

IQWiG Reports – Commission No. A16-23

Ramucirumab (gastric cancer) –

Benefit assessment according to §35a Social Code Book V¹

Extract

¹ Translation of Sections 2.1 to 2.5 of the dossier assessment *Ramucirumab (Magenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 July 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Phone: +49 221 35685-0

Fax: +49 221 35685-1

E-mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice:

- Christoph F. Dietrich, Caritas Hospital, Bad Mergentheim, Germany

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

IQWiG employees involved in the dossier assessment²:

- Helmut Hörn
- Javid Ali
- Catharina Brockhaus
- Thomas Kaiser
- Michaela Florina Kerekes
- Ulrike Lampert
- Miriam Luhn
- Katrin Nink
- Corinna ten Thoren

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

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

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CSR	clinical study report
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
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 29 April 2016.

Research question

The aim of this report was to assess the added benefit of ramucirumab in comparison with the appropriate comparator therapy (ACT) in patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression. The following 2 research questions resulted from the approval:

- combination therapy with paclitaxel after prior platinum and fluoropyrimidine chemotherapy (research question 1)
- monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate (research question 2)

The research questions and the respective ACTs are shown in Table 2.

Table 2: Research questions of the benefit assessment of ramucirumab

Research question	Subindication	Appropriate comparator therapy ^a
1	Combination therapy with ramucirumab and paclitaxel after prior platinum and fluoropyrimidine chemotherapy	Individual treatment specified by the physician under consideration of the respective approval
2	Ramucirumab monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	Best supportive care

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company principally concurred with the ACT specified by the G-BA for both research questions. However, it argued for research question 1 (combination therapy with paclitaxel) that the drugs paclitaxel, docetaxel, irinotecan, and the combination therapy folinic acid + 5-fluorouracil + irinotecan (FOLFIRI), which are not approved for the subindication, were the primary options for the ACT of individual treatment specified by the physician. This contradicts the definition of the G-BA, which explicitly noted that the approval was to be considered and that paclitaxel monotherapy is not approved in the present subindication. The

company's specification was therefore not accepted. The present assessment investigated at study level whether the ACT used concurred with the G-BA's ACT.

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

Results

Research question 1 (combination therapy ramucirumab + paclitaxel)

The company included the randomized controlled trial (RCT) RAINBOW for the assessment of the added benefit of the combination therapy of ramucirumab + paclitaxel. This study was a double-blind, randomized, multicentre approval study on the comparison of ramucirumab + paclitaxel versus placebo + paclitaxel in adult patients with metastatic or unresectable, locally advanced gastric or gastro-oesophageal junction adenocarcinoma; with disease progression during or after first-line platinum and fluoropyrimidine therapy.

The RAINBOW study was unsuitable for the assessment of the added benefit of ramucirumab + paclitaxel in comparison with the ACT because the randomized study treatment for all patients in the control arm consisted of placebo + paclitaxel and the patients therefore received no individual treatment specified by the physician. The company neither showed that paclitaxel was the best treatment for a majority of the study population nor discussed to what extent the excluded drugs might have been more suitable or unsuitable for the treatment of the respective patients. It also did not show that paclitaxel – e.g. due to the patients' prior therapies – was the only usable therapeutic option. Instead, the company itself described that paclitaxel was only one of several different treatment options. Correspondingly, this is found in the guidelines, which list paclitaxel as only one of several drugs – and not as the preferred choice – for the target population.

In addition, paclitaxel monotherapy is not approved for the treatment of advanced gastric cancer with disease progression after prior platinum and fluoropyrimidine chemotherapy, which was explicitly stated in the G-BA's definition of the ACT. The other drugs recommended in the guidelines (e.g. docetaxel, irinotecan, and the combination therapy FOLFIRI) are also not approved in Germany for the second-line treatment of advanced gastric cancer. The drugs approved in Germany (e.g. Teysuno, 5-fluorouracil [5-FU], mitomycin, carmustine, epirubicin, and doxorubicin) are not recommended as second-line treatment of advanced gastric cancer in the guidelines.

The company presented no suitable data for the assessment of the added benefit of ramucirumab + paclitaxel in the dossier. This resulted in no hint of an added benefit of ramucirumab + paclitaxel in comparison with the ACT; an added benefit is therefore not proven.

Research question 2 (ramucirumab monotherapy)

The company included the RCT REGARD for the assessment of the added benefit of ramucirumab monotherapy. This study was a double-blind, randomized, multicentre approval study on the comparison of ramucirumab + best supportive care (BSC) versus placebo + BSC in adult patients with metastatic or unresectable, locally recurrent gastric or gastro-oesophageal junction adenocarcinoma with disease progression during or after first-line treatment for metastatic disease (platinum and fluoropyrimidine combination chemotherapies).

The REGARD study was unsuitable for the assessment of the added benefit of ramucirumab in comparison with the ACT because the REGARD study was not designed to represent the relevant population for the approval in the monotherapy (i.e. patients for whom a combination therapy of ramucirumab + paclitaxel is not appropriate).

The study protocol contained no inclusion or exclusion criteria to limit the study participants to patients for whom treatment in combination with paclitaxel is not appropriate. The company did not address this difference between study population and target population in the dossier. It also provided no evidence that the majority of the patients included were the target population or that the study results can be transferred to the population comprised by the approval for ramucirumab monotherapy.

The large proportion of patients who received chemotherapy after the end of the randomized study treatment showed that chemotherapy would have been an option for a relevant proportion of the study patients. This proportion was 29% in the ramucirumab + BSC arm and 38% in the placebo + BSC arm. Since gastric cancer is a progressive disease and presumably not every patient for whom chemotherapy would have been an option at the start of the study received chemotherapy after the end of the randomized study medication, it can be assumed that the proportion of patients for whom chemotherapy was an option at the start of the study was even higher. This means that the proportion of patients in the REGARD study who fulfilled the requirements of the approval was insufficient to determine the added benefit in comparison with the ACT.

The European Public Assessment Report (EPAR) by the European Medicines Agency (EMA) also shows that the REGARD study was not designed to represent the relevant population for the approval in the monotherapy. It is also criticized in the EPAR that the patients in the REGARD study were not selected on their non-eligibility to any treatment and that 33% of the patients received chemotherapy (third line) after the end of the randomized study medication. It also remains unclear, according to the EPAR, that the effect of ramucirumab monotherapy is so small that it may even be inferior to monochemotherapy in the present treatment situation. The EPAR additionally states that patients for whom chemotherapy would have been an option were possibly under-treated with placebo in the comparator arm. Against the background of the small effect on overall survival, EMA therefore limited the use of monotherapy in second-line treatment to patients for whom a combination therapy with

ramucirumab and paclitaxel is not appropriate. From EMA's point of view, only part of the patients investigated in the study fulfilled the criteria for monotherapy with the size of the proportion being unclear, as shown above. Some members of the Committee for Medicinal Products for Human Use (CHMP) explicitly warned against transferring the results of the study to the approved patient population since the proportion of relevant patients was unknown and necessarily inferior to 66%. The company did not address the problem of lacking transferability in its dossier.

Although the information from the clinical study report (CSR) and the EMA discussion are arguments against the suitability of the REGARD study for the derivation of an added benefit in monotherapy, it was investigated whether the inclusion and exclusion criteria and the patient characteristics in the REGARD study showed that chemotherapy was not indicated for the patients at the start of the study. This investigation also provided no signs that the REGARD study was suitable for the derivation of the added benefit in the present research question.

The company presented no suitable data for the assessment of the added benefit of ramucirumab monotherapy in the dossier. This resulted in no hint of an added benefit of ramucirumab in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

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].

Table 3: Ramucirumab – extent and probability of added benefit

Research question	Subindication	Appropriate comparator therapy ^a	Extent and probability of added benefit
1	Combination therapy with ramucirumab and paclitaxel after prior platinum and fluoropyrimidine chemotherapy	Individual treatment specified by the physician under consideration of the respective approval	Added benefit not proven
2	Ramucirumab monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	Best supportive care	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2015. In this assessment, the G-BA had determined a minor added benefit of ramucirumab for both research questions. However, the deviation was due to the special situation of the orphan assessment at the time. In this case, no ACT is specified by the G-BA, but the extent of added benefit is assessed exclusively on the basis of the approval studies, irrespective of whether the comparator therapy used in the approval study is appropriate.

2.2 Research questions

The aim of this report was to assess the added benefit of ramucirumab in comparison with the ACT in patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression. The following 2 research questions resulted from the approval:

- combination therapy with paclitaxel after prior platinum and fluoropyrimidine chemotherapy (research question 1)
- monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate (research question 2)

The research questions and the respective ACTs are shown in Table 4.

Table 4: Research questions of the benefit assessment of ramucirumab

Research question	Subindication	Appropriate comparator therapy ^a
1	Combination therapy with ramucirumab and paclitaxel after prior platinum and fluoropyrimidine chemotherapy	Individual treatment specified by the physician under consideration of the respective approval
2	Ramucirumab monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	Best supportive care
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company principally concurred with the ACTs specified by the G-BA for both research questions. However, it argued for research question 1 (combination therapy with paclitaxel) that the drugs paclitaxel, docetaxel, irinotecan, and the combination therapy FOLFIRI, which are not approved for the subindication, were the primary options for the ACT of individual treatment specified by the physician. This contradicts the definition of the G-BA, which explicitly noted that the approval was to be considered and that paclitaxel monotherapy is not approved in the present subindication (see Section 2.6.1 of the full dossier assessment). The company's specification was therefore not accepted. The present assessment investigated at study level whether the ACT used concurred with the G-BA's ACT (see Section 2.3.1).

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

For better readability, "gastric cancer or gastro-oesophageal junction adenocarcinoma" is abbreviated to "gastric cancer".

2.3 Research question 1 (combination therapy with paclitaxel)

2.3.1 Information retrieval and study pool (research question 1)

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: 22 February 2016)
- bibliographical literature search on ramucirumab (last search on 5 February 2016)
- search in trial registries for studies on ramucirumab (last search on 5 February 2016)
- bibliographical literature search on ACTs (last search on 16 February 2016)
- search in trial registries for studies on ACTs (last search on 18 February 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ramucirumab (last search on 10 May 2016)

The check of the completeness of the study pool produced no suitable RCTs on the comparison of ramucirumab + paclitaxel versus the ACT. This deviates from the company's approach, which included the RCT RAINBOW for research question 1.

The RAINBOW study [3] was a double-blind, randomized, multicentre approval study on the comparison of ramucirumab + paclitaxel versus placebo + paclitaxel. It included adult patients with metastatic or unresectable, locally advanced gastric or gastro-oesophageal junction adenocarcinoma with disease progression during or within 4 months of first-line platinum and fluoropyrimidine treatment. 665 patients were randomized in a ratio of 1:1, 330 patients to the intervention arm (ramucirumab + paclitaxel) and 335 patients to the control arm (placebo + paclitaxel).

The RAINBOW study was unsuitable for the assessment of the added benefit of ramucirumab + paclitaxel in comparison with the ACT because the randomized study treatment for all patients in the control arm consisted of placebo + paclitaxel and the patients therefore received no individual treatment specified by the physician. It is unclear whether paclitaxel might have been the treatment chosen for some of the patients in the study if there had been several options for the patients included in the studies. The company neither showed that paclitaxel was the best treatment for a majority of the study population nor discussed to what extent the excluded drugs might have been more suitable or unsuitable for the treatment of the respective patients. It also did not show that paclitaxel – e.g. due to the patients' prior therapies – was the only usable therapeutic option. Instead, the company itself described in Module 3 A, Section 3.1, and in Module 4 A, Section 4.2.1, that paclitaxel was only one of several different treatment options. Correspondingly, this is found in the guidelines [4-7],

which list paclitaxel as only one of several drugs – and not as the preferred choice – for the target population.

In addition, paclitaxel monotherapy is not approved for the treatment of advanced gastric cancer with disease progression after prior platinum and fluoropyrimidine chemotherapy, which was explicitly stated in the G-BA's definition of the ACT. The other drugs recommended in the guidelines [4-7] (e.g. docetaxel, irinotecan, and the combination therapy FOLFIRI) are also not approved in Germany for the second-line treatment of advanced gastric cancer. The drugs approved in Germany (e.g. Teysuno, 5-FU, mitomycin, carmustine, epirubicin, and doxorubicin) are not recommended as second-line treatment of advanced gastric cancer in the guidelines [4-7].

Since the patients in the control arm of the RAINBOW study received no individual treatment, the comparator therapy used (paclitaxel) is not approved in the subindication and the G-BA explicitly named the approval as prerequisite and important criterion for the comparator therapy, the RAINBOW study allowed no derivation of the added benefit of ramucirumab + paclitaxel versus the ACT specified by the G-BA.

As can be inferred from the information provided in Module 4 A, the company recognized the problem of the lacking approval of paclitaxel monotherapy and the associated lacking suitability as ACT and aimed to conduct an indirect comparison with the approved drugs, but did not find any relevant studies. Since its search was unsuitable to ensure completeness of the search result, it is unclear whether an indirect comparison would have been possible.

2.3.2 Results on added benefit (research question 1)

The company presented no suitable data for the assessment of the added benefit of ramucirumab + paclitaxel in the dossier. This resulted in no hint of an added benefit of ramucirumab + paclitaxel in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1)

Since the company presented no suitable data for the assessment of the added benefit of ramucirumab + paclitaxel, an added benefit of ramucirumab + paclitaxel is not proven.

This result deviates from that of the company, which derived an indication of considerable added benefit of ramucirumab + paclitaxel on the basis of the data presented by the company.

2.3.4 List of included studies (research question 1)

Not applicable as no studies were included in the benefit assessment.

2.4 Research question 2 (monotherapy)

2.4.1 Information retrieval and study pool (research question 2)

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: 22 February 2016)
- bibliographical literature search on ramucirumab (last search on 5 February 2016)
- search in trial registries for studies on ramucirumab (last search on 5 February 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ramucirumab (last search on 10 May 2016)

The check of the completeness of the study pool produced no suitable RCTs on the comparison of ramucirumab versus the ACT. This deviates from the company's approach, which included the RCT REGARD for research question 2.

The REGARD study [8] was a double-blind, randomized, multicentre approval study on the comparison of ramucirumab + BSC versus placebo + BSC. It included adult patients with metastatic or unresectable, locally recurrent gastric or gastro-oesophageal junction adenocarcinoma with disease progression during or within 4 months of the last dose of first-line treatment for metastatic disease (platinum-containing or fluoropyrimidine-containing combination chemotherapies), or with disease progression during or within 6 months of the last dose of adjuvant treatment. 355 patients were randomized in a ratio of 2:1, 238 patients to the intervention arm (ramucirumab + BSC) and 117 patients to the control arm (placebo + BSC).

The REGARD study was unsuitable for the assessment of the added benefit of ramucirumab in comparison with the ACT because the REGARD study was not designed to represent the relevant population for the approval in the monotherapy (i.e. patients for whom a combination therapy of ramucirumab + paclitaxel is not appropriate).

The study protocol contained no inclusion or exclusion criteria to limit the study participants to patients for whom treatment in combination with paclitaxel is not appropriate. These criteria might have been contraindications to the combination partner paclitaxel, for example, or poor general condition of the patients, which would have made them unsuitable for chemotherapy. The company did not address this difference between study population and target population in the dossier. It also provided no evidence that the majority of the patients included were the target population or that the study results can be transferred to the population comprised by the approval for ramucirumab monotherapy.

The large proportion of patients who received chemotherapy after the end of the randomized study showed that chemotherapy would have been an option for a relevant proportion of the study patients. This proportion was 29% in the ramucirumab + BSC arm and 38% in the placebo + BSC arm. Since gastric cancer is a progressive disease and presumably not every patient for whom chemotherapy would have been an option at the start of the study received chemotherapy after the end of the randomized study medication, it can be assumed that the proportion of patients for whom chemotherapy was an option at the start of the study was even higher. This means that the proportion of patients in the REGARD study who fulfilled the requirements of the approval was insufficient to determine the added benefit in comparison with the ACT.

The EPAR [9] by EMA also shows that the REGARD study was not designed to represent the relevant population for the approval in the monotherapy. The aspects mentioned above are also discussed in the EPAR. It was criticized that the patients in the REGARD study were not selected on their non-eligibility to any treatment and that 33% of the patients received chemotherapy (third line) after the end of the randomized study medication. According to the EPAR, disease progression further lowered the acceptability of chemotherapy at this time point so that possibly more than one third of the patients would have been amenable to an active treatment on second line (i.e. the study treatment) at time of randomization. It remains unclear, according to the EPAR, that the effect of ramucirumab monotherapy is so small that it may even be inferior to monochemotherapy in the present treatment situation [9]. The EPAR additionally states that patients for whom chemotherapy would have been an option were possibly under-treated with placebo in the comparator arm. Against the background of the small effect on overall survival, EMA therefore limited the use of monotherapy in second-line treatment to patients for whom a combination therapy with ramucirumab and paclitaxel is not appropriate. From EMA's point of view, only part of the patients investigated in the study fulfilled the criteria for monotherapy with the size of the proportion being unclear, as shown above. Some members of the CHMP explicitly warned against transferring the results of the study to the approved patient population since the proportion of relevant patients was unknown and necessarily inferior to 66% [9]. The company did not address the problem of lacking transferability in its dossier.

Although the information from the CSR and the EMA discussion are arguments against the suitability of the REGARD study for the derivation of an added benefit in monotherapy, it was investigated whether the inclusion and exclusion criteria and the patient characteristics in the REGARD study showed that chemotherapy was not indicated for the patients at the start of the study. The contraindications from the Summary of Product Characteristics (SPC) were considered and the inclusion and exclusion criteria and the patient characteristics of the studies REGARD and RAINBOW were compared. This investigation had the following results:

- In both studies, $\geq 99\%$ of the patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, indicating a good general condition.
- The inclusion and exclusion criteria of the REGARD study were comparable with the inclusion and exclusion criteria of the RAINBOW study.
 - If there were relevant differences, e.g. in the required neutrophil count at the start of the study ($\geq 1000/\mu\text{L}$ in the REGARD study and the threshold of $\geq 1500/\mu\text{L}$ required according to the SPC of paclitaxel in the RAINBOW study), they did not affect the patient characteristics (see Table 9 in the full dossier assessment).
- Further criteria supporting a non-suitability of paclitaxel in the REGARD study were neither formulated nor could be interpreted from the demographic information.
- The patient characteristics were similar in both studies (see Table 9 in the full dossier assessment).

Since the patients in the RAINBOW study received paclitaxel as part of their combination therapy, it can be assumed due to these similarities that at least a relevant part of the patients in the REGARD study could have also been treated with a combination therapy of ramucirumab + paclitaxel.

Summary

The REGARD study was unsuitable for the derivation of an added benefit of ramucirumab monotherapy in comparison with BSC as ACT because it was not designed to represent the relevant population for the approval in monotherapy and the proportion of the target population in the study was insufficient to determine the added benefit. The company did not address the lack of transferability of the REGARD study in its dossier.

2.4.2 Results on added benefit (research question 2)

The company presented no suitable data for the assessment of the added benefit of ramucirumab monotherapy in the dossier. This resulted in no hint of an added benefit of ramucirumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 2)

Since the company presented no suitable data for the assessment of the added benefit of ramucirumab monotherapy in the dossier, an added benefit of ramucirumab is not proven.

This result deviates from that of the company, which derived an indication of considerable added benefit of ramucirumab monotherapy on the basis of the data presented by the company.

2.4.4 List of included studies (research question 2)

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of ramucirumab in comparison with the ACT is summarized in Table 5.

Table 5: Ramucirumab – extent and probability of added benefit

Research question	Subindication	Appropriate comparator therapy ^a	Extent and probability of added benefit
1	Combination therapy with ramucirumab and paclitaxel after prior platinum and fluoropyrimidine chemotherapy	Individual treatment specified by the physician under consideration of the respective approval	Added benefit not proven
2	Ramucirumab monotherapy after prior platinum or fluoropyrimidine chemotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	Best supportive care	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA assessment in the framework of the market access in 2015 [10,11]. In this assessment, the G-BA had determined a minor added benefit of ramucirumab for both research questions. However, the deviation was due to the special situation of the orphan assessment at the time. In this case, no ACT is specified by the G-BA, but the extent of added benefit is assessed exclusively on the basis of the approval studies, irrespective of whether the comparator therapy used in the approval study is appropriate.

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Please see full dossier assessment for full reference list.

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