IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ramucirumab (lung cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ramucirumab (Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

Medical and scientific advice:

- Ingo Schmidt-Wolf, Bonn University Hospital, Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Katrin Nink
- Christiane Balg
- Catharina Brockhaus
- Gertrud Egger
- Elke Hausner
- Helmut Hörn
- Sarah Mostardt
- Beate Wieseler

Keywords: ramucirumab, carcinoma – non-small-cell lung, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASBI	average symptom burden index
CI	confidence interval
CSR	clinical study report
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-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCSS	Lung Cancer Symptom Scale
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ramucirumab. 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 24 February 2016.

Research question

The aim of this report was to assess the added benefit of ramucirumab in combination with docetaxel compared with the appropriate comparator therapy (ACT) in the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression after platinum-based chemotherapy.

The respective ACT specified by the G-BA is shown in Table 2.

Table 2: Research question of the benefit assessment of ramucirumab

Therapeutic indication	**Appropriate comparator therapy**[a]
Adult patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy[b]	**Docetaxel** or pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib) or crizotinib (only for patients with activating ALK mutations)
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. b: According to the approval, ramucirumab is used in combination with docetaxel. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer	

In accordance with the G-BA's specification, the company chose docetaxel from the ACT options for all patients in the therapeutic indication.

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

Results

Study pool and study characteristics

The studies REVEL and JVCG were included in the benefit assessment. Both studies were randomized, double-blind, controlled studies on the comparison of ramucirumab in combination with docetaxel versus docetaxel. The approval study REVEL was conducted in 216 centres in 26 countries. The JVCG study was conducted in 28 centres exclusively in Japan.

Adult patients with metastatic NSCLC in disease stage IV and disease progression after one prior platinum-based chemotherapy were included. Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at the time point of randomization. The patients were randomly allocated in a ratio of 1:1 to treatment with ramucirumab + docetaxel (REVEL: 628 patients, JVCG: 94 patients) or placebo + docetaxel (REVEL: 625 patients, JVCG: 98 patients). Treatment in both studies was continued until disease progression, unacceptable toxicity, or discontinuation of the study medication by patient or physician.

Overall survival was the primary outcome of the REVEL study. Patient-relevant secondary outcomes were disease symptoms, health status, and adverse events. Primary outcome of the JVCG study was progression-free survival. Patient-relevant secondary outcomes were overall survival, disease symptoms, health status, and adverse events.

Risk of bias

The risk of bias at study level was rated as low for both studies.

For the REVEL study, the risk of bias was rated as low for the outcome “overall survival”, and as high for all other outcomes. For the JVCG study, the risk of bias was rated as low for overall survival and for all AE outcomes and as high for health status recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). The higher outcome-specific certainty of results of the JVCG study versus the REVEL study for AE outcomes resulted from the nearly identical treatment durations in both study arms.

Results

Mortality

For the outcome “overall survival”, the meta-analysis of the studies included showed a statistically significant prolongation in overall survival for treatment with ramucirumab in combination with docetaxel versus docetaxel. Moreover, there was proof of an effect modification by the characteristic “age”. For patients < 65 years, there was proof of an added benefit of ramucirumab + docetaxel versus docetaxel. In the group of patients ≥ 65 years, however, there was no hint of an added benefit of ramucirumab + docetaxel in comparison with docetaxel. An added benefit for the outcome “overall survival” is therefore not proven for patients ≥ 65 years.

Morbidity

- Symptoms (LCSS, ASBI)

No statistically significant difference between the treatment arms was shown for the analysis of the time to deterioration of symptoms recorded with the average symptom burden index (ASBI) of the Lung Cancer Symptom Scale (LCSS) in the REVEL study. The analysis was only based on the REVEL study because the LCSS was recorded in the JVCG study, but no analysis as ASBI was available. Overall, no hint of an added benefit of ramucirumab + docetaxel versus docetaxel could be derived for symptoms. An added benefit for this outcome is therefore not proven.

- Health status (VAS of the EQ-5D)

For the outcome "health status" recorded with the EQ-5D VAS, on the basis of the results of the JVCG study, a statistically significant difference in favour of ramucirumab + docetaxel in comparison with docetaxel was shown for the mean change at the time point 30 days after ending the study medication. The 95% confidence interval (CI) of Hedges' g was not completely above the irrelevance threshold of 0.2, however. Hence it could not be inferred that the effect was relevant; there was no hint of an added benefit of ramucirumab + docetaxel versus docetaxel for health status. An added benefit for this outcome is therefore not proven.

- Health-related quality of life

Health-related quality of life was not recorded in the studies. In the outcome category "quality of life", the company presented data of the questionnaire LCSS and of the EQ-5D VAS. However, the LCSS is not validated for health-related quality of life; the EQ-5D VAS was allocated to morbidity. Hence there was no hint of an added benefit of ramucirumab + docetaxel versus docetaxel for health-related quality of life. An added benefit is therefore not proven.

Side effects

- Serious adverse events

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)". However, there was proof of an effect modification by the characteristic "age", based on the results of the REVEL study. For patients < 65 years, there was a hint of lesser harm from ramucirumab + docetaxel versus docetaxel. In the group of patients ≥ 65 years, however, there was a hint of greater harm from ramucirumab + docetaxel in comparison with docetaxel.

- Severe adverse events (CTCAE grade ≥ 3)

The meta-analysis showed important heterogeneity between both studies for the outcome "severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". In this situation, only the results of the REVEL study and not the ones of the Japanese JVCG study were used in the present assessment. A statistically significant

difference to the disadvantage of ramucirumab + docetaxel versus docetaxel was shown here. This resulted in a hint of greater harm of ramucirumab + docetaxel in comparison with docetaxel for this outcome.

- Discontinuation due to adverse events

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel versus docetaxel for the outcome "discontinuation due to AEs". This resulted in proof of greater harm of ramucirumab + docetaxel in comparison with docetaxel for this outcome.

- Specific adverse events: stomatitis (CTCAE grade ≥ 3) and febrile neutropenia (CTCAE grade ≥ 3)

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel in comparison with docetaxel for each of the AE outcomes "stomatitis" (CTCAE grade ≥ 3) and "febrile neutropenia" (CTCAE grade ≥ 3). There was an indication of greater harm for the outcome "stomatitis" (CTCAE grade ≥ 3) and proof of greater harm for the outcome "febrile neutropenia" (CTCAE grade ≥ 3), in each case from ramucirumab + docetaxel in comparison with docetaxel.

- Specific adverse events: bleeding/haemorrhagic events

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel in comparison with docetaxel for the outcome "bleeding/haemorrhagic events". Moreover, there was proof of an effect modification by the characteristic "histology". For patients with non-squamous cell carcinoma, there was a hint of greater harm from ramucirumab + docetaxel versus docetaxel. In the group of patients with squamous cell carcinoma, however, there was no hint of greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel. Greater or lesser harm for the outcome "bleeding/haemorrhagic events" for patients with squamous cell carcinoma is therefore 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 ramucirumab compared with the ACT is assessed as follows:

[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].

The results showed a relevant effect modification by age for 2 outcomes. Hereinafter, the overall conclusion on the added benefit is derived separately for patients < 65 years and for patients ≥ 65 years.

Patients < 65 years

In the overall consideration, there were positive and negative effects for patients < 65 years. On the positive side, there was proof of an added benefit of considerable extent for the outcome "overall survival" and a hint of lesser harm of considerable extent in the outcome category "SAEs". The lesser harm was subject to additional uncertainty, which did not change the overall conclusion on the added benefit, however. The positive effects were accompanied by negative effects with different extent and different certainty of results. A hint of greater harm with minor extent (severe AEs CTCAE grade ≥ 3), an indication of greater harm of considerable extent (stomatitis CTCAE grade ≥ 3), and proof of greater harm also of considerable extent (febrile neutropenia CTCAE grade ≥ 3) were found in the category "serious/severe side effects". In addition, there were further negative effects in the category "non-serious/non-severe side effects". Overall, the negative effects were not so large as to completely outweigh the mortality advantage of ramucirumab in combination with docetaxel.

In summary, there is proof of a minor added benefit of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients < 65 years.

Patients ≥ 65 years

For patients ≥ 65 years, only negative effects remained in the outcome categories "serious/severe side effects" and "non-serious/non-severe side effects", which were of minor and considerable extent with different probabilities (hint, indication, or proof).

In summary, there is therefore proof of lesser benefit of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients ≥ 65 years.

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

Table 3: Ramucirumab – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Subgroup	Extent and probability of added benefit
Adult patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy[b]	**Docetaxel** or pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib) or crizotinib (only for patients with activating ALK mutations)	< 65 years	Proof of minor added benefit
		≥ 65 years	Proof of lesser benefit

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.
b: According to the approval, ramucirumab is used in combination with docetaxel.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; 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 was to assess the added benefit of ramucirumab in combination with docetaxel compared with the ACT in the treatment of adult patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy.

The respective ACT specified by the G-BA is shown in Table 4.

Table 4: Research question of the benefit assessment of ramucirumab

Therapeutic indication	Appropriate comparator therapy[a]
Adult patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy[b]	**Docetaxel** or pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib) or crizotinib (only for patients with activating ALK mutations)
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. b: According to the approval, ramucirumab is used in combination with docetaxel. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer	

In accordance with the G-BA's specification, the company chose docetaxel from the ACT options listed in Table 4 for all patients in the therapeutic indication.

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 list on ramucirumab (status: 6 January 2016)
- bibliographical literature search on ramucirumab (last search on 19 January 2016)
- search in trial registries for studies on ramucirumab (last search on 12 January 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ramucirumab (last search on 2 March 2016)

No additional relevant study was identified from the check. Deviating from the company, the JVCG study was selected as relevant for the research question, however.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
REVEL (I4T-MC-JVBA)[b]	Yes	Yes	No
I4T-JE-JVCG[c]	No	Yes	No

a: Study for which the company was sponsor.
b: In the following tables and in the text, the study is referred to with its abbreviated form "REVEL".
c: In the following tables and in the text, the study is referred to with its abbreviated form "JVCG".
RCT: randomized controlled trial; vs.: versus

The study pool of the present assessment of the added benefit of ramucirumab deviated from that of the company, which only included the REVEL study. It only presented study I4T-JE-JVCG – hereinafter referred to as "JVCG" – descriptively, however, and did not use it for the derivation of the added benefit. The JVCG study was a randomized controlled study, which was only conducted in Japan. The company justified its approach with the argument that the JVCG study was a so-called bridging study for Japan and that the study design was not aimed at showing statistical differences in efficacy.

Deviating from this approach, the JVCG study was considered to be relevant for the present research question and the assessment of the added benefit of ramucirumab in combination with docetaxel versus docetaxel (see Section 2.7.2.3.2 of the full dossier assessment). Using the subgroup analyses it was possible to identify possible effect modifications by region or ethnicity. In a heterogeneous situation, only the results of the REVEL study were used in the present assessment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
REVEL	RCT, double-blind, parallel	Adult patients[b] (≥ 18 years) with NSCLC (stage IV) and ECOG PS ≤ 1 who experienced disease progression during or after only one single platinum-based chemotherapy, with or without maintenance treatment[d] for advanced/metastatic disease	Ramucirumab + docetaxel (N = 628) placebo + docetaxel (N = 625)	Treatment: one cycle every 3 weeks until disease progression, unacceptable toxicity, discontinuation of the study medication by the patient or the physician Observation: outcome-specific, at most until death, discontinuation of participation in the study or end of study	216 centres in Asia, Europe, North and South America, New Zealand Start: 12/2010 Data cut-off: 12/2013	Primary: overall survival Secondary: health status, symptoms, AEs
JVCG	RCT, double-blind, parallel	Adult patients[e] (≥ 20 years) with NSCLC (stage IV) and ECOG PS ≤ 1 who experienced disease progression during or after only one single platinum-based chemotherapy, with or without maintenance treatment[d] for advanced/metastatic disease	Ramucirumab + docetaxel (N = 98) placebo + docetaxel (N = 99)	Treatment: one cycle every 3 weeks until disease progression, unacceptable toxicity, discontinuation of the study medication by the patient or the physician Observation: outcome-specific, at most until death, discontinuation of participation in the study or end of study	28 centres in Japan Start: 12/2012 Data cut-off for primary analysis: 18 Dec 2014 Data cut-off for final analysis: 20 May 2015	Primary: progression-free survival Secondary: overall survival, health status, symptoms, AEs

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: Stratified by ECOG PS (0 vs. 1), sex, prior maintenance treatment for the advanced disease (yes vs. no), geographical region (Japan/East Asia vs. rest of the world).
c: According to the American Joint Committee on Cancer.
d: Defined as treatment administered within 42 days after the last dose of the platinum-based chemotherapy in patients with maintained clinical advantage after platinum-based first-line induction chemotherapy.
e: Stratified by ECOG PS (0 vs. 1), sex, prior maintenance treatment for the advanced disease (yes vs. no). Patients with prior EGFR-TKI monotherapy were randomized without stratification.
AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; vs.: versus

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

Study	Intervention	Comparison	Prior and concomitant medication
REVEL	Cycles every 3 weeks Day 1 of each cycle[a]: ramucirumab 10 mg/kg IV infusion administered over about 60 minutes[b], followed by docetaxel[d] 75 mg/m^2 BSA IV infusion administered over 60 minutes	Cycles every 3 weeks Day 1 of each cycle[a]: placebo IV infusion administered over about 60 minutes[b], followed by	**Pretreatment:** ▪ one single platinum-based chemotherapy with or without maintenance treatment ▪ also in combination with radiotherapy[c] **Non-permitted pretreatment:** ▪ docetaxel **Concomitant therapy:** ▪ premedication with histamine H1 antagonists (e.g. diphenhydramine hydrochloride) recommended ▪ premedication with corticosteroids (e.g. dexamethasone) ▪ palliative and supportive treatment of the symptoms of the underlying disease and of the toxicity of the study treatment **Non-permitted concomitant therapy:** ▪ additional chemotherapy except the study medication ▪ radiotherapy (with curative intent) ▪ immunomodulators ▪ initiation of treatment with bisphosphonates or RANK-L inhibitors
JVCG	Cycles every 3 weeks Day 1 of each cycle[a]: ramucirumab 10 mg/kg IV infusion administered over about 60 minutes[b], followed by docetaxel 60 mg/m^2 BSA IV infusion administered over 60–90 minutes	Cycles every 3 weeks Day 1 of each cycle[a]: placebo IV infusion administered over about 60 minutes[b], followed by	**Pretreatment:** ▪ one single platinum-based chemotherapy with or without maintenance treatment ▪ also in combination with radiotherapy[e] ▪ monotherapy with EGFR-TKI in patients with activating EGFR mutation **Non-permitted pretreatment:** ▪ EGFR-TKI for patients with EGFR wild type ▪ ALK inhibitors ▪ ramucirumab and/or docetaxel **Concomitant therapy:** ▪ premedication with histamine H1 antagonists (e.g. diphenhydramine hydrochloride) recommended ▪ premedication with corticosteroids (e.g. dexamethasone) ▪ palliative and supportive treatment of the symptoms of the underlying disease and of the toxicity of the study treatment **Non-permitted concomitant therapy:** ▪ additional chemotherapy except the study medication ▪ radiotherapy (with curative intent) ▪ immunomodulators

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

a: The start of the treatment cycle could be delayed by up to 2 weeks to allow recovery from specific adverse events. If delay by more than 2 weeks due to ongoing toxicity was necessary, one or both drugs were to be discontinued. The other drug could be continued if clinically indicated so that the patient remained in the study.
b: A one-hour observation period was required after the ramucirumab/placebo infusion in the first and second treatment cycle. If no signs of infusion-related reaction occurred during the infusions in the first 2 cycles, no observation period was required for the following cycles. If an infusion-related reaction occurred in one of the following cycles, the one-hour observation period was reintroduced.
c: The following periods of time were required between completion of the radiotherapy and randomization: thoracic area ≥ 28 days, focal or palliative treatment ≥ 7 days, central nervous system ≥ 14 days.
d: After the amendment to the protocol from 22 May 2012, the newly included patients in Korea and Taiwan received 60 mg/m^2 BSA docetaxel. Dose reduction was not mandated until occurrence of toxicity in patients in Korea or Taiwan who had started with a starting dose of 75 mg/m^2 BSA docetaxel.
e: The following periods of time were required between completion of the radiotherapy and randomization: thoracic area ≥ 3 months, focal or palliative treatment ≥ 7 days (25% or less of the total bone marrow was radiated), central nervous system ≥ 14 days.
ALK: anaplastic lymphoma kinase; BSA: body surface area; EGFR: epidermal growth factor receptor; IV: intravenous; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; vs.: versus

Study design

Study REVEL

The REVEL study was a randomized, double-blind, controlled approval study on the comparison of ramucirumab in combination with docetaxel versus docetaxel. The study was conducted in 216 centres in 26 countries.

Adult patients with metastatic NSCLC in disease stage IV (according to the American Joint Committee on Cancer, seventh edition) and disease progression after one single prior platinum-based chemotherapy were included. Patients were required to have an ECOG PS of 0 or 1 at the time point of randomization. The population investigated in the REVEL study corresponded to the therapeutic indication of ramucirumab in the present research question. Since the REVEL study included neither patients with disease stage < IV nor with ECOG PS > 1, however, no conclusions can be derived from the available data for these patients. In addition, due to the restriction to patients with one single prior chemotherapy, the conclusion was limited to second-line treatment of the metastatic NSCLC (see Section 2.7.2.4.1 of the full dossier assessment).

A total of 1253 patients were randomly assigned in a ratio of 1:1, either to treatment with ramucirumab + docetaxel (628 patients) or to treatment with placebo + docetaxel (625 patients). Allocation was stratified by ECOG PS (0 versus 1), sex, prior maintenance treatment for the advanced disease (yes versus no), and geographical region (Japan/East Asia versus rest of the world).

The drugs ramucirumab and docetaxel used in the study were administered without relevant deviations from the Summaries of Product Characteristics (SPCs) [3,4]. Following an amendment to the protocol from 11 May 2012, the docetaxel dose was lowered from 75 mg/m^2 body surface area to 60 mg/m^2 for newly included patients from East Asia. This was justified with an increased rate of febrile neutropenia in East Asian patients. The SPC of ramucirumab contains a corresponding recommendation to consider a reduced docetaxel starting dose of 60 mg/m^2 (in combination with ramucirumab) [3]. In total, 28 patients of the 89 East Asian patients included received the lower starting dose. Irrespective of the question which docetaxel dosages for East Asian patients in monotherapy and combination therapy concur with the approval, Asian patients only constituted 7.1% of the study population so that the relevance of the study was not called into question. In each case, treatment was continued until disease progression, unacceptable toxicity, or discontinuation of the study medication by patient or physician (e.g. withdrawal of consent).

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were disease symptoms, health status, and adverse events.

Study JVCG

The JVCG study was also a randomized, double-blind, controlled study on the comparison of ramucirumab in combination with docetaxel versus docetaxel. The study was conducted in 28 centres only in Japan, designed as a so-called bridging study for Japan to mirror the pivotal REVEL study.

The JVCG study also included adult patients with metastatic NSCLC in disease stage IV (according to the American Joint Committee on Cancer, seventh edition) and disease progression after a prior platinum-based chemotherapy. Patients were required to have an ECOG PS of 0 or 1 at the time point of randomization. In addition, the population of the JVCG study was recruited from a primary population in which the patients had received no monotherapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and from an exploratory population with patients with activating EGFR mutations whose pretreatment also included EGFR-TKI monotherapy. Both populations concurred with the therapeutic indication in the present research question (see Sections 2.7.2.1 and 2.7.2.3.2 of the full dossier assessment); the proportion of patients with activating EGFR mutations, with 18 patients in the intervention arm and 17 patients in the comparator arm, was below 20% of the randomized patients.

Since the JVCG study included neither patients with disease stage < IV nor with ECOG PS > 1, however, no conclusions can be derived from the available data for these patients. In addition, due to the restriction to patients with one single prior chemotherapy (with or without EGFR-TKI monotherapy), the conclusion was limited to second-line treatment of the metastatic NSCLC.

A total of 192 patients were randomly assigned in a ratio of 1:1, either to treatment with ramucirumab + docetaxel (94 patients) or to treatment with placebo + docetaxel (98 patients) (35 patients thereof in the exploratory population). Allocation for the primary population was stratified by ECOG PS (0 versus 1), sex, and prior maintenance treatment for the advanced disease (yes versus no). Allocation of the exploratory population was not stratified.

The drug ramucirumab was used in compliance with the approval in the study [3]. In the study, docetaxel was administered in a dose of 60 mg/m^2 body surface area in both study arms. This was in compliance with the recommendations in the SPC of ramucirumab, according to which a starting dose of 60 mg/m^2 body surface area should be considered for docetaxel in combination with ramucirumab in East Asian patients. The SPCs on docetaxel monotherapy valid in Germany do not contain this recommendation, however. According to the information provided in the clinical study report (CSR), this dosage corresponds to the recommended starting dose in Japan and was therefore the adequate dosage of the population included in the study. After amendment, this dose was used for East Asian patients also in the pivotal approval study REVEL (see description of the REVEL study). In each case, treatment was continued until disease progression, unacceptable toxicity, or discontinuation of the study medication by patient or physician (e.g. withdrawal of consent).

Primary outcome of the study was progression-free survival. Patient-relevant secondary outcomes were overall survival, disease symptoms, health status, and adverse events.

Duration of follow-up

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

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

Study **Outcome category** **Outcome**	**Planned follow-up**
REVEL	
Mortality	
Overall survival	Every 2 months (± 7 days) as long as the patient was alive or until the end of the study
Morbidity	
Symptoms (LCSS)	Recorded at the start of the study, on day 21 of each cycle, at the end-of-study visit, and, for the last time, 30 days after discontinuation of the study medication.
Side effects	
All AE outcomes	Up to 30 days after discontinuation of the study medication
JVCG	
Mortality	
Overall survival	At least every 3 months as long as the patient was alive or until the end of the study
Morbidity	
Symptoms (LCSS), health status (EQ-5D VAS)	Recorded at the start of the study, on day 21 of each cycle, at the end-of-study visit, and, for the last time, 30 days after discontinuation of the study medication.
Side effects	
All AE outcomes	Up to 30 days after discontinuation of the study medication
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

In both studies, the planned follow-up of the patients for the outcome "overall survival" was conducted until death. The remaining outcomes were recorded up to 30 days after the end of the study treatment. After discontinuation of the study treatment, the patients in both studies could receive further systemic cancer treatments; switching from the comparator to the intervention group was not envisaged.

The final data cut-off for the REVEL study was planned for the time point when at least 869 patients had died and was conducted on 20 December 2013. 884 patients had died at this time point. The present analyses of the REVEL study were based on this data cut-off.

The first data cut-off for the JVCG study was planned for the time point when 134 patients had received the primary outcome "progression-free survival". The final analysis of overall survival was then to be conducted about one year after the last patient had started the study treatment. The first data-cut off was conducted on 18 December 2014 after 135 patients had reached the primary outcome of the study. The final analysis of overall survival was based on

the data cut-off from 20 May 2015. The results of the final data cut-off were used for the present assessment.

Patient characteristics

Table 9 and Table 10 show the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations (demography) – direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study Characteristics Category	**Ramucirumab + docetaxel**	**Placebo + docetaxel**
REVEL	**N[a] = 628**	**N[a] = 625**
Age [years], mean (SD)	61 (10)	61 (10)
Sex [F/M], %	33/67	34/66
Ethnicity, %		
White	83.8	80.5
Black	2.7	2.6
Asian	11.8	13.8
Others[b]	1.6	3.2
Missing	0.2	0
Region, n (%)		
East Asia/Japan	43 (6.8)	46 (7.4)
Rest of the world	585 (93.2)	579 (92.6)
Smoking status, n (%)		
Smoker	518 (82.5)	483 (77.3)
Never-smoker	109 (17.4)	141 (22.6)
Missing	1 (0.2)	1 (0.2)
Treatment discontinuation, n (%)[c]	613 (97.6)	611 (97.8)
Study discontinuation, n (%)	ND	ND
JVCG	**N[d] = 94**	**N[d] = 98**
Age [years], mean (SD)	64 (9)	64 (9)
Sex [F/M], %	30/70	28/72
Ethnicity, %		
Asian	94 (100)	98 (100)
Region, n (%)		
Japan	94 (100)	98 (100)
Smoking status, n (%)		
Smoker	71 (75.5)	75 (76.5)
Never-smoker	23 (24.5)	23 (23.5)
Missing	0 (0)	0 (0)
Treatment discontinuation[e, f], n (%)	93 (98.9)	97 (99.0)
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients.
b: This group includes native Americans/native Alaskans + Hawaiians/Pacific Islanders.
c: Reasons for treatment discontinuation: progression, AE, patient's decision, death, investigator's decision, sponsor's decision, other.
d: Number of patients in the FAS 2 population.
e: Information on the second data cut-off from 20 May 2015.
f: Reasons for treatment discontinuation: progression, AE, patient's decision, investigator's decision, other.
AE: adverse event; F: female; FAS: full analysis set; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 10: Characteristics of the study populations (disease characteristics) – direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study Characteristics Category	**Ramucirumab + docetaxel**	**Placebo + docetaxel**
REVEL	**N[a] = 628**	**N[a] = 625**
ECOG performance status, n (%)		
0	207 (33.0)	199 (31.8)
1	420 (66.9)	425 (68.0)
Missing	1 (0.2)	1 (0.2)
EGFR status, n (%)		
Mutant	15 (2.4)	18 (2.9)
Wild type	207 (33.0)	197 (31.5)
Unknown	402 (64.0)	406 (65.0)
Missing	4 (0.6)	4 (0.6)
Time between first diagnosis and randomization [months], median [min; max]	8.8 [2; 178]	9.2 [2; 136]
Prior maintenance treatment, n (%)		
Yes	135 (21.5)	143 (22.9)
No	493 (78.5)	482 (77.1)
Prior taxane therapy, n (%)		
Yes	153 (24.4)	149 (23.8)
No	475 (75.6)	476 (76.2)
Prior bevacizumab therapy, n (%)		
Yes	88 (14.0)	92 (14.7)
No	540 (86.0)	533 (85.3)
Number of metastases/site, n (%)		
0	4 (0.6)	3 (0.5)
1	91 (14.5)	82 (13.1)
≥ 2	533 (84.9)	540 (86.4)
CNS	37 (5.9)	24 (3.8)
Liver	139 (22.1)	117 (18.7)
Histology, n (%)		
Non-squamous cell carcinoma	465 (74.2)	447 (71.6)
Adenocarcinoma	377 (60.0)	348 (55.7)
Large-cell carcinoma	14 (2.2)	21 (3.4)
Other	74 (11.8)	78 (12.5)
Squamous cell carcinoma	157 (25.0)	171 (27.4)
Missing	5 (0.8)	6 (1.0)

(continued)

Table 10: Characteristics of the study populations (disease characteristics) – direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

Study Characteristics Category	Ramucirumab + docetaxel	Placebo + docetaxel
JVCG	**N[b] = 94**	**N[b] = 98**
ECOG performance status, n (%)		
0	44 (46.8)	41 (41.8)
1	50 (53.2)	57 (58.2)
EGFR status, n (%)		
Mutant	18 (19.1)	17 (17.3)
Wild type	70 (74.5)	77 (78.6)
Unknown	6 (6.4)	4 (4.1)
Time between first diagnosis and randomization [months], median [min; max]	9.54 [2.6; 67.2]	11.89 [2.3; 182.1]
Prior maintenance treatment, n (%)		
Yes	51 (54.3)	58 (59.2)
No	43 (45.7)	40 (40.8)
Prior taxane therapy, n (%)		
Yes	27 (28.7)	24 (24.5)
No	67 (71.3)	74 (75.5)
Prior bevacizumab therapy, n (%)		
Yes	29 (30.9)	29 (29.6)
No	65 (69.1)	69 (70.4)
Number of metastases, median [min; max]	3 [1; 9]	3 [1; 14]
Histology, n (%)		
Non-squamous cell carcinoma	85 (90.4)	88 (89.8)
Adenocarcinoma	78 (83.0)	81 (82.7)
Large-cell carcinoma	1 (1.1)	1 (1.0)
Other	6 (6.4)	6 (6.1)
Squamous cell carcinoma	9 (9.6)	10 (10.2)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Number of patients in the FAS 2 population.
CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; FAS: full analysis set; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In both studies, the characteristics were balanced between the treatment arms. The mean age of the patients in both studies was over 60 years (REVEL: 61 years, JVCG: 64 years), and, with at least 66%, notably more men than women were included in all treatment arms. Whereas all the patients in the JVCG study were from Japan, the proportion of East Asian patients in the REVEL study was only 7%. Regarding disease characteristics, there were

minor differences between the studies. The physical condition of the patients in the JVCG study was possibly slightly better because the proportion of patients with an ECOG PS of 0 was 44% in the JVCG study versus 32% in the REVEL study. The remaining patients had an ECOG PS of 1. The patients also differed in their pretreatment. Only 22% of the REVEL patients had received prior maintenance treatment versus 57% of the JVCG patients. In addition, more than twice as many patients (30%) had received prior bevacizumab therapy in the JVCG study than in the REVEL study (14%).

Table 11 shows the mean and median treatment duration of the patients and the follow-up period for individual outcomes.

Table 11: Information on the course of the study – direct comparison: Ramucirumab + docetaxel vs. placebo + docetaxel

Study **Duration of the study phase** **Outcome category**	**Ramucirumab + docetaxel**	**Placebo + docetaxel**
REVEL	N = 628	N = 625
Treatment duration [weeks]		
Any treatment		
Median [min; max]	15.0 [3; 118]	12.0 [3; 133]
Mean (SD)	19.7 (16.9)	16.9 (16.0)
Ramucirumab or placebo		
Median [min; max]	15.0 [3; 118]	12.0 [3; 133]
Mean (SD)	19.4 (16.6)	16.8 (16.0)
Docetaxel		
Median [min; max]	14.1 [3; 92]	12.0 [3; 108]
Mean (SD)	17.8 (14.5)	15.9 (14.1)
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Side effects	ND	ND
JVCG	**N = 94**[a]	**N = 98**[a]
Treatment duration[b] [weeks]		
Any treatment	ND	ND
Ramucirumab or placebo		
Median [min; max]	13.0 [3; 97.4]	13.5 [3; 71.3]
Mean (SD)	19.9 (17.6)	20.2 (16.1)
Docetaxel		
Median [min; max]	12.4 [3; 97.4]	13.0 [3; 80.6]
Mean (SD)	18.4 (16.0)	19.1 (15.3)
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Side effects	ND	ND

a: Number of patients in the FAS 2 population.
b: Data of the second data cut-off from 20 May 2015.
AE: adverse event; FAS: full analysis set; max: maximum; min: minimum; n: number of analysed patients; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were generally no large differences in treatment duration between the studies. In the REVEL study, the median treatment duration differed between both study arms. The treatment duration of the patients in the control arm was 80% of the duration of patients in the intervention arm (any treatment). In the JVCG study, the treatment durations had almost the

same durations. No information on the observation period was available for both studies. It can be assumed, however, that the differences were similar to the ones regarding treatment duration because the outcomes on morbidity and side effects were each to be recorded for up to 30 days after the last administration of the study medication.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

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			
REVEL	Yes	Yes	Yes	Yes	Yes	Yes	Low
JVCG	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for both studies. This is in accordance with the assessment of the company.

2.4 Results on added benefit

2.4.1 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 LCSS ASBI
  - health status measured with the EQ-5D VAS
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)

- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study	Outcomes							
	Overall survival	Symptoms (LCSS, ASBI)[a]	Health status (VAS of the EQ-5D)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[e]
REVEL	Yes	Yes	No[b]	No[c]	Yes	Yes	Yes	Yes
JVCG	Yes	No[d]	Yes	No[c]	Yes	Yes	Yes	Yes

a: Measured with the symptom questions (1 to 6) of the LCSS.
b: No usable data available because analyses were based on fewer than 70% of the patients; see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment for a detailed justification.
c: Outcome not recorded (the LCSS symptom score ASBI was allocated to morbidity; the LCSS total score is not validated for quality of life).
d: No usable data available because the ASBI was not analysed in the JVCG study; see Section 2.7.2.4.3 of the full dossier assessment.
e: The following events were considered (MedDRA coding): stomatitis (PT, severe AE CTCAE grade ≥ 3), bleeding/haemorrhagic events (SMQ) and partial analyses on gastrointestinal haemorrhages (according to PT defined a priori, documented in the CSR), febrile neutropenia (PT, severe AE CTCAE grade ≥ 3).
AE: adverse event; ASBI: average symptom burden index; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Study	Study level	Outcomes							
		Overall survival	Symptoms (LCSS, ASBI)[a]	Health status (VAS of the EQ-5D)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[b]
REVEL	L	L	H[f,g]	–[c]	–[d]	H[g]	H[g]	H[e]	H[g]
JVCG	L	L	–[c]	H[f]	–[d]	L	L	L	L

a: Measured with the symptom questions (1 to 6) of the LCSS.
b: The following events were considered (MedDRA coding): stomatitis (PT, severe AE CTCAE grade ≥ 3), bleeding/haemorrhagic events (SMQ) and partial analyses on gastrointestinal haemorrhages (according to PT defined a priori, documented in the CSR), febrile neutropenia (PT, severe AE CTCAE grade ≥ 3).
c: No usable data available.
d: Outcome not recorded (the LCSS symptom score ASBI was allocated to morbidity; the LCSS total score is not validated for quality of life).
e: Potentially different observation periods between the treatment groups with informative censoring in the survival time analysis.
f: High proportion (> 10%) of missing values or difference between the groups in the proportion of patients not considered in the analysis > 5 percentage points.
g: Potentially different observation periods between the treatment groups in an analysis on relative risks.
AE: adverse event; ASBI: average symptom burden index; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LCSS: Lung Cancer Symptom Scale; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale; vs.: versus

For the REVEL study, the risk of bias was rated as low for the outcome "overall survival", and as high for all other outcomes. This concurs with the company's rating. The company did not use the specific AEs "stomatitis" and "febrile neutropenia" (in each case severe AE CTCAE grade ≥ 3) and therefore did not rate the risk of bias.

For the JVCG study, the risk of bias was rated as low for overall survival and for all AE outcomes and as high for health status recorded with the EQ-5D VAS. The assessment concurs with that of the company also in this case. The higher outcome-specific certainty of results of the JVCG study versus the REVEL study for AE outcomes resulted from the nearly identical treatment durations in both study arms.

Reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

In addition, as a result of the systematically shorter observation periods for the outcomes on morbidity and side effects, a conclusion could only be drawn for the time period during which the patients were treated (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Certainty of results

Deviating from the company, the JVCG study was used besides the REVEL study for the assessment of the added benefit of ramucirumab in the present assessment. The risk of bias at study level was rated as low for both studies. Hence depending on the certainty of results at outcome level, at most proof of an added benefit could be derived. This is possible if the risk of bias at outcome level is rated as low for both studies. The derivation of proof is also possible if only one of both studies has a low risk of bias. In this case, there has to be a homogeneous significant effect from both studies and the weight of the study with the low risk of bias has to be at least 25%. This second situation applied to the AE outcomes "discontinuation due to AEs" and "febrile neutropenia" (CTCAE grade ≥ 3).

Handling of the different effect estimates of the AE outcomes

Due to the different observation periods, the company used a hazard ratio (HR) estimated from a Cox proportional hazards model to analyse the results from the REVEL study on adverse events. It can be assumed that the median treatment period in the placebo + docetaxel arm was shorter: It was 80% of the treatment period in the ramucirumab + docetaxel arm. Due to the different observation periods with informative censoring, the company rated the risk of bias of these outcomes as high. This assessment was followed. Since these analyses were not available for the JVCG study, no meta-analysis based on this effect measure was possible. The Institute therefore calculated the relative risk (RR) for these outcomes for the REVEL study to allow the joint consideration of the results for the outcomes "SAEs", "discontinuation due to AEs", "severe AEs" (CTCAE grade ≥ 3), and the specific AEs from both studies. The risk of bias of these results was rated as high because of the different observation periods.

2.4.3 Results

Table 15 to Table 17 summarize the results on the comparison of ramucirumab + docetaxel with docetaxel in patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations, in particular a joint meta-analytical evaluation of both relevant studies was conducted. The corresponding Kaplan-Meier curves can be found in Appendix A, and figures of the meta-analyses in Appendix B of the full dossier assessment.

Table 15: Results (overall survival and symptoms) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome Study	Ramucirumab + docetaxel		Placebo + docetaxel		Ramucirumab + docetaxel vs. placebo + docetaxel
	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]; p-value
Overall survival					
REVEL	628	10.51 [9.53; 11.24] 428 (68.2)	625	9.13 [8.44; 10.02] 456 (73.0)	0.86 [0.75; 0.98][a]; 0.023[b]
JVCG[c]	94	16.95 [13.34; NA] 46 (48.9)	98	14.65 [11.93; 24.18] 56 (57.1)	0.77 [0.52; 1.15][d]; 0.275[b]
Total					0.85 [0.75; 0.97]; 0.012[e]
Morbidity					
LCSS, ASBI[f, g] – time to deterioration of symptoms					
REVEL	628	22.34 [11.76; 22.34] 180 (28.7)	625	9.17 [7.62; NA] 178 (28.5)	0.93 [0.75; 1.15][a]; 0.510[b]
JVCG	94	ND	98	ND	ND

a: Stratified by ECOG PS, sex, geographical region, and prior maintenance treatment.
b: p-value based on stratified log-rank test.
c: Results of the second data cut-off on 20 May 2015.
d: Stratified by ECOG PS, sex, and prior maintenance treatment.
e: Institute's calculation from meta-analysis.
f: Time to deterioration defined as time from randomization to the first increase by at least ≥ 15 mm from the start of the study.
g: Calculated as mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, pain).

ASBI: average symptom burden index; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 16: Results (health status) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome category Outcome Study	Ramucirumab + docetaxel			Placebo + docetaxel			Ramucirumab + docetaxel vs. placebo + docetaxel
	N[a]	Baseline values mean (SD)	Change from baseline mean[b] (SD)	N[a]	Baseline values mean (SD)	Change from baseline mean[b] (SD)	MD [95% CI][c]; p-value
Morbidity							
Health status (VAS of the EQ-5D)[d]							
REVEL	No usable data						
JVCG	78	71.9 (20.1)[e]	-1.9 (16.3)	90	71.4 (19.9)[e]	-8.8 (27.3)	6.90 [0.21; 13.59]; 0.043 Hedges' g[c]: 0.31 [0.01; 0.62]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: At the documentation time 30-day follow-up visit, analysis of the mean difference without imputation of missing values.
c: Institute's calculation.
d: Lower values indicate worse health status.
e: The values at the start of the study are based on the total FAS 2 population.
CI: confidence interval; EQ-5D European Quality of Life-5 Dimensions; FAS: full analysis set; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 17: Results (side effects) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome category Outcome Study	Ramucirumab + docetaxel N	Ramucirumab + docetaxel Median time to event (months) [95% CI] Patients with event n (%)	Placebo + docetaxel N	Placebo + docetaxel Median time to event (months) [95% CI] Patients with event n (%)	Ramucirumab + docetaxel vs. placebo + docetaxel RR [95% CI]; p-value
Side effects					
AEs					
REVEL	627	ND 613 (97.8)	618	ND 594 (96.1)	–
JVCG[a]	94	ND 94 (100)	98	ND 98 (100)	–
SAEs					
REVEL	627	8,3 [5,3; NA] 269 (42.9)	618	6.0 [4.9; 9.8] 262 (42.4)	1.01 [0.89; 1.15][b] *HR: 0.96 [0.81; 1.13]; 0.580*
JVCG[a]	94	ND 30 (31.9)	98	ND 31 (31.6)	1.01 [0.67; 1.53]; 0.967
Total					1.01 [0.89; 1.14]; 0.853[b]
Severe AEs (CTCAE grade ≥ 3)					
REVEL	627	0.3 [0.3; 0.4] 495 (78.9)	618	0.8 [0.4; 1.0] 444 (71.8)	HR: 1.21 [1.06; 1.38]; 0.004 *1.10 [1.03; 1.17][b]*
JVCG[a]	94	ND 90 (95.7)	98	ND 93 (94.9)	*1.01 [0.95; 1.07]; 0.781*
Total	Heterogeneity[b, c]: Q = 5.18; df = 1; p = 0.023; I^2 = 80.7 %				
Discontinuation due to AEs					
REVEL	627	NA 58 (9,3)	618	NA 32 (5,2)	1.79 [1.18; 2.71][b]
JVCG[a]	94	ND 38 (40.4)	98	ND 20 (20.4)	1.98 [1.25; 3.14]; 0.004
Total					1.87 [1.37; 2.55]; < 0.001[b]
Stomatitis CTCAE grade ≥ 3					
REVEL[d]	627	ND 27 (4.3)	618	ND 10 (1.6)	2.66 [1.30; 5.45][b]
JVCG[a, e]	94	ND 6 (6.4)	98	ND 1 (1.0)	6.26 [0.77; 50.98][b]
Total					2.91 [1.48; 5.74]; 0.002[b]

(continued)

Table 17: Results (side effects) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

Outcome category Outcome Study	Ramucirumab + docetaxel N	Ramucirumab + docetaxel Median time to event (months) [95% CI] Patients with event n (%)	Placebo + docetaxel N	Placebo + docetaxel Median time to event (months) [95% CI] Patients with event n (%)	Ramucirumab + docetaxel vs. placebo + docetaxel RR [95% CI]; p-value
Side effects					
Bleeding/haemorrhagic events					
REVEL[f]	627	NA 181 (28,9)	618	NA 94 (15,2)	1.90 [1.52; 2.37][b] *HR: 1.90 [1.48; 2.44]* < 0.001
JVCG[a, g]	94	ND 49 (52.1)	98	ND 30 (30.6)	1.70 [1.19; 2.43] 0.003
Total					1.84 [1.52; 2.22]; < 0.001[b]
Febrile neutropenia CTCAE grade ≥ 3					
REVEL	627	100 (15.9)	618	62 (10.0)	1.59 [1.18; 2.14][b]
JVCG[a]	94	32 (34.0)	98	18 (18.4)	1.85 [1.12; 3.07][b]
Total					1.65 [1.28; 2.14]; < 0.001[b]

Information in italics is only provided as additional information

a: Results of the second data cut-off on 20 May 2015.
b: Institute's calculation from meta-analysis.
c: Due to the heterogeneity, results on this outcome are only used from the REVEL study.
d: Stomatitis of any CTCAE grade, n (%): ramucirumab + docetaxel 146 (23.3); placebo + docetaxel 80 (12.9); SAE: ramucirumab + docetaxel 14 (2.2); placebo + docetaxel 2 (0.3).
e: Stomatitis of any CTCAE grade, n (%): ramucirumab + docetaxel 51 (54.3); placebo + docetaxel 31 (31.6); SAE: ramucirumab + docetaxel 1 (1.1); placebo + docetaxel 0 (0).
f: Bleeding events with CTCAE grade ≥ 3: ramucirumab + docetaxel 15 (2.4); placebo + docetaxel 14 (2.3); gastrointestinal haemorrhages of any CTCAE grade: ramucirumab + docetaxel 17 (2.7); placebo + docetaxel 10 (1.6).
g: Bleeding events with CTCAE grade ≥ 3: ramucirumab + docetaxel 2 (2.1); placebo + docetaxel 0 (0); gastrointestinal haemorrhages of any grade: ramucirumab + docetaxel 6 (6.4); placebo + docetaxel 2 (2.0).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Partly proof, e.g. of an added benefit, could be derived from the available data (see Section 2.4.2).

Mortality

For the outcome "overall survival", the meta-analysis of the studies included showed a statistically significant prolongation in overall survival for treatment with ramucirumab in combination with docetaxel versus docetaxel. Moreover, there was proof of an effect modification by the characteristic "age". For patients < 65 years, there was proof of an added benefit of ramucirumab + docetaxel versus docetaxel. In the group of patients ≥ 65 years,

however, there was no hint of an added benefit of ramucirumab + docetaxel in comparison with docetaxel. An added benefit for the outcome "overall survival" is therefore not proven for patients ≥ 65 years.

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

Morbidity

Symptoms (LCSS, ASBI)

No statistically significant difference between the treatment arms was shown for the analysis of the time to deterioration of symptoms recorded with the LCSS ASBI in the REVEL study. The analysis was only based on the REVEL study because the LCSS was recorded in the JVCG study, but no analysis as ASBI was available. The results of the individual items of the LCSS from the JVCG did not raise doubts about the ASBI results of the REVEL study. Overall, no hint of an added benefit of ramucirumab + docetaxel versus docetaxel could be derived for symptoms. An added benefit for this outcome is therefore not proven. This is in accordance with the assessment of the company.

Health status (VAS of the EQ-5D)

For the outcome "health status" recorded with the EQ-5D VAS, on the basis of the results of the JVCG study, a statistically significant difference in favour of ramucirumab + docetaxel in comparison with docetaxel was shown for the mean change at the time point 30 days after ending the study medication. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2, however. Hence it could not be inferred that the effect was relevant; there was no hint of an added benefit of ramucirumab + docetaxel versus docetaxel for health status. An added benefit for this outcome is therefore not proven. This concurs with the assessment of the company, which based its conclusion on the information of the REVEL study and allocated the EQ-5D to quality of life.

Health-related quality of life

Health-related quality of life was not recorded in the studies. In the outcome category "quality of life", the company presented data of the questionnaire LCSS and of the EQ-5D VAS. The LCSS is not validated for health-related quality of life, however. As the results of the EQ-5D VAS, the results on symptoms recorded with the LCSS ASBI were allocated to the outcome category "morbidity". Hence there was no hint of an added benefit of ramucirumab + docetaxel versus docetaxel for health-related quality of life. An added benefit is therefore not proven.

This concurs with the assessment of the company, which used analyses of the LCSS and of the EQ-5D VAS in the category "quality of life", but derived no added benefit of ramucirumab + docetaxel versus docetaxel.

Side effects

Serious adverse events

The meta-analysis of the included studies showed no statistically significant difference between the treatment groups for the outcome "SAEs". However, there was proof of an effect modification by the characteristic "age", based on the results of the REVEL study. For patients < 65 years, there was a hint of lesser harm from ramucirumab + docetaxel versus docetaxel. In the group of patients ≥ 65 years, however, there was a hint of greater harm from ramucirumab + docetaxel in comparison with docetaxel.

This deviates from the assessment of the company, which derived no hint of greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel for the outcome "SAEs".

Severe adverse events (CTCAE grade ≥ 3)

The meta-analysis showed important heterogeneity between both studies for the outcome "severe AEs (CTCAE grade ≥ 3)". In this situation, only the results of the REVEL study were used in the present assessment. The JVCG study was only conducted in Japan so that, in a heterogeneous situation, the REVEL study has greater relevance for the German health care context. A statistically significant difference to the disadvantage of ramucirumab + docetaxel versus docetaxel was shown here. This resulted in a hint of greater harm of ramucirumab + docetaxel in comparison with docetaxel for this outcome. This is in accordance with the assessment of the company.

Discontinuation due to adverse events

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel versus docetaxel for the outcome "discontinuation due to AEs". This resulted in proof of greater harm of ramucirumab + docetaxel in comparison with docetaxel for this outcome.

This deviates from the assessment of the company, which derived no hint of greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel for the outcome "discontinuation due to AEs". The company's conclusion was only based on the results of the REVEL study and a deviating operationalization of the outcome (see Section 2.7.2.4.3 of the full dossier assessment), for which no significant difference between the treatment arms was shown.

Specific adverse events: stomatitis (CTCAE grade ≥ 3) and febrile neutropenia (CTCAE grade ≥ 3)

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel in comparison with docetaxel for each of the AE outcomes "stomatitis" (CTCAE grade ≥ 3) and "febrile neutropenia" (CTCAE grade ≥ 3). There was an indication of greater harm for the outcome "stomatitis" (CTCAE grade ≥ 3) and proof of greater harm for the outcome "febrile neutropenia" (CTCAE grade ≥ 3), in each case

from ramucirumab + docetaxel in comparison with docetaxel (the justification of the different probability of the results of both outcomes can be found in Section 2.4.2).

This deviates from the company's assessment, which considered no results on these 2 outcomes.

Specific adverse events: bleeding/haemorrhagic events

The meta-analysis of the included studies showed a statistically significant difference to the disadvantage of ramucirumab + docetaxel in comparison with docetaxel for the outcome "bleeding/haemorrhagic events". Moreover, there was proof of an effect modification by the characteristic "histology". For patients with non-squamous cell carcinoma, there was a hint of greater harm from ramucirumab + docetaxel versus docetaxel. In the group of patients with squamous cell carcinoma, however, there was no hint of greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel. Greater or lesser harm for the outcome "bleeding/haemorrhagic events" for patients with squamous cell carcinoma is therefore not proven.

This deviates from the assessment of the company, which, on the basis of the results of the REVEL study, derived an indication of greater harm from ramucirumab + docetaxel in comparison with docetaxel for the total population.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment (see also Section 2.7.2.4.3 of the full dossier assessment):

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- geographical region (Japan/East Asia, rest of the world)
- smoking status (never-smoker, current smoker)
- histology (non-squamous cell carcinoma, squamous cell carcinoma)
- presence of brain metastases (yes, no)

For the REVEL study, analyses were available for the characteristics mentioned on all outcomes for which usable data were available. Exceptions were the outcomes "stomatitis" CTCAE grade ≥ 3 and "febrile neutropenia" CTCAE grade ≥ 3, for which no subgroup analyses were available and the characteristics "smoking status" and "central nervous system metastases", for which subgroup analyses were only available for overall survival. The available analyses were not usable for the outcome "discontinuation due to AEs" because they were not based on the operationalizations relevant for the assessment (see Section 2.7.2.4.3 of the full dossier assessment).

For the JVCG study, the company produced no additional subgroup analyses so that the analyses of the CSR had to be used (see Section 2.7.2.4.3 of the full dossier assessment). They contained the subgroup analyses for the subgroup characteristics mentioned (except brain metastases) for the outcomes “overall survival” and “severe AEs” (CTCAE grade ≥ 3).

In cases where subgroup analyses of both studies were present, deviating from the company, joint interaction tests were calculated.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2.

Hereinafter, results on subgroups with at least an indication of an effect modification and, in addition, a statistically significant and relevant effect in at least one subgroup are presented for the outcomes “overall survival”, “symptoms” LCSS, ASBI”, “SAEs”, “severe AEs”, and in specific AEs for the outcome “bleeding/haemorrhagic events”. Supplementary presentations of the Kaplan-Meier curves can be found in Appendix A, and the figures of the meta-analyses in Appendix B of the full dossier assessment.

Table 18: Subgroups (overall survival) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome Characteristic Study Subgroup	Ramucirumab + docetaxel N	Ramucirumab + docetaxel Median survival time in months [95% CI] Patients with event n (%)	Placebo + docetaxel N	Placebo + docetaxel Median survival time in months [95% CI] Patients with event n (%)	Ramucirumab + docetaxel vs. placebo + docetaxel HR [95% CI]	 p-value
Mortality						
Overall survival						
Age						
REVEL						
< 65 years	391	11.33 [10.28; 12.55] 252 (64.5)	407	8.90 [7.36; 10.18] 301 (74.0)	0.74 [0.62; 0.87]	< 0.001
≥ 65 years	237	9.20 [7.62; 10.32] 176 (74.3)	218	9.26 [8.54; 10.97] 155 (71.1)	1.10 [0.89; 1.36]	0.393
JVCG[a]						
< 65 years	43	26.55 [12.71; NA] 18 (41.9)	47	14.65 [11.43; NA] 25 (53.2)	0.65 [0.35; 1.20]	0.167
≥ 65 years	51	16.20 [12.39; NA] 28 (54.9)	51	13.96 [9.49; 24.44] 31 (60.8)	0.86 [0.51; 1.43]	0.555
Total					Interaction:	0.004[b]
< 65 years					0.73 [0.62; 0.86]	< 0.001
≥ 65 years					1.06 [0.87; 1.29]	0.551

a: Results of the second data cut-off on 20 May 2015.
b: Institute's calculation from meta-analysis.
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 19: Subgroups (side effects: time to first occurrence) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome Characteristic	Ramucirumab + docetaxel		Placebo + docetaxel		Ramucirumab + docetaxel vs. placebo + docetaxel	
Study Subgroup	**N**	**Median time to event (months) [95% CI] Patients with event n (%)**	**N**	**Median time to event (months) [95% CI] Patients with event n (%)**	**HR [95% CI]**	**p-value**
Side effects						
Serious adverse events						
Age						
REVEL						
< 65 years	390	19.3 [8.3; NA] 141 (36.2)	404	5.1 [4.0; 9.8] 175 (43.3)	0.70 [0.56; 0.87]	0.001
≥ 65 years	237	2.8 [1.8; 5.3] 128 (54.0)	214	7.4 [5.5; NA] 87 (40.7)	1.54 [1.17; 2.03]	0.002
JVCG						
Men	66	ND	71	ND	ND	ND
Women	28	ND	27	ND	ND	ND
Total					Interaction:	< 0.001

(continued)

Table 19: Subgroups (side effects: time to first occurrence) – RCT, direct comparison: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

Outcome Characteristic	Ramucirumab + docetaxel		Placebo + docetaxel		Ramucirumab + docetaxel vs. placebo + docetaxel	
Study Subgroup	N	Median time to event (months) [95% CI] Patients with event n (%)	N	Median time to event (months) [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Side effects						
Bleeding/haemorrhagic events						
Sex						
REVEL						
Men	417	14.5 [8.8; NA] 109 (26.1)	411	NA [10.8; NA] 66 (16.1)	1.58 [1.17; 2.15]	0.003
Women	210	14.6 [7.1; NA] 72 (34.3)	207	NA [NA; NA] 28 (13.5)	2.64 [1.71; 4.09]	< 0.001
JVCG						
Men		ND		ND	ND	ND
Women		ND		ND	ND	ND
Total					Interaction:	0.058
Histology						
REVEL						
Non-squamous cell carcinoma	465	14.5 [10.0; NA] 145 (31.2)	411	NA [NA; NA] 66 (16.1)	2.34 [1.73; 3.16]	< 0.001
Squamous cell carcinoma	157	NA [8.8; NA] 36 (22.9)	170	NA [10.2; NA] 33 (19.4)	1.10 [0.68; 1.76]	0.711
JVCG						
Non-squamous cell carcinoma	85	ND	88	ND	ND	ND
Squamous cell carcinoma	9	ND	10	ND	ND	ND
Total					Interaction:	0.008

CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Mortality

There was proof of an effect modification by the characteristic “age” for the outcome “overall survival”. A statistically significant difference in favour of ramucirumab + docetaxel was shown for patients < 65 years. For patients < 65 years, there was proof of an added benefit of ramucirumab + docetaxel versus docetaxel for the outcome “overall survival”. There was no statistically significant difference between the treatment groups in the group of patients ≥ 65 years, however. For patients ≥ 65 years, there was therefore no hint of an added benefit

of ramucirumab + docetaxel in comparison with docetaxel; an added benefit is therefore not proven for this subgroup.

This deviates from the assessment of the company, which, based on the results of the REVEL study, also identified the proof of effect modification by the characteristic "age", but did not consider it to be relevant for the conclusion. It stated that there was no biological or medical rationale for the observed age effect. According to the company, no age-dependent treatment effect was shown in studies with ramucirumab in other therapeutic indications. It added that age was no stratification factor in the REVEL study and possible imbalances regarding prognostic factors between the treatment arms in the age groups could not be excluded. This argument was not followed because this is not to be expected in a randomized study with the present patient number. In addition, the multifactorial analyses conducted by the company post hoc (Cox model under inclusion of different prognostic factors and other cut-off values) showed further different effects by age groups. The detailed analyses of smaller age groups presented by the company or the modelling of age as continuous variable did not raise fundamental doubts about them. Furthermore, the results of the REVEL study regarding the effect modification by age were, at least in their tendency, confirmed by the JVCG study.

Deviating from the present assessment, the company derived an indication of an added benefit of ramucirumab + docetaxel in comparison with docetaxel for the outcome "overall survival" on the basis of the results of the REVEL study for the total population.

Side effects

Serious adverse events

Based on the results of the REVEL study, proof of an effect modification by the characteristic "age" was shown for the outcome "SAEs". A statistically significant difference in favour of ramucirumab + docetaxel was shown for patients < 65 years. For patients < 65 years, this resulted in a hint of lesser harm from ramucirumab + docetaxel versus docetaxel for the outcome "SAEs". In the group of patients ≥ 65 years, however, a significant difference was shown to the disadvantage of ramucirumab + docetaxel versus docetaxel. For patients ≥ 65 years, this resulted in a hint of greater harm from ramucirumab + docetaxel for the outcome "SAEs".

The lesser harm in the subgroup of patients < 65 years was not conclusively comprehensible because the combination treatment with ramucirumab + docetaxel resulted in fewer SAEs than monotherapy with docetaxel. The investigation of the SAEs in the total population (see Table 27 of the full dossier assessment; the dossier contained no detailed information on individual SAEs for the subgroups) showed that they were not caused to a major extent by events that may also be due to disease progression. Hence the effect presumably did not primarily represent a benefit of the combination by preventing disease progression. In the overall consideration, the lesser harm from ramucirumab + docetaxel in comparison with docetaxel for patients < 65 years was subject to increased uncertainty, particularly also

because greater harm from the combination treatment was shown for severe AEs (CTCAE grade ≥ 3) for all age groups.

The separate interpretation of the results for the outcome "SAEs" by age groups deviates from the assessment of the company, which, based on the results of the REVEL study, also identified the proof of effect modification by the characteristic "age", but did not consider it to be relevant for the conclusion.

Deviating from the present assessment, the company derived no greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel for the outcome "SAEs" on the basis of the results of the REVEL study for the total population.

Bleeding/haemorrhagic events

There was both an indication of an effect modification by the characteristic "sex" and proof of an effect modification by the characteristic "histology" for the outcome "bleeding/haemorrhagic events". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Since there was proof of an effect modification by the characteristic "histology", but only an indication of an effect modification by the characteristic "sex", only the results on the characteristic "histology" were considered for the benefit assessment. For the characteristic "sex", concurring with the total population, there were also statistically significant differences to the disadvantage of ramucirumab + docetaxel for men and women.

For the characteristic "histology", a statistically significant difference to the disadvantage of ramucirumab + docetaxel versus docetaxel was shown for patients with non-squamous cell carcinoma for the outcome "bleeding/haemorrhagic events". For patients with non-squamous cell carcinoma, this resulted in a hint of greater harm from ramucirumab + docetaxel for the outcome "bleeding/haemorrhagic events". There was no statistically significant difference between the treatment groups in the group of patients with squamous cell carcinoma, however. Hence there was no hint of greater or lesser harm from ramucirumab + docetaxel in comparison with docetaxel for patients with squamous cell carcinoma; greater or lesser harm is therefore not proven for this subgroup.

This deviates from the assessment of the company, which, based on the results of the REVEL study, also identified the proof of effect modification by the characteristic "histology", but did not consider it to be relevant for the conclusion. The company derived a hint of greater harm of ramucirumab + docetaxel in comparison with docetaxel for the total population.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit 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 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in the following assessments for ramucirumab in combination with docetaxel in comparison with docetaxel:

- proof of an added benefit for overall survival for patients < 65 years
- a hint of lesser harm regarding SAEs for patients < 65 years
- a hint of greater harm regarding SAEs for patients ≥ 65 years
- proof of greater harm for the AE outcomes "discontinuation due to AEs" and "febrile neutropenia" (CTCAE grade ≥ 3), an indication of greater harm for the specific AE "stomatitis" (CTCAE grade ≥ 3) and a hint of greater harm for severe AEs (CTCAE grade ≥ 3)
- a hint of greater harm for the specific AE "bleeding/haemorrhagic events" for patients with non-squamous cell carcinoma

Determination of the outcome category for the outcome "discontinuation due to adverse events"

The assessment of the outcome category of "discontinuations due to AEs" depends on the severity of the AEs that led to discontinuation. In the REVEL study, 50 % of the discontinuations (45 of 90 discontinuations) were discontinuations due to an AE of severity grade ≥ 3 according to CTCAE. This classification by severity grade was not available for the JVCG study. However, there was information on the proportion of discontinuations due to SAEs, which was 31% (18 of 58 discontinuations) and therefore markedly below 50%. The results of the outcome "discontinuation due to AEs" were therefore allocated to the outcome category of non-serious/non-severe side effects.

Determination of the outcome category for the outcome "bleeding/haemorrhagic events"

The assessment of the outcome category of "bleeding/haemorrhagic events" depends on the severity of the AEs. The majority of the events were non-severe bleeding events of CTCAE grade < 3 (see Table 17). The results of the outcome "bleeding/haemorrhagic events" were therefore allocated to the outcome category of non-serious/non-severe side effects.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 20).

Table 20: Extent of added benefit at outcome level: ramucirumab + docetaxel vs. placebo + docetaxel

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + docetaxel vs. placebo + docetaxel** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Age		
< 65 years	Median: 11.33 to 26.55 vs. 8.90 to 14.65 months[c] HR: 0.73 [0.62; 0.86] p < 0.001 probability: "proof"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
≥ 65 years	Median: 9.20 to 16.20 vs. 9.26 to 13.96 months[c] HR: 1.06 [0.87; 1.29] p = 0.551	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (LCSS, ASBI)[d]	Median: 22.34 vs. 9.17 months HR: 0.93 [0.75; 1.15] p = 0.510	Lesser benefit/added benefit not proven
Health status (VAS of the EQ-5D)[e]	mean: −1.9 vs. -8.8 MD: 6.90 [0.21; 13.59] P =0.043 Hedges' g: 0.31 [0.01; 0.62]	Lesser benefit/added benefit not proven
Health-related quality of life		
	No data available	Lesser benefit/added benefit not proven

(continued)

Table 20: Extent of added benefit at outcome level: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + docetaxel vs. placebo + docetaxel** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Serious adverse events		
Age		
< 65 years[d]	Median: 19.3 vs. 5.1 months HR: 0.70 [0.56; 0.87] p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
≥ 65 years[d]	Median: 2.8 vs. 7.4 months HR: 1.54 [1.17; 2.03] HR: 0.65 [0.49; 0.85][f] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Discontinuation due to adverse events	Proportion: 9.3 % to 40.4 % vs. 5.2 % to 20.4 %[c] RR: 1.87 [1.37; 2.55] RR: 0.53 [0.39; 0.73][f] p < 0.001 probability: "proof"[g]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Severe AEs CTCAE grade ≥ 3[h]	Median: 0.3 vs. 0.8 months HR: 1.21 [1.06; 1.38] HR: 0.83 [0.72; 0.94][f] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Side effects		
Stomatitis CTCAE grade ≥ 3	Proportion: 4.3 % to 6.4 % vs. 1.0 % to 1.6 %[c] RR: 2.91 [1.48; 5.74] RR: 0.34 [0.17; 0.68][f] p = 0.002 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"

(continued)

Table 20: Extent of added benefit at outcome level: ramucirumab + docetaxel vs. placebo + docetaxel (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + docetaxel vs. placebo + docetaxel** **Median time to event or proportion of events or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Febrile neutropenia CTCAE grade ≥ 3	Proportion: 15.9 % to 34.0 % vs. 10.0 % to 18.4 %[c] RR: 1.65 [1.28; 2.14] RR: 0.61 [0.47; 0.78][f] p < 0.001 probability: "proof"[g]	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Bleeding/haemorrhagic events		
Histology		
Non-squamous cell carcinoma[d]	Median: 14.5 vs. NA months HR: 2.34 [1.73; 3.16] HR: 0.43 [0.32; 0.58][f] p = < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Squamous cell carcinoma[d]	median: NA vs. NA months HR: 1.10 [0.68; 1.76] p = 0.711	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events or median time to event in each treatment arm in the studies included.
d: Only data from the REVEL study were available.
e: Only data from the JVCG study were available.
f: Institute's calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.
g: In the present situation, the probability "proof" resulted from the presence of a homogeneous significant effect from both studies and, in addition, the weight of at least 25% of the study with a low risk of bias regarding the outcome (JVCG).
h: Data of the JVCG study were not used for the derivation of the 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; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; MD: mean difference; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on the added benefit

Table 21 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of ramucirumab + docetaxel in comparison with placebo + docetaxel

Positive effects	Negative effects
Mortality ▪ overall survival ▫ < 65 years proof of an added benefit – extent: "considerable"	
Serious/severe side effects ▪ SAEs ▫ < 65 years hint of lesser harm – extent: "considerable"	Serious/severe side effects ▪ SAEs ▫ ≥ 65 years hint of greater harm – extent: "considerable" ▪ severe AEs CTCAE grade ≥ 3 hint of greater harm – extent: "minor" ▪ stomatitis CTCAE grade ≥ 3 indication of greater harm – extent: "considerable" ▪ febrile neutropenia CTCAE grade ≥ 3 proof of greater harm – extent: "considerable"
	Non-serious/non-severe side effects ▪ bleeding/haemorrhagic events ▫ non-squamous cell carcinoma hint of greater harm – extent: "considerable" ▪ discontinuation due to AEs proof of greater harm – extent: "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

The results showed a relevant effect modification by age for 2 outcomes. Hereinafter, the overall conclusion on the added benefit is derived separately for patients < 65 years and for patients ≥ 65 years.

Patients < 65 years

In the overall consideration, there were positive and negative effects for patients < 65 years. On the positive side, there was proof of an added benefit of considerable extent for the outcome "overall survival" and a hint of lesser harm of considerable extent in the outcome category "SAEs". The lesser harm was subject to additional uncertainty (see Section 2.4.4), which did not change the overall conclusion on the added benefit, however. The positive effects were accompanied by negative effects with different extent and different certainty of results. A hint of greater harm with minor extent (severe AEs CTCAE grade ≥ 3), an indication of greater harm of considerable extent (stomatitis CTCAE grade ≥ 3), and proof of greater harm also of considerable extent (febrile neutropenia CTCAE grade ≥ 3) were found in the category "serious/severe side effects". In addition, in the category of non-serious/non-

severe side effects, there was proof of greater harm with considerable extent (discontinuation due to AEs) and a hint of greater harm with considerable extent (bleeding/haemorrhagic events) only for patients with non-squamous cell carcinoma. Overall, the negative effects were not so large as to completely outweigh the mortality advantage of ramucirumab in combination with docetaxel.

In summary, there is proof of a minor added benefit of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients < 65 years.

Patients ≥ 65 years

For patients ≥ 65 years, only negative effects remained in the outcome categories "serious/severe side effects" and "non-serious/non-severe side effects", which were of minor and considerable extent with different probabilities (hint, indication, or proof). In summary, there is therefore proof of lesser benefit of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients ≥ 65 years.

The result of the assessment of the added benefit of ramucirumab in comparison with the ACT is summarized in Table 22.

Table 22: Ramucirumab – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Subgroup	Extent and probability of added benefit
Adult patients with locally advanced or metastatic NSCLC with progression after platinum-based chemotherapy[b]	**Docetaxel** or pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib) or crizotinib (only for patients with activating ALK mutations)	< 65 years	Proof of minor added benefit
		≥ 65 years	Proof of lesser benefit

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.
b: According to the approval, ramucirumab is used in combination with docetaxel.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

This deviates from the company's approach, which derived an indication of minor added benefit for the total population.

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

JVCG

Eli Lilly. A study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer: full text view [online]. In: ClinicalTrials.gov. 25.01.2016 [Accessed: 03.03.2016]. URL: https://ClinicalTrials.gov/show/NCT01703091.

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Eli Lilly. A randomized, double-blind, phase 2 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy: study I4T-JE-JVCG; clinical study report [unpublished]. 2015.

Eli Lilly. A randomized, double-blind, phase 2 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy: study I4T-JE-JVCG; clinical study report addendum [unpublished]. 2015.

REVEL

Eli Lilly. A randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy [online]. In: PharmNet.Bund Klinische Prüfung. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Eli Lilly. A study of chemotherapy and ramucirumab versus chemotherapy alone in second line non-small cell lung cancer (NSCLC) participants who received prior first line platinum-based chemotherapy: full text view [online]. In: ClinicalTrials.gov. 20.08.2015 [Accessed: 03.03.2016]. URL: https://ClinicalTrials.gov/show/NCT01168973.

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Garon EB, Cao D, Alexandris E, John WJ, Yurasov S, Perol M. A randomized, double-blind, phase III study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small-cell lung cancer after disease progression after 1 previous platinum-based therapy (REVEL): treatment rationale and study design. Clin Lung Cancer 2012; 13(6): 505-509.

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384(9944): 665-673.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-11-ramucirumab-new-therapeutic-indication-benefit-assessment-according-to-35a-social-code-book-v.7229.html.