IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-10

Ramucirumab (colorectal 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 – 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
FOLFIRI	folinic acid, irinotecan, and 5-fluorouracil
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
MCRC	metastatic colorectal cancer
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 the present report was the assessment of the added benefit of a combination therapy of ramucirumab and FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) in comparison with FOLFIRI as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer (MCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

The G-BA specified FOLFIRI as ACT for the therapeutic indication (see Table 2).

Table 2: Research questions of the benefit assessment of ramucirumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adult patients with MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine[b]	FOLFIRI

a: Presentation of the respective ACT specified by the G-BA.
b: According to the approval, ramucirumab is used in combination with FOLFIRI.
ACT: appropriate comparator therapy; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer

The company used the ACT specified by the G-BA.

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

Results

Study pool and study characteristics

The study RAISE was included in the benefit assessment. This study was a randomized, double-blind, multicentre controlled study on the comparison of ramucirumab in combination with FOLFIRI versus FOLFIRI.

Adult patients with stage IV MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine were included in the study. The metastatic

disease was not potentially curable resectable. Patients were required to be in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) at the time point of randomization. A total of 1072 patients were randomized in a ratio of 1:1, 536 patients to the combination arm (ramucirumab + FOLFIRI) and 536 patients to the FOLFIRI arm.

The study treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the physician to discontinue treatment.

Overall survival was recorded as patient-relevant primary outcome in the study. Patient-relevant secondary outcomes were health-related quality of life, symptoms and adverse events (AEs).

Risk of bias

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

The risk of bias was rated as low for the outcome "overall survival", and as high for all other outcomes.

Results

Mortality

Treatment with ramucirumab in combination with FOLFIRI resulted in a statistically significant prolongation of overall survival in comparison with FOLFIRI. In addition, there was proof of an effect modification by the characteristic "sex" for this outcome. This resulted in an indication of an added benefit of ramucirumab in combination with FOLFIRI in comparison with FOLFIRI for the outcome "all-cause mortality" for women. For men, however, there was no indication of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

Morbidity

- Symptoms

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

For each of the outcomes **"appetite loss"** and **"constipation"**, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for the time to deterioration of symptoms. In addition, there was proof of an effect modification by the characteristic "sex" for both outcomes.

For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, however, there was no hint of lesser benefit or added benefit of ramucirumab in

combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

For the outcome **"fatigue"**, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI, which was no more than marginal, however, for the time to deterioration of symptoms. Hence there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this outcome.

There was no statistically significant difference between the treatment options for the time to deterioration of symptoms for any of the following outcomes: **diarrhoea, dyspnoea, insomnia, nausea and vomiting** and **pain**. This resulted in no hint of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for the time to deterioration for each of the following outcomes: **global health status, physical functioning** and **emotional functioning**. In addition, there was an indication of an effect modification by the characteristic "sex" for all 3 outcomes. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, however, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for the time to deterioration for the outcome **"role functioning"**. In addition, there was proof of an effect modification by the characteristic "sex". For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

No statistically significant difference between the treatment options was shown for the time to deterioration for the outcomes **"cognitive functioning"** and **"social functioning"**. This resulted in no hint of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

Side effects

- Serious adverse events

No statistically significant difference between the treatment options was shown for the outcome "serious adverse events (SAEs)" (time to first event). This resulted in no hint of greater or lesser harm of ramucirumab in combination with FOLFIRI in comparison with the ACT for SAEs; greater or lesser harm is therefore not proven for this outcome.

- Discontinuation due to adverse events, severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for each of the outcomes "discontinuation due AEs" (time to first event) and "severe AEs (Common Terminology Criteria for Adverse events [CTCAE] grade ≥ 3)" (time to first event). This resulted in a hint of greater harm of ramucirumab for both outcomes.

- Specific adverse events

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for each of the following outcomes: **peripheral oedema, palmar-plantar erythrodysaesthesia syndrome, headache, bleeding/haemorrhagic events** as well **bleeding/haemorrhagic events: gastrointestinal bleeding** as part of the bleeding events. This resulted in a hint of greater harm of ramucirumab in combination with FOLFIRI for these outcomes.

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:

The results showed relevant effect modifications by sex for several outcomes of the categories "mortality", "morbidity" and "health related quality of life". Hereinafter, the overall conclusion on the added benefit is therefore derived separately for men and women.

Women

Overall, there were positive and negative effects for women. On the positive side, there was an indication of an added benefit of considerable extent for the outcome "overall survival". This was accompanied by hints of negative effects of different extent. Hints of greater harm of major extent were found in the outcome category "serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs)". In addition, hints of greater harm

[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].

of considerable or minor extent were found in the outcome category "non-serious/non-severe side effects" (different specific AE outcomes). In the present situation, the observed negative effects could not completely outweigh the positive effect in overall survival. In summary, there is an indication of a minor added benefit of ramucirumab in combination with FOLFIRI versus the ACT FOLFIRI for the subgroup of women.

Men

For men, only negative effects remained in the following outcome categories: non-serious/non-severe symptoms/late complications (appetite loss, constipation), health-related quality of life (global health status, physical functioning, role functioning, emotional functioning), serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs) and non-serious/non-severe side effects (specific AE outcomes). In each case, there were hints of different extent. The greatest extent of major greater harm was found in the category of serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs) for both outcomes. In summary, there is a hint of lesser benefit of ramucirumab in combination with FOLFIRI versus the ACT FOLFIRI for the subgroup of men.

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	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Adult patients with MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine[b]	FOLFIRI	Women	Indication of minor added benefit
		Men	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. b: According to the approval, ramucirumab is used in combination with FOLFIRI. ACT: appropriate comparator therapy; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal 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 the present report was the assessment of the added benefit of a combination therapy of ramucirumab and FOLFIRI in comparison with FOLFIRI as ACT in adult patients with MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

The G-BA specified FOLFIRI as ACT for the therapeutic indication (see Table 4).

Table 4: Research questions of the benefit assessment of ramucirumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adult patients with MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine[b]	FOLFIRI

a: Presentation of the respective ACT specified by the G-BA.
b: According to the approval, ramucirumab is used in combination with FOLFIRI.
ACT: appropriate comparator therapy; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal cancer

The company used the ACT specified by the G-BA.

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

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 11 January 2016)
- search in trial registries for studies on ramucirumab (last search on 11 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.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
RAISE (I4T-MC-JVBB)[b]	Yes	Yes	No
a: Study for which the company was sponsor. b: Hereinafter referred to as "RAISE". FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; vs.: versus			

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 + FOLFIRI vs. placebo + FOLFIRI

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RAISE	RCT, double-blind, parallel	Adult patients (≥ 18 years) with MCRC (stage IV), ECOG PS ≤ 1 and disease progression on or after[b] first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine[c]	Ramucirumab + FOLFIRI (N = 536) placebo + FOLFIRI (N = 536)	Treatment: one cycle every 2 weeks until disease progression, unacceptable toxicity, discontinuation of the study medication for other reasons by the patient or the physician Observation: outcome-specific, at most until death, discontinuation of participation in the study or end of study	224 centres in Argentina, Australia, Austria, Belgium, Brazil, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Korea, Netherlands, Portugal, Puerto Rico, Romania, Spain, Sweden, Taiwan, USA 12/2010–7/2014	Primary: overall survival Secondary: health-related quality of life, 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: ≤ 6 months after the last dose of the first-line chemotherapy.
c: Patients were stratified by geographical region, KRAS status (mutant vs. wild type), and time to disease progression after commencing first-line treatment (< 6 months vs. ≥ 6 months).
AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; KRAS: Kirsten rat sarcoma viral oncogene homologue; MCRC: metastatic colorectal cancer; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison	Prior and concomitant medication
RAISE	Cycles every 2 weeks Day 1 of each cycle: ramucirumab 8 mg/kg IV infusion administered over about 60 min[a], followed by	Cycles every 2 weeks Day 1 of each cycle: placebo IV infusion administered over about 60 min, followed[a] by	**Pretreatment:** ▪ combination therapy with bevacizumab, oxaliplatin and a fluoropyrimidine **Non-permitted pretreatment:** ▪ more than 2 different fluoropyrimidines ▪ bevacizumab ≤ 28 days before randomization ▪ chemotherapy ≤ 21 days before randomization ▪ radiotherapy ≤ 14 days before randomization, pelvic radiotherapy ≤ 28 days **Concomitant treatment:** ▪ histamine H1 antagonists (e.g. diphenhydramine hydrochloride) ▪ antiemetics including dexamethasone in combination with 5-HT_3 antagonists ▪ palliative and supportive treatment of the symptoms of the underlying disease and of the toxicity of the study treatment **Non-permitted concomitant treatment:** ▪ additional chemotherapy except the study medication, radiotherapy ▪ immunomodulators, palliative radiotherapy of the areas affected by the underlying disease ▪ initiation of treatment with bisphosphonates or RANK-L inhibitors
	FOLFIRI: irinotecan 180 mg/m² BSA IV infusion over 90 min (± 10), followed by folinic acid 400 mg/m² BSA IV infusion over 120 min (± 10), followed by 5-FU 400 mg/m² BSA IV bolus over 2 to 4 min, followed by 5-FU 2 400 mg/m² BSA IV infusion over 46 to 48 hours		

a: 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.

BSA: body surface area; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; 5-FU: 5-fluorouracil; IV: intravenous, RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; vs. versus

Study design

The RAISE study was a randomized, double-blind, multicentre controlled study on the comparison of ramucirumab in combination with FOLFIRI versus FOLFIRI.

Adult patients with stage IV MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine were included in the study. The metastatic disease was not potentially curable resectable. Patients were required to be in good general condition (ECOG PS ≤ 1) at the time point of randomization. The population investigated in the study corresponded to the therapeutic indication of ramucirumab in the present research

question. Since no patients with ECOG PS > 1 were included, however, no conclusions can be derived from the available data for these patients.

A total of 1072 patients were randomized in a ratio of 1:1, 536 patients to the combination arm (ramucirumab + FOLFIRI) and 536 patients to the FOLFIRI arm. Stratification factors were geographical region, time to progression after commencing first-line treatment, and Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation status.

According to the Summary of Product Characteristics (SPC) [3], ramucirumab is only approved in combination with FOLFIRI. Hence the comparison of ramucirumab + FOLFIRI versus placebo + FOLFIRI investigated in the study concurs with the comparison relevant for this research question. The study was therefore suitable for assessing the added benefit of ramucirumab in comparison with the ACT.

The drug ramucirumab and the drug combination FOLFIRI used in the study were administered without relevant deviations from the respective SPCs [3-6]. Treatment was administered in a 2-week cycle. The study treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the physician to discontinue treatment. After discontinuation of the study treatment, the patients in both studies could receive further cancer treatments; switching from the comparator to the intervention group was not envisaged.

Overall survival was recorded as patient-relevant primary outcome in the study. Patient-relevant secondary outcomes were health-related quality of life, symptoms and AEs.

Follow-up

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

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

Study **Outcome category** **Outcome**	**Planned follow-up**
RAISE	
Mortality	
Overall survival	At least every 3 months (± 14 days) as long as the patient was alive and the study was ongoing
Morbidity	
Symptoms, health status	Up to 30 days (± 3 days) after discontinuation of the study medication
Health-related quality of life	Up to 30 days (± 3 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; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; vs.: versus	

Of the outcomes included, only overall survival was recorded until death. The other outcomes were recorded up to 30 days after the last treatment with the study medication.

The final data cut-off for the RAISE study was planned for the time point when at least 756 patients had died and was conducted on 17 July 2014. 769 patients had died at this time point. The present analyses of the RAISE study were based on this data cut-off.

Characteristics of the study population

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

Table 9: Characteristics of the study populations – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Characteristics Category	**Ramucirumab + FOLFIRI**	**Placebo + FOLFIRI**
RAISE	N[a] = 536	N[a] = 536
Age [years], mean (SD)	60.4 (11.0)	60.5 (10.7)
Sex [F/M], %	46.1/53.9	39.2/60.8
Ethnicity, n (%)		
White	405 (75.6)	410 (76.5)
Asian	111 (20.7)	103 (19.2)
Others[b]	20 (3.7)	23 (4.3)
ECOG PS, n (%)		
0	263 (49.1)	259 (48.3)
1	268 (50.0)	273 (50.9)
≥ 2	1 (0.2)	2 (0.4)
ND	4 (0.7)	2 (0.4)
KRAS status at baseline, n (%)		
Mutation	269 (50.2)	261 (48.7)
Wild type	267 (49.8)	275 (51.3)
Time to progression after commencing first-line treatment, n (%)		
< 6 months	125 (23.3)	129 (24.1)
≥ 6 months	411 (76.7)	407 (75.9)
Location of metastases, n (%)		
Liver	396 (73.9)	403 (75.2)
Lung	294 (54.9)	293 (54.7)
Lymph nodes	158 (29.5)	185 (34.5)
Peritoneum	82 (15.3)	84 (15.7)
Gastrointestinal tract	72 (13.4)	79 (14.7)
Bone	46 (8.6)	40 (7.5)
Liver metastases only, n (%)		
No	444 (82.8)	441 (82.3)
Yes	92 (17.2)	95 (17.7)
Time since first diagnosis [months], median [min; max]	14.3 [1.3; 210.2]	13.0 [0.3; 186.5]
Location of primary tumour, n (%)		
Colon	358 (66.8)	358 (66.8)
Rectum	174 (32.5)	171 (31.9)
Colorectal	4 (0.7)	7 (1.3)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Study Characteristics Category	Ramucirumab + FOLFIRI	Placebo + FOLFIRI
RAISE	N[a] = 536	N[a] = 536
Number of organs/tissues with metastases, n (%)		
1	171 (31.9)	157 (29.3)
2	205 (38.2)	194 (36.2)
≥ 3	157 (29.3)	182 (34.0)
ND	3 (0.6)	3 (0.6)
Treatment discontinuation[c], n (%)	511 (95.3)	513 (95.7)
Study discontinuation, n (%)	ND	ND

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: Other ethnic groups include: black/African American, native Americans or Alaskans, Hawaiians/Pacific islanders, plural ethnicities and others, Institute's calculation.
c: Reasons for treatment discontinuation: progression, AE, patient's decision, investigator's decision, death, withdrawal of consent, sponsor's decision, other.
AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group performance status; F: female; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; KRAS: Kirsten rat sarcoma viral oncogene homologue; M: male; n: number of patients in category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial, SD: standard deviation; vs.: versus

The demographic and disease-specific characteristics of the RAISE study were mostly balanced between the treatment groups. The mean age of the patients was 60 years, and most of them were white. The proportion of women was higher in the ramucirumab + FOLFIRI arm (46%) than in the placebo + FOLFIRI arm (39%). In just under 67%, the location of the primary tumour was in the colon; liver metastases were the most common metastases (over 70%). The median time since the first diagnosis was 14.3 months in the ramucirumab + FOLFIRI arm, and 13 months in the comparator arm. Reasons for treatment discontinuation, which occurred in 95% of the patients, included progression, occurrence of AEs, or death.

Table 10 shows the mean and median treatment duration of the patients.

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

Study **Duration of the study phase** **Outcome category**	**Ramucirumab + FOLFIRI**	**Placebo + FOLFIRI**
RAISE	N = 529	N = 528
Treatment duration component[a] [weeks]		
Median [min; max]	20.4 [2; 167]	18.3 [2; 112]
Mean (SD)	25.9 (21.9)	23.0 (19.1)
Treatment duration ramucirumab/placebo[b]		
Median [min; max]	19.0 [2; 167]	18.0 [2; 112]
Mean (SD)	24.9 (21.7)	22.4 (19.1)
Observation period [months]		
All outcomes considered in the benefit assessment	ND	ND

a: Treatment duration of any component of the combination therapy (ramucirumab, placebo or FOLFIRI).
b: Treatment duration of ramucirumab or placebo.
FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The treatment duration in the RAISE study differed between the 2 treatment arms. In the ramucirumab + FOLFIRI arm, at least one component of the treatment was administered for a median duration of 20 weeks; in the comparator arm for a median duration of 18 weeks. The median duration of the administration of ramucirumab was 19 weeks, and of the administration of placebo 18 weeks. No information on the actual observation period was available for any of the patient-relevant outcomes. 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 recorded for up to 30 days after the last administration of the study medication.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

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**			
RAISE	Yes	Yes	Yes	Yes	Yes	Yes	Low

FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

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 symptom scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30)
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Side effects
  - SAEs
  - discontinuation due to AEs
  - Severe adverse events (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 12 shows for which outcomes data were available in the studies included.

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

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Serious adverse events	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[a]
RAISE	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes

a: The following events (MedDRA coding) are considered: peripheral oedema (PT), palmar-plantar erythrodysaesthesia syndrome (PT), headache (PT), bleeding/haemorrhagic events (SMQ), bleeding/haemorrhagic events: gastrointestinal bleeding (SMQ).
b: No evaluable data available, due to the large proportion of patients not considered (see also Section 2.7.2.4.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; 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 13 shows the risk of bias for the relevant outcomes.

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

Study		Outcomes							
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Serious adverse events	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
RAISE	L	L	H[b, c]	Not applicable	H[b, c]	H[c]	H[c]	H[c]	H[d, e]

a: The following events specific AEs are considered: bleeding/haemorrhagic events (SMQ), bleeding/haemorrhagic events: gastrointestinal bleeding (SMQ), peripheral oedema (PT), palmar-plantar erythrodysaesthesia syndrome (PT), headache (PT).
b: Presumably high proportion (16%) of patients for whom no questionnaires were available after the start of the study.
c: The outcome was no longer recorded 30 days after progression (informative censoring). High proportion of patients with progression during the course of the study (63% in the ramucirumab + FOLFIRI arm vs. 78% in the FOLFIRI arm).
d: A Cox proportional hazards model was available for the specific AEs "bleeding/haemorrhagic events" and "bleeding/haemorrhagic events: gastrointestinal bleeding". The outcome was no longer recorded 30 days after progression (informative censoring). High proportion of patients with progression during the course of the study (63% in the ramucirumab + FOLFIRI arm vs. 78% in the FOLFIRI arm).
e: The relative risk was calculated for the specific AEs "peripheral oedema", "palmar-plantar erythrodysaesthesia syndrome" and "headache". The outcome was no longer recorded 30 days after progression. High proportion of patients with progression during the course of the study (63% in the ramucirumab + FOLFIRI arm vs. 78% in the FOLFIRI arm), who were therefore not observed until the end of the study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low. This concurs with the company's assessment.

The final assessment of the risk of bias was also followed for all other outcomes (high risk of bias), although other reasons than the ones mentioned by the company were relevant for the outcomes "health-related quality of life" and "symptoms".

In addition, as a result of the systematically shorter observation periods for the outcomes "side effects", "morbidity" and "quality of life", 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.

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

2.4.3 Results

Table 14 to Table 18 summarize the results on the comparison of ramucirumab in combination with FOLFIRI with the ACT FOLFIRI in patients with MCRC. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The available Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

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

Study **Outcome**	**Ramucirumab + FOLFIRI**		**Placebo + FOLFIRI**		**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
RAISE					
Overall survival	536	13.3 [12.4; 14.5] 372 (69.4)	536	11.7 [10.8; 12.7] 397 (74.1)	0.84 [0.73; 0.98]; 0.022

a: Cox proportional hazards model stratified by geographical region, time to progression after commencing first-line treatment, KRAS mutation status.
b: Log-rank test stratified by geographical region, time to progression after commencing first-line treatment, KRAS mutation status.
CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 15: Results (morbidity: time to deterioration of symptoms) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Outcome category	Ramucirumab + FOLFIRI		Placebo + FOLFIRI		Ramucirumab + FOLFIRI vs. placebo + FOLFIRI
Outcome Subscale/item	N	Median (months) [95% CI] Patients with event n (%)	N	Median (months) [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
RAISE					
Morbidity					
EORTC QLQ-C30 symptom scales[c]					
Appetite loss	536	2.6 [2.1; 2.9] 338 (63.1)	536	4.9 [3.9; 5.6] 269 (50.2)	1.43 [1.22; 1.68] < 0.001
Diarrhoea	536	4.0 [3.1; 4.8] 286 (53.4)	536	4.2 [3.1; 5.3] 281 (52.4)	0.96 [0.81; 1.13] 0.636
Dyspnoea	536	6.3 [4.9; 8.5] 248 (46.3)	536	7.4 [5.3; 9.9] 225 (42.0)	1.11 [0.93; 1.34] 0.252
Insomnia	536	5.6 [4.5; 8.1] 245 (45.7)	536	5.7 [4.5; 7.6] 246 (45.9)	0.98 [0.82; 1.17] 0.802
Nausea and vomiting	536	4.1 [3.1; 5.3] 284 (53.0)	536	3.0 [2.7; 3.9] 291 (54.3)	0.87 [0.74; 1.03] 0.110
Constipation	536	4.6 [4.0; 5.7] 259 (48.3)	536	7.4 [6.3; 10.2] 224 (41.8)	1.22 [1.02; 1.46] 0.031
Fatigue	536	1.5 [1.4; 1.7] 397 (74.1)	536	2.1 [1.9; 2.7] 346 (64.6)	1.28 [1.11; 1.48] 0.001
Pain	536	2.9 [2.5; 4.0] 324 (60.4)	536	4.2 [3.7; 5.0] 296 (55.2)	1.17 [1.00; 1.37] 0.055

a: Stratified Cox proportional hazards model.
b: Stratified log-rank test.
c: Time to deterioration of the score by at least 10 points versus the baseline value.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire Core-30 (general symptoms of cancer disease); RCT: randomized controlled trial; vs.: versus

Table 16: Results (time to deterioration of health-related quality of life) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Outcome category	Ramucirumab + FOLFIRI		Placebo + FOLFIRI		Ramucirumab + FOLFIRI vs. placebo + FOLFIRI
Outcome Subscale/item	N	Median (months) [95% CI] Patients with event n (%)	N	Median (months) [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
RAISE					
EORTC QLQ-C30 functional scales[c]					
Global health status	536	2.5 [2.0; 3.0] 335 (62.5)	536	4.0 [3.7; 4.8] 292 (54.5)	1.32 [1.13; 1.55] 0.001
Physical functioning	536	3.4 [2.8; 3.9] 313 (58.4)	536	4.8 [3.9; 6.0] 262 (48.9)	1.29 [1.09; 1.52] 0.003
Role functioning	536	2.1 [1.9; 2.6] 372 (69.4)	536	3.2 [2.8; 3.9] 316 (59.0)	1.38 [1.18; 1.61] < 0.001
Emotional functioning	536	6.5 [4.9; 8.8] 245 (45.7)	536	8.8 [6.7; 14.8] 195 (36.4)	1.24 [1.03; 1.50] 0.026
Cognitive functioning	536	4.0 [3.0; 4.6] 298 (55.6)	536	4.3 [3.7; 5.6] 258 (48.1)	1.15 [0.98; 1.37] 0.095
Social functioning	536	2.8 [2.3; 3.4] 327 (61.0)	536	3.7 [2.9; 4.2] 291 (54.3)	1.14 [0.98; 1.34] 0.101

a: Stratified Cox proportional hazards model.
b: Stratified log-rank test.
c: Time to deterioration of the score by at least 10 points versus the baseline value.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire Core-30 (general symptoms of cancer disease); RCT: randomized controlled trial; vs.: versus

Table 17: Results (side effects: time to occurrence of an AE) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Outcome	Ramucirumab + FOLFIRI		Placebo + FOLFIRI		Ramucirumab + FOLFIRI vs. placebo + FOLFIRI
	N	Median (months) [95% CI] Patients with event n (%)	N	Median (months) [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
RAISE					
AEs	529	0.1 [0.1; 0.1] 522 (98.7)	528	0.1 [0.1; 0.1] 519 (98.3)	
SAEs	529	16.4 [11.6; NC] 189 (35.7)	528	21.6 [11.2; NC] 164 (31.1)	1.11 [0.90; 1.37] 0.313
AEs CTCAE grade ≥ 3	529	1.3 [1.1; 1.5] 418 (79.0)	528	3.0 [2.3; 3.7] 329 (62.3)	1.55 [1.34; 1.80] < 0.001
Treatment discontinuation due to an AE[c]	529	18.1 [12.0; NC] 154 (29.1)	528	NC [NC; NC] 70 (13.3)	2.38 [1.79; 3.16] < 0.001
Specific adverse events					
Bleeding/ haemorrhagic events	529	6.9 [5.8; 9.2] 232[d] (43.9)	528	NC [18.4; NC] 120[d] (22.7)	2.15 [1.73; 2.69] < 0.001
Bleeding/ haemorrhagic events: gastrointestinal bleeding	529	NC [NC; NC] 65[e] (12.3)	528	NC [NC; NC] 36[e] (6.8)	1.77 [1.17; 2.65] 0.006

a: Presumably Cox proportional hazards model.
b: Log-rank test.
c: Discontinuation of any component of the study medication.
d: 13 patients in the ramucirumab + FOLFIRI group and 9 patients in the comparator group had bleeding/haemorrhagic events of severity grade ≥ 3 according to CTCAE.
e: 10 patients in the ramucirumab + FOLFIRI group and 6 patients in the comparator group had bleeding/haemorrhagic events: gastrointestinal bleeding of severity grade ≥ 3 according to CTCAE.
CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 18: Results (side effects: specific AEs) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Outcome category	Ramucirumab + FOLFIRI		Placebo + FOLFIRI		Ramucirumab + FOLFIRI vs. placebo + FOLFIRI
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects					
Specific adverse events					
Peripheral oedema (PT)	529	108[b] (20.4)	528	48[b] (9.1)	2.25[c] [1.63; 3.09]; < 0.001
Palmar-plantar erythrodysaesthesia syndrome (PT)	529	68[d] (12.9)	528	29[d] (5.5)	2.34[c] [1.54; 3.55]; < 0.001
Headache (PT)	529	78[e] (14.7)	528	41[e] (7.8)	1.90[c] [1.33; 2.72]; < 0.001

a: Institute's calculation, unconditional exact test (CSZ method according to [7]).
b: 1 patient in the ramucirumab + FOLFIRI group and no patient in the comparator group had oedema of severity grade ≥ 3 according to CTCAE.
c: Institute's calculation, asymptotic.
d: 6 patients in the ramucirumab + FOLFIRI group and 2 patients in the comparator group had palmar-plantar erythrodysaesthesia syndrome of severity grade ≥ 3 according to CTCAE.
e: 3 patients in the ramucirumab + FOLFIRI group and no patient in the comparator group had headache of severity grade ≥ 3 according to CTCAE.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

One relevant study was available for the assessment of ramucirumab in combination with FOLFIRI in the treatment of patients with MCRC. Depending on the risk of bias at outcome level, at most indications, e.g. of an added benefit, could be derived (see Section 2.4.2).

Mortality

Treatment with ramucirumab in combination with FOLFIRI resulted in a statistically significant prolongation of overall survival in comparison with FOLFIRI. In addition, there was proof of an effect modification by the characteristic "sex" for this outcome (see Section 2.4.4). The results for men and women were therefore interpreted separately. This resulted in an indication of an added benefit of ramucirumab in combination with FOLFIRI in comparison with FOLFIRI for the outcome "all-cause mortality" for women. For men, however, there was no indication of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

This deviates from the company's assessment, which considered the proof of an effect modification to be irrelevant for the derivation of the added benefit, and overall derived an indication of an added benefit on the basis of the total population.

Morbidity

Symptoms

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

For each of the outcomes **"appetite loss"** and **"constipation"**, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for the time to deterioration of symptoms. In addition, there was proof of an effect modification by the characteristic "sex" for both outcomes. The results for men and women were therefore interpreted separately (see Section 2.4.4).

For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, however, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. This deviates from the assessment of the company, which considered the effect modification by the characteristic "sex" as not relevant, and derived no lesser benefit for the outcomes "appetite loss" and "constipation" despite a statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

For the outcome **"fatigue"**, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI, which was no more than marginal, however, for the time to deterioration of symptoms (see Section 2.5.1). Hence there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this outcome. This concurs with the company's assessment.

There was no statistically significant difference between the treatment options for the time to deterioration of symptoms for any of the following outcomes: **diarrhoea, dyspnoea, insomnia, nausea and vomiting** and **pain**. This resulted in no hint of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for these outcomes. This concurs with the company's assessment. Although the company found a statistically significant advantage of ramucirumab in combination with FOLFIRI for the outcome **"nausea and vomiting"** on the basis of subgroup analyses for patients < 65 years and patients with ECOG PS of 0, but eventually derived no added benefit from this (see Section 2.7.2.4.3 of the full dossier assessment).

Health-related quality of life

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30. Due to the high risk of bias (see Section

2.7.2.4.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit could be derived for all outcomes in this category.

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for the time to deterioration for each of the following outcomes: **global health status, physical functioning** and **emotional functioning**. In addition, there was an indication of an effect modification by the characteristic "sex" for all 3 outcomes (see Section 2.4.4). For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, however, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. This deviates from the assessment of the company, which considered the effect modification by the characteristic "sex" as not relevant, and derived no lesser benefit for the outcomes also on the basis of statistically significant differences in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for the time to deterioration for the outcome **"role functioning"**. In addition, there was proof of an effect modification by the characteristic "sex" (see Section 2.4.4). For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. This deviates from the assessment of the company, which considered the effect modification by the characteristic "sex" as not relevant, and derived no lesser benefit for the outcome also on the basis of the statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

No statistically significant difference between the treatment options was shown for the time to deterioration for the outcomes **"cognitive functioning"** and **"social functioning"**. This resulted in no hint of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for these outcomes. This concurs with the company's assessment.

Side effects

Due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of greater or lesser harm could be derived for all outcomes in this category.

SAEs

No statistically significant difference between the treatment options was shown for the outcome "SAEs" (time to first event). This resulted in no hint of greater or lesser harm of ramucirumab in combination with FOLFIRI in comparison with the ACT for SAEs; greater or lesser harm is therefore not proven for this outcome. This concurs with the company's assessment.

Discontinuation due to adverse events, severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for each of the outcomes "discontinuation due to AEs" (time to first event) and "severe AEs (CTCAE grade ≥ 3)" (time to first event). This resulted in a hint of greater harm of ramucirumab for both outcomes. This concurs with the company's assessment, which, however, was based on the post-hoc analysis of events classified as symptomatic by the company.

Specific adverse events

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for each of the outcomes **"bleeding/haemorrhagic events"** (time to first event) and **"bleeding/haemorrhagic events: gastrointestinal bleeding"** (time to first event) as part of the bleeding events. There was a hint of greater harm of ramucirumab for the outcomes **"bleeding/haemorrhagic events"** and **"bleeding/haemorrhagic events: gastrointestinal bleeding"** for all patients. This concurs with the company's assessment.

A statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI was shown for each of the outcomes **"peripheral oedema", "palmar-plantar erythrodysaesthesia syndrome"** and **"headache"**. This resulted in a hint of greater harm of ramucirumab in combination with FOLFIRI. This deviates from the company's assessment, which considered no results on these outcomes.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics, which were predefined in the RAISE study, were considered relevant for the present benefit assessment:

- sex (men, women)
- age (< 65 years, ≥ 65 years)
- region (Europe, North America, rest of the world)
- KRAS status (mutant, wild type)
- number of organs/tissues with metastases (1, 2, ≥ 3)
- location of primary tumour (colon, rectum)

Adequate subgroup analyses were available for all outcomes except for some specific AE outcomes (peripheral oedema, palmar-plantar erythrodysaesthesia syndrome, and headache).

Hereinafter, the results on subgroups for which there was at least an indication of an interaction between treatment effect and subgroup characteristic are presented for the outcomes "overall survival", "symptoms" and "health-related quality of life". Subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. In effect modifications with more than 2 categories, the categories of neighbouring

effect estimates were summarized if this was meaningful with regard to content and the heterogeneity test provided a p-value of ≥ 0.2.

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.

Table 19: Subgroups (outcome "overall survival") – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Charac-teristic Sub-group	Ramucirumab + FOLFIRI		Placebo + FOLFIRI		Ramucirumab + FOLFIRI vs. placebo + FOLFIRI	
	N	Median (months) [95% CI] Patients with event n (%)[a]	N	Median (months) [95% CI] Patients with event n (%)[a]	HR [95% CI][b];	p-value[c]
RAISE						
Sex						
Men	289	13.8 [12.6; 15.4] 209 (72.3)	326	12.4 [11.5; 13.9] 229 (70.2)	0.95 [0.78; 1.14]	0.570
Women	247	12.7 [11.6; 15.1] 163 (66.0)	210	10.7 [9.1; 11.7] 168 (80.0)	0.74 [0.59; 0.91]	0.005
					Interaction:	0.049

a: Institute's calculation.
b: Cox proportional hazards model.
c: Log-rank test.
CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 20: Subgroups (morbidity: time to deterioration of symptoms) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	p-value[c]
RAISE						
EORTC QLQ-C30 symptom scales[d]						
Appetite loss						
Sex						
Men	289	2.1 [1.8; 2.6] 198 (68.5)	326	6.0 [4.8; 8.1] 155 (47.6)	1.90 [1.54; 2.35]	< 0.001
Women	247	2.9 [2.4; 4.3] 140 (56.7)	210	3.2 [2.2; 4.5] 114 (54.3)	0.95 [0.74; 1.21]	0.664
					Interaction:	< 0.001
Age						
< 65 years	324	3.0 [2.3; 3.9] 191 (59.0)	321	4.5 [3.5; 5.4] 163 (50.8)	1.19 [0.97; 1.47]	0.098
≥ 65 years	212	2.0 [1.7; 2.6] 147 (69.3)	215	5.4 [3.8; 8.4] 106 (49.3)	1.83 [1.42; 2.35]	< 0.001
					Interaction:	0.008
Location of primary tumour						
Colon	358	2.4 [2.0; 2.9] 229 (64.0)	358	5.3 [3.9; 6.6] 171 (47.8)	1.57 [1.29; 1.92]	< 0.001
Rectum	174	2.9 [2.1; 3.9] 106 (60.9)	171	4.2 [3.0; 5.4] 95 (55.6)	1.16 [0.88; 1.53]	0.295
					Interaction:	0.078
Constipation						
Sex						
Men	289	4.0 [2.8; 5.8] 146 (50.5)	326	8.1 [7.0; 13.6] 128 (39.3)	1.47 [1.16; 1.86]	0.002
Women	247	4.9 [4.2; 6.7] 113 (45.8)	210	4.6 [2.8; 10.2] 96 (45.7)	0.90 [0.68; 1.18]	0.446
					Interaction:	0.008

a: Institute's calculation.
b: Presumably Cox proportional hazards model.
c: Log-rank test.
d: Time to deterioration of the score by at least 10 points versus the baseline value.
CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 21: Subgroups (time to deterioration of health-related quality of life) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Ramucirumab + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Placebo + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	p-value[c]
RAISE						
EORTC QLQ-C30 functional scales[d]						
Global health status						
Sex						
Men	289	2.1 [1.9; 3.0] 182 (63.0)	326	4.4 [3.7; 6.0] 173 (53.1)	1.40 [1.13; 1.72]	0.002
Women	247	2.9 [1.9; 3.9] 153 (61.9)	210	3.8 [2.9; 4.4] 119 (56.7)	1.12 [0.88; 1.42]	0.373
					Interaction:	0.162
Region						
North America	143	1.9 [1.5; 2.6] 91 (63.6)	143	4.6 [3.4; 6.5] 72 (50.3)	1.68 [1.23; 2.29]	0.001
Europe	235	2.9 [1.9; 4.0] 148 (63.0)	235	4.0 [3.0; 5.7] 123 (52.3)	1.27 [1.00; 1.61]	0.051
Rest of the world	158	2.7 [2.0; 4.5] 96 (60.8)	158	3.8 [2.6; 4.8] 97 (61.4)	1.07 [0.80; 1.42]	0.644
					Interaction:	0.124
Physical functioning						
Sex						
Men	289	3.4 [2.6; 4.0] 174 (60.2)	326	5.2 [4.0; 8.1] 154 (47.2)	1.42 [1.14; 1.77]	0.001
Women	247	3.6 [2.6; 4.4] 139 (56.3)	210	4.3 [3.1; 5.1] 108 (51.4)	1.10 [0.85; 1.41]	0.479
					Interaction:	0.125
KRAS status						
Mutant	269	3.3 [2.6; 4.0] 161 (59.9)	261	5.8 [3.5; 9.0] 120 (46.0)	1.47 [1.16; 1.86]	0.002
Wild type	267	3.7 [2.6; 4.9] 152 (56.9)	275	4.6 [3.5; 5.5] 142 (51.6)	1.12 [0.89; 1.41]	0.334
					Interaction:	0.112

(continued)

Table 21: Subgroups (time to deterioration of health-related quality of life) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Ramucirumab + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Placebo + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	p-value[c]
Physical functioning (continued)						
Number of organs/tissues with metastases						
1	171	3.0 [1.9; 4.2] 100 (58.5)	157	5.5 [4.2; 10.6] 76 (48.4)	1.44 [1.07; 1.94]	0.017
2	205	3.4 [2.6; 5.6] 120 (58.5)	194	5.8 [3.5; 12.4] 87 (44.9)	1.44 [1.09; 1.90]	0.009
≥ 3	157	3.8 [2.5; 4.2] 93 (59.2)	182	3.8 [3.0; 5.0] 99 (54.4)	1.03 [0.78; 1.37]	0.837
					Interaction:	0.170
Role functioning						
Sex						
Men	289	2.2 [1.8; 2.8] 201 (69.6)	326	4.0 [3.1; 5.3] 178 (54.6)	1.57 [1.28; 1.92]	< 0.001
Women	247	1.9 [1.7; 2.8] 171 (69.2)	210	2.6 [2.0; 3.1] 138 (65.7)	1.07 [0.86; 1.34]	0.565
					Interaction:	0.013
Emotional functioning						
Sex						
Men	289	5.2 [4.2; 8.1] 142 (49.1)	326	9.4 [7.0; 16.1] 121 (37.1)	1.41 [1.11; 1.80]	0.005
Women	247	8.2 [5.5; 10.6] 103 (41.7)	210	7.4 [5.7; NC] 74 (35.2)	1.07 [0.80; 1.45]	0.644
					Interaction:	0.186
Age						
< 65 years	324	9.1 [5.5; 12.0] 134 (41.4)	321	9.1 [6.6; NC] 111 (34.6)	1.13 [0.88; 1.45]	0.348
≥ 65 years	212	4.9 [3.3; 7.9] 111 (52.4)	215	8.8 [5.5; 13.6] 84 (39.1)	1.46 [1.10; 1.94]	0.008
					Interaction:	0.173

(continued)

Table 21: Subgroups (time to deterioration of health-related quality of life) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Ramucirumab + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Placebo + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	p-value[c]
Emotional functioning (continued)						
Number of organs/tissues with metastases						
1	171	12.9 [6.3; NC] 66 (38.6)	157	9.1 [5.6; 16.1] 61 (38.9)	1.02 [0.72; 1.44]	0.926
2	205	5.7 [4.4; 9.1] 104 (50.7)	194	NC [6.7; NC] 64 (33.0)	1.58 [1.16; 2.16]	0.004
≥ 3	157	5.5 [4.1; 8.1] 75 (47.8)	182	7.0 [4.7; 9.4] 70 (38.5)	1.21 [0.87; 1.67]	0.259
					Interaction:	0.152
Cognitive functioning						
Sex						
Men	289	3.7 [2.8; 4.9] 157 (54.3)	326	5.1 [3.8; 8.1] 151 (46.3)	1.29 [1.03; 1.61]	0.026
Women	247	4.2 [3.0; 5.4] 141 (57.1)	210	3.7 [3.0; 5.4] 107 (51.0)	0.98 [0.76; 1.26]	0.858
					Interaction:	0.137
Age						
< 65 years	324	4.5 [3.3; 5.9] 167 (51.5)	321	4.3 [3.4; 6.7] 148 (46.1)	1.06 [0.85; 1.32]	0.623
≥ 65 years	212	2.9 [2.3; 4.2] 131 (61.8)	215	4.3 [3.3; 5.8] 110 (51.2)	1.36 [1.05; 1.75]	0.019
					Interaction:	0.140
Number of organs/tissues with metastases						
1	171	4.5 [2.8; 6.5] 91 (53.2)	157	4.2 [2.6; 6.7] 81 (51.6)	1.06 [0.78; 1.43]	0.723
2	205	3.7 [2.6; 4.6] 124 (60.5)	194	5.6 [3.8; NC] 85 (43.8)	1.53 [1.16; 2.01]	0.003
≥ 3	157	4.1 [3.0; 5.2] 83 (52.9)	182	3.9 [2.8; 5.0] 92 (50.6)	0.95 [0.71; 1.28]	0.753
					Interaction:	0.051

(continued)

Table 21: Subgroups (time to deterioration of health-related quality of life) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Ramucirumab + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Placebo + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	p-value[c]
Cognitive functioning (continued)						
Location of primary tumour						
Colon	358	3.7 [2.8; 4.2] 197 (55.0)	358	4.8 [3.7; 6.05.95] 164 (45.8)	1.29 [1.05; 1.59]	0.016
Rectum	174	4.7 [3.0; 6.5] 98 (56.3)	171	4.1 [2.8; 5.6] 89 (52.1)	1.00 [0.75; 1.33]	0.994
					Interaction:	0.132
Social functioning						
Age						
< 65 years	324	3.6 [2.7; 4.6] 184 (56.8)	321	3.7 [2.5; 4.2] 176 (54.8)	1.03 [0.84; 1.27]	0.753
≥ 65 years	212	2.2 [1.9; 2.8] 143 (67.5)	215	3.7 [2.9; 5.2] 115 (53.5)	1.38 [1.08; 1.77]	0.010
					Interaction:	0.073
Region						
North America	143	2.9 [1.9; 3.6] 89 (62.2)	143	4.1 [3.0; 6.8] 71 (49.7)	1.57 [1.15; 2.15]	0.005
Europe	235	2.8 [1.9; 3.6] 147 (62.6)	235	2.8 [2.0; 4.0] 130 (55.3)	1.10 [0.87; 1.40]	0.420
Rest of the world	158	2.8 [2.2; 5.5] 91 (57.6)	158	3.9 [2.8; 5.7] 90 (57.0)	0.98 [0.74; 1.32]	0.917
					Interaction:	0.100
Location of primary tumour						
Colon	358	2.4 [2.0; 3.0] 216 (60.3)	358	3.9 [2.8; 4.6] 188 (52.5)	1.26 [1.04; 1.53]	0.021
Rectum	174	3.9 [2.3; 5.1] 108 (62.1)	171	3.1 [2.5; 5.6] 100 (58.5)	0.98 [0.75; 1.29]	0.898
					Interaction:	0.156

a: Institute's calculation.
b: Presumably Cox proportional hazards model.
c: Log-rank test.
d: Time to deterioration of the score by at least 10 points versus the baseline value.

CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; n: number of patients with ≥ 1 event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 22: Subgroups (AEs) – RCT, direct comparison: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Study Characteristic Subgroup	Ramucirumab + FOLFIRI N	Ramucirumab + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Placebo + FOLFIRI N	Placebo + FOLFIRI Median (months) [95% CI] Patients with event n (%)[a]	Ramucirumab + FOLFIRI vs. placebo + FOLFIRI HR [95% CI][b];	 p-value[c]
RAISE						
Bleeding/haemorrhagic events						
Number of organs/tissues with metastases						
1	171	5.6 [3.6; 7.9] 90 (52.6)	155	NC [18.4; NC] 32 (20.7)	3.22 [2.15; 4.83]	< 0.001
≥ 2	358[a]	ND [ND; ND] 142[a] (39.7)	373[a]	ND [ND; ND] 88[a] (23.6)	1.77 [1.28; 2.44][a]	< 0.001[a]
2	*203*	*7.0 [5.8; 10.2]* *86 (42.4)*	*192*	*NC [13.7; NC]* *42 (21.9)*	*2.07 [1.43; 3.00]*	*< 0.001*
≥ 3	*155*	*NC [5.7; NC]* *56 (36.1)*	*181*	*NC [11.7; NC]* *46 (25.4)*	*1.49 [1.01; 2.20]*	*0.044*
					Interaction:	0.024[d]
Bleeding/haemorrhagic events: gastrointestinal bleeding						
Age						
< 65 years	320	NC [NC; NC] 38 (11.9)	316	NC [NC; NC] 26 (8.2)	1.35 [0.82; 2.23]	0.236
≥ 65 years	209	NC [NC; NC] 27 (12.9)	212	NC [NC; NC] 10 (4.7)	2.88 [1.39; 5.96]	0.003
					Interaction:	0.095
Number of organs/tissues with metastases						
1	171	NC [NC; NC] 30 (17.5)	155	NC [NC; NC] 9 (5.8)	3.17 [1.50; 6.67]	0.001
≥ 2	358[a]	ND [ND; ND] 35[a] (9.8)	373[a]	ND [ND; ND] 27[a] (7.2)	1.32 [0.80; 2.18][a]	0.281[a]
2	*203*	NC [NC; NC] *17 (8.4)*	*192*	NC [NC; NC] *12 (6.3)*	*1.23 [0.59; 2.57]*	*0.588*
≥ 3	*155*	NC [NC; NC] *18 (11.6)*	*181*	NC *[13.5; NC]* *15 (8.3)*	*1.40 [0.70; 2.77]*	*0.337*
					Interaction:	0.174[d]

a: Institute's calculation.
b: Presumably Cox proportional hazards model.
c: Log-rank test.
d: Test for the interaction of the 3 subgroup characteristics 1, 2 and ≥ 3.
CI: confidence interval; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; vs.: versus

Interpretation of the subgroup results with presence of several effect modifications for one outcome

Proof and indications of effect modifications from several subgroup characteristics were shown for the EORTC symptom scale "appetite loss", for the EORTC quality of life scales "global health status", "physical functioning", "emotional functioning", "cognitive functioning" and "social functioning", and for AEs. Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes and several outcome categories (mortality, symptoms and health-related quality of life) was only shown for the characteristic "sex", so that only subgroup results for the characteristic "sex" were considered for the benefit assessment.

Interpretation of the subgroup results in the presence of an indication of an effect modification

In the EORTC functional scales for the recording of health-related quality of life, indications of effect modifications were shown for several scales. In these situations, the result of the total population was also considered in the interpretation besides the result in the respective subgroup. If the subgroup differed from the total population regarding the presence of statistical significance, the certainty of results in this subgroup was reduced. In situations where only a hint was derived for the respective outcome already at the level of the total population, no added benefit or lesser benefit could then be derived for the subgroup.

Overall survival

There was proof of an effect modification by the characteristic "sex" for the outcome "overall survival".

There was a statistically significant difference in favour of ramucirumab in combination with FOLFIRI for women. For men, however, there was no statistically significant difference between both treatment groups. This resulted in an indication of an added benefit of ramucirumab in combination with FOLFIRI compared with the ACT for women. For male patients, however, there was no hint of an added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which also identified the proof of effect modification by the characteristic "sex", but did not consider it to be relevant for the conclusion. The company argued that part of the sex-related effect could be explained by the fact that there was a different distribution of subsequent therapies after completion of the study treatment (post-discontinuation therapy) in the subgroups of men and women. It additionally argued that the sex-specific difference was not shown in studies on other therapeutic indications of ramucirumab. This rationale was not followed. A different distribution of subsequent therapies was of lesser importance in the present situation and in the existing magnitude. Different subsequent therapies are part of a respective therapeutic

strategy. The use of a subsequent therapy is therefore not clearly caused by a patient characteristic such as sex, for example. If this was indeed the case, however, this would actually reflect sex-specific differences. Moreover, treatment effects and potential effect modifications can take on different forms for different therapeutic indications and comparator therapies.

Deviating from the present assessment, the company derived an indication of an added benefit of ramucirumab + FOLFIRI in comparison with FOLFIRI for the outcome "overall survival" for the total population.

Morbidity

Symptom scales of the EORTC QLQ-C30

Proof of an effect modification by the characteristics "sex" and "age" and an indication of an effect modification by the characteristic "location of primary tumour" were shown for the outcome **"appetite loss"**. As explained above, only the effect modification by the characteristic "sex" was considered in this situation.

There was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. There was no statistically significant difference between both treatment groups for female patients. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For female patients, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

There was proof of an effect modification by the characteristic "sex" for the outcome **"constipation"**. There was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. For women, there was no statistically significant difference between both treatment groups.

For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, however, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant disadvantage in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

Health-related quality of life

Functional scales of the EORTC QLQ-C30

An indication of an effect modification by the characteristics '"sex" and "region" was shown for the outcome **"global health status"**. As explained above, only the effect modification by the characteristic "sex" was considered in this situation. As in the total population, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. For women, however, deviating from the total population, there was no statistically significant difference between both treatment groups. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

An indication of an effect modification by the characteristics "sex", "KRAS mutation status", and "number of organs/tissues with metastases" was shown for the outcome **"physical functioning"**. As explained above, only the effect modification by the characteristic "sex" was considered in this situation. As in the total population, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. For women, however, deviating from the total population, there was no statistically significant difference between both treatment groups. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

There was proof of an effect modification by the characteristic "sex" for the outcome **"role functioning"**. There was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. For women, there was no statistically significant difference between both treatment groups. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant difference in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

An indication of an effect modification by the characteristics "sex", "age", and "number of organs/tissues with metastases" was shown for the outcome **"emotional functioning"**. As explained above, only the effect modification by the characteristic "sex" was considered in

this situation. As in the total population, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. For women, however, deviating from the total population, there was no statistically significant difference between both treatment groups. For men, there was a hint of lesser benefit of ramucirumab in combination with FOLFIRI. For women, there was no hint of lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT; an added benefit is therefore not proven for this subgroup. The company considered the effect modification as not relevant, and derived no lesser benefit also on the basis of the statistically significant disadvantage in the total population to the disadvantage of ramucirumab (see Section 2.7.2.4.3 of the full dossier assessment).

An indication of an effect modification by the characteristics "sex", "age", "number of organs/tissues with metastases", and "location of primary tumour" was shown for the outcome **"cognitive functioning"**. As explained above, only the effect modification by the characteristic "sex" was considered in this situation. Deviating from the total population, there was a statistically significant difference to the disadvantage of ramucirumab in combination with FOLFIRI for men. Since no statistically significant effect was observed in the total population, and there was only an indication of an effect modification, the certainty of results of the effect was reduced in the subgroup of men. Since only hints were possible already at the level of the total population, no lesser benefit was derived from the subgroup result. For women, however, as in the total population, there was no statistically significant difference between both treatment groups. For both groups, no lesser benefit or added benefit of ramucirumab in combination with FOLFIRI in comparison with the ACT was derived in the present situation; an added benefit is therefore not proven for these subgroups. This concurs with the company's assessment.

An indication of an effect modification by the characteristics '"age", "region", and "location of primary tumour" was shown for the outcome **"social functioning"**. As explained above, only an effect modification by the characteristic "sex" was considered and interpreted for the present study. Since there was no statistically significant difference between the treatment groups for the total population, no added benefit was derived overall for the outcome. This concurs with the company's assessment.

Side effects

Specific adverse events

Proof of an effect modification by the characteristic "number of organs/tissues with metastases" was shown for the outcome **"bleeding/haemorrhagic events"** (time to first event), and an indication of an effect modification for the outcome "**bleeding/haemorrhagic events: gastrointestinal bleeding"** (time to first event). As explained above, only an effect modification by the characteristic "sex" was considered for the present study. Since there was a statistically significant effect to the disadvantage of ramucirumab in combination with FOLFIRI for the total population, there was a hint of greater harm of ramucirumab for both outcomes. This concurs with the company's assessment.

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 assessment for ramucirumab in combination with FOLFIRI in comparison with FOLFIRI:

- an indication of an added benefit for overall survival for women
- a hint of lesser benefit regarding symptoms (appetite loss, constipation) for men
- a hint of lesser benefit regarding health-related quality of life (global health status, physical functioning, role functioning, and emotional functioning) for men
- a hint of greater harm for the following AE outcomes: severe AEs (CTCAE ≥ 3), treatment discontinuation due to AEs, bleeding/haemorrhagic events, bleeding/haemorrhagic events: gastrointestinal bleeding, peripheral oedema, palmar-plantar erythrodysaesthesia syndrome, and headache

Determination of the outcome category for the EORTC symptom scales

The outcomes “appetite loss”, “constipation” and “fatigue” were allocated to the outcome category of non-serious/non-severe side effects because there was no sign that these were mainly severe symptoms.

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 RAISE study, 63% of the discontinuations (142 of 224) were discontinuations due to an AE of severity grade ≥ 3 according to CTCAE. The results of the outcome “discontinuation due to AEs” were therefore allocated to the outcome category of serious/severe side effects.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 23).

Table 23: Extent of added benefit at outcome level: ramucirumab + FOLFIRI vs. placebo + FOLFIRI

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI** **Time to event (median) or proportion of patients with event (%)** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival		
Sex		
Men	13.8 vs. 12.4 months HR: 0.95 [0.78; 1.14] p = 0.570	Lesser benefit/added benefit not proven
Women	12.7 vs. 10.7 months HR: 0.74 [0.59; 0.91] p = 0.005 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent "considerable"
Morbidity		
EORTC QLQ-C30 symptom scales: time to deterioration of symptoms		
Appetite loss		
Sex		
Men	2.1 vs. 6.0 months HR: 1.90 [1.54; 2.35] HR: 0.53 [0.43; 0.65][c] p = < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: "considerable"
Women	2.9 vs. 3.2 HR: 0.95 [0.74; 1.21] p = 0.664	Lesser benefit/added benefit not proven
Diarrhoea	4.0 vs. 4.2 months HR: 0.96 [0.81; 1.13] p = 0.636	Lesser benefit/added benefit not proven
Dyspnoea	6.3 vs. 7.4 months HR: 1.11 [0.93; 1.34] p = 0.252	Lesser benefit/added benefit not proven
Insomnia	5.6 vs. 5.7 months HR: 0.98 [0.82; 1.17] p = 0.802	Lesser benefit/added benefit not proven

(continued)

Table 23: Extent of added benefit at outcome level: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI** **Time to event (median) or proportion of patients with event (%)** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity (continued)		
EORTC QLQ-C30 symptom scales: time to deterioration of symptoms (continued)		
Nausea and vomiting	4.1 vs. 3.0 months HR: 0.87 [0.74; 1.03] p = 0.110	Lesser benefit/added benefit not proven
Constipation		
Sex		
Men	4.0 vs. 8.1 months HR: 1.47 [1.16; 1.86] HR: 0.68 [0.54; 0.86][c] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: "minor"
Women	4.9 vs. 4.6 months HR: 0.90 [0.68; 1.18] p = 0.446	Lesser benefit/added benefit not proven
Fatigue	1.5 vs. 2.1 months HR: 1.28 [1.11; 1.48] HR: 0.78 [0.67; 0.90] p = 0.001	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1$ Lesser benefit/added benefit not proven[d]
Pain	2.9 vs. 4.2 months HR: 1.17 [1.00; 1.37] p = 0.055	Lesser benefit/added benefit not proven

(continued)

Table 23: Extent of added benefit at outcome level: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI** **Time to event (median) or proportion of patients with event (%)** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 functional scales: time to deterioration		
Global health status		
Sex		
Men	2.0 vs. 4.4 months HR: 1.40 [1.13; 1.72] HR: 0.71 [0.58; 0.89][c] p = 0.002 probability: "hint"	Outcome category: quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: "considerable"
Women	2.9 vs. 3.8 months HR: 1.12 [0.88; 1.42] p = 0.373	Lesser benefit/added benefit not proven
Physical functioning		
Sex		
Men	3.4 vs. 5.2 months HR: 1.42 [1.14; 1.77] HR: 0.70 [0.56; 0.88][c] p = 0.001 probability: "hint"	Outcome category: quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: "considerable"
Women	3.6 vs. 4.3 months HR: 1.10 [0.85; 1.41] p = 0.479	Lesser benefit/added benefit not proven
Role functioning		
Sex		
Men	2.2 vs. 4.0 months HR: 1.57 [1.28; 1.92] HR: 0.64 [0.52; 0.78][c] p < 0.001 probability: "hint"	Outcome category: quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: "considerable"
Women	1.9 vs. 2.6 months HR: 1.07 [0.86; 1.34] p = 0.565	Lesser benefit/added benefit not proven

(continued)

Table 23: Extent of added benefit at outcome level: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI** **Time to event (median) or proportion of patients with event (%)** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life (continued)		
EORTC QLQ-C30 functional scales: time to deterioration (continued)		
Emotional functioning		
Sex		
Men	5.2 vs. 9.4 months HR: 1.41 [1.11; 1.80] HR: 0.71 [0.56; 0.903][c] p = 0.005 probability: "hint"	Outcome category: quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
Women	8.2 vs. 7.4 months HR: 1.07 [0.80; 1.45] p = 0.644	Lesser benefit/added benefit not proven
Cognitive functioning	4.0 vs. 4.3 months HR: 1.15 [0.98; 1.37] p = 0.095	Lesser benefit/added benefit not proven
Social functioning	2.8 vs. 3.7 months HR: 1.14 [0.98; 1.34] p = 0.101	Lesser benefit/added benefit not proven
Side effects		
SAEs	16.4 vs. 21.6 months HR: 1.11 [0.90; 1.37] p = 0.313	Greater/lesser harm not proven
AEs CTCAE grade ≥ 3	1.3 vs. 3.0 months HR: 1.55 [1.34; 1.80] HR: 0.64 [0.56; 0.745][c] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Treatment discontinuation due to an AE	18.1 months vs. NC HR: 2.38 [1.79; 3.16] HR: 0.42 [0.32; 0.56][c] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

(continued)

Table 23: Extent of added benefit at outcome level: ramucirumab + FOLFIRI vs. placebo + FOLFIRI (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ramucirumab + FOLFIRI vs. placebo + FOLFIRI** **Time to event (median) or proportion of patients with event (%)** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects (continued)		
Specific adverse events		
Bleeding/haemorrhagic events	6.9 months vs. NC HR: 2.15 [1.73; 2.69] HR: 0.47 [0.37; 0.58][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Bleeding/haemorrhagic events: gastrointestinal bleeding	NC vs. NC HR: 1.77 [1.17; 2.65] HR: 0.56 [0.38; 0.85][c] p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Peripheral oedema	20.4% vs. 9.1% RR: 2.25 [1.63; 3.09] RR: 0.44 [0.32; 0.61][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Palmar-plantar erythrodysaesthesia syndrome	12.9% vs. 5.5% RR: 2.34 [1.54; 3.55] RR: 0.43 [0.28; 0.65][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Headache	14.7% vs. 7.8% RR: 1.90 [1.33; 2.72] RR: 0.53 [0.37; 0.75][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: Lesser benefit or added benefit is not proven because the effect size was only marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; NC: not calculable; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 24 and Table 25 summarize the results considered in the overall conclusion about the extent of added benefit.

Table 24: Positive and negative effects from the assessment of ramucirumab + FOLFIRI in comparison with placebo + FOLFIRI – subgroup of women

Positive effects	**Negative effects**
Mortality overall survival: indication of an added benefit – extent: “considerable”	
	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: “major” ▪ discontinuation due to an AE: hint of greater harm – extent “major”
	Non-serious/non-severe side effects ▪ bleeding/haemorrhagic events: hint of greater harm – extent “considerable” ▪ bleeding/haemorrhagic events (gastrointestinal bleeding): hint of greater harm – extent “minor” ▪ peripheral oedema: hint of greater harm – extent “considerable” ▪ palmar-plantar erythrodysaesthesia syndrome: hint of greater harm – extent “considerable” ▪ headache: hint of greater harm, extent: “considerable”
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan	

Table 25: Positive and negative effects from the assessment of ramucirumab + FOLFIRI in comparison with placebo + FOLFIRI – subgroup of men

Positive effects	**Negative effects**
–	Non-serious/non-severe symptoms/late complications ▪ EORTC QLQ-C30 symptom scales: ▫ appetite loss: hint of lesser benefit – extent: "considerable" ▫ constipation: hint of lesser benefit – extent: "minor"
–	Health-related quality of life ▪ EORTC QLQ-C30 functional scales: ▫ global health status: hint of lesser benefit – extent: "considerable" ▫ physical functioning: hint of lesser benefit – extent: "considerable" ▫ role functioning: hint of lesser benefit – extent: "considerable" ▫ emotional functioning: hint of lesser benefit – extent: "minor"
–	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major" ▪ discontinuation due to an AE: hint of greater harm – extent "major"
–	Non-serious/non-severe side effects ▪ bleeding/haemorrhagic events: hint of greater harm – extent "considerable" ▪ bleeding/haemorrhagic events (gastrointestinal bleeding): hint of greater harm – extent "minor" ▪ peripheral oedema: hint of greater harm – extent "considerable" ▪ palmar-plantar erythrodysaesthesia syndrome: hint of greater harm – extent "considerable" ▪ headache: hint of greater harm, extent: "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan	

The results showed relevant effect modifications by sex for several outcomes of the categories "mortality", "morbidity" and "health related quality of life". Hereinafter, the overall conclusion on the added benefit is derived separately for men and women.

Women

Overall, there were positive and negative effects for women. On the positive side, there was an indication of an added benefit of considerable extent for the outcome "overall survival". This was accompanied by hints of negative effects of different extent. Hints of greater harm

of major extent were found in the outcome category "serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs)". In addition, hints of greater harm of considerable or minor extent were found in the outcome category "non-serious/non-severe side effects" (different specific AE outcomes). It has to be taken into account in the balancing of benefit and harm that regarding severe AEs (CTCAE grade ≥ 3), apart from neutropenia and hypertension, no AE stood out particularly. The discontinuations due to AEs were therefore at a rather low level. Hence in the present situation, the observed negative effects could not completely outweigh the positive effect in overall survival. In summary, there is an indication of a minor added benefit of ramucirumab in combination with FOLFIRI versus the ACT FOLFIRI for the subgroup of women.

Men

For men, only negative effects remained in the following outcome categories: non-serious/non-severe symptoms/late complications (appetite loss, constipation), health-related quality of life (global health status, physical functioning, role functioning, emotional functioning), serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs) and non-serious/non-severe side effects (specific AE outcomes). In each case, there were hints of different extent. The greatest extent of major greater harm was found in the category of serious/severe side effects (severe AEs CTCAE grade ≥ 3, treatment discontinuation due to AEs) for both outcomes. In summary, there is a hint of lesser benefit of ramucirumab in combination with FOLFIRI versus the ACT FOLFIRI for the subgroup of men.

The result of the assessment of the added benefit of ramucirumab in comparison with the ACT is summarized in Table 26.

Table 26: Ramucirumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Adult patients with MCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine[b]	FOLFIRI	Women	Indication of minor added benefit
		Men	Hint of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. b: According to the approval, ramucirumab is used in combination with FOLFIRI. ACT: appropriate comparator therapy; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; G-BA: Federal Joint Committee; MCRC: metastatic colorectal 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

RAISE

Eli Lilly. A study in second line metastatic colorectal cancer: full text view [online]. In: ClinicalTrials.gov. 01.02.2016 [accessed: 03.03.2016]. URL: https://clinicaltrials.gov/ct2/show/study/NCT01183780.

Eli Lilly. A study for people with advanced colorectal cancer who have been treated with a specific chemotherapy regimen (bevacizumab, oxaliplatin, and a fluoropyrimidine) which was ineffective in stopping the spread of the colorectal cancer: study participants will receive a different chemotherapyregimen (irinotecan, folinic acid, and 5-fluorouracil) and be randomly andunknowingly assigned to also receive the study drug (ramucirimab) or a non-active compound (placebo) [online]. In: EU Clinical Trials Register. [Accessed: 03.03.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-021037-32.

Eli Lilly. A study in second line metastatic colorectal cancer: study results [online]. In: ClinicalTrials.gov. 01.02.2016 [Accessed: 03.03.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01183780.

Eli Lilly. A randomized, double-blind, multicenter phase 3 study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients with metastatic colorectal carcinoma progressive during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine: study I4T-MC-JVBB; clinical study report [unpublished]. 2014.

Eli Lilly. A randomized, double-blind, multicenter phase 3 study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab or placebo in patients with metastatic colorectal carcinoma progressive during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine: study I4T-MC-JVBB; Zusatzanalysen [unpublished]. 2015.

Eli Lilly. A study for people with advanced colorectal cancer who have been treated with a specific chemotherapy regimen (bevacizumab, oxaliplatin, and a fluoropyrimidine) which was ineffective in stopping the spread of the colorectal cancer: study participants will receive a different chemotherapyregimen (irinotecan, folinic acid, and 5-fluorouracil) and be randomly andunknowingly assigned to also receive the study drug (ramucirimab) or a non-active compound (placebo) [online]. In: PharmNet.Bund Klinische Prüfungen. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015; 16(5): 499-508.

References for English extract

Please see full dossier assessment for full reference list.

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2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. Lilly. Cyramza 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 01.2016 [Accessed: 22.04.2016]. URL: http://www.fachinfo.de/.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-10-ramucirumab-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v.7302.html.