IQWiG Reports – Commission No. A20-13

Ramucirumab (NSCLC, combination with erlotinib) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ramucirumab (NSCLC, Kombination mit Erlotinib) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] 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
ASBI	Average Symptom Burden Index
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EQ-5D	European Quality of Life Questionnaire – 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)
LCSS	Lung Cancer Symptom Score
N	number of randomized patients
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	Visual Analogue Scale

2 Benefit assessment

2.1 Extract of dossier 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 ramucirumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 February 2020.

Research question

The aim of this report is to assess the added benefit of ramucirumab in combination with erlotinib (hereinafter referred to as "ramucirumab + erlotinib") in comparison with the appropriate comparator therapy (ACT) in previously untreated adult patients with metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of ramucirumab

Research question	**Therapeutic indication**	**ACT[a]**
1	First-line treatment of adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R	Afatinib or gefitinib or **erlotinib** or osimertinib
2	First-line treatment of adult patients with metastatic NSCLC with activating EGFR mutations other than del 19 or L858R	Individualized therapy depending on the activating EGFR mutation, given the following options: ▪ Afatinib, gefitinib, erlotinib, osimertinib ▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) (see Pharmaceutical Guideline, Section K, Annex VI) ▪ Carboplatin in combination with nab paclitaxel and ▪ Gemcitabine or vinorelbine monotherapy (only in patients with ECOG Performance Status 2, as an alternative to platinum-based combination therapy)

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.

ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients with the EGFR mutation del 19 or L858R
- Research question 2: Patients with EGFR mutations other than del 19 or L858R

The company followed the G-BA's specification of the ACT and chose erlotinib from the above options for research question 1. For research question 2, the company used the ACT of individualized therapy.

The assessment was conducted using patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of any added benefit. This concurs with the company's inclusion criteria.

Research question 1: Patients with the EGFR mutation del 19 or L858R

Study pool and study characteristics

The study pool for research question 1 consists of the RELAY study. The RELAY study is a double-blind, randomized, multicentre study comparing ramucirumab + erlotinib with placebo + erlotinib.

The study included previously untreated adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R. Patients with recurrent metastatic disease were eligible for study inclusion, provided that adjuvant or neoadjuvant therapy had been completed ≥ 12 months before metastasis.

Worldwide, a total of 449 patients were allocated in a 1:1 ratio to treatment with ramucirumab + erlotinib (N = 224) or placebo + erlotinib (N = 225). The study treatment corresponds to the specifications of the Summaries of Product Characteristics (SPCs) for ramucirumab and erlotinib, respectively.

Patient treatment continued until disease progression, unacceptable toxicity, withdrawal of consent to study participation, or discontinuation of therapy upon the physician's discretion.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were outcomes from the categories of mortality, morbidity (symptoms, health status), and adverse events (AEs).

Risk of bias

The risk of bias across outcomes was rated as low for the RELAY study. The risk of bias for the outcomes of overall survival and discontinuation due to AEs was likewise rated as low. For the results on the outcomes from the morbidity and AE categories, the risk of bias was assessed as high.

Results

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

Morbidity

Symptoms (recorded with the Average Symptom Burden Index [ASBI] of the Lung Cancer Symptom Score [LCSS])

For the outcome of symptoms, recorded with the LCSS ASBI, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

Health status (recorded with the Visual Analogue Scale [VAS]) of the European Quality of Life Questionnaire – 5 Dimensions ([EQ-5D])

For the outcome of health status, recorded with EQ-5D VAS, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

AEs

Serious Adverse Events (SAEs), discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, no statistically significant difference between treatment arms was found. Neither of the two outcomes of SAEs and discontinuation due to AEs resulted in a hint of greater or lesser harm of ramucirumab + erlotinib in comparison with erlotinib. Greater or lesser harm is therefore not proven.

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

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference between treatment arms was found to the disadvantage of ramucirumab + erlotinib. For this outcome, this results in a hint of greater harm of ramucirumab + erlotinib in comparison with erlotinib.

Specific AEs: Peripheral oedema, diarrhoea, hypertension, infections and infestations

For the outcomes of peripheral oedema, diarrhoea, hypertension, as well as infections and infestations, a statistically significant difference between each treatment arm was found to the disadvantage of ramucirumab + erlotinib. For each of the outcomes of peripheral oedema, diarrhoea, hypertension, as well as infections and infestations, there is a hint of greater harm of ramucirumab + erlotinib in comparison with erlotinib.

Research question 2: Patients with EGFR mutations other than del 19 or L858R

No data are available for assessing the added benefit of ramucirumab + erlotinib in comparison with the ACT of individualized therapy in previously untreated adult patients with metastatic

NSCLC with activating EGFR mutations other than del 19 or L858R. Consequently, there is no hint of added benefit of ramucirumab + erlotinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, the probability and extent of added benefit of the drug ramucirumab in comparison with the ACT are assessed as follows:

For research question 1, the RELAY study revealed exclusively negative effects in the AE outcome category. For serious/severe AEs, there are multiple hints of greater harm, the majority of considerable extent. A hint of greater harm of considerable extent was additionally found for non-serious/non-severe AEs.

In summary, for previously untreated adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R, there is a hint of lesser benefit of ramucirumab + erlotinib in comparison with the ACT of erlotinib.

No data are available for research question 2. There is no proof of an added benefit of ramucirumab + erlotinib in comparison with the ACT in previously untreated adult patients with metastatic NSCLC with EGFR mutations other than del 19 or L858R.

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

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

Table 3: Ramucirumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R[b]	Afatinib or gefitinib or **erlotinib** or osimertinib	Hint of lesser benefit
First-line treatment of adult patients with metastatic NSCLC with activating EGFR mutations other than del 19 or L858R	Individualized therapy depending on the activating EGFR mutation, given the following options: ▪ Afatinib, gefitinib, erlotinib, osimertinib ▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) (see Pharmaceutical Guideline, Section K, Annex VI) ▪ Carboplatin in combination with nab paclitaxel and ▪ Gemcitabine or vinorelbine monotherapy (only in patients with ECOG Performance Status 2, as an alternative to platinum-based combination therapy)	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the RELAY study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer

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

2.2 Research question

The aim of this report is to assess the added benefit of ramucirumab in combination with erlotinib (hereinafter referred to as "ramucirumab + erlotinib") in comparison with the ACT in previously untreated patients with metastatic NSCLC with activating EGFR mutations.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ramucirumab

Research question	Therapeutic indication	ACT[a]
1	First-line treatment of adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R	Afatinib or gefitinib or **erlotinib** or osimertinib
2	First-line treatment of adult patients with metastatic NSCLC with activating EGFR mutations other than del 19 or L858R	Individualized therapy depending on the activating EGFR mutation, given the following options: ▪ Afatinib, gefitinib, erlotinib, osimertinib ▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabin or docetaxel or paclitaxel or pemetrexed) (see Pharmaceutical Guideline, Section K, Annex VI [3]) ▪ Carboplatin in combination with nab paclitaxel and ▪ Gemcitabine or vinorelbine monotherapy (only in patients with ECOG Performance Status 2, as an alternative to platinum-based combination therapy)

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.

ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer

Research questions 1 and 2 of the present benefit assessment correspond to subpopulation A and subpopulation B in the company's dossier. To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients with the EGFR mutation del 19 or L858R
- Research question 2: Patients with EGFR mutations other than del 19 or L858R

The company followed the G-BA's specification of the ACT and chose erlotinib from the above options for research question 1. For research question 2, the company used the ACT of individualized therapy.

The assessment was conducted using patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of any added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: Patients with the EGFR mutation del 19 or L858R

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on ramucirumab + erlotinib (status: 17 January 2020)
- Bibliographic literature search on ramucirumab + erlotinib (most recent search on 10 January 2020)
- Search in trial registries for studies on ramucirumab + erlotinib (most recent search on 19 December 2019)

To check the completeness of the study pool:

- Search in trial registries for studies on ramucirumab + erlotinib (most recent search on 02 March 2020)

The check did not identify any additional relevant studies.

2.3.1.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: Ramucirumab + erlotinib versus placebo + erlotinib

Study	Study category			Available sources		
	Approval study for the drug to be assessed (Yes/No)	Sponsored study[a] (Yes/No)	Third-party study (Yes/No)	Clinical study report (Yes/No [reference])	Registry entries[b] (Yes/No [reference])	Publication (Yes/No [reference])
I4T-MC-JVCY (RELAY[c])	Yes	Yes	No	Yes [4]	Yes [5-9]	Yes [10-12]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this short name.

RCT: randomized controlled trial

The study pool for the present benefit assessment of ramucirumab + erlotinib in comparison with the ACT consists of the RELAY study, coinciding with the study pool of the company.

2.3.1.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
RELAY	RCT, double-blind, parallel-group	Previously untreated adult patients with metastatic NSCLC[b] with activating EGFR mutation L858R or del 19 and an ECOG-PS of 0 or 1	Ramucirumab + erlotinib (N = 224) Placebo + erlotinib (N = 225)	Screening: 21 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent to study participation, or discontinuation of therapy upon the physician's discretion. Follow-up[c]: outcome-specific, at most until death or end of the study	100 centres in: Canada, France, Germany, Hong Kong, Italy, Japan, Romania, South Korea, Spain, Taiwan, Turkey, United Kingdom, USA 01/2016–ongoing Data cut-off dates: 23/01/2019[d] 25/09/2019[e]	Primary: PFS Secondary: Overall survival, symptoms, health status, AEs

a. Data on primary outcomes were included irrespective of their relevance for this benefit assessment. Data on secondary outcomes were included only concerning available outcomes relevant for this benefit assessment.
b. Cytologically or histologically confirmed.
c. Outcome-specific information is provided in Table 8.
d. Prespecified data cut-off after 280 events for the outcome of PFS (the planned number of 270 events was exceeded).
e. As requested by the EMA, interim analysis for the outcome of PFS and estimated time of the final analysis of overall survival.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; N: number of randomized patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characterization of the interventions – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study	Intervention	Comparison
RELAY	Ramucirumab, 10 mg/kg, i.v. as a 60-minute infusion every 2 weeks + Erlotinib 150 mg once daily p.o.[a]	Placebo, i.v. as a 60-minute infusion every 2 weeks + Erlotinib 150 mg once daily p.o.[a]
	Dose modifications <u>Ramucirumab/placebo</u> ▪ Dose reductions due to AEs were allowed: ▫ Dose reduction after the 2-week treatment cycle - From 10 mg/kg to 8 mg/kg - From 8 mg/kg to 6 mg/kg - From 6 mg/kg to 5 mg/kg ▪ Dose delays were allowed <u>Erlotinib</u> ▪ Dose reductions due to AEs were allowed: ▫ From 150 mg to 100 mg ▫ From 100 mg to 50 mg	
	Premedication ▪ Histamine-H_1 antagonists 30 to 60 minutes before infusion ▪ Further premedication upon the investigator's discretion	
	Permitted pretreatment ▪ Radiotherapy for the local alleviation or prevention of symptoms, provided it had been completed ≥ 7 days before study inclusion ▪ Thoracic radiotherapy, provided it had been completed ≥ 28 days before study inclusion ▪ In patients with recurrent metastatic disease, any adjuvant or neoadjuvant therapy had to have been completed ≥ 12 months before metastasis. Prior adjuvant or neoadjuvant therapy was not required, however. **Non-permitted pretreatment** ▪ Major surgery ≤ 28 days before study inclusion ▪ Long-term treatment with NSAIDs or platelet aggregation inhibitors ≤ 7 days before the first dose of the study drug[b] ▪ Treatment with a non-approved intervention within a clinical study ≤ 30 days before study inclusion ▪ Systemic therapy for NSCLC stages IIIB/IV ▪ CYP3A4 inducers or strong CYP3A4 inhibitors **Permitted concomitant treatment** ▪ Palliative and supportive therapy (e.g. including: antidiarrhoeal drugs, antiemetic drugs, analgesic drugs, appetite stimulants, G-CSF, erythropoiesis-stimulating factors, bisphosphonates) **Non-permitted concomitant treatment** ▪ Chemotherapy, experimental drug therapies, immunotherapies, hormonal cancer therapies, radiation, cancer-related surgeries, or other cancer therapies ▪ CYP3A4 inducers or strong CYP3A4 inhibitors, anticoagulants, H_2-receptor antagonists, antacids, proton pump inhibitors	

a. During the first 2 cycles, on the ramucirumab or placebo infusion days, erlotinib administration was allowed only after a 1-hour observation phase and only if no infusion-related reactions occurred.
b. Aspirin up to a dose of 325 mg/day was allowed.

AE: adverse event; CYP3A4: cytochrome P_{450} 3A4; G-CSF: granulocyte colony-stimulating factor; i.v.: intravenous; NSAID: nonsteroidal antiinflammatory drug; NSCLC; non-small cell lung cancer; p.o.: peroral; RCT: randomized controlled trial

Study design

The RELAY study is a double-blind, randomized, multicentre study comparing ramucirumab + erlotinib with placebo + erlotinib.

The study included previously untreated adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R. Patients with recurrent metastatic disease were eligible for study inclusion, provided that adjuvant or neoadjuvant therapy had been completed ≥ 12 months before metastasis. In addition, patients' general health had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Hence, no data are available for patients with an ECOG-PS ≥ 2.

Worldwide, a total of 449 patients were allocated in a 1:1 ratio to treatment with ramucirumab + erlotinib (N = 224) or placebo + erlotinib (N = 225). Randomization was stratified by sex (male/female), region (East Asia / rest of the world), EGFR mutation type (del 19 / L858R), and EGFR test method (therascreen or cobas / other polymerase chain reaction [PCR] based and sequence based procedure). Being randomized to ramucirumab, 3 patients actually received no treatment for the following reasons: revocation of study participation (n = 1), the physician deciding against the treatment (n = 1), and occurrence of AEs (n = 1).

Patients received a 60-minute infusion with ramucirumab or placebo every 2 weeks as well as a daily dose of erlotinib. The study treatment therefore corresponds to the specifications of the SPCs of ramucirumab and erlotinib [13,14]. In addition, patients were premedicated with histamine H1 antagonists in accordance with the ramucirumab SPC.

Patient treatment continued until disease progression, unacceptable toxicity, withdrawal of consent to study participation, or discontinuation of therapy upon the physician's discretion.

Primary outcome of the study was PFS. Patient-relevant secondary outcomes were outcomes from the categories of mortality, morbidity (symptoms, health status), and adverse events.

The primary analysis of all outcomes had been planned to take place after 270 PFS events and was actually conducted after 280 events, on 23 January 2019. The final analysis of the outcome of overall survival will be carried out when about 300 deaths have occurred. Upon request by the European Medicines Agency, an additional interim analysis was conducted on 25 September 2019 only for the outcome of PFS. Additionally, an estimate was requested of the final analysis date for overall survival. It is expected to be conducted in the end of 2023.

For the present benefit assessment, the analyses of the data cut-off on 23 January 2019 were used.

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
RELAY	
Mortality	
Overall survival	Until death or study end
Morbidity	
Symptoms (LCSS ASBI)	Until 30 days after the last dose of the study medication (±3 days)
Health status (EQ-5D)	Until 30 days after the last dose of the study medication (±3 days)
AEs	
AEs, SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs	Until 30 days after the last dose of the study medication (±3 days)

AE: adverse event; ASBI: Average Symptom Burden Index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event

The durations of follow-up observation for outcomes of the categories of morbidity and AEs are systematically shortened since they were surveyed only for the period of treatment with the study drug (plus 30 days). However, to be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire study period.

There were no restrictions with regard to treatment after the end of the study medication. In the intervention arm, 54% of patients received subsequent systemic therapy versus 69% in the comparator arm (see Table 22 in Appendix A of the full dossier assessment).

Characterization of the study population

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

Table 9: Characterization of the study population – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib (multi-page table)

Study Characteristics Category	**Ramucirumab + erlotinib N = 224**	**Placebo + erlotinib N = 225**
RELAY study		
Age [years], mean (SD)	64 (10)	63 (10)
Sex [f/m], %	63/37	63/37
Geographic region, n (%)		
East Asia	166 (74.1)	170 (75.6)
Rest of the world	58 (25.9)	55 (24.4)
Race/ethnicity, n (%)		
Asian	172 (76.8)	174 (77.3)
Caucasian	52 (23.2)	48 (21.3)
Other	0 (0)	2 (0.9)
Missing	0 (0)	1 (0.4)
Histology, n (%)		
Adenocarcinoma	215 (96.0)	218 (96.9)
Not further specified	9 (4.0)	7 (3.1)
Smoking status, n (%)		
Never smoked	134 (59.8)	139 (61.8)
Smoker	64 (28.6)	73 (32.4)
Unknown	26 (11.6)	13 (5.8)
EGFR mutation type, n (%)		
Exon 19 deletion	123 (54.9)	120 (53.3)
Exon 21 L858R substitution	99 (44.2)	105 (46.7)
Other	1 (0.4)	0 (0)
Missing	1 (0.4)	0 (0)
ECOG Performance Status, n (%)		
0	116 (51.8)	119 (52.9)
1	108 (48.2)	106 (47.1)
Disease stage at diagnosis		
IA	9 (4.0)	10 (4.4)
IIA	11 (4.9)	11 (4.9)
IIIA	8 (3.6)	12 (5.3)
IIIB	1 (0.4)	1 (0.4)
IV	195 (87.1)	189 (84.0)
Unknown	0 (0)	2 (0.9)
Liver metastases at study start, n (%)		
Yes	21 (9.4)	24 (10.7)
No	203 (90.6)[a]	201 (89.3)[a]

Table 9: Characterization of the study population – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib (multi-page table)

Study Characteristics Category	**Ramucirumab + erlotinib N = 224**	**Placebo + erlotinib N = 225**
Disease duration: period from initial diagnosis to randomization [months], mean (SD)	6.5 (17.2)	7.0 (19.0)
Treatment discontinuation[b], n (%)	157 (70.1)	182 (80.9)
Study discontinuation, n (%)	14[a] (6.3)	9[a] (4.0)

a. IQWiG calculations.
b. Main reason for treatment discontinuation was disease progression (ramucirumab + erlotinib: 68% vs. placebo + erlotinib: 80%).

f: female; m: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the study population were sufficiently balanced between the two treatment arms.

Patients included in the RELAY study had a mean age of about 63 years, and most were female. The majority of patients was Asian. Most patients never smoked. At study inclusion, about half of the patients had an ECOG-PS of 0. The majority of patients were in disease stage IV at the time of diagnosis. On average, the time between diagnosis and study inclusion was about 7 months.

The percentage of patients who discontinued therapy was higher in the control arm than in the intervention arm. In both treatment arms, the main reason for treatment discontinuation was disease progression. The proportion of patients who discontinued the study was 6% in the intervention arm and 4% in the control arm.

Table 10 shows the median duration of patient treatment as well as the median duration of follow-up observation for individual outcomes.

Table 10: Data on the course of the study – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study **Duration of the study phase** **Outcome category**	**Ramucirumab + erlotinib** **N = 224**	**Placebo + erlotinib** **N = 225**
RELAY study		
Treatment duration [months]		
Ramucirumab or placebo		
Median [Q1; Q3]	11.0 [4.2; 15.6]	9.7 [3.7; 15.6]
Mean (SD)	11.1 (7.9)	10.9 (8.6)
Erlotinib		
Median [Q1; Q3]	14.1 [6.5; 20.3]	11.2 [5.8; 17.9]
Mean (SD)	14.3 (8.7)	12.4 (8.3)
Follow-up observation [months]		
Overall survival		
Median [Q1; Q3]	20.4 [15.5; 27.3]	20.8 [16.1; 27.2]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	Not recorded	
Adverse events	ND	ND

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: Standard deviation

In case of unacceptable toxicity or at the patient's request, it was possible to discontinue treatment with one component of the combination therapy (ramucirumab/placebo or erlotinib) and continue with the remaining medication. Consequently, the various therapies within a treatment arm differ in treatment duration.

At 11 months, the median ramucirumab treatment duration in the intervention arm is about 1 month longer than the duration of placebo treatment in the control arm. At about 14 months, erlotinib treatment was administered almost 3 months longer in the intervention arm than in the control arm.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, indirect comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Providers			
RELAY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the RELAY study. This concurs with the company's assessment.

Transferability of the study results to the German healthcare context

In Module 4 A, Section 4.3.1.2.1, the company reports that the patients in the study largely match patients in the general population with regard to the characteristics of sex, smoking status, EGFR mutation type, disease stage, and histology. The only cited difference between the study population and the German general population pertains to the characteristic of race/ethnicity since it included a high percentage of Asian patients; however, this attribute did not show any effect modification. Given the general similarity of patient characteristics in the study with the target population in Germany, the company assumes that there is full transferability to the German healthcare context.

The company has not presented any further information on the transferability of study results to the German healthcare context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms (recorded with the Average Symptom Burden Index [ASBI] of the LCSS)
  - Health status (recorded with the visual analogue scale [VAS]) of the EQ-5D
- AEs
  - SAEs

- discontinuation due to AEs
- severe AEs (CTCAE grade ≥ 3)
- further specific AEs, if any

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

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

Table 12: Matrix of outcomes – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study	Outcomes							
	Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
RELAY	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	Yes

a. The following events are considered (MedDRA coding): "oedema, peripheral (PT, AE)", "diarrhoea (PT, severe AEs [CTCAE grade ≥ 3]), "hypertension (PT, severe AEs CTCAE grade ≥ 3), and "infections and infestations (SOC, severe AEs CTCAE grade ≥ 3)".
b. Outcome not recorded.

AE: adverse event; ASBI: Average Symptom Burden Index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

2.3.2.2 Risk of bias

Table 13 presents the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias at study and outcome levels – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study	Study level	Outcomes							
		Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
RELAY	L	L	H[b]	H[b]	-[c]	H[b]	L[d]	H[b]	H[b]

a. The following events are considered (MedDRA coding): oedema, peripheral (PT, AEs), diarrhoea (PT, severe AEs CTCAE grade ≥ 3), hypertension (PT, severe AEs CTCAE grade ≥ 3), and infections and infestations (SOC, severe AEs CTCAE grade ≥ 3).
b. Incomplete observations for potentially informative reasons.
c. Outcome not recorded.
d. Despite a low risk of bias, the certainty of results is assumed to be on the lower end for the outcome of discontinuation due to AEs.

AE: adverse event; ASBI: Average Symptom Burden Index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; h: high; LCSS: Lung Cancer Symptom Score; MedDRA: Medical Dictionary for Regulatory Activities; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

In agreement with the company, the risk of bias for the outcomes of overall survival and discontinuation due to AEs was rated as low.

For the outcome of discontinuation due to AEs, the certainty of results is at the lower end, despite a low risk of bias.

Again in agreement with the company, the risk of bias of results for any of the remaining outcomes from the AE category was rated as high due to incomplete observations for potentially informative reasons.

The company rated the risk of bias for the results on the outcomes of symptoms (recorded with the ASBI of LCSS) and health status (recorded with VAS of EQ-5D) as low. This rating ignored the fact that the outcome recording was likewise directly linked to duration of treatment, which might lead to incomplete observations for potentially informative reasons. In deviation from the company, the risk of bias is therefore rated as high for these outcomes as well.

2.3.2.3 Results

Table 14 and Table 15 summarize the results of the comparison of ramucirumab + erlotinib with placebo + erlotinib in previously untreated adult patients with metastatic NSCLC with the EGFR mutation del 19 or L858R. Event-time analyses on the outcomes of symptoms (LCSS ASBI) and health status (EQ-5D VAS) are shown in Appendix B of the full dossier assessment. Tables with common AEs, SAEs, severe AEs, and discontinuation due to AEs are found in Appendix C of the full dossier assessment. Kaplan-Meier curves are shown in Appendix D of the full dossier assessment.

Table 14: Results (mortality, adverse events) – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study Outcome category Outcome	Ramucirumab + erlotinib N	Ramucirumab + erlotinib Median time to event in months [95% CI] Patients with event n (%)	Placebo + erlotinib N	Placebo + erlotinib Median time to event in months [95% CI] Patients with event n (%)	Ramucirumab + erlotinib vs. placebo + erlotinib HR [95% CI]; p-value[a]
RELAY					
Mortality					
Overall survival	224	NA 37 (16.5)	225	NA 42 (18.7)	0.83 [0.53; 1.30] 0.421
AEs					
AEs (supplementary)	221	0.2 [0.1; 0.2] 221 (100)	225	0.2 [0.1; 0.2] 225 (100)	-
SAEs	221	NA [25.8; NC]) 65 (29.4)	225	NA 47 (20.9)	1.40 [0.96; 2.03] 0.081
Severe AEs (CTCAE grade ≥ 3)	221	3.9 [2.5; 4.3] 159 (71.9)	225	12.0 [6.2; 20.9] 121 (53.8)	1.58 [1.25; 2.00]; < 0.001
Discontinuation due to AEs	221	NA 28 (12.7)	225	NA 24 (10.7)	1.13 [0.66; 1.96]; 0.650
Peripheral oedema (PT, AEs)	221	33.1 [33.1; NC] 50 (22.6)	225	NA 10 (4.4)	5.24 [2.65; ND[b]]; < 0.001
Diarrhoea (PT, severe AEs [CTCAE grade ≥ 3])	221	NA 16 (7.2)	225	NA 3 (1.3)	5.36 [1.56; ND[b]]; 0.003
Hypertension (PT, severe AEs [CTCAE grade ≥ 3])	221	NA 52 (23.5)	225	NA 12 (5.3)	4.56 [2.43; 8.54]; < 0.001
Infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])	221	33.4 [33.4; NC] 38 (17.2)	225	NA 15 (6.7)	2.52 [1.39; 4.59]; 0.002

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; overall survival: each stratified by EGFR mutation type, sex, region and EGFR test method; outcomes of the AE category: each non-stratified.
b. > 9.99 according to the company

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: Hazard Ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Table 15: Results (morbidity) – RCT, direct comparison: ramucirumab + erlotinib vs. placebo + erlotinib

Study Outcome category Outcome	Ramucirumab + erlotinib			Placebo + erlotinib			Ramucirumab + erlotinib vs. placebo + erlotinib
	N[a]	Values at study start Mean (SD)	Mean change across follow-up Mean[b] (SE)	N[a]	Values at study start Mean (SD)	Mean change across follow-up Mean[b] (SE)	MD [95% CI]; p-value[b]
RELAY							
Morbidity							
Symptoms (LCSS ASBI)[c]	216	21.1 (15.2)	−4.6 (0.7)	216	18.3 (14.6)	−5.2 (0.7)	0.58 [−1.43; 2.59]; 0.572
Health status (EQ-5D VAS)[d]	218	75.1 (17.1)	2.6 (0.9)	219	77.6 (16.7)	1.6 (0.9)	1.00 [−1.37; 3.38]; 0.408

a. Number of patients included in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers.
b. Mean and SE (mean change across follow-up per treatment group) as well as mean, 95% CI, and p-value (between-group comparison): MMRM; adjusted for value at baseline.
c. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for the intervention.
d. Higher (increasing) values represent a better health status; positive effects (intervention minus control) mean an advantage for the intervention.

ASBI: Average Symptom Burden Index; CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; LCSS: Lung Cancer Symptom Scale; mean difference; MMRM: mixed effects model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

Due to the high risk of bias, the available data can be used to derive at most an indication, e.g. of added benefit, for the outcome of overall survival, and at most hints for the outcomes of symptoms, health status, and AEs.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (LCSS ASBI)

For the outcome of symptoms, recorded with the LCSS ASBI, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

For the outcome of health status, recorded with EQ-5D VAS, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of ramucirumab + erlotinib in comparison with erlotinib. An added benefit is therefore not proven.

This concurs with the company's assessment.

Adverse events

SAEs, discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, no statistically significant difference between treatment arms was found. Neither of the two outcomes of SAEs and discontinuation due to AEs resulted in a hint of greater or lesser harm of ramucirumab + erlotinib in comparison with erlotinib. Greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference between treatment arms was found to the disadvantage of ramucirumab + erlotinib. For this outcome, this results in a hint of greater harm of ramucirumab + erlotinib in comparison with erlotinib.

This concurs with the company's assessment.

Specific AEs

Peripheral oedema, diarrhoea, hypertension, infections and infestations

For the outcomes of peripheral oedema, diarrhoea, hypertension, as well as infections and infestations, a statistically significant difference between each respective treatment arm was found to the disadvantage of ramucirumab + erlotinib. For the each of the outcomes of peripheral oedema, diarrhoea, hypertension, as well as infections and infestations, there is a hint of greater harm of ramucirumab + erlotinib in comparison with erlotinib.

For the outcomes of diarrhoea, hypertension as well as infections and infestations, this concurs with the company's assessment. The company did not use the outcome of oedema to derive an added benefit.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 65 / ≥ 65 years)
- Sex (male/female)

The above subgroups were all prespecified. Subgroup analyses regarding the above characteristics are available for all relevant outcomes.

Interaction tests are performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

No effect modification was found in the available subgroup analyses.

2.3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the General Methods of IQWiG [1].

The approach for deriving an overall conclusion on the 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.

2.3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 16).

Determination of the outcome category for outcomes on AEs

Not for all outcomes considered in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. In these cases, the categorizations made are explained below.

Events for specific AE outcomes, except for the outcome of peripheral oedema, were severe (CTCAE grade ≥ 3). Hence, these outcomes were categorized as serious/severe AEs. The outcome of peripheral oedema was categorized as non-serious/non-severe AEs since the majority of the events in this outcome were non-serious/non-severe.

Table 16: Extent of added benefit at outcome level: ramucirumab + erlotinib vs. erlotinib (multi-page table)

Outcome category **Outcome**	**Ramucirumab + erlotinib vs. placebo + erlotinib** **Median time to event (months) or mean value of average changes across follow-up** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: NA vs. NA HR: 0.83 [0.53; 1.30] p < 0.421	Lesser/added benefit not proven
Morbidity		
Symptoms (LCSS ASBI)	Mean: −4.6 vs. −5.2 MD: 0.58 [−1.43; 2.59] p < 0.572	Lesser/added benefit not proven
Health status (EQ-5D VAS)	Mean: 2.6 vs. 1.6 MD: 1.00 [−1.37; 3.38] p = 0.408	Lesser/added benefit not proven
Health-related quality of life		
No outcomes of this category recorded		
AEs		
SAEs	Median: NA vs. NA HR: 1.40 [0.96; 2.03] p = 0.081	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 3.9 vs. 12.0 months HR: 1.58 [1.25; 2.00] HR: 0.63 [0.50; 0.80][c] p < 0.001 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm; extent: considerable
Discontinuation due to AEs	Median: NA vs. NA HR: 1.13 [0.66; 1.96] p = 0.650	Greater/lesser harm not proven
Peripheral oedema (PT, AEs)	Median: 33.1 vs. NA HR: 5.24 [2.65; ND] HR: 0.19 [ND; 0.38][c] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Diarrhoea (PT, severe AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 5.36 [1.56; ND] HR: 0.19 [ND; 0.64][c] p = 0.003 Probability: hint	Outcome category: serious/severe AEs $CI_u < 0.75$ and risk ≥ 5% Greater harm: extent: considerable

Table 16: Extent of added benefit at outcome level: ramucirumab + erlotinib vs. erlotinib (multi-page table)

Outcome category **Outcome**	**Ramucirumab + erlotinib vs. placebo + erlotinib** **Median time to event (months) or mean value of average changes across follow-up** **Effect estimate [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Hypertension (PT, severe AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 4.56 [2.43; 8.54] HR: 0.22 [0.12; 0.41][c] p < 0.001 Probability: hint	Outcome category: serious/severe AEs CI_u < 0.75 and risk ≥ 5% Greater harm; extent: considerable
Infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])	Median: 33.4 vs. NA HR: 2.52 [1.39; 4.59] HR: 0.40 [0.22; 0.72][c] p = 0.002 Probability: hint	Outcome category: serious/severe AEs CI_u < 0.75 and risk ≥ 5% Greater harm; extent: considerable

a. Probability given if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u).
c. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.

AE: adverse event; ASBI: Average Symptom Burden Index; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: Hazard Ratio; LCSS: Lung Cancer Symptom Score; MD: mean difference; NA: not achieved; ND: no data; PT: preferred term; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

2.3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of ramucirumab + erlotinib in comparison with erlotinib

Positive effects	**Negative effects**
-	Serious/severe AEs ▪ Severe AEs (CTCAE grade ≥ 3) Hint of greater harm – extent: considerable ▫ Diarrhoea (PT), hypertension (PT), as well as infections and infestations (SOC): for each, hint of greater harm – extent: considerable
-	Non-serious/non-severe AEs ▪ Peripheral oedema (PT, AEs) Hint of greater harm – extent: considerable

AEs: adverse events; CTCAE: Common Terminology Criteria for Adverse Events; PT: preferred term; SOC: System organ class

In the overall assessment, there are exclusively unfavourable effects in the outcome category of AEs. For serious/severe AEs, there are multiple hints of greater harm, most of considerable extent. Furthermore, a hint of greater harm of considerable extent was found for non-serious/non-severe AEs.

In summary, for previously untreated adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R, there is a hint of lesser benefit of ramucirumab + erlotinib in comparison with the ACT of erlotinib.

The above assessment deviates from that of the company, which derived an indication of minor added benefit.

2.4 Research question 2: Patients with EGFR mutations other than del 19 or L858R

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on ramucirumab + erlotinib (status: 17 January 2020)
- Bibliographic literature search on ramucirumab + erlotinib (most recent search on 10 January 2020)
- Search in trial registries for studies on ramucirumab + erlotinib (most recent search on 19 December 2019)

To check the completeness of the study pool:

- Search in trial registries for studies on ramucirumab + erlotinib (most recent search on 02 March 2020)

The company's dossier did not present any study on research question 2. The check for completeness did not reveal any relevant study either.

2.4.2 Results on added benefit

No data are available for assessing the added benefit of ramucirumab + erlotinib in comparison with the ACT of individualized therapy in previously untreated adult patients with metastatic NSCLC with activating EGFR mutations other than del 19 or L858R. Consequently, there is no hint of added benefit of ramucirumab + erlotinib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company did not present any data for assessing the added benefit of ramucirumab + erlotinib in comparison with the ACT in previously untreated adult patients with metastatic

NSCLC with EGFR mutations other than del 19 or L858R, an added benefit of ramucirumab + erlotinib is not proven for these patients.

This concurs with the company's assessment.

2.5 Probability and extent of added benefit – summary

Table 18 presents a summary of the probability and extent of added benefit of ramucirumab.

Table 18: Ramucirumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of adult patients with metastatic NSCLC with the activating EGFR mutation del 19 or L858R[b]	Afatinib or gefitinib or **erlotinib** or osimertinib	Hint of lesser benefit
First-line treatment of adult patients with metastatic NSCLC with activating EGFR mutations other than del 19 or L858R	Individualized therapy depending on the activating EGFR mutation, given the following options: ▪ Afatinib, gefitinib, erlotinib, osimertinib ▪ Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabin or docetaxel or paclitaxel or pemetrexed) (see Pharmaceutical Guideline, Section K, Annex VI [3]) ▪ Carboplatin in combination with nab paclitaxel and ▪ Gemcitabin or vinorelbine monotherapy (only in patients with ECOG Performance Status 2, as an alternative to platinum-based combination treatment)	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the RELAY study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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