small cell lung cancer) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Osimertinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 October 2018). Please note: This document was translated by an external translator and 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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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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 osimertinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 5 July 2018.

Research question

The aim of this report is to assess the added benefit of osimertinib in comparison with the appropriate comparator therapy (ACT) as first-line therapy in adult patients with local advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations in the epidermal growth factor receptor (EGFR).

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

Table 2[2]: Research questions for the benefit assessment of osimertinib

Research question	Indication	ACT[a]
1	First-line therapy in adult patients with locally advanced or metastatic NSCLC with activating mutations in the EGFR	Afatinib or **erlotinib** or **gefitinib**

a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer

The company followed the G-BA's specification of the ACT; from the 3 options named by the G-BA, it selected treatment with either erlotinib or gefitinib.

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

Results

Study pool and study characteristics

The multicentre, double-blind, randomized controlled trial (RCT) FLAURA, which compared osimertinib with erlotinib or gefitinib, was used for the benefit assessment.

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

The study included patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. Patients were randomized in a 1:1 ratio to the osimertinib or erlotinib/gefitinib arm. Before participating in the study, the study sites chose either erlotinib or gefitinib as the ACT. Patients received 80 mg osimertinib orally once daily in the osimertinib arm or either 250 mg gefitinib or 150 mg erlotinib orally once daily in the comparator arm; all dosing regimens conformed to the marketing authorization. To ensure blinding, all patients received 2 tablets (1 verum and 1 placebo) once daily during the blinded treatment phase. In accordance with the approval, erlotinib is to be taken separately from meals, i.e. at least 1 hour before or 2 hours after meals. However, the study protocol did not ensure that erlotinib was taken on an empty stomach as required by the approval. This results in about 1/3 of patients in the comparator arm potentially not having been treated as approved.

Risk of bias

The risk of bias at study level is assessed as low. The risk of bias at outcome level for the outcomes of overall survival and discontinuation due to AEs is rated as low. The outcomes of serious adverse events (SAEs), severe AEs, and specific AEs (elevated alanine transferase, diseases of the skin and subcutaneous tissue, and acneiform dermatitis) each have a high risk of bias.

Certainty of conclusions

The high percentage of patients in the erlotinib/gefitinib arm who may potentially not have been treated as approved may influence the results of all outcomes. Therefore, any effects on outcomes which were demonstrated on the basis of the FLAURA study can be used to infer only hints, for example of added benefit, with the extent being non-quantifiable.

Results

Mortality

- Overall survival

For the outcome of overall survival, a statistically significant effect in favour of osimertinib was found. Consequently, there is a hint of added benefit for osimertinib in comparison with erlotinib/gefitinib.

Morbidity and health-related quality of life

Morbidity and health-related quality of life were measured using the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 (EORTC QLQ-LC13) and the function scales of EORTC QLQ-C30. However, the data presented by the company are incomplete and therefore unusable. Consequently, there is no hint of an added benefit of osimertinib in comparison with erlotinib/gefitinib; an added benefit is therefore not proven.

Adverse events

- SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of osimertinib in comparison with erlotinib/gefitinib; greater or lesser harm is therefore not proven.

- Severe AEs (Common-Terminology-Criteria-for-Adverse-Events[CTCAE] grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant effect in favour of osimertinib in comparison with erlotinib/gefitinib was found. An effect modification by the attribute sex was found for this outcome. For men, this results in a hint of lesser harm of osimertinib in comparison with erlotinib/gefitinib, while for women, there is no proof of greater or lesser harm of osimertinib in comparison with erlotinib/gefitinib.

- Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant effect in favour of osimertinib was found. Consequently, there is a hint of lesser harm of osimertinib in comparison with erlotinib/gefitinib.

- Specific AEs

For each of the specific AEs of elevated alanine aminotransferase (CTCAE grade ≥ 3), diseases of the skin and subcutaneous tissue (CTCAE grade ≥ 3), and acneiform dermatitis, a statistically significant effect in favour of osimertinib in comparison with erlotinib/gefitinib was found. Consequently, there is a hint of lesser harm of osimertinib in comparison with erlotinib/gefitinib.

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 osimertinib compared with the ACT is assessed as follows:

Overall, there are exclusively positive effects of osimertinib regarding overall survival and AE outcomes of various severities. On the basis of the available data, there is a hint of non-quantifiable added benefit of osimertinib in comparison with erlotinib/gefitinib for patients with

[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].

locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutation.

No data are available for patients with other activating EGFR mutations in NSCLC; consequently, there is no proof of added benefit for these patients.

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

Table 3: Osimertinib – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**[b]
First-line therapy in adult patients with locally advanced or metastatic NSCLC with activating mutations in the EGFR	Afatinib or **erlotinib** or **gefitinib**	*EGFR mutation exon 21 (L858R) or exon 19 deletion:* Hint of non-quantifiable added benefit *Other activating EGFR mutations:* Added benefit not proven
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. b: Patients with an WHO-PS of 0 or 1 were included in the relevant study. It remains unclear whether the observed effects translate to patients with WHO-PS ≥ 1. ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer; WHO-PS: World Health Organization Performance Status		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 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

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-45-osimertinib-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.10223.html.