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 August 2015). 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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[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	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
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
QLQ	Quality of Life Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TKI	tyrosine-kinase inhibitor
UICC	Union for International Cancer Control
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 13 May 2015.

The company submitted a first dossier of the drug to be evaluated on 15 November 2013 for the early benefit assessment. In this procedure, by decision of 8 May 2014, the G-BA limited its decision until 15 May 2015.

Research question

The aim of the present report was to assess the added benefit of afatinib in comparison with the appropriate comparator therapy (ACT) in epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR-TKI)-naive patients with locally advanced and/or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. This ACT is shown in Table 2.

Table 2: Appropriate comparator therapy for the benefit assessment of afatinib

Research question	Subpopulation[a]	Appropriate comparator therapy[b]
1	Treatment-naive patients or treatment-naive patients with ECOG PS 0, 1 or 2	**Gefitinib** or **erlotinib**[c] or **cisplatin** in combination with a third-generation cytostatic agent (vinorelbine or **gemcitabine** or docetaxel or paclitaxel or **pemetrexed**) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced AEs in the framework of a combination therapy)
	treatment-naive patients with ECOG PS 2	as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Patients after pretreatment with platinum-based chemotherapy	**Gefitinib** or **erlotinib** or docetaxel or pemetrexed

a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy.
b: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: Gefitinib or erlotinib are to be considered as ACT for the total patient group, irrespective of the ECOG PS.
ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

In its choice of the ACT, the company followed the G-BA's specification. For treatment-naive patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, the company chose the combination therapy of cisplatin + pemetrexed as comparator therapy. In addition, the company named cisplatin + gemcitabine as comparator therapy. For treatment-naive patients with an ECOG PS of 2, the company specified erlotinib or gefitinib as comparator therapy.

For the subpopulation of patients pretreated with platinum-based chemotherapy, the company chose gefitinib or erlotinib as comparator therapy, thus also following the ACT specified by the G-BA.

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

Results

Research question 1: treatment-naive patients

The LUX-Lung 3 study (approval study of afatinib) was included in the benefit assessment. This study was already presented in the dossier from 15 November 2013 for the first benefit assessment of afatinib (Commission A13-41). For the present benefit assessment, the company presented the results of a new data cut-off of the LUX-Lung 3 study in its dossier from 13 May 2015.

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 used in an initial dose of 40 mg/day. Dose adjustments were allowed and were conducted without relevant deviation from the requirements of the Summary of Product Characteristics (SPC). 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 (AEs) 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 body surface area, pemetrexed in a dose of 500 mg/m² body surface area.

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 discontinuation of the study medication and possible treatment switching. 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 health-related quality of life were recorded up to disease progression or treatment switching.

Overall, data on 3 data cut-offs were available: The first data cut-off (February 2012) and the third data cut-off (November 2013) were primarily planned for the final analysis of PFS and overall survival. The regulatory authorities requested an additional data cut-off (second data cut-off, January 2013) for the recording of overall survival. This data cut-off and the first data cut-off were the basis for the first benefit assessment of afatinib (Commission A13-41). For the present benefit assessment, the data of the third data cut-off were primarily used. Only for the outcome "overall survival", the results of the second data cut-off were additionally considered to increase the informative value of the results.

Only treatment-naive adenocarcinoma patients with ECOG PS 0 or 1, but not with ECOG PS 2, were included in the LUX-Lung 3 study. Correspondingly, only data on the subpopulation of treatment-naive patients with ECOG PS 0 or 1 were available for research question 1.

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 the present benefit assessment, the risk of bias for the outcome "overall survival" was rated as high for the third data cut-off. The decisive reason for this assessment was the relevant influence of the targeted treatment switching of patients in the chemotherapy arm to afatinib treatment, which was possible at this time point. In contrast, the risk of bias for the outcome "overall survival" at the second data cut-off was rated as low. For these reasons, the results of the outcome "overall survival" were assessed in the overall consideration of the second and third data cut-off.

The risk of bias for the outcomes of symptoms and health-related quality of life was rated as high. The decisive reasons for this assessment were the open-label study design as well as the combination of potentially informative censorings and large differences in treatment periods (median: 336 days in the afatinib arm, and 105 days in the cisplatin + pemetrexed arm), which were probably associated with large differences in observation periods because the outcomes on symptoms and health-related quality of life were only recorded until progression occurred or subsequent therapy was initiated. Hence no more than hints were derived for these outcomes.

The differences in observation periods between the treatment groups were probably more important for AEs than for the outcomes on morbidity and health-related quality of life because AEs were only recorded within the predefined period of time of 28 days after the end of treatment (336 + 28 days in the afatinib arm versus 105 + 28 days in the cisplatin + pemetrexed arm). Therefore no quantitative conclusion on the extent of harm from afatinib was drawn in the present benefit assessment. The qualitative conclusions drawn in the report were based on the naive proportions for the outcomes regarding harm that were considered as relevant.

Results

Mortality

For overall survival, there was proof of an effect modification by the patients' EGFR mutation so that conclusions are only meaningful on the basis of the corresponding subgroup results. For patients with the EGFR mutation Del19, there was an indication of an added benefit of afatinib in comparison with cisplatin + pemetrexed for the outcome "overall survival" in the overall consideration of the second and third data cut-off. For patients with the EGFR mutation L858R, there was no hint of an added benefit; an added benefit is

therefore not proven for these patients. For patients with other EGFR mutations, there was a hint of a lesser benefit in the overall consideration of the second and third data cut-off.

Morbidity (symptoms)

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaires European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13).

For the outcomes **"dyspnoea", "nausea and vomiting"**, **"cough"** and **"alopecia"**, there was a statistically significant difference in favour of afatinib for the time to worsening. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT for each of the symptoms "nausea and vomiting", "cough" and "alopecia". In addition, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome **"dyspnoea"**. For patients with Del19 or L858R EGFR mutation, this resulted in a hint of an added benefit of afatinib in comparison with the ACT. For patients with other EGFR mutations, no hint of an added benefit was shown; an added benefit for this outcome is therefore not proven for these patients.

For the outcomes **"fatigue"** and **"pain (chest)"**, there was also a statistically significant difference in favour of afatinib for the time to worsening. The extent of the effect in these non-serious/non-severe outcomes was no more than marginal.

For the outcomes **"pain"** and **"constipation"**, there was no statistically significant difference between the treatment groups for the time to worsening. At the same time, there was proof of an effect modification by the characteristic "age" for **pain**, and by the characteristic "ethnicity" for **constipation**. As a result, there was a hint of an added benefit for pain in patients in the age group < 65 years, and no hint of an added benefit for patients ≥ 65 years; an added benefit is therefore not proven. There was a hint of an added benefit for the outcome "constipation" in non-Asian patients; and no hint of an added benefit for this outcome in Asian patients; an added benefit is therefore not proven.

For the outcomes **"diarrhoea", "sore mouth"** and **"dysphagia"**, there was a statistically significant difference to the disadvantage of afatinib for the time to worsening. Hence there was a hint of lesser benefit of afatinib in comparison with the ACT for these outcomes.

There was no statistically significant difference between the treatment groups for the time to worsening for the following outcomes: **insomnia, appetite loss, haemoptysis, pain (arm/shoulder), pain (other)** and **peripheral neuropathy**. In addition, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome **"appetite loss"**. There were no statistically significant differences between the treatment groups or more than marginal effects in any of the subgroups. Hence there was no hint of an added benefit for any of the outcomes; an added benefit is therefore not proven for these outcomes.

Morbidity (health status)

The results on the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) were not used in the present benefit assessment because the company presented no subgroup results for it, although relevant effect modifications were shown in symptoms (category: morbidity) using the EORTC QLQ-C30 and the EORTC QLQ-LC13. Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

Health-related quality of life

Health-related quality of life was recorded with the functional scales of the EORTC QLQ-C30 questionnaire.

For the outcome **"physical functioning"**, there was a statistically significant difference in favour of afatinib for the time to worsening. The outcome-specific risk of bias for this outcome was rated as high. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT.

There was no statistically significant difference between the treatment groups for the time to worsening for the following outcomes: **global health status, emotional functioning, cognitive functioning, role functioning** and **social functioning**. As a result, there was no hint of an added benefit for the outcomes "emotional functioning", "cognitive functioning", "role functioning" and "social functioning"; an added benefit is therefore not proven. In addition, there was proof of an effect modification by the characteristic "age" for the outcome **"global health status"**. There was a hint of lesser benefit of afatinib in comparison with the ACT for patients in the age group ≥ 65 years. For patients < 65 years, there was no hint of an added benefit; an added benefit is therefore not proven.

Adverse events

The considerable difference in observation period 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 on the basis of the naive proportions were drawn for AEs in the present benefit assessment.

Regarding the outcomes **"serious AEs (SAEs)", "discontinuation due to AEs"** and **"severe AEs"** (Common Terminology Criteria for Adverse Events [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 difference to the disadvantage of afatinib despite the considerably longer observation period of afatinib. Hence greater or lesser harm from afatinib than from cisplatin + pemetrexed is not proven for these outcomes.

Research question 2: patients pretreated with platinum-based chemotherapy

There were no evaluable data for the research question of afatinib versus erlotinib or gefitinib in patients pretreated with platinum-based chemotherapy. 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 versus the ACT is assessed as follows:

Research question 1: treatment-naive patients

The results showed a relevant effect modification by EGFR mutation status for the outcome "overall survival". Hereinafter, the overall conclusion on the added benefit for treatment-naive patients with ECOG PS 0 or 1 is therefore presented separately for the 3 different mutation statuses.

There is an indication of a major added benefit for the outcome "overall survival" for patients with Del19 EGFR mutation. Regarding symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib for this subgroup with a higher number of positive effects. Extent and probability of the effects were smaller for all outcomes in these 2 categories than for the outcome "overall survival". Only some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Hence 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 EGFR mutation.

In the subgroup of patients with L858R EGFR mutation, neither added benefit nor lesser benefit was proven for the outcome "overall survival". Regarding symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib for this subgroup with a higher number of positive effects. Only some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Overall, there is therefore a hint of a minor added benefit for patients with L858R EGFR mutation.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

For patients with other EGFR mutations than Del19 or L858R, there was a hint of lesser benefit of afatinib for the outcome "overall survival". Regarding morbidity and health-related quality of life, there were hints of positive and negative effects of afatinib with a higher number of positive effects. However, this is insufficient to completely outweigh the negative effects, particularly regarding overall survival. Some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Overall, there is a hint of lesser benefit of afatinib versus the ACT for the subgroup of patients with other EGFR mutations than Del19 or L858R.

There were no relevant data on the comparison of afatinib with the ACT for the subpopulation of treatment-naive patients with ECOG PS of 2. An added benefit of afatinib versus the ACT is therefore not proven for these patients.

Research question 2: patients pretreated with platinum-based chemotherapy

There were no evaluable data for the research question of afatinib versus erlotinib or gefitinib in patients pretreated with platinum-based chemotherapy. Hence an added benefit of afatinib versus the ACT is not proven.

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

Table 3: Afatinib – extent and probability of added benefit

Line of treatment	**Patient group**	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Treatment-naive patients	ECOG PS 0-1	Gefitinib or erlotinib or **cisplatin +** (vinorelbine, **gemcitabine**, docetaxel, paclitaxel or **pemetrexed**) or carboplatin + (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed)	EGFR mutation Del19	Indication of a major added benefit
			EGFR mutation L858R	Hint of a minor added benefit
			Other[b] EGFR mutations	Hint of lesser benefit
	ECOG PS 2	**Gefitinib** or **erlotinib** or as an alternative to the combination therapies shown for ECOG PS 0-1: monotherapy with gemcitabine or vinorelbine	Added benefit not proven	
Patients after pretreatment with platinum-based chemotherapy		**Gefitinib** or **erlotinib** or docetaxel or pemetrexed	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 a comparator therapy from several options, the respective choice of the company is printed in bold. The company used the comparator therapy cisplatin + gemcitabine for comparison.
b: Not only L858R EGFR mutation, not only Del19 EGFR mutation.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

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 the present report was to assess the added benefit of afatinib in comparison with the ACT in EGFR-TKI-naive patients with locally advanced and/or metastatic NSCLC with activating EGFR mutations.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. This ACT is shown in Table 4.

Table 4: Appropriate comparator therapy for the benefit assessment of afatinib

Research question	Subpopulation[a]	Appropriate comparator therapy
1	Treatment-naive patients or treatment-naive patients with ECOG PS 0, 1 or 2	Gefitinib or erlotinib[b] or cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced AEs in the framework of a combination therapy)
	treatment-naive patients with ECOG PS 2	as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Patients after pretreatment with platinum-based chemotherapy	Gefitinib or erlotinib or docetaxel or pemetrexed
a: It is assumed for the present therapeutic indication that the NSCLC patients are in disease stage IIIB to IV (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. b: Gefitinib or erlotinib are to be considered as ACT for the total patient group, irrespective of the ECOG PS. ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control		

In its choice of the ACT, the company followed the G-BA's specification even though it did not consider all options specified by the G-BA as appropriate. For treatment-naive patients with an ECOG PS of 0 or 1, the company chose the combination therapy of cisplatin + pemetrexed as comparator therapy. In addition, the company named cisplatin + gemcitabine as comparator therapy (see Section 2.7.1 of the full dossier assessment). For treatment-naive patients with an ECOG PS of 2, the company opened a separate research question and specified erlotinib or gefitinib as comparator therapy (see Section 2.7.1 of the full dossier assessment). The comparator therapies chosen by the company were therefore among the options specified by the G-BA for the respective subpopulations.

For the subpopulation of patients pretreated with platinum-based chemotherapy, the company chose gefitinib or erlotinib as comparator therapy (see Section 2.7.1. of the full dossier assessment), thus following the ACT specified by the G-BA. However, the company included all patients with second and subsequent line of treatment for this research question and did not limit the patient population to those patients pretreated with only one platinum-based chemotherapy.

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

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on afatinib (status: 17 February 2015)
- bibliographical literature search on afatinib (last search on 16 February 2015)
- search in trial registries for studies on afatinib (last search on 17 February 2015)

To check the completeness of the study pool:

- search in trial registries for studies on afatinib (last search on 29 May 2015)

No additional relevant study was identified from the check.

2.3.1 Research question 1: treatment-naive patients

2.3.1.1 Studies included

The LUX-Lung 3 study listed in the following table was included in the benefit assessment. This study was already presented in the dossier from 15 November 2013 for the first benefit assessment of afatinib (Commission A13-41 [3]). For the present benefit assessment, the company presented the results of a new data cut-off of the LUX-Lung 3 study in its dossier from 13 May 2015.

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			

Only treatment-naive adenocarcinoma patients with ECOG PS 0 or 1, but not with ECOG PS 2, were included in the LUX-Lung 3 study. Correspondingly, only data on the subpopulation of treatment-naive patients with ECOG PS 0 or 1 were available for research question 1.

Besides the LUX-Lung 3 study, the company included another randomized controlled trial (RCT) (LUX-Lung 6) in its assessment. This study was a comparison of afatinib with cisplatin + gemcitabine, also in treatment-naive 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 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 presented no suitable analyses to prove the transferability of the results of the LUX-Lung 6 study 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 studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

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	Treatment-naive adult patients with lung adenocarcinoma (stage IIIB or IV), EGFR mutation, ECOG PS 0 or 1, 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: until 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: 8/2009 Data cut-offs: 2/2012[c] 1/2013[d] 11/2013[e]	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 this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Apart from (neo)adjuvant chemotherapy if at least 12 months before randomization.
c: Planned after 217 cases of disease progression (first data cut-off).
d: This data cut-off was not predefined in the clinical study report, but was additionally requested by the regulatory authorities for the outcome "overall survival" for 21 January 2013, and is hereinafter referred to as "second data cut-off".
e: Planned after 209 deaths (third data cut-off).
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	Prior and concomitant medication
LUX-Lung 3	Afatinib: starting dose 40 mg/day, orally, once daily	Pemetrexed: 500 mg/m² body surface area IV + cisplatin: 75 mg/m² body surface area IV	▪ symptomatic treatment of AEs and tumour-associated symptoms ▪ bisphosphonates
	administration in 21-day cycles until disease progression or intolerance	on every first day of a 21-day treatment cycle until disease progression or intolerance, at most 6 treatment cycles of 21 days	Only with cisplatin + pemetrexed: ▪ administration of corticosteroid on the day before, during and after the infusion ▪ hydration before and after the infusion ▪ folic acid[c] daily, orally ▪ vitamin B12 1000 mg IM before the first and after every third treatment cycle ▪ leucovorin rescue medication in case of extreme toxicity
	up-titration to 50 mg/day possible after 21 days in case of good tolerability dose reduction[a] to 20 mg/day in case of intolerance	dose reduction or postponement of treatment possible in case of intolerance[b]	

a: According to a fixed regimen.
b: According to the SPC.
c: 7 days before treatment is started until 3 weeks after end of pemetrexed treatment.
AE: adverse events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IM: intramuscular; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study design

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. General condition 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 ethnicity (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 [4,5]. 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, i.e. if certain prespecified AEs did not occur [6]. Dose reduction to a minimum dose of 20 mg/day according to a prespecified scheme in compliance with the SPC was possible if important AEs 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 AEs 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 body surface area, pemetrexed in a dose of 500 mg/m² body surface area. Dose reduction or postponing treatment was possible if drug-related AEs 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 in the chemotherapy arm could also receive tumour-targeted subsequent therapies (if possible monochemotherapy or a TKI [including afatinib]) after the end of the study treatment or disease progression. The study documents contained no further information on the circumstances under which afatinib could be used in subsequent therapy.

Duration of follow-up

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes in the LUX-Lung 3 study.

Table 8: Planned duration of follow-up – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study **Outcome category**	**Planned follow-up**
LUX-Lung 3	
Overall survival	until death
Symptoms and health-related quality of life	until progression or initiation of subsequent therapy[a]
Adverse events	until 28 days after the last treatment with the study medication
a: All patients had their first obligatory follow-up visit 21 (± 7) days after the end-of-treatment visit (0–14 days after the last study medication), also if subsequent therapy had already been initiated at this time point. b: Data underlying the planned analyses; AEs that occurred later were only documented (until the last follow-up visit). ECOG PS: Eastern Cooperative Oncology Group Performance Status; RCT: randomized controlled trial; vs.: versus	

The data of all patients were included in the analysis of overall survival also after discontinuation of the study medication and possible treatment switching. 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 health-related quality of life were recorded up to disease progression or treatment switching.

Analysis dates of the LUX-Lung 3 study

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 the outcome "overall survival" were performed at this time point. This data cut-off provided the data underlying the first benefit assessment of afatinib for all outcomes except overall survival [3]. On 21 January 2013, an additional data cut-off was performed for the recording of overall survival at the regulatory authorities' request. This data cut-off was also used for the first benefit assessment of afatinib and is hereinafter referred to as "second data cut-off". The final analysis of the outcome "overall survival" was planned after 209 deaths and was performed after occurrence of 213 events (14 November 2013; third data cut-off). The company presented the results of this third data cut-off for the present benefit assessment, but used them only for the assessment of the outcome "overall survival". For the other outcomes, the company still considered the data of the first data cut-off (9 February 2012). In the present benefit assessment, the results of the third data cut-off on 14 November 2013 were used as the basis of the benefit assessment. For the reasons described in Section 2.7.2.4.2 of the full dossier assessment, the results of the outcome "overall survival" were assessed in the overall consideration of the second and third data cut-off.

Patient characteristics

Table 9 shows the characteristics of the patients in the study included.

Table 9: 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], %	36/64	33/67
Ethnicity, n (%)		
Asian	166 (72)	83 (72)
Non-Asian	64 (28)	32 (28)
ECOG PS, n (%)		
0	92 (40)	41 (36)
1	138 (60)	73 (64)
2	0 (0)	1 (1)[a]
Tumour stage, n (%)		
Stage IIIB	20 (9)	17 (15)
Stage IV	210 (91)	98 (85)
EGFR mutation, n (%)		
L858R[b]	91 (40)	47 (41)
Del19[b]	112 (49)	57 (50)
Other	27[c] (12)	11 (10)
Proportion of patients with adenocarcinoma only, n (%)	227 (99)	111 (97)
Smoking status		
Never-smoker	155 (67)	81 (70)
Ex-smoker	70 (30)	32 (28)
Current smoker	5 (2)	2 (2)
Brain metastases present	27 (12)	15 (13)
Treatment discontinuations, n (%)		
First data cut-off[e]	164 (71)[f]	51 (44)[f,g]
Third data cut-off[h]	209 (91)[f]	51 (44)[f,g]
Study discontinuations, n (%)	ND	ND

a: Patient with ECOG PS 0 at screening; worsened to 2 even before treatment started.
b: Patients with L858R EGFR mutation only (or with Del19 EGFR mutation only).
c: Includes one patient with wild-type EGFR mistakenly included in the study.
d: Adenocarcinoma predominated in 6 additional patients, a different carcinoma predominated in one other patient.
e: Predefined data cut-off on 9 February 2012.
f: Percentages: Institute's calculation.
g: 60 patients had completed treatment at the time point of the first data cut-off already after 6 cycles according to the study protocol.
h: Predefined data cut-off on 14 November 2013.
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; ND: no data; RCT: randomized controlled trial; SD: standard deviation; 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; with the number of women being nearly twice as high as the number of men in both arms. According to the inclusion criteria of the study, almost all carcinomas of the patients were histologically classified as adenocarcinomas. About 12% and 13% of the patients had brain metastases. The majority of the patients had tumour stage IV.

Ethnicity (Asian or non-Asian) and EGFR mutation status (Del19, L858R or other) were mainly equally distributed due to the stratified randomization. About 72% of 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 was reflected by the high proportion of never-smokers (just below 70%).

At the time point of the third data cut-off on 14 November 2013, 91% of the patients in the afatinib arm had discontinued treatment, and 44% of the patients under chemotherapy had discontinued treatment. This can be explained by the differences in planned treatment duration (afatinib: without defined end of treatment, cisplatin + pemetrexed: 6 treatment cycles maximum).

Table 10 shows the median treatment duration in the LUX-Lung 3 study.

Table 10: Information on the course of the study – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study **Duration of the study phase** **Outcome category**	**Afatinib** **N = 230**	**Cisplatin + pemetrexed** **N = 115**
LUX-Lung 3		
Treatment duration, [days]		
First data cut-off[a]		
Median [min–max]	336 [7–827]	105 [1-157]
Mean (SD)	335.4 (210.5)	85.0 (42.5)
Third data cut-off[b]		
Median [min–max]	336 [7-1471]	105 [1-157]
Mean (SD)	436.1 (362.2)	85.0 (42.5)
Observation period, [days]		
All outcomes considered in the benefit assessment	ND	ND

a: Predefined data cut-off on 9 February 2012.
b: Predefined data cut-off on 14 November 2013.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration in the LUX-Lung 3 study was considerably longer for patients in the afatinib arm (336 days) than in the cisplatin + pemetrexed arm (105 days). This can be explained by the differences in specified treatment duration (afatinib: without defined end of treatment, cisplatin + pemetrexed: maximum 6 treatment cycles of 21 days). There was no information on the actual observation period, which could differ greatly due to the different criteria for follow-up depending on the outcome. For AEs however, the observation period can be estimated on the basis of the data on median treatment duration because AEs were predefined to be recorded up to 28 days after the last study medication. Under the assumption that all patients used these 28 days of follow-up, the resulting median observation period was approximately 364 days in the afatinib arm, and approximately 133 days in the cisplatin + pemetrexed arm. The observation period in the cisplatin + pemetrexed arm was therefore only about one third of the observation period in the afatinib arm. The differences in median observation period were probably more moderate for the outcomes on symptoms and health-related quality of life because these were followed up not only until 28 days after the end of treatment, but until progression or initiation of subsequent therapy.

Table 11 shows the risk of bias at study level.

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

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

ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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. Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.3.2 Research question 2: patients pretreated with platinum-based chemotherapy

There was no evaluable study for the assessment of the added benefit of afatinib in patients pretreated with platinum-based chemotherapy. 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 1: treatment-naive patients

2.4.1.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A). Further information can be found in Section 2.7.2.4.3 of the full dossier assessment.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed, ECOG PS 0-1

Study	Outcomes						
	Overall survival	Symptoms[a]	Health status (VAS of the EQ-5D)[b]	Health-related quality of life (disease-specific instrument)[c]	SAEs[d]	Severe AEs (CTCAE grade ≥ 3)[d]	Discontinuation due to AEs[d]
LUX-Lung 3	Yes	Yes	No	Yes	Yes	Yes	Yes

a: Measured with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: No data presented on subgroups.
c: Measured with the EORTC QLQ-C30.
d: Due to the high risk of bias, only a qualitative assessment of the outcomes on AEs was conducted.

AE: adverse event; 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: European Quality of Life-5 Dimensions; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.1.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study	Outcomes							
	Study level	Overall survival	Symptoms[a]	Health status (VAS of the EQ-5D)	Health-related quality of life (disease-specific instrument)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	discontinuation due to AEs
LUX-Lung 3	L	H[c]	H[d]	-[e]	H[d]	-[f]	-[f]	-[f]

a: Measured with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13).
b: Measured with the EORTC QLQ-C30.
c: Assessment for the third data cut-off (9 to 11 patients [7.8% to 9.5%] of the chemotherapy arm received afatinib as subsequent therapy). The risk of bias for the second data cut-off was rated as low (see Section 2.7.2.4.2 of the full dossier assessment).
d: Patient-reported outcome in open-label study; potentially great differences in observation periods in informative censoring.
e: No data presented on subgroups.
f: No data evaluable for quantitative conclusion available. Therefore only qualitative consideration in the present benefit assessment. For reasons, see Section 2.7.2.4.2 of the full dossier assessment.

AE: adverse event; 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: European Quality of Life-5 Dimensions; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

For all outcomes considered to be relevant for the assessment, data were available in the dossier. The available data were not used for the benefit assessment for the outcome "health status", however, because the company presented no results on subgroup analyses (see Section 2.7.2.4.3 of the full dossier assessment).

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 [1]. Hence at most indications, e.g. of an added benefit, could be derived from the data. This assessment deviates from that of the company, which for most outcomes derived proof of an added benefit of afatinib versus cisplatin + pemetrexed from the LUX-Lung 3 study if the LUX-Lung 6 study showed effects in the same direction.

In the present benefit assessment, the risk of bias for the outcome "overall survival" was rated as high for the third data cut-off of the LUX-Lung 3 study. The targeted treatment switching from the chemotherapy arm to afatinib treatment was decisive in this situation. This concurs

with the assessment of the company, which also rated the risk of bias of bias as high for the outcome “overall survival”. The company provided a different justification, however (see Section 2.7.2.4.2 of the full dossier assessment). The risk of bias for the outcome “overall survival” at the second data cut-off was rated as low (see dossier assessment A13-41 [3]). There were fewer patients who switched treatment at this data cut-off, and it can be assumed that the patients who had switched treatment had not received afatinib treatment for as long, particularly because all patients who switched treatment received afatinib as third-line therapy. Detailed justification for the 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 the outcomes of symptoms and health-related quality of life was rated as high. The decisive reasons for this assessment were the open-label study design as well as the combination of potentially informative censorings and large differences in treatment periods, which were probably associated with large differences in observation periods (see Section 2.7.2.4.2 of the full dossier assessment). Hence no more than hints were derived for these outcomes.

In the case of AEs, no quantitative conclusion on the extent of harm from afatinib was therefore drawn in the present benefit assessment. This is mainly due to the drastically different observation periods in the study arms (336 + 28 days in the afatinib arm and 105 + 28 days in the cisplatin + pemetrexed arm). Hence both relative risks and the incidence density ratios used by the company only allowed limited, qualitative or no 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 estimations to account for the different lengths in observation period.

2.4.1.3 Results

The results on the comparison of afatinib with cisplatin + pemetrexed in treatment-naive NSCLC patients with ECOG PS 0 or 1 are summarized in the following tables. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations. An overview of the most common AEs, severe AEs (CTCAE grade ≥ 3), SAEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Table 14: Results (mortality) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
LUX-Lung 3					
Overall survival					
First data cut-off: 9 Feb 2012	230	NC [22.6; NC] 67 (29.1)	115	NC [21.6; NC] 31 (27.0)	1.12 [0.73; 1.73]; 0.605
Second data cut-off[c]: 21 Jan 2013	230	28.1 [24.6; 33.0] 116 (50.4)	115	28.2 [20.7; 33.2] 59 (51.3)	0.91 [0.66; 1.25]; 0.546
Third data cut-off: 14 Nov 2013	230	28.2 [24.6; 33.6] 140 (60.9)	115	28.2 [20.7; 33.2] 73 (63.5)	0.88 [0.66; 1.17]; 0.385

a: Cox model stratified by EGFR mutation status and ethnicity.
b: Log-rank test stratified by EGFR mutation status and ethnicity.
c: This data cut-off was not predefined in the clinical study report, but was additionally requested by the regulatory authorities for 21 January 2013.

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

Table 15: Results (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome category Outcome Subscale/item	Afatinib N	Afatinib Median (months) [95% CI] Patients with event n (%)	Cisplatin N	Cisplatin Median (months) [95% CI] Patients with event n (%)	Afatinib vs. cisplatin + pemetrexed HR [95% CI][a]; p-value[b]
LUX-Lung 3					
Morbidity					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms[c,d]					
Dyspnoea	230	27.6 [14.6; NC] 88 (38.3)	115	5.2 [2.8; 10.5] 55 (47.8)	0.48 [0.33; 0.68]; < 0.001
Fatigue	230	3.0 [2.2; 5.6] 152 (66.1)	115	1.7 [1.1; 2.6] 80 (69.6)	0.69 [0.52; 0.91]; 0.007
Insomnia	230	10.4 [6.9; 17.1] 116 (50.4)	115	20.5 [3.6; NC] 45 (39.1)	0.98 [0.69; 1.39]; 0.886
Pain	230	4.2 [2.8; 5.6] 147 (63.9)	115	3.1 [2.2; 4.0] 72 (62.6)	0.83 [0.62; 1.10]; 0.188
Appetite loss	230	3.8 [2.8; 8.3] 140 (60.9)	115	2.8 [2.0; 3.8] 69 (60.0)	0.84 [0.62; 1.13]; 0.234
Diarrhoea	230	0.8 [0.8; 0.8] 210 (91.3)	115	13.7 [11.3; NC] 30 (26.1)	7.80 [5.18; 11.75]; < 0.001
Nausea and vomiting	230	7.4 [4.8; 12.4] 130 (56.5)	115	2.1 [1.6; 2.9] 74 (64.3)	0.55 [0.40; 0.74]; < 0.001
Constipation	230	17.7 [9.7; 20.8] 108 (47.0)	115	7.6 [3.6; NC] 48 (41.7)	0.73 [0.52; 1.04]; 0.079
EORTC QLQ-LC13 symptom scales – time to worsening of symptoms[c,d]					
Dyspnoea	230	10.4 [5.6; 15.9] 121 (52.6)	115	2.9 [2.2; 4.9] 67 (58.3)	0.68 [0.50; 0.93]; 0.013
Haemoptysis	230	NC [NC; NC] 46 (20.0)	115	NC [NC; NC] 11 (9.6)	1.75 [0.89; 3.45]; 0.100
Cough	230	27.0 [19.2; NC] 82 (35.7)	115	8.0 [4.4; NC] 44 (38.3)	0.59 [0.40; 0.87]; 0.006
Pain (arm/shoulder)	230	12.1 [7.6; 20.8] 110 (47.8)	115	28.2 [4.4; NC] 44 (38.3)	0.92 [0.64; 1.31]; 0.627
Pain (chest)	230	42.2 [20.1; NC] 83 (36.1)	115	8.3 [5.8; NC] 45 (39.1)	0.64 [0.44; 0.93]; 0.018
Pain (other parts)	230	4.9 [3.4; 6.7] 131 (57.0)	115	6.2 [3.6; 8.8] 49 (42.6)	1.08 [0.78; 1.51]; 0.636
Alopecia	230	3.5 [2.8; 4.1] 154 (67.0)	115	1.7 [1.5; 2.0] 77 (67.0)	0.61 [0.46; 0.80]; < 0.001

(continued)

Table 15: Results (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1 (continued)

Study **Outcome category**	**Afatinib**		**Cisplatin**		**Afatinib vs. cisplatin + pemetrexed**
Outcome **Subscale/item**	**N**	**Median (months)** **[95% CI]** **Patients with event** **n (%)**	**N**	**Median (months)** **[95% CI]** **Patients with event** **n (%)**	**HR [95% CI][a]; p-value[b]**
Sore mouth	230	0.8 [0.8; 0.8] 194 (84.3)	115	2.9 [2.4; 3.7] 68 (59.1)	2.55 [1.90; 3.41]; < 0.001
Peripheral neuropathy	230	2.9 [2.2; 4.2] 159 (69.1)	115	5.1 [4.2; 5.8] 64 (55.7)	1.24 [0.92; 1.66]; 0.160
Dysphagia	230	2.8 [1.5; 5.8] 147 (63.9)	115	10.4 [5.6; NC] 43 (37.4)	1.84 [1.30; 2.59]; < 0.001

a: Cox model stratified by EGFR mutation status and ethnicity.
b: Log-rank test stratified by EGFR mutation status and ethnicity.
c: Data of the third data cut-off on 14 November 2013.
d: 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; 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-specific symptoms); RCT: randomized controlled trial; vs.: versus

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

Study Outcome Subscale	Afatinib N	Afatinib Median (months) [95% CI] Patients with event n (%)	Cisplatin N	Cisplatin Median (months) [95% CI] Patients with event n (%)	Afatinib vs. cisplatin + pemetrexed HR [95% CI][a]; p-value[b]
LUX-Lung 3					
EORTC QLQ-C30 functional scales – time to worsening of health-related quality of life[c, d]					
Global health status	230	3.5 [2.8; 5.6] 144 (62.6)	115	3.8 [2.8; 5.8] 65 (56.5)	1.00 [0.74; 1.35]; 0.997
Emotional functioning	230	12.1 [7.7; 17.1] 114 (49.6)	115	8.5 [5.5; NC] 45 (39.1)	0.91 [0.64; 1.30]; 0.612
Cognitive functioning	230	4.9 [3.5; 8.3] 144 (62.6)	115	3.1 [2.1; 4.2] 69 (60.0)	0.77 [0.57; 1.03]; 0.078
Physical functioning	230	5.6 [3.5; 9.5] 139 (60.4)	115	2.8 [2.1; 4.4] 70 (60.9)	0.73 [0.54; 0.98]; 0.031
Role functioning	230	2.9 [2.2; 4.9] 157 (68.3)	115	2.4 [1.7; 3.5] 70 (60.9)	0.92 [0.69; 1.23]; 0.585
Social functioning	230	4.8 [2.8; 7.6] 136 (59.1)	115	3.5 [2.4; 7.1] 62 (53.9)	0.98 [0.72; 1.33]; 0.891

a: Cox model stratified by EGFR mutation status and ethnicity.
b: Log-rank test stratified by EGFR mutation status and ethnicity.
c: Data of the third data cut-off on 14 November 2013.
d: 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; 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); RCT: randomized controlled trial; vs.: versus

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

Study Outcome	Afatinib		Cisplatin + pemetrexed	
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)
LUX-Lung 3				
Adverse events[a]				
SAEs	229	71 (31.0)	111	25 (22.5)
Treatment discontinuations due to AEs	229	37 (16.2)	111	17 (15.3)
AEs of CTCAE grade ≥ 3	229	143 (62.4)	111	63 (56.8)
CTCAE grade 3	229	119 (52.0)	111	49 (44.1)
CTCAE grade 4	229	9 (3.9)	111	11 (9.9)

a: Data of the third data cut-off on 14 November 2013.

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

Mortality

Overall survival

The second and third data cut-offs were used for assessing the outcome "overall survival" (see Section 2.7.2.4.3 of the full dossier assessment). The results on the first data cut-off were presented as additional information only.

In the LUX-Lung 3 study, there were no statistically significant differences in overall survival between afatinib and cisplatin + pemetrexed in any of the 3 data cut-offs. Due to effect modifications for the characteristic "EGFR mutation status", the overall estimator of the LUX-Lung 3 study could not be meaningfully interpreted, however (see Section 2.4.1.4). For patients with the EGFR mutation Del19, there was an indication of an added benefit of afatinib in comparison with cisplatin + pemetrexed for the outcome "overall survival" in the overall consideration of the second and third data cut-off. For patients with the EGFR mutation L858R, there was no hint of an added benefit; an added benefit is therefore not proven for these patients. For patients with other EGFR mutations, there was a hint of a lesser benefit in the overall consideration of the second and third data cut-off.

For patients with the EGFR mutations Del19 and other EGFR mutations, this deviates from the company's assessment. The company saw proof of an added benefit for patients with Del19 EGFR mutation, and no proof of added benefit for patients with other EGFR mutations.

Morbidity

Symptoms (time to worsening)

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13. Due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit could be derived for all outcomes in this category.

For the outcomes **"dyspnoea", "nausea and vomiting"**, **"cough"** and **"alopecia"**, there was a statistically significant difference in favour of afatinib for the time to worsening. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT for each of the symptoms "nausea and vomiting", "cough" and "alopecia". In addition, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome **"dyspnoea"** (see Section 2.4.1.4). For patients with Del19 or L858R EGFR mutation, this resulted in a hint of an added benefit of afatinib in comparison with the ACT. For patients with other EGFR mutations, no hint of an added benefit was shown; an added benefit for this outcome is therefore not proven for these patients. This deviates from the company's assessment, which derived proof of an added benefit for each of the outcomes "dyspnoea", "nausea and vomiting", "cough" and "alopecia" for the total target population.

For the outcomes **"fatigue"** and **"pain (chest)"**, there was also a statistically significant difference in favour of afatinib for the time to worsening. The extent of the effect in these non-serious/non-severe outcomes was no more than marginal. This deviates from the company's assessment, which derived an indication in the overall consideration of the outcomes on pain, and proof of an added benefit for the outcome "fatigue".

For the outcomes **"pain"** and **"constipation"**, there was no statistically significant difference between the treatment groups for the time to worsening. At the same time, there was proof of an effect modification by the characteristic "age" for **pain**, and by the characteristic "ethnicity" for **constipation** (see Section 2.4.1.4). As a result, there was a hint of an added benefit for pain in patients in the age group < 65 years, and no hint of an added benefit for patients ≥ 65 years; an added benefit is therefore not proven. There was a hint of an added benefit for the outcome "constipation" in non-Asian patients; and no hint of an added benefit for this outcome in Asian patients; an added benefit is therefore not proven. This deviates from the company's assessment, which derived an indication of added benefit for the total population in the overall consideration of the outcomes on pain and for the outcome "constipation".

For the outcomes **"diarrhoea", "sore mouth"** and **"dysphagia"**, there was a statistically significant difference to the disadvantage of afatinib for the time to worsening. Hence there was a hint of lesser benefit of afatinib in comparison with the ACT for these outcomes. This deviates from the company's assessment, which derived proof of lesser benefit of afatinib for these outcomes.

There was no statistically significant difference between the treatment groups for the time to worsening for the following outcomes: **insomnia, appetite loss, haemoptysis, pain (arm/shoulder), pain (other)** and **peripheral neuropathy**. In addition, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome **"appetite loss"**. There were no statistically significant differences between the treatment groups or more than marginal effects in any of the subgroups. Hence there was no hint of an added benefit for any of the outcomes; an added benefit is therefore not proven for these outcomes. This partly deviates from the company's assessment. The company also saw no proof of an added benefit for the outcomes "insomnia" and "haemoptysis". The company derived an indication of an added benefit of afatinib in the overall consideration of the outcomes on pain and for the outcomes "peripheral neuropathy" and "appetite loss".

Health status

The results on EQ-5D VAS were not used in the present benefit assessment because the company presented no subgroup results for it, although relevant effect modifications were shown in symptoms (category: morbidity) using the EORTC QLQ-C30 and the EORTC QLQ-LC13. Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

Health-related quality of life (time to worsening)

Health-related quality of life was recorded with the functional scales of the EORTC QLQ-C30 questionnaire.

For the outcome **"physical functioning"**, there was a statistically significant difference in favour of afatinib for the time to worsening. The outcome-specific risk of bias for this outcome was rated as high. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT. This deviates from the company's assessment, which claimed proof of an added benefit for this outcome.

There was no statistically significant difference between the treatment groups for the time to worsening for the following outcomes: **global health status, emotional functioning, cognitive functioning, role functioning** and **social functioning**. As a result, there was no hint of an added benefit for the outcomes "emotional functioning", "cognitive functioning", "role functioning" and "social functioning"; an added benefit is therefore not proven. In addition, there was proof of an effect modification by the characteristic "age" for the outcome **"global health status"** (see Section 2.4.1.4). There was a hint of lesser benefit of afatinib in comparison with the ACT for patients in the age group ≥ 65 years. For patients < 65 years, there was no hint of an added benefit; an added benefit is therefore not proven. This deviates from the company's assessment, which derived an indication of an added benefit of afatinib for the total population for all of these outcomes. However, this was based on the results of the LUX-Lung 6 study, which was not relevant for the present benefit assessment.

Adverse events

The considerable difference in observation period 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 periods by presenting the incidence density ratio as effect estimate. Since in this case the median observation period was drastically (by about the factor 3) longer in the afatinib arm than in the chemotherapy arm, the incidence density ratio as well as the relative risk were not considered to be adequate analysis procedures (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, discontinuation due to adverse events and severe adverse events (CTCAE grade ≥ 3)

Regarding the outcomes **"SAEs", "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 difference to the disadvantage of afatinib despite the considerably longer observation period 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 an added benefit for SAEs; and an indication or proof of an added benefit for discontinuation due to AEs and severe AEs on the basis of the LUX-Lung 3 study and the LUX-Lung 6 study.

2.4.1.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age at baseline (< 65 years versus ≥ 65 years)
- sex
- ECOG PS at baseline (0 versus 1)
- EGFR mutations:
  - L858R versus Del19 versus other
- ethnicity (Asian versus non-Asian)
- smoking status (never-smoker versus non-smoker/little smoker versus smoker)
- brain metastases at baseline (yes versus no)
- geographical region (Europe/North America/Asia/other)

All subgroup characteristics mentioned and their dimension and cut-off values were defined beforehand in the LUX-Lung 3 study.

Based on the available data, it was not possible to draw a comprehensive, differentiated conclusion on added benefit for the different other EGFR mutation groups (Exon 20/L861Q/G719S/A/C/T790M/S768I/other) (see Section 2.7.2.4.3 of the full dossier assessment). The results on the distribution of the different other mutations in both treatment arms as well as the subresults on treatment effects for the outcome "overall survival" in the different other mutation groups calculated by the company are presented in Appendix C of the full dossier assessment.

Hereinafter, for the outcome "overall survival" for the second and third data cut-off, only the results for subgroups are presented for which at least an indication of an effect modification was shown. There was a high risk of bias of possibly different degree in the subgroups for the outcomes of morbidity and health-related quality of life because of the different observation periods and informative censorings. Only subgroup analyses with proof of an interaction ($p < 0.05$) were included in the present benefit assessment to account for the uncertainty of these results (see Section 2.7.2.4.2 of the full dossier assessment).

There were relevant effect modifications by more than one factor for some outcomes. However, there were no further analyses to investigate the mutual dependencies of these effect modifiers. No final conclusion on the results in these subgroups could therefore be drawn. The results of the individual subgroups are therefore not presented. The result of the total population was assumed in the situations described. Moreover, subgroup characteristics were only considered if a relevant effect modification was shown in several outcomes.

No effect modifications were investigated for AEs because, due to the different observation periods, only qualitative conclusions could be drawn already for the total population.

In principle, subgroup analyses on a characteristic are only presented hereinafter if at least one of the subgroups showed a result deviating from the total population regarding statistical significance.

Table 18: Subgroups (outcome "overall survival") – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome Characteristic Subgroup	Afatinib N	Afatinib Median survival time in months [95% CI] Patients with event n (%)	Cisplatin + pemetrexed N	Cisplatin + pemetrexed Median survival time in months [95% CI] Patients with event n (%)	Afatinib vs. cisplatin + pemetrexed HR [95% CI][a]; p-value[b]
LUX-Lung 3					
Overall survival					
EGFR mutation					
First data cut-off: 9 Feb 2012					
L858R	91	NC [17.7; NC] 28 (30.8)	47	NC [21.6; NC] 9 (19.1)	1.77 [0.84; 3.76]; 0.130
Del19	113	NC [NC; NC] 24 (21.2)	57	NC [18.8; NC] 18 (31.6)	0.58 [0.31; 1.07]; 0.075
Other	26	15.4 [7.5; 24.9] 15 (57.7)	11	19.7 [6.8; NC] 4 (36.4)	1.99 [0.66; 6.01]; 0.213
				Interaction:	p = 0.033
Second data cut-off: 21 Jan 2013					
L858R	91	27.2 [19.8; NC] 46 (50.5)	47	NC [24.3; NC] 19 (40.4)	1.30 [0.76; 2.23]; 0.332
Del19	113	31.6 [26.7; 37.5] 51 (45.1)	57	21.1 [16.3; 29.1] 36 (63.2)	0.55 [0.36; 0.85]; 0.006
Other	26	15.9 [7.5; 24.6] 19 (73.1)	11	NC [6.8; NC] 4 (36.4)	3.08 [1.04; 9.15]; 0.034
				Interaction:	p = 0.002
Third data cut-off:14 Nov 2013					
L858R	91	27.6 [19.8; 41.7] 56 (61.5)	47	40.3 [24.3; NC] 23 (48.9)	1.30 [0.80; 2.11]; 0.292
Del19	112[c]	33.3 [26.8; 41.5] 63 (56.3)	57	21.1 [16.3; 30.7] 43 (75.4)	0.54 [0.36; 0.79]; 0.002
Other	27[c]	15.4 [7.5; 24.6] 21 (77.8)	11	40.8 [6.8; 42.3] 7 (63.6)	2.42 [0.96; 6.11]; 0.054
				Interaction:	p = 0.001

a: Cox model.
b: Log-rank test. Interaction p-value from Cox model, which includes interaction term between treatment and subgroup characteristic.
c: One patient with wild-type mutation was included in the Del19 subgroup until the third data cut-off. For the third data cut-off, this patient was allocated to the subgroup of patients with other mutations. Result of the sensitivity analysis on the subgroup of patients with other mutations without patient with wild-type mutation (N = 26): HR [95% CI] = 2.35 [0.93; 5.96]; p = 0.065.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 19: Subgroups (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome Characteristic Subgroup	Afatinib N	Afatinib Median in months [95% CI] Patients with event n (%)	Cisplatin + pemetrexed N	Cisplatin + pemetrexed Median in months [95% CI] Patients with event n (%)	Afatinib vs. cisplatin + pemetrexed HR [95% CI][a]; p-value[b]
LUX-Lung 3					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms[c, d]					
Dyspnoea					
EGFR mutation					
L858R or Del19[e]					0.38 [0.26; 0.55]; 0.001[f]
L858R	91	22.2 [13.7; NC] 34 (37.4)	47	3.6 [2.2; 10.5] 24 (51.1)	0.39 [0.23; 0.67]; p < 0.001
Del19	112	37.4 [17.7; NC] 39 (34.8)	57	5.4 [2.4; NC] 28 (49.1)	0.37 [0.22; 0.63]; 0.001
Other	27	5.6 [2.2; 10.4] 15 (55.6)	11	NC [2.8; NC] 3 (27.3)	2.98 [0.86; 10.33]; 0.070
				Interaction:	p = 0.009[g]
Pain					
Age					
< 65 years	140	6.2 [4.7; 11.1] 84 (60.0)	71	2.9 [1.5; 3.8] 46 (64.8)	0.54 [0.37; 0.78]; < 0.001
≥ 65 years	90	1.5 [1.4; 2.2] 63 (70.0)	44	3.6 [2.4; 6.4] 26 (59.1)	1.46 [0.92; 2.31]; 0.099
				Interaction:	p = 0.003
Appetite loss					
EGFR mutation					
L858R or Del19[e]					0.71 [0.52; 0.98]; 0.035[f]
L858R	91	8.9 [3.1; 14.2] 54 (59.3)	47	2.1 [1.5; 4.4] 28 (59.6)	0.61 [0.38; 0.98]; 0.035
Del19	112	4.9 [1.5; 13.9] 66 (58.9)	57	2.8 [1.7; 4.2] 35 (61.4)	0.81 [0.53; 1.23]; 0.304
Other	27	1.5 [0.8; 3.0] 20 (74.1)	11	3.8 [0.8; NC] 6 (54.5)	2.31 [0.92; 5.79]; 0.062
				Interaction:	p = 0.048[g]

(continued)

Table 19: Subgroups (morbidity: time to worsening of symptoms) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1 (continued)

Study Outcome Characteristic Subgroup	Afatinib N	Afatinib Median in months [95% CI] Patients with event n (%)	Cisplatin + pemetrexed N	Cisplatin + pemetrexed Median in months [95% CI] Patients with event n (%)	Afatinib vs. cisplatin + pemetrexed HR [95% CI][a]; p-value[b]
Constipation					
Ethnicity					
Non-Asian	64	NC [9.4; NC] 23 (35.9)	32	2.8 [1.6; 13.0] 16 (50.0)	0.37 [0.19; 0.72]; 0.003
Asian	166	12.4 [9.0; 20.1] 85 (51.2)	83	NC [3.8; NC] 32 (38.6)	0.90 [0.60; 1.37]; 0.628
				Interaction:	p = 0.019
EORTC QLQ-LC13 symptom scales – time to worsening of symptoms[c, d]					
Dyspnoea					
EGFR mutation					
L858R or Del19[e]					0.54 [0.39; 0.76]; 0.001[f]
L858R	91	14.5 [6.3; 20.1] 45 (49.5)	47	2.7 [1.5; 5.5] 28 (59.6)	0.48 [0.30; 0.78]; 0.002
Del19	112	15.8 [5.6; NC] 54 (48.2)	57	3.4 [1.6; 8.3] 33 (57.9)	0.61 [0.39; 0.95]; 0.025
Other	27	1.5 [1.2; 5.5] 22 (81.5)	11	4.4 [1.6; NC] 6 (54.5)	2.47 [1.00; 6.12] 0.041
				Interaction:	p = 0.007[g]

a: Cox model.
b: Log-rank test. Interaction p-value from Cox model, which includes interaction term between treatment and subgroup characteristic.
c: Data of the third data cut-off on 14 November 2013.
d: Time to worsening of the score by at least 10 points versus the baseline value.
e: Since there was no important heterogeneity for the subgroups Del19 and L858R, these categories were combined. See text for results from the interaction tests.
f: From meta-analysis, Institute's calculation.
g: Interaction p-value for the categories of the EGFR mutation status: L858R vs. Del19 vs. other.

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; 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-specific symptoms); RCT: randomized controlled trial; vs.: versus

Table 20: Subgroups (time to worsening of health-related quality of life) – RCT, direct comparison: afatinib vs. cisplatin + pemetrexed; ECOG PS 0-1

Study Outcome	Afatinib		Cisplatin + pemetrexed		Afatinib vs. cisplatin + pemetrexed
Characteristic Subgroup	N	Median in months [95% CI] Patients with event n (%)	N	Median in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
LUX-Lung 3					
EORTC QLQ-C30 functional scales – time to worsening of health-related quality of life[c, d]					
Global health status					
Age					
< 65 years	140	4.9 [3.4; 12.5] 81 (57.9)	71	3.8 [2.1; 6.6] 42 (59.2)	0.71 [0.48; 1.04]; 0.071
≥ 65 years	90	2.1 [1.5; 4.1] 63 (70.0)	44	3.6 [2.8; NC] 23 (52.3)	1.64 [1.02; 2.66]; 0.038
				Interaction:	p = 0.008

a: Cox model.
b: Log-rank test. Interaction p-value from Cox model, which includes interaction term between treatment and subgroup characteristic.
c: Data of the third data cut-off on 14 November 2013.
d: 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; 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); RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

There was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome "overall survival" (Table 18) at all 3 data cut-offs.

A statistically significant effect in favour of afatinib in comparison with cisplatin + pemetrexed was shown in the second and third data cut-off for patients with Del19 EGFR mutation. Hence for patients with Del19 EGFR mutation, there was an indication of an added benefit of afatinib in comparison with the ACT for the outcome "overall survival" in the overall consideration of the second and third data cut-off.

There was no statistically significant difference between the treatment groups for patients with L858R EGFR mutation. As a result, there was no hint of an added benefit for patients with L858R EGFR mutation; an added benefit is therefore not proven for these patients.

A statistically significant effect to the disadvantage of afatinib was shown in the second data cut-off for patients with other EGFR mutations. There was no statistically significant

difference between the treatment groups in the third data cut-off. Due to the higher uncertainty of data of the outcome "overall survival" at the third data cut-off, these were unsuitable to completely outweigh the results of the second data cut-off, which was more certain. Hence in the overall conclusion of the second and third data cut-off, there is therefore a hint of lesser benefit of afatinib for the outcome "overall survival" for these patients.

This partly deviates from the company's assessment. The company also derived no added benefit for the outcome "overall survival" for patients with L858R EGFR mutation. In contrast, the company saw proof of a major added benefit for patients with Del19 EGFR mutation, and no proof of added benefit for patients with other EGFR mutations.

Morbidity

Symptoms (time to worsening)

Table 19 shows the results for the outcome category "morbidity (time to worsening of symptoms)" for which there was proof of an effect modification. Due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit could be derived for all outcomes in this category.

Dyspnoea

For the time to worsening, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome "dyspnoea". Since there was no important heterogeneity for the subgroups Del19 and L858R (interaction test p = 0.903 [EORTC QLQ-C30]; p = 0.489 [EORTC QLQ-LC13]), these categories were combined. There was a statistically significant difference in favour of afatinib for patients with Del19 or L858R EGFR mutation. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT. There was no statistically significant difference between the treatment groups for patients with other EGFR mutations. This resulted in no hint of an added benefit; an added benefit for this outcome is therefore not proven for these patients.

This deviates from the company's assessment, which derived proof of an added benefit for this outcome for the total population.

Pain

For the time to worsening, there was proof of an effect modification by the characteristic "age" for the outcome "pain". There was a statistically significant difference in favour of afatinib for patients in the age group < 65 years. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT. There was no statistically significant difference between the treatment groups for patients ≥ 65 years. This resulted in no hint of an added benefit; an added benefit for this outcome is therefore not proven for these patients.

This deviates from the company's assessment, which derived an indication of an added benefit for the outcome "pain" for the total population.

Appetite loss

For the time to worsening, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome "appetite loss". Since there was no important heterogeneity for the subgroups Del19 and L858R (interaction test $p = 0.380$), these categories were combined. There was a statistically significant difference in favour of afatinib for patients with Del19 or L858R EGFR mutation. The extent in this non-serious/non-severe outcome was no more than marginal. There was no statistically significant difference between the treatment groups for patients with other EGFR mutations. This resulted in no hint of an added benefit for both subgroups; an added benefit for this outcome is therefore not proven for these patients.

This deviates from the company's assessment, which derived an indication of an added benefit for this outcome for the total population.

Constipation

For the time to worsening, there was proof of an effect modification by the characteristic "ethnicity" for the outcome "constipation". There was a statistically significant difference in favour of afatinib for non-Asian patients. As a result, there was a hint of an added benefit of afatinib in comparison with the ACT. There was no statistically significant difference between the treatment groups for Asian patients. This resulted in no hint of an added benefit; an added benefit for this outcome is therefore not proven for these patients.

This deviates from the company's assessment, which derived an indication of an added benefit for this outcome for the total population.

Health-related quality of life (time to worsening)

Global health status

For the time to worsening, there was proof of an effect modification by the characteristic "age" for the outcome "global health status". There was a statistically significant difference to the disadvantage of afatinib for patients in the age group ≥ 65 years. As a result, there was a hint of lesser benefit of afatinib in comparison with the ACT. There was no statistically significant difference between the treatment groups for patients < 65 years. This resulted in no hint of an added benefit; an added benefit for this outcome is therefore not proven for these patients.

Moreover, there was proof of an effect modification by the characteristic "EGFR mutation status" for the outcome "global health status". Since there was no important heterogeneity for the subgroups L858R and Del19, as well as for the subgroups L858R and other (interaction test $p = 0.292$ and $p = 0.121$), it was not necessary to present the results of the outcome "global health status" separately for EGFR mutation status.

The present assessment deviates from the company's assessment, which derived an indication of an added benefit of afatinib for the total population for this outcome. However, this was

based on the results of the LUX-Lung 6 study, which was not relevant for the present benefit assessment.

General comment on the company's assessment

The assessments mentioned above deviate from those of the company insofar as the company only used subgroups for the outcomes on morbidity if proof of effect modification was observed in the LUX-Lung 3 study and in the LUX-Lung 6 study. The company only presented descriptive presentation of all other subgroups for which indications or proof of an effect modification were available. This approach was not relevant for the present benefit assessment however because the LUX-Lung 6 study was not used for the benefit assessment.

2.4.2 Research question 2: patients pretreated with platinum-based chemotherapy

There were no evaluable data for the research question of afatinib versus erlotinib or gefitinib in patients pretreated with platinum-based chemotherapy. Hence an added benefit of afatinib versus the ACT is not proven.

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 1: treatment-naive patients

2.5.1.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in proof of effect modifications for treatment-naive patients with ECOG PS 0 or 1 for the characteristics "EGFR mutation status", "age" and "ethnicity". Indications and hints of an added benefit of afatinib in comparison with cisplatin + pemetrexed were shown (partly only in subgroups) for the following outcomes: overall survival, dyspnoea, pain, nausea and vomiting, constipation, cough, alopecia, and physical functioning. Hints of lesser benefit were shown (partly only in subgroups) for diarrhoea, sore mouth, dysphagia, and global health status. The extent of the respective added benefit at outcome level was estimated from these results (see Table 21).

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (treatment-naive patients with ECOG PS 0-1)

Outcome category **Outcome** **Subgroup**	**Afatinib vs. cisplatin + pemetrexed** **Proportion of events/median times to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Del19	*Second data cut-off* median survival [months]: 31.6 vs. 21.1 HR: 0.55 [0.36; 0.848]; p = 0.006	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
	Third data cut-off median survival [months]: 33.3 vs. 21.1 HR: 0.54 [0.36; 0.79]; p = 0.002	
	Summarizing assessment of the second and third data cut-off[c]*:* probability: "indication"	
L858R	*Second data cut-off* median survival [months]: 27.2 vs. NC HR: 1.30 [0.76; 2.23]; p = 0.332	Lesser benefit/added benefit not proven
	Third data cut-off median survival [months]: 27.6 vs. 40.3 HR: 1.30 [0.80; 2.11]; p = 0.292	
Other	*Second data cut-off* median survival [months]: 15.9 vs. NC HR: 3.08 [1.04; 9.15]; p = 0.034 HR: 0.32 [0.11; 0.96][d]	Outcome category: mortality $CI_u < 1.00$ lesser benefit, extent: "minor"
	Third data cut-off median survival [months]: 15.4 vs. 40.8 HR: 2.42 [0.96; 6.11]; p = 0.054	
	Summarizing assessment of the second and third data cut-off[c]*:* probability: "hint"	

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (treatment-naive patients with ECOG PS 0-1) (continued)

Outcome category **Outcome** **Subgroup**	**Afatinib vs. cisplatin + pemetrexed** **Proportion of events/median times to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
EORTC QLQ-C30 and QLQ-LC13: time to worsening of symptoms		
Dyspnoea		
Del19 and L858R	*QLQ-C30*: Del19: 37.4 vs. 5.4 months L858R: 22.2 vs. 3.6 months HR: 0.38 [0.26; 0.55][e]; p < 0.001 *QLQ-LC13*: Del19: 15.8 vs. 3.4 months L858R: 14.5 vs. 2.7 months HR: 0.54 [0.39; 0.76][e]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ added benefit, extent: "considerable"
Other	*QLQ-C30*: 5.6 months vs. NC HR: 2.98 [0.86; 10.33]; p = 0.070 *QLQ-LC13*: 1.5 vs. 4.4 months HR: 2.47 [1.00; 6.12]; p = 0.041 HR: 0.40 [0.16; 1.00][d] probability: "hint"	*QLQ-C30*: lesser benefit/added benefit not proven QLQ-LC13: outcome category: non-serious/non-severe symptoms $0.90 < CI_u$ lesser benefit/added benefit not proven[f]
Fatigue	3.0 vs. 1.7 months HR: 0.69 [0.52; 0.91]; p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u$ lesser benefit/added benefit not proven[f]
Insomnia	10.4 vs. 20.5 months HR: 0.98 [0.69; 1.39]; p = 0.886	Lesser benefit/added benefit not proven
Pain		
< 65 years	6.2 vs. 2.9 months HR: 0.54 [0.37; 0.78]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ added benefit, extent: "considerable"
≥ 65 years	1.5 vs. 3.6 months HR: 1.46 [0.92; 2.31]; p = 0.099	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (treatment-naive patients with ECOG PS 0-1) (continued)

Outcome category **Outcome** **Subgroup**	**Afatinib vs. cisplatin + pemetrexed** **Proportion of events/median times to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Appetite loss		
Del19 and L858R	Del19: 4.9 vs. 2.8 months L858R: 8.9 vs. 2.1 months HR: 0.71 [0.52; 0.98][e]; p = 0.035 probability: "hint"	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u$ lesser benefit/added benefit not proven[f]
Other	1.5 vs. 3.8 months HR: 2.31 [0.92; 5.79]; p = 0.062	Lesser benefit/added benefit not proven
Diarrhoea	0.8 vs. 13.7 months HR: 7.80 [5.18; 11.75]; p < 0.001 HR: 0.13 [0.09; 0.19][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: "considerable"
Nausea and vomiting	7.4 vs. 2.1 months HR: 0.55 [0.40; 0.74]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ added benefit, extent: "considerable"
Constipation		
Non-Asian	NC vs. 2.8 months HR: 0.37 [0.19; 0.72]; p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ added benefit, extent: "considerable"
Asian	12.4 months vs. NC HR: 0.90 [0.60; 1.37]; p = 0.628	Lesser benefit/added benefit not proven
Haemoptysis	NC vs. NC HR: 1.75 [0.89; 3.45]; p = 0.100	Lesser benefit/added benefit not proven
Cough	27.0 vs. 8.0 months HR: 0.59 [0.40; 0.87]; p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.90$ added benefit, extent: "minor"
Pain (arm/shoulder)	12.1 vs. 28.2 months HR: 0.92 [0.64; 1.31]; p = 0.627	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (treatment-naive patients with ECOG PS 0-1) (continued)

Outcome category **Outcome** **Subgroup**	**Afatinib vs. cisplatin + pemetrexed** **Proportion of events/median times to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Pain (chest)	42.2 vs. 8.3 months HR: 0.64 [0.44; 0.93]; p = 0.018 probability: "hint"	Outcome category: non-serious/non-severe symptoms $0.90 < CI_u$ lesser benefit/added benefit not proven[f]
Pain (other parts)	4.9 vs. 6.2 months HR: 1.08 [0.78; 1.51]; p = 0.636	Lesser benefit/added benefit not proven
Alopecia	3.5 vs. 1.7 months HR: 0.61 [0.46; 0.802]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.90$ added benefit, extent: "minor"
Sore mouth	0.8 vs. 2.9 months HR: 2.55 [1.90; 3.41]; p < 0.001 HR: 0.39 [0.29; 0.53][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: "considerable"
Peripheral neuropathy	2.9 vs. 5.1 months HR: 1.24 [0.92; 1.66]; p = 0.160	Lesser benefit/added benefit not proven
Dysphagia	2.8 vs. 10.4 months HR: 1.84 [1.30; 2.59]; p < 0.001 HR: 0.54 [0.39; 0.77][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms $CI_u < 0.80$ lesser benefit, extent: "considerable"
EORTC QLQ-C30 functional scales, time to worsening		
Global health status		
< 65 years	4.9 vs. 3.8 months HR: 0.71 [0.48; 1.04]; p = 0.071	Lesser benefit/added benefit not proven
≥ 65 years	2.1 vs. 3.6 months HR: 1.64 [1.02; 2.66]; p = 0.038 HR: 0.61 [0.38; 0.98][d] probability: "hint"	Outcome category: health-related quality of life $CI_u < 1.00$ lesser benefit, extent: "minor"
Emotional functioning	12.1 vs. 8.5 months HR: 0.91 [0.64; 1.30]; p = 0.612	Lesser benefit/added benefit not proven
Cognitive functioning	4.9 vs. 3.1 months HR: 0.77 [0.57; 1.03]; p = 0.078	Lesser benefit/added benefit not proven

(continued)

Table 21: Extent of added benefit at outcome level: afatinib vs. cisplatin + pemetrexed (treatment-naive patients with ECOG PS 0-1) (continued)

Outcome category **Outcome** **Subgroup**	**Afatinib vs. cisplatin + pemetrexed** **Proportion of events/median times to event** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Physical functioning	5.6 vs. 2.8 months HR: 0.73 [0.54; 0.98]; p = 0.031 probability: "hint"	Outcome category: health-related quality of life $CI_u < 1.00$ added benefit, extent: "minor"
Role functioning	2.9 vs. 2.4 months HR: 0.92 [0.69; 1.23]; p = 0.585	Lesser benefit/added benefit not proven
Social functioning	4.8 vs. 3.5 months HR: 0.98 [0.72; 1.33]; p = 0.891	Lesser benefit/added benefit not proven
Adverse events		
SAEs	31.0% vs. 22.5%	Greater/lesser harm not proven[g]
Treatment discontinuations due to AEs	16.2% vs. 15.3%	Greater/lesser harm not proven[g]
Severe AEs (CTCAE grade ≥ 3)	62.4% vs. 56.8%	Greater/lesser harm not proven[g]

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: For the outcome "overall survival", the derivation of extent was conducted under consideration of the results of the second (21 January 2013) and the third data cut-off (14 November 2013).
d: Proportion of events afatinib vs. chemotherapy (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
e: Hazard ratio pooled for the subgroups Del19 and L858R.
f: Lesser benefit or added benefit is not proven because the effect size was only marginal.
g: Qualitative interpretation on the basis of the naive proportions of the patients with AEs.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; 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; HR: hazard ratio; NC: not calculable; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.5.1.2 Overall conclusion on added benefit

The results showed a relevant effect modification by EGFR mutation status for the outcome "overall survival". Hereinafter, the overall conclusion on the added benefit for treatment-naive patients with ECOG PS 0 or 1 is therefore presented separately for the 3 different mutation statuses. The respective effect modifications due to age or ethnicity, these were integrated in the tables. The tables present all outcomes included in the overall conclusion on the extent of added benefit of afatinib.

EGFR mutation Del19

Table 22 shows the positive and negative effects of 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); treatment-naive patients with ECOG PS 0-1

Positive effects	**Negative effects**
Mortality: ▪ overall survival; indication, extent: "major"	
Non-serious/non-severe symptoms (in each case "hint"): ▪ dyspnoea; extent: "considerable" ▪ nausea and vomiting; extent: "considerable" ▪ alopecia; extent: "minor" ▪ cough; extent: "minor" ▪ pain ▫ < 65 years; extent: "considerable" ▪ constipation ▫ non-Asian; extent: "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea; extent: "considerable" ▪ sore mouth; extent: "considerable" ▪ dysphagia; extent: "considerable"
Health-related quality of life (in each case "hint"): ▪ physical functioning; extent: "minor"	Health-related quality of life (in each case "hint"): ▪ global health status ▫ ≥ 65 years; extent: "minor"
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor	

There is an indication of a major added benefit for the outcome "overall survival" for patients with Del19 EGFR mutation. Regarding symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib for this subgroup with a higher number of positive effects. Extent and probability of the effects were smaller for all outcomes in these 2 categories than for the outcome "overall survival". Only some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Hence 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 EGFR mutation.

EGFR mutation L858R

Table 23 shows the positive and negative effects of 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); treatment-naive patients with ECOG PS 0-1

Positive effects	**Negative effects**
Non-serious/non-severe symptoms (in each case "hint"): ▪ dyspnoea; extent: "considerable" ▪ nausea and vomiting; extent: "considerable" ▪ alopecia; extent: "minor" ▪ cough; extent: "minor" ▪ pain ▫ < 65 years; extent: "considerable" ▪ constipation ▫ non-Asian; extent: "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea; extent: "considerable" ▪ sore mouth; extent: "considerable" ▪ dysphagia; extent: "considerable"
Health-related quality of life (in each case "hint"): ▪ physical functioning; extent: "minor"	Health-related quality of life (in each case "hint"): ▪ global health status ▫ ≥ 65 years; extent: "minor"
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor	

In the subgroup of patients with L858R EGFR mutation, neither added benefit nor lesser benefit was proven for the outcome "overall survival". Regarding symptoms and health-related quality of life, there were hints of positive and negative effects of afatinib for this subgroup with a higher number of positive effects. Only some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Overall, there is therefore a hint of a minor added benefit for patients with L858R EGFR mutation.

Other EGFR mutations

Table 24 shows the positive and negative effects of 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); treatment-naive patients with ECOG PS 0-1

Positive effects	**Negative effects**
	Mortality: ▪ overall survival; hint, extent: "minor"
Non-serious/non-severe symptoms (in each case "hint"): ▪ nausea and vomiting; extent: "considerable" ▪ alopecia; extent: "minor" ▪ cough; extent: "minor" ▪ pain ▫ < 65 years; extent: "considerable" ▪ constipation ▫ non-Asian; extent: "considerable"	Non-serious/non-severe symptoms (in each case "hint"): ▪ diarrhoea; extent: "considerable" ▪ sore mouth; extent: "considerable" ▪ dysphagia; extent: "considerable"
Health-related quality of life (in each case "hint"): ▪ physical functioning; extent: "minor"	Health-related quality of life (in each case "hint"): ▪ global health status ▫ ≥ 65 years; extent: "minor"
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor	

For patients with other EGFR mutations than Del19 or L858R, there was a hint of lesser benefit of afatinib for the outcome "overall survival". Regarding morbidity and health-related quality of life, there were hints of positive and negative effects of afatinib with a higher number of positive effects. However, this is insufficient to completely outweigh the negative effects, particularly regarding overall survival. Some of the effects depended on age and ethnicity, but did not lead to a different assessment of the added benefit for the subgroups considered. Overall, there is a hint of lesser benefit of afatinib versus the ACT for the subgroup of patients with other EGFR mutations than Del19 or L858R.

2.5.2 Research question 2: patients pretreated with platinum-based chemotherapy

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

2.5.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of afatinib in comparison with the ACT is summarized in Table 25.

Table 25: Afatinib – extent and probability of added benefit

Line of treatment	**Patient group**	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Treatment-naive patients	ECOG PS 0-1	Gefitinib or erlotinib or **cisplatin +** (vinorelbine, **gemcitabine**, docetaxel, paclitaxel or **pemetrexed**) or carboplatin + (vinorelbine, gemcitabine, docetaxel, paclitaxel or pemetrexed)	EGFR mutation Del19	Indication of a major added benefit
			EGFR mutation L858R	Hint of a minor added benefit
			Other[b] EGFR mutations	Hint of lesser benefit
	ECOG PS 2	**Gefitinib** or **erlotinib** or as an alternative to the combination therapies shown for ECOG PS 0-1: monotherapy with gemcitabine or vinorelbine	Added benefit not proven	
Patients after pretreatment with platinum-based chemotherapy		**Gefitinib** or **erlotinib** or docetaxel or pemetrexed	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 a comparator therapy from several options, the respective choice of the company is printed in bold. The company used the comparator therapy cisplatin + gemcitabine for comparison.
b: Not only L858R EGFR mutation, not only Del19 EGFR mutation.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

In summary, there is an indication of major added benefit of afatinib in comparison with the ACT cisplatin + pemetrexed for EGFR-TKI-naive adult patients with locally advanced and/or metastatic NSCLC with ECOG PS 0 or 1 and activating Del19 EGFR mutations. For patients with L858R EGFR mutation, there is a hint of a minor added benefit of afatinib. In contrast, there is a hint of lesser benefit in patients with other EGFR mutations.

An added benefit of afatinib is not proven for treatment-naive patients with ECOG PS 2 as well as for patients pretreated with platinum-based chemotherapy.

This deviates from the company's approach, which derived proof of considerable added benefit for treatment-naive patients with ECOG PS 0 or 1, and a hint of a non-quantifiable added benefit for treatment-naive patients with ECOG PS 2 and for patients pretreated with chemotherapy.

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

2.6 List of included studies

Boehringer Ingelheim. 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: 15 July 2015]. URL: http://ClinicalTrials.gov/show/NCT00949650.

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Boehringer Ingelheim Pharma. 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 (analysis of overall survival) [unpublished]. 2014.

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Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16(2): 141-151.

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Please see full dossier assessment for full reference list.

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