IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Afatinib (NSCLC of squamous histology) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Afatinib (NSCLC mit Plattenepithelhistologie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 July 2016). 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Ingo Schmidt-Wolf, Centre for Integrated Oncology (CIO), Bonn University Hospital, 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]:

- Klaus Gossens
- Getrud Egger
- Ulrich Grouven
- Sarah Mostardt
- Regine Potthast
- Dorothea Sow
- Beate Wieseler
- Min Zhou

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[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
BSC	best supportive care
EGFR	epidermal growth factor receptor
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)
SPC	Summary of Product Characteristics

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 afatinib. 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 27 April 2016.

Research question

The aim of the present report was to assess the added benefit of afatinib in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of squamous histology progressing on or after platinum-based chemotherapy. The research questions and the respective ACTs specified that resulted from the G-BA's requirements are presented in Table 2.

Table 2: Research questions of the benefit assessment of afatinib

Research question	Therapeutic indication[a]	ACT[b]
1	Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated	Docetaxel
2	Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated	BSC

a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC, without indication for curative resection, radiotherapy or radiochemotherapy).
b: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BSC: best supportive care; 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 docetaxel as ACT for adult patients with squamous cell carcinoma progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated. For patients for whom no further chemotherapy is indicated, the G-BA specified best supportive care (BSC) as ACT.

The company expanded the ACT on research question 1 with erlotinib and assessed the added benefit of afatinib in comparison with erlotinib.

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

Results

Research question 1: patients for whom further chemotherapy is indicated

The data presented by the company were unsuitable to draw conclusions on the added benefit of afatinib in comparison with the ACT. This concerned both the study of direct comparison and the indirect comparison presented.

Direct comparison

The company expanded the G-BA's specification of the ACT with erlotinib and derived an added benefit of afatinib in comparison with erlotinib on the basis of the LUX-Lung-8 study presented. This study was a randomized controlled trial (RCT) comparing afatinib with erlotinib in adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom second-line treatment was indicated.

The company justified its expansion of the ACT by claiming that, from the company's point of view, erlotinib has a comparable therapeutic value to docetaxel in the present therapeutic indication. However, the company presented no sufficient evidence from which a therapeutic equivalence of erlotinib and docetaxel for the present therapeutic indication could be derived. Erlotinib was therefore unsuitable as ACT. The LUX-Lung 8 study presented by the company was therefore not used for the assessment of the added benefit of afatinib in comparison with the ACT.

Indirect comparison

In addition to the direct comparison, the company described an adjusted indirect comparison between afatinib and docetaxel with the common comparator erlotinib for research question 1. On the afatinib side, the company identified the LUX-Lung 8 study, and on the docetaxel side, the TAILOR study. The latter was an RCT directly comparing erlotinib with docetaxel in second-line treatment after platinum-based chemotherapy in patients without activating epidermal growth factor receptor (EGFR) mutations. The company did not use the indirect comparison to derive an added benefit of afatinib, however. The company justified this by claiming that the TAILOR study was unsuitable for a valid and methodologically correct comparison.

The information about the study design and relevant patient characteristics on the TAILOR study was insufficient to allow a check of the comparability of the TAILOR and the LUX-Lung 8 study. Furthermore, the dosing regimen of docetaxel used in the TAILOR study did not concur completely with the Summary of Product Characteristics (SPC). Finally, the TAILOR study reported results only on one patient-relevant outcome (overall survival) for the relevant patient population.

Concurring with the company, the indirect comparison was not used for the derivation of an added benefit of afatinib because of these deficiencies.

Research question 2: patients for whom no further chemotherapy is indicated

In its dossier, the company presented no data on the comparison of afatinib with BSC for research question 2.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug afatinib versus the ACT is assessed as follows:

Table 3: Afatinib – extent and probability of added benefit

Therapeutic indication[a]	Appropriate comparator therapy	Extent and probability of added benefit
Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated	Docetaxel	Added benefit not proven
Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated	BSC	Added benefit not proven
a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC, without indication for curative resection, radiotherapy or radiochemotherapy). BSC: best supportive care; 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.

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of afatinib in comparison with the ACT in adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. The research questions and the respective ACTs specified that resulted from the G-BA's specifications are presented in Table 4.

Table 4: Research questions of the benefit assessment of afatinib

Research question	Therapeutic indication[a]	Appropriate comparator therapy[b]
1	Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated	Docetaxel
2	Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated	BSC

a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC, without indication for curative resection, radiotherapy or radiochemotherapy).
b: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BSC: best supportive care; 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 docetaxel as ACT for adult patients with squamous cell carcinoma progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated. For patients for whom no further chemotherapy is indicated, the G-BA specified BSC as ACT.

The company followed the G-BA's research questions, but expanded the ACT on research question 1 with erlotinib and assessed the added benefit of afatinib in comparison with erlotinib. This approach was not accepted. The ACT specified by the G-BA was used for the present benefit assessment.

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 further chemotherapy is indicated

The data identified by the company for research question 1 were unsuitable to draw conclusions on the added benefit of afatinib in comparison with the ACT. This concerned both the study of direct comparison and the indirect comparison presented. The study pool of the company is described below. The reasons why the respective data were unsuitable for the derivation of the added benefit are explained.

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 list on afatinib (status: 2 March 2016)
- bibliographical literature search on afatinib (last search on 1 March 2016)
- search in trial registries for studies on afatinib (last search on 3 March 2016)
- bibliographical literature search on the ACT (last search on 1 March 2016)
- search in trial registries for studies on the ACT (last search on 3 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on afatinib (last search on 13 May 2016)
- search in trial registries for studies on the ACT (last search on 18 May 2016)

No additional relevant study was identified from the check.

Direct comparison

The company presented one study of direct comparison for research question 1. This was the RCT LUX-Lung 8 [3]. This open-label, active controlled phase 3 study compared afatinib with erlotinib in adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom second-line treatment was indicated. Further information on the LUX-Lung 8 study can be found in Table 10 in Appendix A of the full dossier assessment.

Assessment of the evidence presented by the company on the direct comparison

The company's approach to use the LUX-Lung 8 study for the assessment of the added benefit of afatinib was not followed. The company expanded the G-BA's specification of the ACT with erlotinib and derived an added benefit of afatinib in comparison with erlotinib on the basis of the study presented. It justified its approach by claiming that, from the company's point of view, erlotinib has a comparable therapeutic value to docetaxel in the present therapeutic indication. However, the company presented no sufficient evidence from which a therapeutic equivalence of erlotinib and docetaxel for the present therapeutic indication could be derived (see Section 2.6.1 of the full dossier assessment). Erlotinib was therefore unsuitable as ACT. The LUX-Lung 8 study presented by the company was therefore not used for the assessment of the added benefit of afatinib in comparison with the ACT.

Indirect comparison

In addition to the direct comparison, the company described an adjusted indirect comparison between afatinib and docetaxel with the common comparator erlotinib for research question 1

(see Figure 1). On the afatinib side, the company identified the LUX-Lung 8 study, and on the docetaxel side, the TAILOR study [4]. The latter was an RCT directly comparing erlotinib with docetaxel in second-line treatment after platinum-based chemotherapy in patients without activating EGFR mutations. The company did not use the indirect comparison to derive an added benefit of afatinib, however. The company justified this by claiming that the TAILOR study was unsuitable for a valid and methodologically correct comparison (see Section 2.6.2.3.2 of the full dossier assessment).

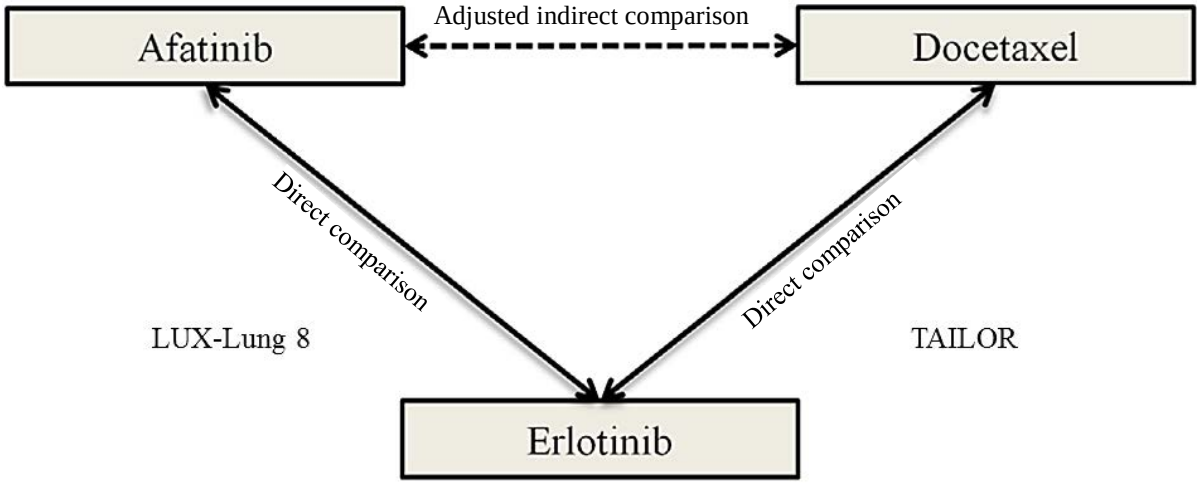

Figure 1: Study pool of the company for the indirect comparison between afatinib and docetaxel

Assessment of the evidence presented by the company on the indirect comparison

The company's approach not to use the indirect comparison for the derivation of the added benefit of afatinib was followed. The information about the study design and relevant patient characteristics on the TAILOR study was insufficient to allow a check of the comparability of the TAILOR and the LUX-Lung 8 study. Furthermore, the dosing regimen of docetaxel used in the TAILOR study did not concur completely with the SPC. Besides the approved dosage of 75 mg/m^2 docetaxel every 21 days, a dosage of 35 mg/m^2 docetaxel on days 1, 8, and 15 every 28 days was also used, which is not in compliance with the approval [5]. Finally, the TAILOR study reported results only on one patient-relevant outcome (overall survival) for the relevant patient population.

The indirect comparison was not used for the derivation of an added benefit of afatinib because of these deficiencies.

2.3.2 Results on added benefit

In its dossier, the company presented no suitable data on the comparison of afatinib with docetaxel for research question 1. Hence there was no hint of an added benefit of afatinib in comparison with docetaxel. An added benefit of afatinib is not proven for patients with locally

advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated.

2.3.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of afatinib in adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated. An added benefit of afatinib for these patients is not proven.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question 2: patients for whom no further chemotherapy is indicated

In its dossier, the company presented no data on the comparison of afatinib with BSC for research question 2.

2.4.1 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 list on afatinib (status: 2 March 2016)
- bibliographical literature search on afatinib (last search on 1 March 2016)
- search in trial registries for studies on afatinib (last search on 3 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on afatinib (last search on 13 May 2016)

Concurring with the company, no relevant study was identified.

2.4.2 Results on added benefit

In its dossier, the company presented no data on the comparison of afatinib with BSC for research question 2. Hence there was no hint of an added benefit of afatinib in comparison with BSC. An added benefit of afatinib is not proven for adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated.

2.4.3 Extent and probability of added benefit

The company presented no data for the assessment of the added benefit of afatinib in adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated. An added benefit of afatinib for these patients is not proven.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit

Table 5 presents a summary of the extent and probability of the added benefit of afatinib.

Table 5: Afatinib – extent and probability of added benefit

Therapeutic indication[a]	**Appropriate comparator therapy**	**Extent and probability of added benefit**
Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated	Docetaxel	Added benefit not proven
Adult patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy for whom no further chemotherapy is indicated	BSC	Added benefit not proven
a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC, without indication for curative resection, radiotherapy or radiochemotherapy). BSC: best supportive care; 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 company's approach, which derived an indication of considerable added benefit of afatinib in comparison with erlotinib for patients with squamous cell carcinoma progressing on or after platinum-based chemotherapy for whom further chemotherapy is indicated. The company derived a non-quantifiable added benefit for patients for whom further chemotherapy is not indicated.

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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