IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Afatinib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 February 2014). 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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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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[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] 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
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
EQ-5D	EuroQol-5D
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
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UICC	Union for International Cancer Control
TKI	tyrosine-kinase inhibitor
VAS	visual analogue scale

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 15 November 2013.

Research question

The aim of this benefit assessment is to assess the added benefit of afatinib in epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI)-naive adult patients with locally advanced and/or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations.

The assessment was conducted in comparison with the appropriate comparator therapy (ACT). The G-BA specified the ACT presented in Table 2.

Table 2: ACT for the benefit assessment of afatinib

Research question	Line of treatment	ACT
1	Non-pretreated patients	▪ Gefitinib or erlotinib or
1a	Non-pretreated patients with ECOG PS 0 or 1	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed) in accordance with the respective approved therapeutic indication
1b	Non-pretreated patients with ECOG PS 2	▪ Gemcitabine
2	Patients pretreated with one chemotherapy or several chemotherapies	▪ Gefitinib or erlotinib
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status		

In principle, the company concurred with the G-BA's specification. In research question 1 (non-pretreated patients), it chose the second option offered by the G-BA (differentiation of the ACT according to Eastern Cooperative Oncology Group Performance Status [ECOG PS]).

The assessment was based on patient-relevant outcomes. One comparative randomized controlled trial (RCT) was included in the assessment.

Results

Research question 1a: non-pretreated patients with ECOG PS 0 to 1

The LUX-Lung 3 study (approval study of afatinib) was included in the assessment.

Study characteristics

The LUX-Lung 3 study is an ongoing, randomized, open-label, multicentre, active-controlled approval study. TKI-naive adult patients with stage IIIB or IV lung adenocarcinoma with activating EGFR mutations and baseline ECOG PS of 0 or 1 were enrolled. The patients were randomly assigned 2:1 (afatinib : chemotherapy). A total of 345 patients were randomized (afatinib: 230 patients; chemotherapy: 115 patients).

In the study, afatinib was compared with a combination treatment of cisplatin and pemetrexed. Afatinib was used in an initial dose of 40 mg/day. Afatinib treatment was continued until disease progression occurred, treatment was no longer tolerated, or the investigator or the patient requested treatment discontinuation. The comparator therapy cisplatin + pemetrexed was administered for a maximum of 6 cycles of 21 days each. Treatment could be discontinued prematurely if disease progression or unacceptable adverse events occurred or at the patient's or investigator's request or in case of intolerance. Cisplatin was administered in a dose of 75 mg/m², pemetrexed in a dose of 500 mg/m².

Progression-free survival (PFS) was the primary outcome of the LUX-Lung 3 study. The data of all patients were included in the analysis of overall survival also after the end of the study treatment. The recording of other data was conducted outcome-specific beyond the end of treatment. Adverse events (AEs) were recorded up to 28 days after the end of treatment, data on symptoms and quality of life were recorded up to disease progression or treatment switching.

Risk of bias

The risk of bias at study level was rated as low for the LUX-Lung 3 study. At most "indications", e.g. of an added benefit, could be derived from this study. In addition, there was a high risk of bias of the study results for all outcomes except overall survival because of the different treatment durations in the afatinib arm and the cisplatin + pemetrexed arm. Hence no more than hints were derived for these outcomes. The differences in observation durations between the treatment groups were probably more important for adverse events than for the outcomes on morbidity and health-related quality of life because these were only recorded within a predefined period of time after the end of treatment. Therefore no quantitative conclusion on the extent of harm from afatinib can be drawn in the present benefit assessment. This is mainly due to the drastically different treatment durations in the study arms. The median treatment duration was 336 days in the afatinib arm and 105 days in the cisplatin + pemetrexed arm because afatinib was used up to disease progression or unacceptable intolerance, whereas the chemotherapy ended after 6 cycles of 21 days each at

the latest. The qualitative conclusions drawn in the report were based on the naive proportions for the outcomes on adverse events.

Results

Mortality

For overall survival, there was proof of an effect modification by the patient's EGFR mutation so that conclusions are only meaningful on the basis of the corresponding subgroup results. For patients with Del19 mutation, there was an indication of an added benefit of afatinib compared with cisplatin + pemetrexed. For patients with L858R mutation, treatment with afatinib did not result in a statistically significant difference between the treatment groups. For patients with different mutations (non-Del19 and non-L858R), there was an indication of lesser benefit of afatinib for overall survival.

Morbidity

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13). The rate of patients with clinically relevant improvement and the time to the worsening of symptoms were analysed. There were hints of an added benefit of afatinib for the following symptoms: dyspnoea, nausea and vomiting, coughing (both analyses), fatigue and alopecia. Effects were observed for pain in chest (time to worsening) and pain in arm/shoulder (improvement), but these were no more than marginal so that no added benefit of afatinib could be derived from them. There was a hint of lesser benefit for each of the following symptoms: diarrhoea (both analyses), sore mouth and dysphagia (time to worsening). There was no statistically significant difference between the treatment groups in the following symptom scales: pain, pain (other than chest or arm/shoulder), insomnia, appetite loss, constipation, haemoptysis and peripheral neuropathy.

Due to effect modifications, some of the effects described were only observed in individual subgroups. This was taken into account in the overall conclusion on added benefit.

Health-related quality of life

Health-related quality of life was recorded with the functional scales of the EORTC QLQ-C30 questionnaire. The rate of patients with clinically relevant improvement and the time to the worsening of symptoms were analysed.

For the outcomes "physical functioning", "role functioning" and "global health status", there were indications of effect modifications by the factor "age", and in the case of physical functioning also by EGFR mutation status. Both analyses resulted in a hint of an added benefit of afatinib in patients < 65 years with regards to physical functioning and role functioning. In contrast, in patients ≥ 65 years, there was a hint of lesser benefit of afatinib for

improvement in role functioning. For patients with Del19 mutation, both analyses resulted in a hint of an added benefit of afatinib with regards to physical functioning; for L858R and other mutations, there were no statistically significant differences between the treatment groups.

There was no statistically significant difference between the treatment groups in the outcomes "emotional functioning" and "cognitive functioning".

For health-related quality of life measured with the EuroQol-5D (EQ-5D), no results were available for the individual scales of the questionnaire. The visual analogue scale (VAS) data were not used because the company presented no subgroup results for them, although relevant effect modifications were observed in the recording of health-related quality of life with the EORTC QLQ-C30.

Adverse events

The considerable difference in observation duration between the treatment arms did not allow a quantitative assessment of the potential harm from afatinib versus the ACT on the basis of the available data. Only qualitative conclusions could be drawn on the basis of the naive proportions. Overall, with regards to adverse events, there was neither an advantage nor a disadvantage of afatinib versus the ACT on this basis. Overall, greater or lesser harm from afatinib in comparison with cisplatin + pemetrexed is therefore not proven.

Research question 1b: non-pretreated patients with ECOG PS 2

There were no relevant data for the research question of afatinib versus gemcitabine in non-pretreated patients with ECOG PS 2. Hence an added benefit of afatinib versus the ACT is not proven.

Research question 2: patients pretreated with one chemotherapy or several chemotherapies

There were no relevant data for the research question of afatinib versus erlotinib or gefitinib in patients pretreated with one chemotherapy or several chemotherapies. Hence an added benefit of afatinib versus the ACT is not proven.

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 compared with the ACT is assessed as presented in Table 3:

Table 3: Patient groups, ACTs and extent and probability of added benefit of afatinib in TKI-naive adult patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations

Line of treatment	**Patient group**	**ACT[a]**	**Subgroup**	**Extent and probability of added benefit**
Non-pretreated patients	ECOG PS 0-1	Gefitinib or erlotinib or **cisplatin +** (vinorelbine, gemcitabine, docetaxel, paclitaxel or **pemetrexed**)	EGFR mutation Del19	Indication of a major added benefit
			EGFR mutation L858R, age < 65 age ≥ 65	Hint of a minor added benefit Added benefit not proven
			Other[b] EGFR mutations	Indication of a lesser benefit
	ECOG PS 2	Gefitinib or erlotinib or **gemcitabine**	Added benefit not proven	
Patients pretreated with one chemotherapy or several chemotherapies		Erlotinib or gefitinib	Added benefit not proven	

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose an ACT from several options, the respective choice of the company is printed in bold.
b: Non-L858R, non-Del19 mutation

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; TKI: tyrosine-kinase inhibitor

There was an indication of a major added benefit for the outcome "overall survival" for patients with Del19 mutation; age dependence was not shown. There were mainly hints of positive effects of afatinib with regards to symptoms and health-related quality of life for this subgroup. Some of them were age-dependent. There were only individual cases of negative

[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), see [1]. 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), see [2].

effects of afatinib. In the overall assessment of the effects, there is an indication of a major added benefit of afatinib versus cisplatin + pemetrexed for the subgroup of patients with Del19 mutation.

In the subgroup of patients with L858R mutation, there were hints of positive and negative effects of afatinib with regards to symptoms and health-related quality of life, with a predominance of the positive effects. Some of these effects were age-dependent. Overall, there is a hint of a minor added benefit of afatinib for patients < 65 years. There is no proof of added benefit for patients ≥ 65 years.

For patients with different EGFR mutations than Del19 or L858R, there was an indication of lesser benefit of afatinib for the outcome "overall survival". This effect was not age-dependent. With regards to symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib. Some of them were age-dependent without showing clear advantages of afatinib versus the ACT. In this case, the age-dependent effects had no important influence on the overall conclusion, and therefore did not result in a different assessment of the added benefit for the age groups considered. Overall, there is an indication of lesser benefit of afatinib versus cisplatin in combination with pemetrexed for the subgroup of patients with different EGFR mutations than Del19 or L828R.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this benefit assessment is to assess the added benefit of afatinib in EGFR-TKI-naive adult patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations.

The G-BA specified the ACT presented in Table 4.

Table 4: ACT for the benefit assessment of afatinib

Research question	Line of treatment	ACT
1	Non-pretreated patients	▪ Gefitinib or erlotinib or
1a	Non-pretreated patients with ECOG PS 0 or 1	▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed) in accordance with the respective approved therapeutic indication
1b	Non-pretreated patients with ECOG PS 2	▪ Gemcitabine
2	Patients pretreated with one chemotherapy or several chemotherapies	▪ Gefitinib or erlotinib
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status		

In principle, the company concurred with this specification. For non-pretreated patients with ECOG PS of 0 or 1 (research question 1a), the company chose cisplatin + pemetrexed as comparator therapy. The company additionally named cisplatin + gemcitabine as comparator therapy; but this was of no importance for the assessment because the study included by the company for this comparison was not relevant (see Section 2.3). For non-pretreated patients with ECOG PS 2 (research question 1b), the company concurred with the ACT gemcitabine specified by the G-BA.

The company divided the subpopulation of pretreated patients (research question 2) in patients who were pretreated with one chemotherapy (second-line) and in patients who were pretreated with several chemotherapies (third- and higher lines). However, the company specified the same comparator therapy (gefitinib or erlotinib) for both populations and therefore concurred with the ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 afatinib (studies completed up to 21 August 2013)
- search in trial registries for studies on afatinib (last search on 21 August 2013)
- bibliographical literature search on the ACT (last search on 3 September 2013)
- search in trial registries for studies on the ACT (last search on 22 August 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on afatinib (last search on 29 November 2013)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Research question 1a: non-pretreated patients with ECOG PS 0 to 1

2.3.1.1 Studies included

The LUX-Lung 3 study listed in Table 5 was included in the benefit assessment of afatinib in non-pretreated patients with ECOG PS 0 or 1.

Table 5: Study pool – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
LUX-Lung 3	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

Apart from the LUX-Lung 3 study, the company included another RCT (LUX-Lung 6) in its assessment. This study was a comparison of afatinib with cisplatin + gemcitabine, also in non-pretreated adenocarcinoma patients with ECOG PS 0 or 1 and activating EGFR mutations. According to the company, the results of this study were presented as additional information to provide an overview of the entire available evidence for this patient population. However, in the LUX-Lung 6 study, gemcitabine (in combination therapy with cisplatin) was administered in a dosage of 1000 mg/m² body surface area. According to the information provided in the Summary of Product Characteristics (SPC), the approval-compliant dosage of

gemcitabine is 1250 mg/m² body surface area for the combined treatment with cisplatin (see Section 2.7.2.3.2 of the full dossier assessment). The company did not explain in how far the results of the LUX-Lung 6 study are transferable to patients treated in compliance with the approval. Hence the LUX-Lung 6 study presented by the company was unsuitable for drawing conclusions on the added benefit of afatinib versus the ACT and was not included in the benefit assessment.

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.1.2 Study characteristics

Characteristics of the study and of the interventions

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
LUX-Lung 3	RCT, open-label, active-controlled, parallel	Non-pretreated patients with lung adenocarcinoma (stage IIIB or IV, EGFR mutation, ECOG PS 0 or 1, ≥ 18 years, no previous chemotherapy[b]	Afatinib (N = 230) cisplatin + pemetrexed (N = 115)	Treatment with afatinib: up to disease progression or intolerance; chemotherapy: 6 cycles or up to disease progression or intolerance; follow-up up to progression or initiation of different cancer treatment; overall survival recorded until the patients' death	133 centres in 25 countries in Asia, Australia, Europe, North and South America start: 08/2009 data cut-offs: 02/2012[c] 01/2013[d]	Primary outcome: progression-free survival secondary outcomes: overall survival, symptoms, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.
b: Apart from (neo)adjuvant chemotherapy if at least 12 months before randomization.
c: Planned after disease progression or death in 217 patients.
d: At the regulatory authorities' request, only data on overall survival

ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed, ECOG PS 0-1

Study	Intervention	Comparison	Concomitant medication
LUX-Lung 3	Afatinib: starting dose 40 mg/day[a] orally, once daily, use up to disease progression or intolerance; up-titration to 50 mg/day possible after 21 days in case of good tolerability; dose reduction to 20 mg/day in case of intolerance[b]	Cisplatin: 75 mg/m² IV, on the first day of each 21-day treatment cycle pemetrexed: 500 mg/m² IV, on the first day of each 21-day treatment cycle[b] maximum 6 treatment cycles of 21 days[b]	Only with cisplatin + pemetrexed: ▪ antiemetics ▪ administration of corticosteroid on the day before, during and after the infusion ▪ daily oral administration of folic acid ▪ 1000 mg vitamin B12 IM before the first and after every third treatment cycle ▪ hydration
ECOG PS: Eastern Cooperative Oncology Group Performance Status; IM: intramuscular; IV: intravenous; RCT: randomized controlled trial; vs.: versus			

The LUX-Lung 3 study is an ongoing, randomized, open-label, multicentre, active-controlled approval study. TKI-naive adult patients with stage IIIB or IV lung adenocarcinoma (Union for International Cancer Control [UICC], 6th edition), which corresponds to the locally advanced or metastatic stage according to the SPC of afatinib, were enrolled. Patients had to have activating EGFR mutations. Disease severity at the start of the study had to correspond to an ECOG PS of 0 or 1. Patients pretreated with chemotherapy due to relapsed and/or metastatic NSCLC were excluded from the study. Adjuvant/neoadjuvant chemotherapy was only allowed if at least 12 months had passed between the end of treatment and randomization.

Patients were randomly assigned 2:1 (afatinib : chemotherapy), stratified by ethnic group (Asian or non-Asian) and EGFR mutation (Del19, L858R or other). A total of 345 patients were randomized (afatinib: 230 patients; chemotherapy: 115 patients). Patients or treating staff were not blinded for the patient-relevant outcomes considered in the present benefit assessment.

The drugs used in the study, i.e. afatinib or a combination therapy of cisplatin and pemetrexed, were administered in treatment regimens without relevant deviation from the requirements specified in the respective SPC [3-5]. Afatinib was used at a starting dose of 40 mg/day with the option to increase the dose to a maximum of 50 mg/day after 21 days at the earliest, if the drug was tolerated well during this time, i.e. if certain prespecified adverse events did not occur [3]. Dose reduction to a minimum dose of 20 mg/day according to a prespecified scheme in compliance with the SPC was possible if important side effects

occurred. Afatinib treatment was continued until disease progression occurred, treatment was no longer tolerated, or the investigator or the patient requested treatment discontinuation.

The comparator therapy cisplatin + pemetrexed was administered for a maximum of 6 cycles of 21 days each. Treatment could be discontinued prematurely if disease progression or unacceptable adverse events occurred or at the patient's or investigator's request or in case of intolerance. Both drugs, one after the other, were administered intravenously on the first day of each cycle. Cisplatin was administered in a dose of 75 mg/m², pemetrexed in a dose of 500 mg/m². Dose reduction or postponing treatment was possible if adverse events caused by drugs occurred.

PFS was the primary outcome of the LUX-Lung 3 study. The patients discontinued the use of afatinib when progression occurred. Afterwards, patients could switch to a suitable subsequent therapy, if possible chemotherapy. Patients of the chemotherapy arm could also receive tumour-targeted subsequent therapies (if possible monochemotherapy or a TKI) after the end of the study treatment or disease progression. The data of all patients were included in the analysis of overall survival also after switching treatment. The recording of other data was conducted outcome-specific beyond the end of treatment. AEs were recorded up to 28 days after the end of treatment, data on symptoms and quality of life were recorded up to disease progression or treatment switching.

The LUX-Lung 3 was not yet completed at the time of the benefit assessment. Analyses on several data cut-offs were available. The first data cut-off (9 February 2012) was planned after 217 cases of disease progression and was conducted after the occurrence of 221 events. The final confirmatory analysis of the primary outcome "PFS" and an interim analysis for overall survival were performed at this time point. The data in the dossier are based on the analyses of this data cut-off. For the results on overall survival, the company additionally presented the results of a second data cut-off, which was conducted on 21 January 2013 at the regulatory authorities' instigation. The results of both data cut-offs are presented in the present benefit assessment. The extent of added benefit with regards to overall survival was determined on the basis of the second data cut-off, however, because these data were more informative. The final analysis of the outcome "overall survival" is to be conducted when 209 deaths have been observed. This was not yet the case at the time point of the second data cut-off.

Characteristics of the study population

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study **Characteristics** **Category**	**Afatinib** **N = 230**	**Cisplatin + pemetrexed** **N = 115**
LUX-Lung 3		
Age [years]: mean (SD)	60.5 (10.1)	59.9 (10.0)
Sex: [M/F], %	36.1/63.9	33.0/67.0
Ethnic group, n (%)		
Asian	166 (72.2)	83 (72.2)
Non-Asian	64 (27.8)	32 (27.8)
ECOG PS, n (%)		
0	92 (40.0)	41 (35.7)
1	138 (60.0)	73 (63.5)
2	0 (0.0)	1 (0.9)[a]
UJCC tumour stage, n (%)		
Stage IIIB	20 (8.7)	17 (14.8)
Stage IV	210 (91.3)	98 (85.2)
EGFR mutation, n (%)		
L858R	91 (39.6)	47 (40.9)
Del19	113 (49.1)	57 (49.6)
Other	26 (11.3)	11 (9.6)
Proportion of patients with lung adenocarcinoma, n (%)[b]	227 (98.7)	111 (96.5)
Smoking status		
Never-smoker	155 (67.4)	81 (70.4)
Ex-smoker	70 (30.4)	32 (27.8)
Current smoker	5 (2.2)	2 (1.7)
Brain metastases present	27 (11.7)	15 (13.0)
Treatment discontinuations[c], n (%)	164 (71.3)[d]	51 (44.3)[d]

a: One patient had ECOG PS 0 at screening, but worsened to ECOG PS 2 even before treatment started.
b: Adenocarcinoma predominated in 6 patients, a different carcinoma predominated in one other patient.
c: Treatment discontinuations at data cut-off 1.
d: Institute's calculation of percentages.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; UJCC: Union for International Cancer Control; vs.: versus

The population of the LUX-Lung 3 study comprised 230 patients in the afatinib treatment arm and 115 patients in the chemotherapy arm; and there were nearly twice as many women as men in both arms. According to the inclusion criteria of the study, almost all carcinomas of the patients could be histologically classified as adenocarcinomas. 11.7% and 13% of the patients had brain metastases. The vast majority of the patients had tumour stage IV.

The ethnic group (Asian or non-Asian) and EGFR mutation status (Del19, L858R or other) were mainly equally distributed due to the stratified randomization. About 72% of the patients were of Asian origin. The most common EGFR mutations were the mutations Del19 (just below 50% in both groups) and L858R (about 40% in both groups).

Smoking is not the primary risk factor for this type of NSCLC. This is reflected in the high proportion of never-smokers (just below 70%).

At the time point of the second data cut-off, 71.3% of the patients in the afatinib arm had discontinued treatment, and 44.3% of the patients under chemotherapy had discontinued treatment. This can be explained by the different treatment duration (afatinib: without defined ending, cisplatin + pemetrexed: 6 treatment cycles maximum).

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
LUX-Lung 3	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the LUX-Lung 3 study. This concurs with the company's assessment. Outcome-specific limitations, which resulted from the open-label study design among other things, are described in Section 2.4 with the outcome-specific risk of bias.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.3.2 Research question 1b: non-pretreated patients with ECOG PS 2

The company presented no relevant study on the assessment of the added benefit of non-pretreated patients with ECOG PS 2.

2.3.3 Research question 2: patients pretreated with one chemotherapy or several chemotherapies

There was no relevant study for the assessment of the added benefit of afatinib in pretreated patients. The one-arm LUX-Lung 2 study presented by the company was unsuitable for drawing conclusions on the added benefit of afatinib versus the ACT (erlotinib, gefitinib) (see Section 2.7.2.3.2 of the full dossier assessment). The study characteristics and the patient population are therefore not described.

2.4 Results on added benefit

2.4.1 Research question 1a: non-pretreated patients with ECOG PS 0 to 1

2.4.1.1 Outcomes included

The following patient-relevant outcomes were included in the assessment of the added benefit of afatinib in non-pretreated patients with ECOG PS 0 or 1:

- mortality: overall survival
- morbidity: symptoms, recorded with the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13
  - improvement
  - time to worsening
- health-related quality of life, recorded with the functional scales of the questionnaire EORTC QLQ-C30 and with the generic instrument EQ-5D
  - improvement
  - time to worsening
- AEs
  - serious AEs (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - AEs that led to treatment discontinuation
  - common severe events

See Sections 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment for more details on the choice of outcomes.

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment). Particularly the outcomes “PFS” and “tumour response” were not used for the present benefit assessment because these outcomes were recorded using imaging techniques. The company did not prove the validity of a surrogate characteristic of both outcomes, which

would have been irrelevant in this case however, because overall survival and symptoms were recorded directly.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study	Outcomes							
	All-cause mortality	Symptoms[a]	Health-related quality of life (disease-specific instrument)[b]	Health-related quality of life (generic instrument)[c]	Serious adverse events	Severe adverse events (CTCAE Grade ≥ 3)	Treatment discontinuations due to adverse events	Common severe adverse events[d]
LUX-Lung 3	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

a: Recorded with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: Recorded using the EORTC QLQ-C30.
c: Recorded in the LUX-Lung 3 study using the EQ-5D; but no data on subgroups were provided.
d: Adverse events with CTCAE grade = 3 and a frequency of ≥ 5% in at least one treatment arm.
CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: EuroQol-5D; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; vs.: versus

2.4.1.2 Risk of bias at outcome level

Table 11 shows the risk of bias for these outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study		Outcomes							
	Study level	All-cause mortality	Symptoms[a]	Health-related quality of life (disease-specific instrument)[b]	Health-related quality of life (generic instrument)[c]	Serious adverse events	Severe adverse events (CTCAE grade ≥ 3)	Treatment discontinuations due to adverse events	Common severe adverse events[d]
LUX-Lung 3	L	L	H	H	-	H	H	H	H

a: Recorded with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: Recorded using the EORTC QLQ-C30.
c: Recorded in the LUX-Lung 3 study using the EQ-5D; but no data on subgroups were provided.
d: CTCAE grade 3 adverse events that occurred in ≥ 5% of the patients in one treatment arm.
CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: EuroQol-5D; H: high; L: low; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; vs.: versus

For all outcomes considered to be relevant for the assessment, data were available in the dossier.

Only one study was available for the assessment of afatinib. The LUX-Lung 3 study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [6]. Hence, at most indications – e.g. of an added benefit – could be derived from the data. Moreover, due to the open-label study design and the drastically different treatment durations between the afatinib arm and the cisplatin + pemetrexed arm, there was a high risk of bias of the study results for all outcomes except overall survival (the median treatment durations were 336 days in the afatinib arm and 105 days in the cisplatin + pemetrexed arm). Hence no more than hints could be derived for these outcomes, and no more than an indication could be derived for overall survival. This assessment deviates from that of the company, which derived proofs of an added benefit of afatinib versus cisplatin + pemetrexed from the LUX-Lung 3 study.

The risk of bias for the outcome “overall survival” was rated as low in the present benefit assessment. This deviates from the company’s assessment, which rated this as high because the patients could switch to a different therapy after the end of the treatment, and subsequent therapies were distributed unevenly between the treatment groups. However, this is to be considered as part of the overall therapeutic strategy both in the afatinib and in the

chemotherapy treatment. More details on this rating can be found in Section 2.7.2.4.2 of the full dossier assessment.

Concurring with the ratings of the company in the dossier, the risk of bias for all other outcomes was rated as high. The main reasons were the open-label study design and the considerable differences in observation duration in the 2 study arms.

In case of the AEs, no quantitative conclusion on the extent of harm from afatinib could be drawn in the present benefit assessment because of the high risk of bias. This is mainly due to the drastically different treatment durations in the study arms (336 days in the afatinib arm and 105 days in the cisplatin + pemetrexed arm). Hence both relative risks and the incidence density ratios used by the company only allowed limited conclusions on possible treatment effects. The qualitative conclusions drawn in the report were based on the naive proportions for the outcomes regarding harm that were considered as relevant. This deviates from the company's approach, which chose the incidence density ratio of the events as effect estimate to account for the different lengths in observation duration.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.1.3 Results

The results on the comparison of afatinib with cisplatin + pemetrexed in non-pretreated NSCLC patients with ECOG PS 0 or 1 are summarized in the following tables. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations.

2.4.1.3.1 Overall survival

Table 12 shows the results on overall survival from the LUX-Lung 3 study.

Table 12: Results (overall survival) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study **Outcome**	**Afatinib**		**Cisplatin + pemetrexed**		**Afatinib vs. cisplatin + pemetrexed**	
Data cut-off	**N**	**Median survival time in months [95% CI]**	**N**	**Median survival time in months [95% CI]**	**HR [95% CI]**	**p-value**
LUX-Lung 3						
Overall survival						
First data cut-off: 9 Feb 2012	230	NC [22.64; NC]	115	NC [21.62; NC]	1.12 [0.73; 1.73]	p = 0.605
Second data cut-off: 21 Jan 2013	230	28.1[a]	115	28.2[a]	0.91 [0.66; 1.25]	p = 0.546

a: No CIs provided.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

There was no statistically significant difference in overall survival between afatinib and cisplatin + pemetrexed in both data cut-offs. Due to effect modifications, the overall estimator of the LUX-Lung 3 study cannot be meaningfully interpreted, however (see Section 2.4.1.4). The company did not draw any conclusion on added benefit for the outcome "overall survival" because it considered it not to be evaluable yet due to the lack of the final analysis.

2.4.1.3.2 Morbidity (symptoms)

Table 13 and Table 14 show the results for the outcomes on morbidity.

Table 13: Results (morbidity: improvement of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Patients with events[b] n (%)	N	Patients with events[b] n (%)	RR [95% CI][c]; p-value
LUX-Lung 3					
EORTC QLQ-C30 symptom scales – improvement of symptoms					
Dyspnoea	218	94 (43.1)	107	31 (29.0)	0.67 [0.48; 0.93]; p = 0.020
Fatigue	218	77 (35.3)	107	27 (25.2)	0.71 [0.49; 1.04]; p = 0.077
Insomnia	218	100 (45.9)	106	40 (37.7)	0.82 [0.62; 1.09]; p = 0.178
Pain	218	74 (33.9)	107	30 (28.0)	0.83 [0.58; 1.18]; p = 0.292
Appetite loss	218	64 (29.4)	107	27 (25.2)	0.86 [0.58; 1.27]; p = 0.442
Diarrhoea	218	11 (5.0)	107	16 (15.0)	2.94 [1.43; 6.25]; p = 0.004
Nausea and vomiting	218	48 (22.0)	107	9 (8.4)	0.38 [0.19; 0.75]; p = 0.005
Constipation	218	69 (31.7)	106	25 (23.6)	0.75 [0.50; 1.11]; p = 0.144
EORTC QLQ-LC13 symptom scales – improvement of symptoms					
Dyspnoea	218	89 (40.8)	107	26 (24.3)	0.60 [0.41; 0.86]; p = 0.006
Haemoptysis	218	24 (11.0)	107	11 (10.3)	0.93 [0.48; 1.82]; p = 0.842
Coughing	218	121 (55.5)	105	38 (36.2)	0.65 [0.49; 0.86]; p = 0.003
Pain (arm/shoulder)	218	66 (30.3)	107	19 (17.8)	0.59 [0.37; 0.93]; p = 0.022
Pain (chest)	218	91 (41.7)	107	36 (33.6)	0.81 [0.59; 1.10]; p = 0.171
Pain (other parts)	207	66 (31.9)	98	30 (30.6)	0.96 [0.67; 1.37]; p = 0.824
Alopecia	218	20 (9.2)	107	6 (5.6)	0.61 [0.25; 1.47]; p = 0.274
Sore mouth	216	16 (7.4)	106	9 (8.5)	1.15 [0.52; 2.50]; p = 0.733
Peripheral neuropathy	218	22 (10.1)	107	9 (8.4)	0.83 [0.40; 1.75]; p = 0.630

(continued)

Table 13: Results (morbidity: improvement of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1 (continued)

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Patients with events[b] n (%)	N	Patients with events[b] n (%)	RR [95% CI][c]; p-value
Dysphagia	218	17 (7.8)	107	12 (11.2)	1.43 [0.71; 2.94]; p = 0.310

a: Data of the first data cut-off on 9 February 2012.
b: Responder analysis: proportion of patients who, during the course of the study, achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire.
c: Proportion of events afatinib/chemotherapy; reciprocals of the effect estimates and the CI limits to illustrate the direction of the effect in comparison with the operationalization “time to worsening of symptoms”; values < 1 in favour of afatinib.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; n: number of patients with event; QLQ-C30: Quality of Life Questionnaire-Core 30 (general symptoms of cancer disease); QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13 (lung cancer-specific symptoms); RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Median (months) [95% CI][b] patients with events n (%)	N	Median (months) [95% CI][b] patients with events n (%)	HR [95% CI][c]; p-value
LUX-Lung 3					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms					
Dyspnoea	230	NC 83 (36.1)	115	5.2 55 (47.8)	0.48 [0.33; 0.68]; p < 0.001
Fatigue	230	3.0 146 (63.5)	115	1.7 80 (69.6)	0.69 [0.52; 0.92]; p = 0.009
Insomnia	230	9.7 114 (49.6)	115	20.5 45 (39.1)	1.00 [0.70; 1.43]; p = 0.993
Pain	230	4.2 [2.79; 5.59] 144 (62.6)	115	3.09 [2.17; 3.98] 72 (62.6)	0.82 [0.62; 1.10]; p = 0.191
Appetite loss	230	3.8 136 (59.1)	115	2.8 69 (60.0)	0.84 [0.62; 1.13]; p = 0.241
Diarrhoea	230	0.8 208 (90.4)	115	13.7 30 (26.1)	7.74 [5.15; 11.63]; p < 0.001
Nausea and vomiting	230	7.4 123 (53.5)	115	2.1 74 (64.3)	0.55 [0.40; 0.74]; p < 0.001
Constipation	230	14.1 102 (44.3)	115	7.6 48 (41.7)	0.73 [0.51; 1.04]; p = 0.077
EORTC QLQ-LC13 symptom scales – time to worsening of symptoms					
Dyspnoea	230	10.3 [5.59; 15.80] 118 (51.3)	115	2.9 [2.17; 4.90] 67 (58.3)	0.68 [0.50; 0.93]; p = 0.015
Haemoptysis	230	NC 45 (19.6)	115	NC 11 (9.6)	1.75 [0.89; 3.43]; p = 0.101
Coughing	230	NC [15.2; NC] 78 (33.9)	115	8.0 [4.44; NC] 44 (38.3)	0.60 [0.41; 0.87]; p = 0.007
Pain (arm/shoulder)	230	10.4 109 (47.4)	115	NC 43 (37.4)	0.94 [0.65; 1.34]; p = 0.721
Pain (chest)	230	NC 79 (34.3)	115	8.3 45 (39.1)	0.65 [0.44; 0.94]; p = 0.023
Pain (other parts)	230	4.9 129 (56.1)	115	6.2 49 (42.6)	1.09 [0.78; 1.52]; p = 0.621
Alopecia	230	3.5 154 (67)	115	1.7 77 (67)	0.61 [0.46; 0.81]; p < 0.001
Sore mouth	230	0.8 194 (84.3)	115	2.9 68 (59.1)	2.47 [1.86; 3.28]; p < 0.001

(continued)

Table 14: Results (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1 (continued)

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Median (months) [95% CI][b] Patients with events n (%)	N	Median (months) [95% CI][b] Patients with events n (%)	HR [95% CI][c]; p-value
Peripheral neuropathy	230	2.9 155 (67.4)	115	5.1 64 (55.7)	1.24 [0.92; 1.67]; p = 0.156
Dysphagia	230	2.8 142 (61.7)	115	10.4 43 (37.4)	1.85 [1.31; 2.61]; p < 0.001

a: Data of the first data cut-off on 9 February 2012.
b: 95% CI of the median time to worsening provided if available.
c: Time to worsening of the score by at least 10 points versus the baseline value.
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30 (general symptoms of cancer disease); QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13 (lung cancer-specific symptoms); RCT: randomized controlled trial; vs.: versus

Aspects of morbidity were recorded in the LUX-Lung 3 study using the symptom scales of the disease-specific questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13. The operationalizations "improvement" and "time to worsening of symptoms" were analysed for both measurement instruments. No opposing effects (in terms of respective statistical significance) were shown between the operationalizations in any of the individual symptom scales (see the joint presentation of the effect estimates of both scales in Appendix B of the full dossier assessment for more details).

For the outcomes **"dyspnoea", "nausea and vomiting"** and **"coughing"**, there was a statistically significant difference in favour of afatinib both for improvement and for time to worsening of the symptom. Hence there is a hint of an added benefit of afatinib for all 3 symptoms; however because of effect modifications, this hint partially only applies to subgroups (see Section 2.4.1.4). This deviates from the company's assessment, which claimed proof of an added benefit for each of the symptoms "dyspnoea" and "coughing". The outcome "nausea and vomiting" was not considered specifically by the company.

For each of the outcomes **"fatigue"** and **"alopecia"**, there was a statistically significant difference in favour of afatinib for the time to worsening of the symptom. This results in a hint of an added benefit of afatinib (for fatigue, this is limited to subgroups because of effect modification, see Section 2.4.1.4). This deviates from the company's assessment, which claimed proof of an added benefit for the outcome "fatigue". The outcome "alopecia" was not considered specifically by the company.

There was a statistically significant difference in favour of afatinib for the outcome **"pain (arm or shoulder)"** for improvement of the symptom and for the outcome **"pain (chest)"** for the time to worsening. However, the effect was not more than marginal in both cases. There was no statistically significant difference between the treatment groups for each of the outcomes **pain** and **pain (other parts)**. Overall, no added benefit of afatinib could be derived for any outcome from the category "pain". This deviates from the company's assessment, which claimed an indication of a minor added benefit for the outcome "pain", justified, however, by the aggregation with pain (arm/shoulder) and pain (chest).

For the outcome **"diarrhoea"**, there was a statistically significant difference in favour of cisplatin + pemetrexed both for improvement and for time to worsening of the symptom. This led to a hint of lesser benefit of afatinib. This outcome was not considered specifically by the company.

For each of the outcomes **"sore mouth"** and **"dysphagia"**, there was a statistically significant difference in favour of cisplatin + pemetrexed for the time to worsening of the symptom. This led to a hint of lesser benefit of afatinib in each case. This deviates from the company's assessment, which derived proof of lesser benefit for the outcome "dysphagia". The outcome "sore mouth" was not considered specifically by the company.

There was no statistically significant difference between the treatment groups for any of the outcomes **"insomnia", "appetite loss", "constipation", "haemoptysis"** and **"peripheral neuropathy"**. Hence an added benefit of afatinib is not proven for these outcomes. For the symptoms "haemoptysis" and "insomnia", this corresponds to the company's assessment. The outcomes "appetite loss", "constipation" and "peripheral neuropathy" were not considered specifically by the company.

2.4.1.3.3 Health-related quality of life

Disease-specific instrument (EORTC QLQ-C30)

Table 15 and Table 16 show the results of the outcomes on health-related quality of life. For a joint presentation of the effect estimates of both scales, see Appendix B of the full dossier assessment.

Table 15: Results (health-related quality of life; improvement) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Patients with events[b] n (%)	N	Patients with events[b] n (%)	RR [95% CI][c]; p-value
LUX-Lung 3					
Global health status	218	57 (26.1)	107	22 (20.6)	0.79 [0.51; 1.22]; p = 0.278
Emotional functioning	218	77 (35.3)	107	35 (32.7)	0.93 [0.67; 1.28]; p = 0.644
Cognitive functioning	218	38 (17.4)	107	17 (15.9)	0.91 [0.54; 1.54]; p = 0.728
Physical functioning	218	53 (24.3)	107	12 (11.2)	0.46 [0.26; 0.83]; p = 0.009
Role functioning	218	65 (29.8)	107	28 (26.2)	0.88 [0.60; 1.28]; p = 0.498
Social functioning	217	62 (28.6)	107	30 (28.0)	0.98 [0.68; 1.43]; p = 0.920

a: Data of the first data cut-off on 9 February 2012.
b: Responder analysis: proportion of patients who, during the course of the study, achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire.
c: Proportion of events afatinib/chemotherapy; reciprocals of the effect estimates and the CI limits to illustrate the direction of the effect in comparison with the operationalization “time to worsening of health-related quality of life”; values < 1 in favour of afatinib.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 16: Results (health-related quality of life; time to worsening) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Median (months) [95% CI][c] Patients with events n (%)	N	Median (months) [95% CI][c] Patients with events n (%)	HR [95% CI][d]; p-value
LUX-Lung 3					
Global health status	230	3.5 142 (61.7)	115	3.8 65 (56.5)	1.01 [0.75; 1.37]; p = 0.930
Emotional functioning	230	11.1 112 (48.7)	115	8.5 45 (39.1)	0.93 [0.65; 1.32]; p = 0.677
Cognitive functioning	230	4.9 142 (61.7)	115	3.1 68 (59.1)	0.77 [0.57; 1.04]; p = 0.086
Physical functioning	230	5.6 135 (58.7)	115	2.8 70 (60.9)	0.73 [0.54; 0.98]; p = 0.035
Role functioning	230	2.9 152 (66.1)	115	2.4 70 (60.9)	0.93 [0.70; 1.24]; p = 0.617
Social functioning	230	4.8 133 (57.8)	115	3.5 62 (53.9)	0.97 [0.71; 1.31]; p = 0.823

a: Data of the first data cut-off on 9 February 2012.
b: 95% CI of the median time to worsening provided if available.
c: Time to worsening of the score by at least 10 points versus the baseline value.
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

The company included the functional scales of the EORTC QLQ-C30 questionnaire for health-related quality of life. The recording of the outcomes was operationalized in an identical manner for the analysis of the symptom scales. Also in this case, exclusively the operationalizations described in the previous section (improvement and time to worsening of symptoms) were included in the benefit assessment.

For the outcome **"physical functioning"**, there was a statistically significant difference in favour of afatinib both for improvement and for time to worsening of the functioning. This led to a hint of an added benefit of afatinib. Due to effect modifications, this hint was limited to individual subgroups, however (see Section 2.4.1.4). This deviates from the company's assessment, which claimed proof of an added benefit for this outcome in each case.

There was no statistically significant difference between the treatment groups for the outcomes **"global health status", "emotional functioning", "cognitive functioning"** and **"social functioning"**. An added benefit of afatinib for these outcomes is therefore not proven.

This deviates from the company's assessment, which claimed an indication of an added benefit for each of these outcomes. However, this was based on the results of the LUX-Lung 6 study, which was not relevant for the benefit assessment.

There was no statistically significant difference between the treatment groups for the outcome **"role functioning"**. An added benefit of afatinib with regards to the total population is therefore not proven. Due to effect modifications, there were deviating results in individual subgroups, which were also different with regards to the direction of the effects (see Section 2.4.1.4). This deviates from the company's assessment, which claimed an indication of an added benefit for each of these outcomes. However, this was based on the results of the LUX-Lung 6 study, which was not relevant for the benefit assessment.

Generic instrument (EQ-5D)

For health-related quality of life measured with the EQ-5D, no results were available for the individual scales of the questionnaire. The VAS data were not used because the company presented no subgroup results on them, although relevant effect modifications were observed in the recording of health-related quality of life with the EORTC QLQ-C30.

2.4.1.3.4 Adverse events

Table 17 shows the overall rates of SAEs, treatment discontinuations due to AEs of the severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and AEs of CTCAE grade 3 that occurred in ≥ 5% of the patients in one treatment group. For an overview of CTCAE grade 3 AEs that occurred in ≥ 1% of the patients, see Appendix D of the full dossier assessment.

Table 17: Results (AEs) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome[a]	Afatinib		Cisplatin + pemetrexed	
	N	Patients with events n (%)	N	Patients with events n (%)
LUX-Lung 3				
AEs				
Overall rate of SAEs	229	66 (28.8)	111	25 (22.5)
Treatment discontinuation due to AEs	229	32 (14.0)	111	17 (15.3)
AEs of CTCAE grade ≥ 3	229	139 (60.7)	111	63 (56.8)
CTCAE grade 3	229	117 (51.1)	111	49 (44.1)
CTCAE grade 4	229	9 (3.9)	111	11 (9.9)
CTCAE grade 3 AEs that occurred in ≥ 5% of all patients in one treatment group.				
Diarrhoea	229	34 (14.8)	111	2 (1.8)
Skin rash	229	30 (13.1)	111	0 (0.0)
Paronychia	229	26 (11.4)	111	0 (0.0)
Fatigue	229	5 (2.2)	111	11 (9.9)
Neutropenia	229	2 (0.9)	111	18 (16.2)
Leukopenia	229	1 (0.4)	111	9 (8.1)

a: Data of the first data cut-off on 9 February 2012.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The considerable difference in observation duration between the treatment arms did not allow a quantitative assessment of the potential harm from afatinib versus the ACT on the basis of the available data. The company tried to include the different observation durations by presenting the incidence density ratio as effect estimate. Since in this case the median observation duration was drastically (by about the factor 3) longer in the afatinib arm than in the chemotherapy arm, the incidence density was considered to be highly biased as was the relative risk (see Section 2.7.2.4.2 of the full dossier assessment for more details). Only qualitative conclusions on the basis of the naive proportions were drawn for AEs in the present benefit assessment.

Serious adverse events, treatment discontinuation due to adverse events and severe adverse events (CTCAE grade ≥ 3)

Regarding the outcomes “SAEs”, “treatment discontinuation due to AEs” and “severe AEs” (CTCAE grade ≥ 3), there were no important differences between the respective rates of the afatinib and of the chemotherapy arm on the basis of the naive proportions. It could only be concluded for these outcomes that the data presented showed no greater harm despite the

considerably longer observation duration of afatinib. Hence greater or lesser harm from afatinib than from cisplatin + pemetrexed is not proven for these outcomes.

This result deviates from the company's assessment, which derived an indication of a considerable added benefit on the basis of the incidence density ratio for each of the outcomes regarding harm mentioned.

Common severe adverse events (CTCAE grade 3; ≥ 5% of the patients in at least one study arm)

Most of the severe AEs of CTCAE grade ≥ 3 that occurred in the LUX-Lung 3 study were of severity grade 3 (see Table 17). The severe grade 3 AEs that occurred in ≥ 5% of the patients in at least one study arm are therefore presented for the consideration of the common severe AEs.

The events "diarrhoea", "skin rash" and "paronychia" almost exclusively occurred in the afatinib arm. Their rates were between 11.4% and 14.8%. These results did not occur in the chemotherapy arm (skin rash, paronychia) or in only 2 patients (1.8% diarrhoea). Due to the very low rates in the chemotherapy arm in comparison with the afatinib arm, it can be assumed that this difference would be the same also if the observation duration was almost the same in both treatment arms.

The situation is the other way around with regards to the events "fatigue", "neutropenia" and "leukopenia". These events were mainly observed in the patients of the chemotherapy arm (between 8.1% and 16.2%), whereas the rates in the afatinib arm were comparably low (between 0.4% and 2.2%). Lesser harm from afatinib can be assumed for these events.

Summary

Overall, with regards to adverse events, there was neither an advantage nor a disadvantage of afatinib versus the ACT. Overall, greater or lesser harm from afatinib in comparison with cisplatin + pemetrexed is therefore not proven.

2.4.1.4 Subgroups and other effect modifiers

To discover possible effect differences between the patient groups, the following potential effect modifiers were investigated: EGFR mutation (L858R, Del19, others), ethnic group (Asian and non-Asian), baseline ECOG PS (0 or 1), age (< 65 years, ≥ 65 years).

Possible effect modification was investigated for all outcomes with the exception of AEs. Due to the different observation durations, only qualitative conclusions could be drawn for AEs already for the total population.

A statistically significant interaction test ($p < 0.05$) is the precondition for proof of different effects for the outcome "all-cause mortality". A p-value between 0.05 and 0.2 provides an indication of different effects.

For each of the outcomes "morbidity" and "health-related quality of life", 2 operationalizations were available from the questionnaires EORTC QLQ-C30 and QLQ-LC13 (responder analysis on improvement and time to worsening). This offered the opportunity that there was an indication ($p < 0.2$) or proof ($p < 0.05$) of an interaction with regards to an outcome for one operationalization, but not for the other – or that there was an indication instead of proof, for example. To provide greater certainty for conclusions on individual outcomes that include both operationalizations and to consider the high risk of bias for these outcomes, subgroup results are only presented under the following condition: Of the p-values of both interaction tests (for the operationalizations "improvement of symptoms" and "time to worsening"), one p-value had to be below 0.05 (proof of interaction), and the second p-value had to be below 0.2 (indication of interaction). An overall indication of interaction was derived in this case. The presence of proof in each of the 2 operationalizations was considered overall to be proof of an interaction.

2.4.1.4.1 Overall survival

Table 18 shows the subgroups on overall survival with at least an indication of an effect modification.

Table 18: Subgroups (dichotomous outcomes): Outcome "overall survival" by the characteristic "EGFR mutation (Del19/L858R/other)", RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study **Outcome**	**Afatinib**		**Cisplatin + pemetrexed**		**Afatinib vs. cisplatin + pemetrexed**	
Characteristic *Time point*	**N**	**Median survival time in months [95% CI]**	**N**	**Median survival time in months [95% CI]**	**HR [95% CI]**	**p-value**
LUX-Lung 3						
Overall survival						
EGFR mutation						
First data cut-off: 9 Feb 2012						
L858R	91	NC [17.71; NC]	47	NC [21.2; NC]	1.77 [0.84; 3.76]	0.130
Del19	113	NC [NC; NC]	57	NC [18.79; NC]	0.58 [0.31; 1.07]	0.075
Other	26	15.41 [7.49; 24.90]	11	19.65 [6.77; NC]	1.99 [0.66; 6.01]	0.213
Interaction						0.033
Second data cut-off: 21 Jan 2013						
L858R	91	27.17[a]	47	NC[a]	1.30 [0.76; 2.23]	0.332
Del19	113	31.57[a]	57	21.13[a]	0.55 [0.36; 0.85]	0.006
Other	26	15.93[a]	11	NC[a]	3.08 [1.04; 9.15]	0.034
Interaction						0.002
Brain metastases compared with baseline[b]						
No	182	NC [NC; NC]	93	NC [21.26; NC]	0.84 [0.50; 1.40]	0.499
Yes	27	18.60 [14.03; 24.90]	15	NC [13.96; NC]	1.83 [0.59; 5.69]	0.288
Interaction						0.189

a: CIs not provided.
b: Only data at first data cut-off available.
CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; HR: hazard ratio, N: number of analysed patients, NC: not calculable; RCT: randomized controlled trial, vs.: versus

There was proof of an effect modification by the subgroup characteristic "EGFR mutation" for the outcome "overall survival" at both data cut-offs. However, only the results at the second data cut-off showed statistically significant differences between the treatment groups. The following conclusions on added benefit are exclusively based on this data cut-off because the second data cut-off was more informative because of the greater number of events.

For patients with L858R mutation, treatment with afatinib did not result in a statistically significant difference for overall survival in comparison with cisplatin + pemetrexed. Hence for patients with L858R mutation, there is no proof of an added benefit of afatinib in comparison with the ACT for this outcome.

For patients with Del19 mutation, treatment with afatinib resulted in a statistically significant prolongation of overall survival in comparison with cisplatin + pemetrexed. Hence for patients with Del19 mutation, there is an indication of an added benefit of afatinib in comparison with the ACT for this outcome.

For patients with different mutations (non-Del19 and non-L858R), there was a statistically significant effect in favour of cisplatin + pemetrexed for overall survival. This results in an indication of a lesser benefit of afatinib versus the ACT for this outcome.

With regards to the presence or lack of brain metastases, there was an indication of an interaction, but the treatment arms did not differ significantly in the individual subgroups.

These assessments partly deviate from those of the company, which also derived an indication of an added benefit of afatinib for patients with Del19 mutation, but which did not derive lesser benefit of afatinib for the subgroup with different mutations.

2.4.1.4.2 Morbidity (symptoms)

Table 19 shows the effect estimates of the subgroups on symptoms with an indication of effect modification. The event rates for the individual outcomes are presented in Appendix C of the full dossier assessment.

Table 19: Overview of the effect estimates of the relevant subgroups on the different operationalizations of symptoms – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome Characteristic	Morbidity: improvement of symptoms[a]		Morbidity: time to worsening of symptoms[b]	
	EORTC QLQ-C30 symptom scales	EORTC QLQ-LC13 symptom scales	EORTC QLQ-C30 symptom scales	EORTC QLQ-LC13 symptom scales
	RR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)		HR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)	
LUX-Lung 3				
Dyspnoea				
EGFR mutation				
L858R + Del19	0.59 [0.41; 0.85]; 0.005	0.51 [0.34; 0.78]; 0.002	0.39 [0.27; 0.56]; < 0.001	0.55 [0.40; 0.77]; < 0.001
Other	2.08 [0.76; 5.88]; 0.152	1.75 [0.68; 4.55]; 0.249	2.84 [0.82; 9.83]; 0.086	2.37 [0.96; 5.85]; 0.055
Interaction	p = 0.021	p = 0.020	p = 0.002	p = 0.003
Ethnic group				
Asian	0.51 [0.33; 0.79]; 0.001	NP[c]	0.42 [0.28; 0.62]; < 0.001	0.58 [0.41; 0.81]; 0.002
Non-Asian	1.20 [0.72; 2.00]; 0.474	NP[c]	0.75 [0.35; 1.62]; 0.459	1.00 [0.53; 1.89]; 0.997
Interaction	p = 0.010	p = 0.570	p = 0.196	p = 0.182
Fatigue				
EGFR mutation				
L858R	1.10 [0.65; 1.85]; 0.720		0.69 [0.43; 1.11]; 0.122	
Del19	0.38 [0.20; 0.72]; 0.003		0.55 [0.37; 0.80]; 0.002	
Other	2.08 [0.64; 6.67]; 0.223		1.56 [0.69; 3.51]; 0.282	
Interaction	p = 0.009		p = 0.077	
Pain				
Age				
< 65 years	0.68 [0.43; 1.08]; 0.095		0.55 [0.38; 0.79]; 0.001	
≥ 65 years	1.19 [0.67; 2.13]; 0.551		1.46 [0.92; 2.31]; 0.106	
Interaction	p = 0.133		p = 0.002	

(continued)

Table 19: Overview of the effect estimates of the relevant subgroups on the different operationalizations of symptoms – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1 (continued)

Study Outcome Characteristic	Morbidity: improvement of symptoms[a]		Morbidity: time to worsening of symptoms[b]	
	EORTC QLQ-C30 symptom scales	EORTC QLQ-LC13 symptom scales	EORTC QLQ-C30 symptom scales	EORTC QLQ-LC13 symptom scales
	RR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)		HR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)	
Constipation				
ECOG PS				
0	1.35 [0.74; 2.50]; 0.329		1.07 [0.59; 1.92]; 0.830	
1	0.52 [0.30; 0.88]; 0.015		0.56 [0.36; 0.87]; 0.009	
Interaction	p = 0.019		p = 0.097	
Coughing				
Age				
< 65 years		0.47 [0.31; 0.71]; < 0.001		0.40 [0.24; 0.66]; < 0.001
≥ 65 years		1.01 [0.68; 1.49]; 0.947		0.86 [0.48; 1.55]; 0.622
Interaction		p = 0.007		p = 0.098

a: Responder analysis: proportion of patients who, during the course of the study, achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire; reciprocals of the effect estimates and the CI limits to illustrate the direction of the effect; values < 1 in favour of afatinib; Institute's calculation.
b: Time to worsening of the score by at least 10 points versus the baseline value.
c: Not presented by the company in the dossier because no indication of effect modification.
CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NP: not provided; QLQ-C30: Quality of Life Questionnaire-Core 30 (general symptoms of cancer disease); QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13 (lung cancer-specific symptoms); RCT: randomized controlled trial; RR: relative risk; vs.: versus

Dyspnoea

The subgroups L858R and Del19 were summarized for the outcome "dyspnoea" because these categories did not show an indication of an interaction in a statistical test on pairwise interaction of the subgroups both for improvement and for the time to worsening of symptoms.

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of symptoms in

both symptom scales for patients with L858R or Del19 mutation. This led to a hint of an added benefit of afatinib.

For patients with different EGFR mutations, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of symptoms in both symptom scales. An added benefit of afatinib is therefore not proven.

For patients of Asian origin, treatment with afatinib resulted in a statistically significant difference in favour of afatinib with regards to improvement in the EORTC QLQ-C30 symptom scale; there was no indication of effect modification for the QLQ-LC13 scale. With regards to the time to worsening of symptoms, treatment with afatinib resulted in a statistically significant difference in favour of afatinib in both symptom scales. This led to a hint of an added benefit of afatinib.

For patients of non-Asian origin, treatment with afatinib did not result in a statistically significant difference between the treatment arms with regards to improvement or with regards to the time to worsening of symptoms. For improvement, an indication of effect modification was only present for the EORTC QLQ-C30 scale. An added benefit of afatinib is therefore not proven.

Fatigue

There was an indication of effect modification by EGFR mutation status for the outcome “fatigue”.

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of symptoms for patients with Del19 mutation. This led to a hint of an added benefit of afatinib.

For patients with L858R mutation and different EGFR mutations, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of symptoms. An added benefit of afatinib is therefore not proven.

Pain

There was an indication of effect modification by the patients’ age for the outcome “pain”.

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib with regards to the time to worsening of symptoms for patients aged under 65 years. The treatment did not result in a statistically significant difference for the improvement of symptoms. This results in a hint of an added benefit of afatinib for the time to worsening of symptoms.

For patients aged 65 years or older, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of symptoms. An added benefit of afatinib is therefore not proven.

Constipation

There was an indication of effect modification by baseline ECOG PS for the outcome "constipation".

For patients with ECOG PS 0, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of symptoms. An added benefit of afatinib is therefore not proven.

For patients with ECOG PS 1, treatment with afatinib resulted in a statistically significant difference in favour of afatinib with regards to improvement or with regards to the time to worsening of symptoms. This led to a hint of an added benefit of afatinib.

Coughing

There was an indication of effect modification by the patients' age for the outcome "coughing".

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of symptoms for patients under the age of 65 years. This led to a hint of an added benefit of afatinib.

For patients aged 65 years or older, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of symptoms. An added benefit of afatinib is therefore not proven.

Assessment by the company

The assessments mentioned above deviate from those of the company insofar as the company only provided descriptive presentations of subgroups with indications or proof of effect modification for the outcomes on morbidity, but did not use them for the benefit assessment if no proof of effect modification was observed in the LUX-Lung 3 study and in the LUX-Lung 6 study. However, this exception was not relevant for the present benefit assessment because the LUX-Lung 6 study was not relevant.

2.4.1.4.3 Health-related quality of life

Table 20 shows the effect estimates of the subgroups on health-related quality of life with at least an indication of effect modification. The event rates for the individual outcomes are presented in Appendix C of the full dossier assessment.

Table 20: Overview of the effect estimates of the relevant subgroups on the different operationalizations of health-related quality of life – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome Characteristic	EORTC QLQ-C30 functional scales – improvement of health-related quality of life[a]	EORTC QLQ-C30 functional scales – time to worsening of health-related quality of life[b]
	RR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)	HR [95% CI]; p-value (afatinib vs. cisplatin + pemetrexed)
LUX-Lung 3		
Role functioning		
Age		
< 65 years	0.53 [0.30; 0.92]; 0.025	0.60 [0.41; 0.87]; 0.006
≥ 65 years	1.82 [1.02; 3.23]; 0.042	1.46 [0.92; 2.31]; 0.107
Interaction	p = 0.002	p = 0.005
Global health status		
Age		
< 65 years	0.58 [0.32; 1.05]; 0.074	0.72 [0.49; 10.5]; 0.082
≥ 65 years	1.25 [0.65; 7.14]; 0.511	1.65 [1.02; 2.66]; 0.040
Interaction	p = 0.091	p = 0.009
Physical functioning		
Age		
< 65 years	0.36 [0.17; 0.76]; 0.007	0.54 [0.37; 0.79]; 0.001
≥ 65 years	0.81 [0.30; 2.13]; 0.662	1.03 [0.65; 1.63]; 0.900
Interaction	p = 0.197	p = 0.033
EGFR mutation		
L858R	0.44 [0.16; 1.20]; 0.110	0.85 [0.53; 1.36]; 0.492
Del19	0.33 [0.13; 0.81]; 0.015	0.49 [0.32; 0.74]; < 0.001
Other	1.56 [0.42; 5.88]; 0.502	1.98 [0.79; 4.94]; 0.137
Interaction	p = 0.143	p = 0.006

a: Responder analysis: proportion of patients who, during the course of the study, achieved an average improvement of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire; reciprocals of the effect estimates and the CI limits to illustrate the direction of the effect; values < 1 in favour of afatinib; Institute's calculation.
b: Time to worsening of the score by at least 10 points versus the baseline value.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; QLQ-C30: Quality of Life Questionnaire-Core 30 (general symptoms of cancer disease); RCT: randomized controlled trial; RR: relative risk; vs.: versus

Role functioning

There was proof of effect modification by the patients' age for the outcome "role functioning".

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of the functioning for patients < 65 years. This led to a hint of an added benefit of afatinib.

Treatment with afatinib resulted in a statistically significant difference in favour of cisplatin + pemetrexed with regards to improvement of the functioning for patients ≥ 65 years. This led to a hint of lesser benefit of afatinib. There was no statistically significant difference between the treatment groups with regards to the time to worsening.

Physical functioning

In each case, there was an indication of effect modification by the categories “patients’ age” and “EGFR mutation” for the outcome “physical functioning”.

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of the functioning for patients < 65 years. This led to a hint of an added benefit of afatinib.

Treatment with afatinib did not result in a statistically significant difference between the treatment groups both with regards to improvement and with regards to the time to worsening of the functioning for patients ≥ 65 years. An added benefit of afatinib is therefore not proven.

For patients with L858R mutation, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of the functioning. An added benefit of afatinib is therefore not proven.

Treatment with afatinib resulted in a statistically significant difference in favour of afatinib both with regards to improvement and with regards to the time to worsening of the functioning for patients with Del19 mutation. This led to a hint of an added benefit of afatinib.

For patients with different EGFR mutations, treatment with afatinib did not result in a statistically significant difference between the treatment groups with regards to improvement or with regards to the time to worsening of the functioning. An added benefit of afatinib is therefore not proven.

Global health status

There was an indication of effect modification by the patients’ age for the outcome “global health status”. However, since only a hint of an added benefit could be derived for this outcome at the level of the total population and no statistically significant difference between the treatment groups was detectable for improvement or for the time to worsening, no subgroup results are presented here.

Assessment by the company

The assessments mentioned above deviate from those of the company insofar as the company only provided descriptive presentations of subgroups with indications or proof of effect modification for the outcomes of health-related quality of life, but did not use them for the benefit assessment if no proof of effect modification was observed in the LUX-Lung 3 study and in the LUX-Lung 6 study. However, this exception was not relevant for the present benefit assessment because the LUX-Lung 6 study was not relevant.

2.4.1.4.4 Summary of the subgroup results for outcomes on morbidity and health-related quality of life

As can be seen in Sections 2.4.1.4.2 and 2.4.1.4.3, the characteristics "EGFR mutation", "age", "ethnic group" and "ECOG PS" appeared as effect modifiers for the outcomes on morbidity and health-related quality of life. It became evident that of the characteristics "ethnic group" and "ECOG PS" each only appeared once as effect modifier (for the outcomes "dyspnoea" and "constipation" respectively). In contrast, there were several instances of effect modification for the characteristics "EGFR mutation (Del19, L858R and others)" and "age (< 65 years and ≥ 65 years)". For this reason, only these 2 characteristics were included in the assessment of the extent of added benefit of afatinib.

2.4.2 Research question 1b: non-pretreated patients with ECOG PS 2

There were no relevant data for the research question of afatinib versus gemcitabine in non-pretreated patients with ECOG PS 2. Hence an added benefit of afatinib versus the ACT is not proven.

2.4.3 Research question 2: patients pretreated with one chemotherapy or several chemotherapies

There were no relevant data for the research question of afatinib versus erlotinib or gefitinib in patients pretreated with one chemotherapy or several chemotherapies. Hence an added benefit of afatinib versus the ACT is not proven.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the General Methods of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Research question 1a: non-pretreated patients with ECOG PS 0 or 1

2.5.1.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.1 resulted in indications of effect modifications for non-pretreated patients with ECOG PS 0 or 1 for the following subgroup characteristics.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 21). An overall investigation will then be performed to find out whether there are different conclusions on the extent of added benefit for the individual patient groups.

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed

Outcome category **Outcome**		**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality			
Overall survival (second data cut-off)			
	L858R	HR: 1.30 [0.76; 2.23] median survival (months): 27.17 vs. NC p = 0.332	Lesser benefit/added benefit not proven
	Del19	HR: 0.55 [0.36; 0.848] median survival (months): 31.57 vs. 21.13 p = 0.006 Indication	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
	Other	HR: 3.08 [1.04; 9.15] 0.32 [0.11; 0.96][c] median survival (months): 15.93 vs. NC p = 0.034 Indication	Outcome category: mortality CI_u < 1.00 lesser benefit, extent: “minor”
Morbidity			
EORTC QLQ-C30 and QLQ-LC13: improvement/time to worsening of symptoms			
Dyspnoea			
Improvement	L858R + Del19	*QLQ-C30*: RR: 0.59 [0.41; 0.855] 45.6% vs. 27.1% p = 0.005 *QLQ-LC13*: RR: 0.51 [0.34; 0.78] 42.6% vs. 21.9% p = 0.002 hint	Outcome category: non-serious/non-severe symptoms added benefit, extent: “minor”
	Other	*QLQ-C30*: RR: 2.08 [0.76; 5.88] 21.7% vs. 45.5% p = 0.152 *QLQ-LC13*: RR: 1.75 [0.68; 4.55] 26.1% vs. 45.5% p = 0.249	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**		**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Dyspnoea			
Time to worsening	L858R + Del19	*QLQ-C30*: HR: 0.39 [0.27; 0.56] p < 0.001 *QLQ-LC13*: HR: 0.55 [0.40; 0.76] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 added benefit, extent: "considerable"
	Other	*QLQ-C30*: HR: 2.84 [0.82; 9.83] p = 0.086 *QLQ-LC13*: HR: 2.37 [0.96; 5.85] p = 0.055	Lesser benefit/added benefit not proven
Coughing			
Improvement	< 65 years	RR: 0.47 [0.31; 0.71] 60.7% vs. 28.6% p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 added benefit, extent: "considerable"
	≥ 65 years	RR: 1.01 [0.68; 1.49] 47.0% vs. 47.6% p = 0.947	Lesser benefit/added benefit not proven
Time to worsening	< 65 years	HR: 0.40 [0.24; 0.66] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 added benefit, extent: "considerable"
	≥ 65 years	HR: 0.86 [0.48; 1.55] p = 0.662 hint	Lesser benefit/added benefit not proven
Nausea and vomiting			
Improvement		RR: 0.38 [0.19; 0.75] 22.0% vs. 8.4% p = 0.005 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 added benefit, extent: "considerable"

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**		**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Nausea and vomiting			
Time to worsening		HR: 0.55 [0.40; 0.74] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 added benefit, extent: “considerable”
Fatigue			
Improvement		RR: 0.71 [0.49; 1.04] 35.3% vs. 25.2% p = 0.077	Lesser benefit/added benefit not proven
Time to worsening	L858R	HR: 0.69 [0.43; 1.11] p = 0.122	Lesser benefit/added benefit not proven
	Del19	HR: 0.55 [0.37; 0.80] p = 0.002 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.90 added benefit, extent: “minor”
	Other	HR: 1.56 [0.69; 3.51] p = 0.282	Lesser benefit/added benefit not proven
Alopecia			
Improvement		RR: 0.61 [0.25; 1.47] 9.2% vs. 5.6% p = 0.274	Lesser benefit/added benefit not proven
Time to worsening		HR: 0.61 [0.46; 0.81] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.90 added benefit, extent: “minor”
Pain (arm/shoulder)			
Improvement		RR: 0.59 [0.37; 0.93] 30.3% vs. 17.8% p = 0.022 hint	Outcome category: non-serious/non-severe symptoms 0.90 < CI_u Added benefit not proven
Time to worsening		HR: 0.94 [0.65; 1.34] p = 0.721	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Pain (chest)		
Improvement	RR: 0.81 [0.59; 1.10] 41.7% vs. 33.6% p = 0.171	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.65 [0.44; 0.94] p = 0.023 hint	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u$ Added benefit not proven
Pain		
Improvement	RR: 0.83 [0.58; 1.18]; 33.9% vs. 28.0% p = 0.292	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.82 [0.62; 1.10] p = 0.191	Lesser benefit/added benefit not proven
Pain (other parts)		
Improvement	RR: 0.96 [0.67; 1.37] 31.9% vs. 30.6% p = 0.824	Lesser benefit/added benefit not proven
Time to worsening	HR: 1.09 [0.78; 1.52] p = 0.621	Lesser benefit/added benefit not proven
Diarrhoea		
Improvement	RR: 2.94 [1.43; 6.25] 0.34 [0.16; 0.70][c] 5.0% vs. 15.0% p = 0.004 hint	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: “considerable”
Time to worsening	HR: 7.74 [5.15; 11.63] 0.13 [0.09; 0.19][c] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: “considerable”

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Sore mouth		
Improvement	RR: 1.15 [0.52; 2.5] 7.4% vs. 8.5% p = 0.733	Lesser benefit/added benefit not proven
Time to worsening	HR: 2.47 [1.86; 3.28] 0.40 [0.30; 0.54][c] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 lesser benefit, extent: “considerable”
Dysphagia		
Improvement	RR: 1.43 [0.71; 2.94] 7.8% vs. 11.2% p = 0.310	Lesser benefit/added benefit not proven
Time to worsening	HR: 1.85 [1.31; 2.61] 0.54 [0.38; 0.76][c] p < 0.001 hint	Outcome category: non-serious/non-severe symptoms CI_u < 0.80 lesser benefit, extent: “considerable”
Insomnia		
Improvement	RR: 0.82 [0.62; 1.09] 45.9% vs. 37.7% p = 0.178	Lesser benefit/added benefit not proven
Time to worsening	HR: 1.00 [0.70; 1.43] p = 0.993	Lesser benefit/added benefit not proven
Appetite loss		
Improvement	RR: 0.86 [0.58; 1.27] 29.4% vs. 25.2% p = 0.442	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.84 [0.62; 1.13] p = 0.241	Lesser benefit/added benefit not proven
Constipation		
Improvement	RR: 0.75 [0.50; 1.11] 31.7% vs. 23.6% p = 0.144	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.73 [0.51; 1.04] p = 0.077	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**		**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Haemoptysis			
Improvement		RR: 0.93 [0.48; 1.82] 11.0% vs. 10.3% p = 0.842	Lesser benefit/added benefit not proven
Time to worsening		HR: 1.75 [0.89; 3.43] p = 0.101	Lesser benefit/added benefit not proven
Peripheral neuropathy			
Improvement		RR: 0.83 [0.40; 1.75] 10.1% vs. 8.4% p = 0.630	Lesser benefit/added benefit not proven
Time to worsening		HR: 1.24 [0.92; 1.67] p = 0.156	Lesser benefit/added benefit not proven
Health-related quality of life			
EORTC QLQ-C30: functional scales, improvement/ of quality of life/time to worsening			
Physical functioning			
Improvement	< 65 years	RR: 0.36 [0.17; 0.76] 30.4% vs. 11.0% p = 0.007 hint	Outcome category: health-related quality of life $CI_u < 0.90$ added benefit, extent: “considerable”
	≥ 65 years	RR: 0.81 [0.30; 2.13] 14.5% vs. 11.6% p = 0.662	Lesser benefit/added benefit not proven
	L858R	RR: 0.44 [0.16; 1.20] 22.7% vs. 10.0% p = 0.110	Lesser benefit/added benefit not proven
	Del19	RR: 0.33 [0.13; 0.81] 27.1% vs. 8.9% p = 0.015 hint	Outcome category: health-related quality of life $CI_u < 0.90$ added benefit, extent: “considerable”
	Other	RR: 1.56 [0.42; 5.88] 17.4% vs. 27.3% p = 0.502	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**		**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Physical functioning			
Time to worsening	< 65 years	HR: 0.54 [0.37; 0.79] p = 0.001 hint	Outcome category: health-related quality of life CI_u < 0.90 added benefit, extent: “considerable”
	≥ 65 years	HR: 1.03 [0.65; 1.63] p = 0.900	Lesser benefit/added benefit not proven
	L858R	HR: 0.85 [0.53; 1.36] p = 0.492	Lesser benefit/added benefit not proven
	Del19	HR: 0.49 [0.32; 0.74] p < 0.001 hint	Outcome category: health-related quality of life CI_u < 0.75 added benefit, extent: “major”
	Other	HR: 1.98 [0.79; 4.94] p = 0.137	Lesser benefit/added benefit not proven
Role functioning			
Improvement	< 65 years	RR: 0.53 [0.30; 0.92] 35.6% vs. 18.8% p = 0.025 hint	Outcome category: health-related quality of life CI_u < 1.00 added benefit, extent: “minor”
	≥ 65 years	RR: 1.82 [1.02; 3.23] 0.55 [0.31; 0.98][c] 20.5% vs. 37.2% p = 0.042 hint	Outcome category: health-related quality of life CI_u < 1.00 lesser benefit, extent: “minor”
Time to worsening	< 65 years	HR: 0.60 [0.41; 0.87] p = 0.006 hint	Outcome category: health-related quality of life CI_u < 0.90 added benefit, extent: “considerable”
	≥ 65 years	HR: 1.46 [0.92; 2.31] p = 0.107	Lesser benefit/added benefit not proven
Global health status			
Improvement		RR: 0.79 [0.51; 1.22] 26.1% vs. 20.6% p = 0.278	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Global health status		
Time to worsening	HR: 1.01 [0.75; 1.37] p = 0.930	Lesser benefit/added benefit not proven
Emotional functioning		
Improvement	RR: 0.93 [0.67; 1.28] 35.3% vs. 32.7% p = 0.644	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.93 [0.65; 1.32] p = 0.677	Lesser benefit/added benefit not proven
Cognitive functioning		
Improvement	RR: 0.91 [0.54; 1.54] 17.4% vs. 15.9% p = 0.728	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.77 [0.57; 1.04] p = 0.086	Lesser benefit/added benefit not proven
Social functioning		
Improvement	RR: 0.98 [0.68; 1.43] 28.6% vs. 28.0% p = 0.920	Lesser benefit/added benefit not proven
Time to worsening	HR: 0.97 [0.71; 1.31] p = 0.823	Lesser benefit/added benefit not proven
Adverse events		
Serious adverse events	28.8% vs. 22.5%	Greater/lesser harm not proven[d]
Treatment discontinuations due to adverse events	14.0% vs. 15.3%	Greater/lesser harm not proven[d]
Severe adverse events (CTCAE grade ≥ 3)	60.7% vs. 56.8%	Greater/lesser harm not proven[d]

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Afatinib vs. cisplatin + pemetrexed** **effect estimates [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Common adverse events of CTCAE grade 3	Diarrhoea: 14.8% vs. 1.8% skin rash: 13.1% vs. 0.0% paronychia: 11.4% vs. 0.0% fatigue: 2.2% vs. 9.9% neutropenia: 0.9% vs. 16.2% leukopenia: 0.4% vs. 8.1%	Greater/lesser harm not proven[d]

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Proportion of events afatinib vs. chemotherapy (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
d: Qualitative interpretation on the basis of the naive proportions of the patients with adverse events.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NC: not calculable; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

The results show that relevant effect modifications for the characteristic “EGFR mutation” occurred in the outcomes “overall survival”, “dyspnoea”, “fatigue” (time to worsening) and “physical functioning”. For the characteristic “age”, there was a relevant effect modification in the outcomes “coughing”, “physical functioning”, “role functioning” and “global health status”. The consideration of the individual subgroups showed a different extent of added benefit at outcome level in each case. Separate conclusions on added benefit are therefore necessary both for patients with the EGFR mutations L858R, Del19 and others and for the 2 age groups.

The conclusions on added benefit per outcome by subgroups are summarized in the table presented in the following Section for the categories “age” and “EGFR mutation”.

2.5.1.2 Overall conclusion on added benefit

The overall conclusion on added benefit is presented below separately for the 3 different mutation status. If effect modifications due to age exist, these are integrated in the tables. All outcomes for which there is an added benefit of afatinib for patients with the respective mutation are presented in the tables.

EGFR mutation Del19

Table 22 shows the positive and negative effects of a treatment with afatinib versus cisplatin + pemetrexed in patients with EGFR mutation Del19.

Table 22: Effects of afatinib for the subgroup characteristic "Del19" (category: EGFR mutation)

Positive effects	**Negative effects**
Mortality: ▪ overall survival; indication: "major"	
Non-serious/non-severe symptoms (in each case "hint"): ▪ dyspnoea ▫ improvement; "minor" ▫ time to worsening; "considerable" ▪ fatigue ▫ time to worsening; "minor" ▪ nausea and vomiting ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ alopecia ▫ time to worsening; "minor" ▪ coughing (< 65 years) ▫ improvement; "considerable" ▫ time to worsening; "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ sore mouth ▫ time to worsening; "considerable" ▪ dysphagia ▫ time to worsening; "considerable"
Health-related quality of life (in each case "hint"): ▪ physical functioning (< 65 years) ▫ improvement; "considerable" ▫ time to worsening; "major" ▪ role functioning (< 65 years) ▫ improvement; "minor" ▫ time to worsening; "considerable"	Health-related quality of life (in each case "hint"): ▪ role functioning (≥ 65 years) ▫ improvement; "minor"

There is an indication of a major added benefit for the outcome "overall survival" for patients with Del19 mutation. This added benefit is not age-dependent. There were mainly hints of positive effects of afatinib with regards to symptoms and health-related quality of life for this subgroup. Some of them were age-dependent. There were only individual cases of negative effects of afatinib. In the overall assessment of the effects, there is a hint of a major added benefit of afatinib versus cisplatin + pemetrexed for the subgroup of patients with Del19 mutation.

EGFR mutation L858R

Table 23 shows the positive and negative effects of a treatment with afatinib versus cisplatin + pemetrexed in patients with EGFR mutation L858R.

Table 23: Effects of afatinib for the subgroup characteristic "L858R" (category: EGFR mutation)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms (in each case "hint"): ▪ dyspnoea ▫ improvement; "minor" ▫ time to worsening; "considerable" ▪ nausea and vomiting ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ alopecia ▫ time to worsening; "minor" ▪ coughing (< 65 years) ▫ improvement; "considerable" ▫ time to worsening; "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ sore mouth ▫ time to worsening; "considerable" ▪ dysphagia ▫ time to worsening; "considerable"
Health-related quality of life (in each case "hint"): ▪ role functioning (< 65 years) ▫ improvement; "minor" ▫ time to worsening; "considerable"	Health-related quality of life (in each case "hint"): ▪ role functioning (≥ 65 years) ▫ improvement; "minor"

In the subgroup of patients with L858R mutation, there were hints of positive and negative effects of afatinib with regards to symptoms and health-related quality of life, with a predominance of positive effects. Some of these effects were age-dependent. Overall, there is a hint of a minor added benefit of afatinib for patients < 65 years. There is no proof of added benefit for patients ≥ 65 years.

Other EGFR mutations

Table 24 shows the positive and negative effects of a treatment with afatinib versus cisplatin + pemetrexed in patients with other EGFR mutations than Del19 or L858R.

Table 24: Effects of afatinib for the subgroup characteristic "other" (category: EGFR mutation)

Positive effects	**Negative effects**
	Mortality: ▪ overall survival; indication: "minor"
Non-serious/non-severe symptoms (in each case "hint"): ▪ nausea and vomiting ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ alopecia ▫ time to worsening; "minor" ▪ coughing (< 65 years) ▫ improvement; "considerable" ▫ time to worsening; "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea ▫ improvement; "considerable" ▫ time to worsening; "considerable" ▪ sore mouth ▫ time to worsening; "considerable" ▪ dysphagia ▫ time to worsening; "considerable"
Health-related quality of life (in each case "hint"): ▪ role functioning (< 65 years) ▫ improvement; "minor" ▫ time to worsening; "considerable"	Health-related quality of life (in each case "hint"): ▪ role functioning (≥ 65 years) ▫ improvement; "minor"

For patients with different EGFR mutations than Del19 or L858R, there was an indication of lesser benefit of afatinib for the outcome "overall survival". This effect was not age-dependent. With regards to symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib without showing clear advantages or disadvantages of afatinib versus the ACT. In this case, the age-dependent effects had no important influence on the overall conclusion, and therefore did not result in a different assessment of the added benefit for the age groups considered. Overall, there is an indication of lesser benefit of afatinib versus the ACT for the subgroup of patients with different EGFR mutations than Del19 or L828R.

2.5.2 Research question 1b: non-pretreated patients with ECOG PS 2

An added benefit of afatinib is not proven for this subpopulation because the company did not present any relevant data on afatinib versus gemcitabine for non-pretreated patients with ECOG PS 2.

2.5.3 Research question 2: patients pretreated with one chemotherapy or several chemotherapies

An added benefit of afatinib is not proven for this subpopulation because the company did not present any data on afatinib in comparison with erlotinib or gefitinib for patients pretreated with at least one chemotherapy.

2.5.4 Extent and probability of added benefit – summary

The added benefit for TKI-naive adult patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations, which results from the assessment of afatinib versus the ACT, is displayed in Table 25.

Table 25: Patient groups, ACTs and extent and probability of added benefit of afatinib in TKI-naive adult patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations

Line of treatment	**Patient group**	**ACT[a]**	**Subgroup**	**Extent and probability of added benefit**
Non-pretreated patients	ECOG PS 0-1	Gefitinib or erlotinib or **cisplatin +** (vinorelbine, gemcitabine, docetaxel, paclitaxel or **pemetrexed**)	EGFR mutation Del19	Indication of a major added benefit
			EGFR mutation L858R, age < 65 age ≥ 65	Hint of a minor added benefit added benefit not proven
			Other[b] EGFR mutations	Indication of a lesser benefit
	ECOG PS 2	Gefitinib or erlotinib or **gemcitabine**	Added benefit not proven	
Patients pretreated with one chemotherapy or several chemotherapies		Erlotinib or gefitinib	Added benefit not proven	

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose an ACT from several options, the respective choice of the company is printed in bold.
b: Non-L858R, non-Del19 mutation.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; TKI: tyrosine-kinase inhibitor

The overall assessment deviates considerably from that of the company. Overall, the company claimed proof of considerable added benefit of afatinib versus the comparator therapy cisplatin + pemetrexed for non-pretreated patients with ECOG PS 0 or 1.

For non-pretreated patients with ECOG PS 2, the company claimed a hint of a non-quantifiable added benefit.

For patients pretreated with one chemotherapy or several chemotherapies, the company claimed a hint of a non-quantifiable added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

2.6.1 Research question 1a: non-pretreated patients with ECOG PS 0 or 1

LUX-Lung 3

Boehringer Ingelheim Pharmaceuticals. BIBW 2992 (afatinib) versus chemotherapy as first line treatment in NSCLC with EGFR mutation: full text view [online]. In: Clinicaltrials.gov. 5 December 2013 [accessed: 10 December 2013]. URL: http://clinicaltrials.gov/ct2/show/NCT00949650.

Boehringer Ingelheim. LUX-Lung 3: a randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation [online]. In: EU Clinical Trials Register. [accessed: 10 December 2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-005615-18.

Boehringer Ingelheim. LUX-Lung 3: a randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation; study 1200.32; clinical trial report (primary analysis) (revision 1) [unpublished]. 2013.

Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31(27): 3327-3334.

Yang JC, Hirsh V, Schuler M, Yamamoto N, O'Byrne KJ, Mok TS et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31(27): 3342-3350.

2.6.2 Research question 1b: non-pretreated patients with ECOG PS 2

No relevant studies included.

2.6.3 Research question 2: patients pretreated with one chemotherapy or several chemotherapies

No relevant studies included.

References for English extract

Please see full dossier assessment for full reference list.

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