IQWiG Reports – Commission No. A20-122

Lenvatinib (renal cell carcinoma) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Lenvatinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2021). 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
eCRF	electronic case report form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSKCC	Memorial Sloan Kettering Cancer Center
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

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 lenvatinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 December 2020.

According to the justification of the decision of 16 March 2017, the reason for the limitation of the decision was that the evidence submitted by the company was rated as insufficient in terms of both scope and certainty of conclusions to assess the added benefit of lenvatinib in comparison with the appropriate comparator therapy (ACT). For the reassessment after expiry of the decision, data on all patient-relevant outcomes – mortality, morbidity, health-related quality of life and side effects – were to be recorded on the basis of comparative clinical studies compared with the ACT. Covering an adequate sample size, the data were to guarantee a sufficiently high statistical power of the study and allow drawing conclusions on disease-specific morbidity, health-related quality of life as well as more reliable conclusions on side effects. In addition, it was requested that the study population also included patients with brain metastases and that it sufficiently corresponded to the actual German health care setting by also including patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2 or higher.

Research question

The aim of the present report is the assessment of the added benefit of lenvatinib in combination with everolimus (hereinafter "lenvatinib + everolimus") in comparison with the ACT in adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Table 2: Research questions of the benefit assessment of lenvatinib + everolimus

Therapeutic indication	**ACT**[a]
Adult patients with advanced renal cell carcinoma[b] following one prior vascular endothelial growth factor (VEGF)-targeted therapy	**Cabozantinib** or nivolumab

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

From the options presented, the company chose cabozantinib as comparator therapy, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

No randomized controlled trial (RCT) of direct comparison was identified for the assessment of the added benefit of lenvatinib in combination with everolimus in comparison with the comparator therapy cabozantinib. The company presented an adjusted indirect comparison using the common comparator everolimus, with the study E7080-G000-205 (hereinafter referred to as "study 205") on the lenvatinib side and the study METEOR on the cabozantinib side.

Study 205 (study with lenvatinib + everolimus)

Study 205 is a randomized, open-label, active-controlled phase 1b/2 study for the approval of lenvatinib + everolimus. Adult patients with unresectable advanced or metastatic, mainly clear-cell, renal cell carcinoma were included in the phase 2 study. The patients' disease must have progressed within 9 months after previous treatment. In addition, the patients had to have disease progression after one prior VEGF-targeted therapy of the unresectable advanced or metastatic disease. This VEGF-targeted therapy did not have to be the last therapy before study inclusion. Patients had to be in good general condition (ECOG PS of 0 or 1). Since no patients with an ECOG PS of > 1 were included, it remains unclear whether the results of the study are valid for this patient group. Since only one patient with non-clear-cell renal cell carcinoma was included in the study, no conclusion can be derived for this patient group.

A total of 153 patients were randomly assigned in a 1:1:1 ratio to the treatment arms lenvatinib + everolimus (N = 51), lenvatinib (N = 52) or everolimus (N = 50). The study arm with the lenvatinib + everolimus combination and the study arm with everolimus monotherapy are relevant for the present benefit assessment.

The patients in the lenvatinib + everolimus arm and in the everolimus arm were treated in compliance with the Summaries of Product Characteristics (SPCs).

Treatment with lenvatinib + everolimus or everolimus was to be continued in both study arms at most until disease progression or occurrence of unacceptable toxicity. After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies.

Primary outcome of the study was progression-free survival (PFS); relevant secondary outcomes were overall survival and side effects. Health-related quality of life was not recorded in study 205.

There were 3 data cut-offs for study 205. The third data cut-off on 31 July 2015 is relevant for the benefit assessment. This data cut-off was conducted post hoc following a recommendation by the regulatory authorities to obtain more precise data with greater informative value.

METEOR (study with cabozantinib)

The METEOR is a randomized, open-label, active-controlled approval study on the comparison of cabozantinib and everolimus. Adult patients with advanced, metastatic and clear-cell renal cell carcinoma who had received at least one prior VEGF-targeted therapy were included in the study. The prior VEGF-targeted therapy had to be a tyrosine kinase inhibitor (TKI); prior therapy with a monoclonal antibody (e.g. bevacizumab) as only pretreatment was not sufficient for study inclusion.

Patients had to have radiological documentation of tumour progression during or within 6 months after the most recent prior VEGF-targeted therapy. In addition, the patients had to be in good general condition (Karnofsky performance status of ≥ 70%). Since no patients with a Karnofsky performance status of < 70% (equivalent to an ECOG PS of > 1) were included, it remains unclear whether the results of the study are valid for this patient group.

Since no patients with non-clear-cell renal cell carcinoma were included in the study, no conclusion can be derived for this patient group. This also applies to patients who had only been treated with the VEGF-targeted therapy bevacizumab in their prior therapy.

A total of 658 patients were randomly allocated in a ratio of 1:1 to treatment with cabozantinib (N = 330) or everolimus (N = 328).

The patients in the cabozantinib arm and in the everolimus arm were treated in compliance with the SPCs. Treatment was continued in both study arms as long as there was a clinical benefit and treatment was tolerated; patients were also allowed to continue treatment beyond disease progression. There were no restrictions regarding subsequent therapies.

Primary outcome of the study was PFS; relevant secondary outcomes were overall survival, morbidity and side effects.

There were 3 data cut-offs for the METEOR study. The third data cut-off on 2 October 2016 is relevant for the benefit assessment. This is the time of the prespecified final analysis of overall survival after at least 408 events.

Similarity of the studies for the indirect comparison

The check of the similarity of the studies 205 and METEOR revealed a number of ambiguities or uncertainties regarding the similarity of the studies presented for the indirect comparison. These include differences in the proportion of patients enrolled in Europe, differences in the specifications regarding treatment duration, and differences in pretreatment, among others. Overall, however, these differences did not lead to a fundamental questioning of the similarity of the studies.

Risk of bias

The risk of bias across outcomes was rated as low for both studies. The risk of bias for the outcome "overall survival" was also rated as low for both studies. However, the results of all other outcomes recorded in both studies of the indirect comparison had a high risk of bias. This means that the requirement for the certainty of results for conducting an adjusted indirect comparison was not met for the following outcomes: serious adverse events (SAEs), severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and discontinuation due to AEs. No indirect comparison was therefore conducted for these outcomes.

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of lenvatinib + everolimus versus cabozantinib, the consistency assumption could not be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib; an added benefit is therefore not proven.

Morbidity

No patient-relevant outcomes of the category of morbidity were recorded in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib for the outcome category of morbidity; an added benefit is therefore not proven.

Health-related quality of life

There were no data for an indirect comparison for the outcome "health-related quality of life", as this outcome was not recorded in the studies 205 and METEOR. Hence, there was no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib; an added benefit is therefore not proven.

Side effects

Due to insufficient certainty of results in both studies, no indirect comparison was calculated for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs".

Hence, there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with cabozantinib; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, probability and extent of the added benefit of the drug lenvatinib in comparison with the ACT are assessed as follows:

Overall, based on the adjusted indirect comparison using the common comparator everolimus, there are neither positive nor negative effects of lenvatinib + everolimus in comparison with cabozantinib.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival". There is no hint of an added benefit of lenvatinib + everolimus for this outcome, as the indirect comparison showed no statistically significant difference. Outcomes on morbidity and health-related quality of life were not recorded on at least one side of the indirect comparison. No usable data for an indirect comparison are available for the outcome category of side effects, as the certainty of results was not sufficient for an indirect comparison.

In summary, there is no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib for adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy.

Table 3 presents a summary of the extent and probability of the added benefit of lenvatinib + everolimus.

Table 3: Lenvatinib + everolimus – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients[b] with advanced renal cell carcinoma following one prior VEGF-targeted therapy	**Cabozantinib** or nivolumab	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Only patients with clear-cell renal cell carcinoma with an ECOG PS of 0 or 1 were included in the studies 205 and METEOR (except for one patient in study 205). It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with non-clear cell renal cell carcinoma.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

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

The approach for the derivation of an overall conclusion on the 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 is the assessment of the added benefit of lenvatinib in combination with everolimus (hereinafter "lenvatinib + everolimus") in comparison with the ACT in adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy.

Table 4: Research questions of the benefit assessment of lenvatinib + everolimus

Therapeutic indication	**ACT[a]**
Adult patients with advanced renal cell carcinoma[b] following one prior vascular endothelial growth factor (VEGF)-targeted therapy	**Cabozantinib** or nivolumab

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the therapeutic decision and that treatment is palliative.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

From the options presented, the company chose cabozantinib as comparator therapy, thus following the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of 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 lenvatinib (status: 15 November 2020)
- bibliographical literature search on lenvatinib (last search on 9 October 2020)
- search in trial registries/trial results databases for studies on lenvatinib (last search on 24 October 2020)
- search on the G-BA website for lenvatinib (last search on 22 October 2020)
- bibliographical literature search on ACTs (last search on 5 November 2020)
- search in trial registries/trial results databases for studies on ACTs (last search on 5 November 2020)
- search on the G-BA website for ACTs (last search on 11 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on lenvatinib (last search on 11 January 2021)

- search in trial registries for studies on cabozantinib (last search on 14 January 2021)

Concurring with the company, no relevant RCT on the direct comparison of lenvatinib + everolimus versus cabozantinib was identified from the check of the completeness of the study pool.

- The company presented an adjusted indirect comparison according to Bucher [3] for the assessment of lenvatinib + everolimus in comparison with cabozantinib using the common comparator everolimus.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

2.3.1 Studies included

Since there was only one RCT with lenvatinib + everolimus in the relevant therapeutic indication and this RCT used everolimus as comparison, in agreement with the company, everolimus was the only possible common comparator for an adjusted indirect comparison.

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

Table 5: Study pool – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study with lenvatinib + everolimus vs. everolimus						
Study E7080-G000-205 (study 205[d])	Yes	Yes	No	No[e]	Yes [4,5]	Yes [6-13]
Study with cabozantinib vs. everolimus						
NCT01865747 (METEOR[d])	No	No	Yes	No	Yes [14,15]	Yes [16-29]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; vs.: versus

The study pool for the benefit assessment concurred with that of the company. Study 205 was already submitted and assessed for the previous benefit assessment A16-63 of lenvatinib [13]. The second study included in the indirect comparison, study METEOR, was also already

submitted and assessed for previous benefit assessments of cabozantinib in the therapeutic indication (dossier assessment A16-69 and addendum A17-10 [23,29] as well as dossier assessment A17-59 and addenda A18-13 and A18-18 [24-26].

Figure 1 shows a schematic representation of the indirect comparison.

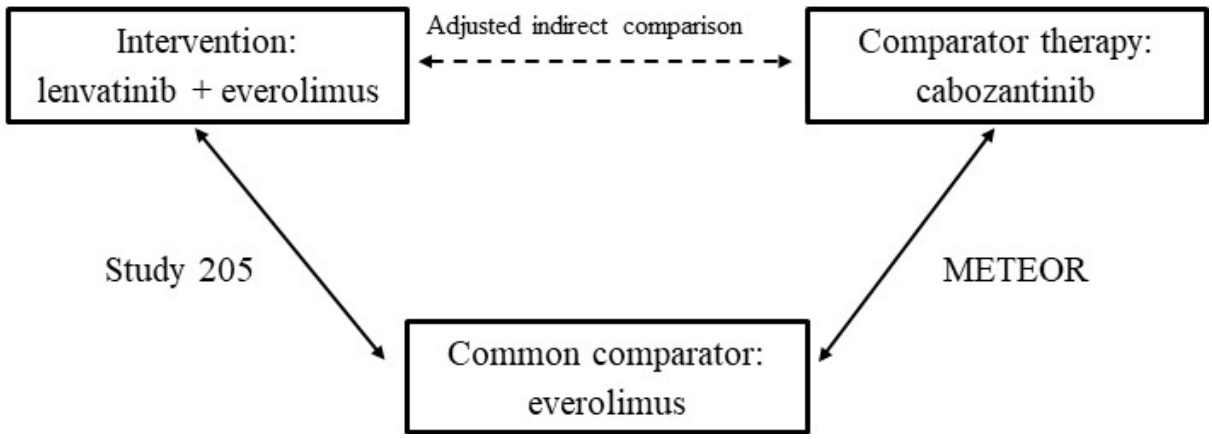

Figure 1: Study pool for the indirect comparison between lenvatinib + everolimus and the ACT cabozantinib

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, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with lenvatinib + everolimus vs. everolimus						
205	RCT, open-label, parallel	Adults (≥ 18 years) with unresectable advanced or metastatic, mainly clear-cell RCC ▪ after one prior VEGF-targeted therapy and ▪ radiological documentation of disease progression within 9 months after the most recent prior therapy ▪ disease progression after one prior VEGF-targeted therapy in the advanced stage ▪ ECOG PS 0 or 1	Lenvatinib + everolimus (N = 51) lenvatinib (N = 52)[b] everolimus (N = 50)	Screening: ≤ 21 days Treatment: until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision Observation[c]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	37 centres in Czech Republic, Poland, Spain, United Kingdom, United States 3/2012–2/2018 First data cut-off (primary analysis)[d]: 13 June 2014 Second data cut-off (post hoc): 10 December 2014 Third data cut-off (post hoc)[e]: 31 July 2015	Primary: PFS Secondary: overall survival, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with cabozantinib vs. everolimus						
METEOR	RCT, open-label, parallel	Adults (≥ 18 years) with advanced, metastatic and clear-cell RCC ▪ after ≥ 1 prior VEGF-targeted therapy and ▪ radiological documentation of tumour progression during or within 6 months after the most recent prior VEGF-targeted therapy ▪ Karnofsky performance status ≥ 70%	Cabozantinib (N = 330) everolimus (N = 328)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision Observation[c]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	173 study centres in Argentina, Austria, Australia, Belgium, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Republic of Korea, Russia, Slovak Republic, Spain, Sweden, Taiwan, Turkey, United Kingdom, USA 8/2013–10/2016 First data cut-off (primary analysis)[f]: 22 May 2015 Second data cut-off (interim analysis)[e]: 31 December 2015 Third data cut-off (final analysis)[g]: 2 October 2016	Primary: PFS Secondary: overall survival, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The arm is not relevant for the assessment and is no longer presented in the following tables.
c. Outcome-specific information is provided in Table 8.
d. Predefined primary analysis after at least 90 progression events across all study arms and at least 60 events for each of the prespecified comparisons between the study arms.
e. Data cut-off conducted post hoc on the recommendation of the regulatory authorities; METEOR study: interim data cut-off for the outcome "overall survival".
f. Predefined primary analysis after at least 259 progression events.
g. Predefined final analysis of overall survival after at least 408 events.

Table 6: Characteristics of the studies included – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; PFS: progression-free survival; RCC: renal cell carcinoma; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; vs.: versus						

Table 7: Characteristics of the interventions – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	Intervention/comparator therapy	Common comparator
Study with lenvatinib + everolimus vs. everolimus		
205	Lenvatinib 18 mg + everolimus 5 mg/day, orally	Everolimus 10 mg/day, orally
	Dose reduction according to the SPC or dose interruption in case of grade 2 or 3 toxicity allowed	
	Permitted pretreatment ▪ one VEGF-targeted therapy (e.g. sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, vatalanib) **Non-permitted pretreatment** ▪ mTOR inhibitors (everolimus, temsirolimus) ▪ anticancer therapies ≤ 21 days or investigational agents ≤ 30 days prior to first dose of study medication ▪ major surgery ≤ 3 weeks before first dose of study medication **Permitted concomitant treatment** ▪ treatment of disease-related symptoms (including transfusions, antibiotics, antidiarrhoeal drugs, etc.) ▪ short-term corticosteroids ▪ G-CSF, erythropoietin ▪ bisphosphonates ▪ low molecular weight heparin ▪ acetylsalicylic acid, nonsteroidal anti-inflammatory drugs restricted **Non-permitted concomitant treatment** ▪ CYP3A4 and/or P-gp inhibitors, inducers and substrates ▪ any other anticancer treatment except the study medication ▪ corticosteroids for the palliative treatment of symptoms	
Study with cabozantinib vs. everolimus		
METEOR	Cabozantinib 60 mg/day, orally	Everolimus 10 mg/day, orally
	Dose reduction and interruption in compliance with the SPC was possible at any time in case of unacceptable toxicity	Dose reduction and interruption in compliance with the SPC was possible in case of severe or intolerable adverse reactions[a]
	Permitted pretreatment ▪ ≥ 1 prior systemic VEGF-targeted therapy (e.g. sorafenib, sunitinib, axitinib, pazopanib or tivozanib) ▪ other antineoplastic therapies, including cytokines (e.g. interleukin 2, interferon alpha), monoclonal antibodies (VEGF-, PD-1- or PD-L1/L2[b]-targeted therapies) and cytotoxic chemotherapies without restriction in the number of treatments **Non-permitted pretreatment** ▪ everolimus or another specific or selective mTOR inhibitor (e.g. temsirolimus) ▪ cabozantinib **Concomitant treatment** ▪ treatment to control bone metabolism (e.g. bisphosphonates, denosumab) if initiated before randomization **Non-permitted concomitant treatment** ▪ avoidance of local antineoplastic treatments (e.g. palliative radiation or surgery) until the last tumour assessment with imaging techniques ▪ further systemic antineoplastic treatments	

Table 7: Characteristics of the interventions – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	Intervention/comparator therapy	Common comparator
a. According to the SPC [30], dose reductions are allowed; the recommended daily dose must not be lower than 5 mg daily, however (implementation in the METEOR study: dose reductions for everolimus contrary to the SPC below 5 mg in 1.6% of the patients). b. The proportion of patients of the study population who had received prior PD-1- or PD-L1/L2-targeted therapy was limited to a maximum of 10%. CYP3A4: cytochrome P450 3A4; G-CSF: granulocyte colony-stimulating factor; mTOR: mechanistic target of rapamycin; P-gp: P-glycoprotein; PD-1: programmed cell death 1; PD-L: programmed cell death ligand; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; VEGF: vascular endothelial growth factor; vs.: versus		

Study design

Study 205 (study with lenvatinib + everolimus)

Study 205 is a randomized, open-label, active-controlled phase 1b/2 study for the approval of lenvatinib + everolimus. The first part of the study (approval phase 1b) for dose finding was not used for the present benefit assessment. The patients in this phase 1b were not included in the second part of the study. In the second part of the study (approval phase 2), the patients were treated in 3 study arms: lenvatinib + everolimus, everolimus monotherapy, and lenvatinib monotherapy. This part of the study was used for the present benefit assessment.

Adult patients with unresectable advanced or metastatic, mainly clear-cell, renal cell carcinoma were included in the phase 2 study. The patients' disease must have progressed within 9 months after previous treatment. In addition, the patients had to have disease progression after one prior VEGF-targeted therapy of the unresectable advanced or metastatic disease. This VEGF-targeted therapy did not have to be the last therapy before study inclusion. Patients had to be in good general condition (ECOG PS of 0 or 1). Since no patients with an ECOG PS of > 1 were included, it remains unclear whether the results of the study are valid for this patient group. Since only one patient with non-clear-cell renal cell carcinoma was included in the study, no conclusion can be derived for this patient group.

The population investigated in the study largely corresponded to the therapeutic indication of lenvatinib + everolimus.

A total of 153 patients were stratified by haemoglobin levels (≤ 13 g/dL versus > 13 g/dL for men and ≤ 11.5 g/dL versus > 11.5 g/dL for women) and corrected serum calcium levels (≥ 10 mg/dL versus < 10 mg/dL) and randomly assigned in a ratio of 1:1:1 to the treatment arms lenvatinib + everolimus (N = 51), lenvatinib (N = 52) or everolimus (N = 50). The study arm with the lenvatinib + everolimus combination and the study arm with everolimus monotherapy are relevant for the present benefit assessment.

The patients in the lenvatinib + everolimus arm and in the everolimus arm were treated in compliance with the SPCs [30,31]. Treatment with lenvatinib + everolimus or everolimus was

to be continued in both study arms at most until disease progression or occurrence of unacceptable toxicity.

Previous medication that was considered necessary for the patients' health could be continued. In addition, all patients could receive concomitant supportive treatment of disease-related symptoms. All medications which were not expected to influence the analysis or to interact with the drugs of the study were allowed as prior or concomitant medication. No other anticancer treatments such as chemotherapy, endocrine therapy, radiotherapy or immunotherapy were allowed.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies. There is no information regarding restriction of the subsequent therapy. A switch of patients from the everolimus arm to treatment with lenvatinib + everolimus was not planned.

At the time point of the third data cut-off (31 July 2015), 18 (35%) patients in the lenvatinib + everolimus arm and 18 (36%) patients in the everolimus arm were receiving subsequent antineoplastic therapy. The most common subsequent treatments were axitinib (12%) and everolimus (9.8%) in the lenvatinib + everolimus arm and axitinib (24%) in the everolimus arm (see Table 29 in the full dossier assessment).

Primary outcome of the study was PFS; patient-relevant secondary outcomes were overall survival and AEs. Health-related quality of life was not recorded in study 205.

METEOR (study with cabozantinib)

The METEOR is a randomized, open-label, active-controlled approval study on the comparison of cabozantinib and everolimus.

Adult patients with advanced, metastatic and clear-cell renal cell carcinoma who had received at least one prior VEGF-targeted therapy were included in the study. The prior VEGF-targeted therapy had to be a TKI; prior therapy with a monoclonal antibody (e.g. bevacizumab) as only pretreatment was not sufficient for study inclusion.

Patients had to have radiological documentation of tumour progression during or within 6 months after the most recent prior VEGF-targeted therapy. In addition, the patients had to be in good general condition (Karnofsky performance status of ≥ 70%). Since no patients with a Karnofsky performance status of < 70% (equivalent to an ECOG PS of > 1) were included, it remains unclear whether the results of the study are valid for this patient group. Since no patients with non-clear-cell renal cell carcinoma were included in the study, no conclusion can be derived for this patient group. This also applies to patients who had only been treated with the VEGF-targeted therapy bevacizumab in their prior therapy.

The inclusion criteria for the population included in the METEOR study corresponded to the therapeutic indication of cabozantinib in the present research question.

Randomization was stratified by the following factors: number of prior VEGF-targeted therapies (1 versus ≥ 2) and number of Memorial Sloan Kettering Cancer Center (MSKCC) risk factors (0 versus 1 versus 2 to 3; according to electronic case report form [eCRF]). A total of 658 patients were randomly allocated in a ratio of 1:1 to treatment with cabozantinib (N = 330) or everolimus (N = 328).

The patients in the cabozantinib arm and in the everolimus arm were treated in compliance with the SPCs [30,32]. Treatment was continued in both study arms as long as there was a clinical benefit and treatment was tolerated; patients were also allowed to continue treatment beyond disease progression.

Further systemic antineoplastic therapies as concomitant treatment to the study treatment were prohibited. Local antineoplastic treatment (palliative radiation, or surgery with impact on tumour lesions) had to be avoided until completion of the tumour assessment with imaging techniques. Treatment with impact on bone metabolism (e.g. with bisphosphonates or denosumab) was allowed if this had been initiated before randomization.

There were no restrictions regarding subsequent therapies; treatment switching from the comparator intervention everolimus to the experimental intervention cabozantinib was not permitted, however. At the time point of the third data cut-off (2 October 2016), 187 (57%) patients in the cabozantinib arm and 205 (63%) patients in the everolimus arm were receiving subsequent antineoplastic therapy. The most common subsequent treatments in the cabozantinib arm were everolimus (33%), axitinib (20%) and nivolumab (13%). In comparison, the subsequent treatments in the everolimus were distributed between axitinib (30%), nivolumab (15%), sunitinib (11%) and sorafenib (10%) (see Table 29 in the full dossier assessment).

Primary outcome of the study was PFS; patient-relevant secondary outcomes were overall survival, morbidity and AEs.

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients in the studies 205 and METEOR for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Study with lenvatinib + everolimus vs. everolimus	
205	
Mortality	
Overall survival	Every 8 weeks until the primary analysis, then[a] every 12 weeks until death, end of study or withdrawal of consent to be contacted
Morbidity	No data suitable for the indirect comparison are available[b]
Health-related quality of life	No data suitable for the indirect comparison are available[c]
Side effects	
All outcomes in the category of side effects	Until 30 days after the last dose of the study medication
Study with cabozantinib vs. everolimus	
METEOR	
Mortality	
Overall survival	Every 8 weeks (± 7 days) until death, withdrawal of consent or due to the sponsor's decision to end data recording, at most until the final analysis of overall survival
Morbidity	
Symptoms (FKSI-DRS)	
Health status (EQ-5D VAS)	No data suitable for the indirect comparison are available[d]
Skeletal-related events	
Health-related quality of life	No data suitable for the indirect comparison are available[c]
Side effects	
All outcomes in the category of side effects	Until 30 (+ 14) days after permanent treatment discontinuation

a. Patients who were under treatment at the time point of the primary analysis continued treatment according to randomization.
b. No patient-relevant outcomes recorded in this category.
c. Not recorded. The questionnaires FKSI-15 and FKSI-19 used in the study are not suitable to represent the complex construct of health-related quality of life or are considered unvalidated, see also Section 2.7.2.4.3 of dossier assessment A17-56 [24].
d. The outcomes were recorded only in the METEOR study.

EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the side effect outcomes of both studies were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on morbidity, health-related quality of life and AEs over 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.

Data cut-offs

Study 205

Three data cut-offs are available for study 205.

- first data cut-off: 13 June 2014 (prespecified primary analysis of PFS)
- second data cut-off: 10 December 2014 (post hoc, update of the data on overall survival)
- third data cut-off: 31 July 2015 (post hoc, recommendation of the Food and Drug Administration [FDA])

In Module 4 A, the company presented analyses based on the third data cut-off of 31 July 2015 for the outcome categories of mortality and side effects, and analyses based on the first data cut-off of 13 June 2014 for the morbidity outcomes included by the company.

The third data cut-off was considered decisive for the present benefit assessment because the data were more recent and it can be assumed that the time point of the data cut-off was not data-driven.

METEOR

Three data cut-offs are available for the METEOR study:

- first data cut-off: 22 May 2015 (prespecified analysis of the primary outcome "PFS" and first interim analysis for the outcome "overall survival")
- second data cut-off: 31 December 2015 (post hoc second interim data cut-off for overall survival in consultation with the European Medicines Agency [EMA])
- third data cut-off: 2 October 2016 (prespecified, final analysis of overall survival after at least 408 events)

In Module 4 A, the company presented analyses for all used outcomes based on the third data cut-off from 2 October 2016.

The present benefit assessment is based on the data cut-off from 2 October 2016.

Study population

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

Table 9: Characteristics of the study populations – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	205		METEOR	
Characteristic Category	Lenvatinib + everolimus	Everolimus	Cabozantinib	Everolimus
	N = 51	N = 50	N = 330	N = 328
Age [years], mean (SD)	62 (8)	59 (9)	62 (10)	61 (11)
Sex [F/M], %	31/69	24/76	23/77	26/73
Family origin, n (%)				
White	50 (98)	47 (94)	269 (82)	263 (80)
Asian	1 (2)	2 (4)	46 (14)	42 (13)
No data	0 (0)	1 (2)	15 (4.5)	23 (7)
Region, n (%)				
Europe	46 (90)	36 (72)	167 (51)	153 (47)
North America	5 (10)	14 (28)	118 (36)	122 (37)
Asia-Pacific	0 (0)	0 (0)	39 (12)	47 (14)
South America	0 (0)	0 (0)	6 (1.8)	6 (1.8)
Time between first diagnosis and randomization [months], median [min; max]	31.8 [5.1; 215.9]	26.0 [2.0; 147.2]	33.6 [0; 360]	30.0 [0; 396]
ECOG PS[a], n (%)				
0	27 (53)	28 (56)	226 (68)	216 (66)
1	24 (47)	22 (44)	104 (32)	112 (34)
Number of prior VEGF-targeted therapies, n (%)				
1	51 (100)	50 (100)	235 (71)	229 (70)
≥ 2	0 (0)	0 (0)	95 (29)	99 (30)
Previous nephrectomy, n (%)				
Yes	44 (86)[b]	48 (96)[b]	283 (86)	279 (85)
No	ND	ND	47 (14)	49 (15)
RCC diagnosis classification, n (%)				
Clear-cell	50 (98.0)	50 (100)	330 (100)	328 (100)
Other	1 (2.0)[c]	0	0	0
Extent of RCC at baseline, n (%)				
Unresectable advanced	4 (7.8)	1 (2.0)	ND	ND
Metastatic	47 (92.2)	49 (98.0)	ND	ND
Disease stage, n (%)				
Stage IV	ND	ND	272 (82)	287 (88)
Stage III	ND	ND	34 (10)	24 (7.3)
Unknown or missing	ND	ND	24 (7.3)	17 (5.2)
MSKCC risk score[d] at baseline, n (%)				
Favourable (0)	12 (24)	12 (24)	150 (45)	150 (46)
Intermediate (1)	19 (37)	19 (38)	139 (42)	135 (41)
Poor (2–3)	20 (39)	19 (38)	41 (12)	43 (13)

Table 9: Characteristics of the study populations – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Study	205		METEOR	
Characteristic Category	Lenvatinib + everolimus	Everolimus	Cabozantinib	Everolimus
	N = 51	N = 50	N = 330	N = 328
Heng criteria[e], n (%)				
Favourable (value 0)	8 (16)	9 (18)	66 (20)	62 (19)
Intermediate (value 1 or 2)	32 (64)	29 (58)	210 (64)	214 (65)
Poor (value ≥ 3)	10 (20)	12 (24)	54 (16)	52 (16)
Treatment discontinuation, n (%)	49 (96[f])[g]	49 (98[f])[g]	294 (89)[h]	320 (98)[h]
Study discontinuation, n (%)	ND[i]	ND[i]	17 (5.2)[h]	25 (7.6)[h]

a. For the METEOR study calculated from Karnofsky performance status.
b. Data from the EPAR [33] or the publication Motzer 2015 [7]. Discrepant information on this in Module 4 A of the dossier. In Module 4 A of the dossier, previous nephrectomy is reported for 55% of patients in the lenvatinib + everolimus arm and for 56% in the everolimus arm.
c. Partially clear-cell, partially papillary renal cell carcinoma.
d. The overall risk score is based on 3 prognostic factors: ECOG PS, haemoglobin level and corrected serum calcium at baseline.
e. The overall risk score is based on 6 prognostic factors: ECOG PS, haemoglobin level, corrected serum calcium, neutrophil count, platelet count at baseline and time from diagnosis to randomization.
f. Institute's calculation.
g. Third data cut-off 31 July 2015.
h. Third data cut-off 2 October 2016.
i. No information on the third data cut-off from 31 July 2015; at the first data cut-off from 13 June 2014, there was one study discontinuation in the lenvatinib + everolimus arm and one in the everolimus arm.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; EPAR: European Public Assessment Report; F: female; M: male; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients in the category; N: number of randomized patients; ND: no data; RCC: renal cell carcinoma; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor; vs.: versus

The demographic and disease-specific characteristics of the patients within the individual studies are largely balanced. There are differences between the 2 studies, however.

The mean age of the patients in both studies was between 59 and 62 years, about 3 quarters of the patients were male and most patients were of white family origin. Only patients in good general condition (ECOG PS of 0 or 1) were included in the 2 studies. About 2 thirds of the patients had an intermediate risk profile according to the Heng criteria [34,35] and about 40% had an intermediate MSKCC score. The majority of the patients had metastatic renal cell carcinoma.

At the decisive third data cut-off, almost all patients in the everolimus arm of both studies and in the lenvatinib + everolimus arm of study 205 had discontinued therapy. At this point, 89% of the patients in the METEOR study had completed therapy with cabozantinib. Therapy discontinuations in the METEOR study were mainly due to progression of the underlying

disease. According to the information on the first data cut-off [13], treatment discontinuations in study 205 were mainly due to radiological disease progression or AEs.

Differences between the studies resulted from the inclusion and exclusion criteria of the studies. For example, pretreatment with VEGF-targeted therapy was defined differently in the 2 studies. A notable difference can also be seen in the proportion of patients included in Europe. These aspects are discussed in Section 2.3.3 on the examination of similarity.

Treatment duration and observation period

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study **Data cut-off** **Duration of the study phase** **Outcome category**	**Lenvatinib + everolimus or cabozantinib**	**Everolimus**
Study with lenvatinib + everolimus vs. everolimus		
Study 205	N = 51	N = 50
Data cut-off 31 July 2015		
Treatment duration	ND	
Observation period [months]		
Overall survival	ND	
Morbidity	No patient-relevant outcomes recorded in this category	
Health-related quality of life	Not recorded	
Side effects		
Median [min; max]	8.8 [0.5; 32.4]	5.3 [0.9; 33.6]
Mean (SD)	11.9 (9.2)	7.3 (6.8)
Study with cabozantinib vs. everolimus		
METEOR	N = 331[a]	N = 322[a]
Data cut-off: 2 October 2016		
Treatment duration [months]		
Median [min; max]	8.3 [0.3; 36.9]	4.4 [0.2; 32.2]
Mean (SD)	11.2 (8.2)	6.8 (6.5)
Observation period [months]		
Overall survival	ND	
Morbidity	ND	
Health-related quality of life	Not recorded[b]	
Side effects	ND	

a. One patient assigned to treatment with everolimus received treatment with cabozantinib.
b. The questionnaires FKSI-15 and FKSI-19 used in the study are not suitable to represent the complex construct of health-related quality of life or are considered unvalidated, see also Section 2.7.2.4.3 of dossier assessment A17-56 [24].

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

At the time of the third data cut-off in each case, there were differences in the treatment or observation durations between the treatment arms for the outcomes of the category of side effects within the 2 studies 205 and METEOR. In the METEOR study, the median treatment duration was almost twice as long in the cabozantinib arm as in the everolimus arm (8.3 months vs. 4.4 months). No information on treatment duration at the relevant data cut-off is available for study 205. However, the median observation period for the outcomes of the category of side effects was notably longer in the lenvatinib + everolimus arm than in the everolimus arm (8.8 months versus 5.3 months). There were no notable differences between the studies 205 and

METEOR for the common comparator everolimus with regard to the median observation period for side effects (recorded up to 30 days after the last dose of study medication) in study 205 compared with the median treatment duration in the METEOR study (5.3 months versus 4.4 months).

2.3.3 Similarity of the studies for the indirect comparison

From the study characteristics described in the previous Section 2.3.2, several aspects concerning the similarity of studies arise. These are discussed in more detail below.

Similarity of study conduct

Study design

Both included studies are multicentre, open-label RCTs that differ in the number of randomized patients, participating centres and countries. In contrast to study 205, the METEOR study was also conducted in study centres in the regions Asia-Pacific and South America. However, the difference in the proportion of patients with Asian/non-white family origin between the 2 studies is only about 10 percentage points and thus has no relevant significance for the indirect comparison of lenvatinib + everolimus versus cabozantinib. A greater difference can be seen with regard to the region. The proportion of patients included in Europe was significantly lower in the METEOR study, at about 50%, compared with about 70% and 90% respectively in study 205. In subgroup analyses of the METEOR study, effect modifications were observed for various outcomes by the characteristic of region (see also Section 2.4.4. of dossier assessment A17-56 [24]). However, these effect modifications did not affect the outcome "overall survival", the only outcome for which an indirect comparison with sufficient certainty of results is possible in this dossier assessment. Overall, the differences regarding regions did not affect the indirect comparison of lenvatinib + everolimus versus cabozantinib.

Treatment duration and observation period

Patients in study 205 were treated at most until progression, unacceptable toxicity or withdrawal of consent. In the METEOR study, treatment with cabozantinib or everolimus was continued in both study arms as long as there was a clinical benefit and treatment was tolerated; treatment could also be continued beyond disease progression.

It is not known how many patients in the METEOR study continued treatment beyond disease progression. It is also unclear whether and how continuation of treatment affected the patient-relevant outcomes. However, it is not evident that the different specifications on the duration of treatment had a significant impact on treatment duration. At the third data cut-off, in the common comparator arm everolimus, the median treatment duration for the METEOR study of 4.4 months is sufficiently comparable with 5.3 months for the median observation period of AEs in study 205, which included a planned duration of follow-up observation up to 30 days after the last dose of study medication.

Similarity of the patient population

Patient characteristics

The demographic and clinical characteristics of the included patients regarding age, sex and risk assessment according to Heng criteria [34,35] are comparable between the studies 205 and METEOR. However, there are differences between the studies regarding other characteristics (see Table 9).

The proportion of patients with an ECOG PS of 0 in study 205 was, at about half, somewhat lower than in the METEOR study, in which about 2 thirds of the patients had an ECOG PS of 0. However, since all patients in both studies were in good general condition overall (ECOG PS 0 or 1), it is assumed that the study populations were sufficiently similar with regard to this aspect.

At just under 40%, the proportion of patients with a poor MSKCC risk score was notably higher in study 205 than in the METEOR study. Here, just over 10% of patients had a poor MSKCC risk score. In addition to the prognostic model of the MSKCC, both studies used the so-called Heng criteria [34,35] for risk assessment, which are considered to have greater informative value [36]. Since the latter showed a sufficiently comparable risk profile of the patients, the difference in the MSKCC risk scores did not have any impact on the similarity of the patient population.

The vast majority of all patients included in the indirect comparison had stage IV renal cell carcinoma at baseline. This disease stage includes the terms “unresectable advanced renal cell carcinoma” and “metastatic renal cell carcinoma”, which are used interchangeably, also according to the opinion of the EMA. All patients in study 205 had unresectable advanced or metastatic renal cell carcinoma. In contrast, disease stage III was reported for 7.3% and 10% of the patients in the METEOR study. Information on the disease stage is missing for 5.2% and 7% of the patients, and 82% and 88% were in disease stage IV. Due to the predominance of stage IV disease in both studies, the study populations are assumed to be sufficiently similar with regard to this aspect.

Pretreatment

There were differences between the studies 205 and METEOR in the targeted pretreatment of the patients. In contrast to study 205, pretreatment with more than one VEGF-targeted therapy was permitted in the METEOR study. About 30% of the patients in both treatment arms of the METEOR study had already been pretreated with ≥ 2 VEGF-targeted therapies at the time of study inclusion. It is therefore not possible to assess the similarity of the patients included in the indirect comparison of the 2 studies with regard to pretreatment with VEGF-targeted and other therapies. In particular, there is a lack of information on the assessment of the comparability of previous systemic therapies and lines of therapy.

For pretreatment by means of previous nephrectomy, there is discrepant information for study 205 between Module 4 A of the dossier and the European Public Assessment Report (EPAR) [33] as well as in the publication on the study, Motzer 2015 [7]. The data presented in the

dossier (Module 4 A) showed a difference of about 30 percentage points in the proportion of patients with previous nephrectomy between the studies 205 and METEOR (about half of the patients in study 205 compared with about 86% in the METEOR study). However, at 86% and 96% (lenvatinib + everolimus and everolimus, respectively), the data in the EPAR on the proportion of patients with this pretreatment in study 205 are comparable to the data from the METEOR study. Due to the different data, the proportion of patients with previous nephrectomy is unclear. Based on the information in the EPAR and in the publication on the study, Motzer 2015 [7], the similarity of the patients included in the indirect comparison of the 2 studies is therefore considered to be sufficiently comparable.

Subsequent therapies

The studies 205 and METEOR also differ with regard to the documented subsequent therapies. For example, subsequent therapy was recorded for a notably larger proportion of patients in the METEOR study than in study 205 (about 60% compared with 35%). About 15% of these patients in the METEOR study received subsequent therapy with checkpoint inhibitors, which were not yet used in study 205.

Similarity of the common comparator

For the common comparator everolimus, there was sufficient similarity between study 205 and the METEOR study. There were no important differences in study design, dosage in compliance with the SPC, or possible dose reduction or interruption.

Summary on the comparability of the studies

In the overall consideration, there are a number of ambiguities or uncertainties regarding the similarity of the studies presented for the indirect comparison. However, these differences do not lead to a fundamental questioning of the similarity of the studies.

2.3.4 Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Lenvatinib + everolimus vs. everolimus							
Study 205	Yes	Yes	No	No	Yes	Yes	Low
Cabozantinib vs. everolimus							
METEOR	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the opinion of the company, the results of study 205 are transferable to the German health care context due to the study design, the study population and the intervention. According to the company, 97.4% of the patients belonged to the ethnic group of Caucasians and 4 of the 5 countries with study centres were European countries. Patients in centres in the USA were treated with the high standards comparable to Europe. The therapy recommendations of the German and European or international guidelines were comparable.

The company noted, however, that the mean age of the patients in study 205, 61 years, was lower than the mean age of disease onset in Germany, which was 68 years for men and 72 years for women in 2016, the last reported year. Available subgroup analyses for the outcome "overall survival" showed no interaction with respect to age.

Regarding the transferability of the results of the METEOR study, the company referred to dossier assessment A16-69 [23], according to which there were no indications that the study results cannot be transferred to the German health care context with regard to the investigated patient population.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - skeletal-related events
  - symptoms (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS])
  - health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])
- Health-related quality of life
- side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - further specific AEs, if any

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

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

Table 12: Matrix of outcomes – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study	Outcomes								
	Overall survival	Skeletal-related events	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs
Study with lenvatinib + everolimus vs. everolimus									
Study 205	Yes	No[a]	No[a]	No[a]	No[a]	Yes	Yes	Yes	No[b]
Study with cabozantinib vs. everolimus									
METEOR	Yes	Yes[c]	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Indirect comparison possible	Yes	No[d]	No[d]	No[d]	No[d]	No[e]	No[e]	No[e]	No[e]

a. Outcome or category not recorded.
b. The company presented only a choice of specific AEs for the indirect comparison.
c. Composite outcome consisting of the following individual components: pathological fractures, spinal cord compression, surgery to bone or radiation therapy to bone.
d. There are no results suitable for the indirect comparison.
e. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Table 13 and Section 2.4.3).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

As the requirement for the certainty of results to conduct an adjusted indirect comparison for the side effect outcomes is not met (see Section 2.4.3) and the company presented only a choice of specific AEs for the indirect comparison, no choice of specific AEs was made.

2.4.2 Risk of bias

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

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib

Study	Study level	Outcomes								
		Overall survival	Skeletal-related events	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Specific AEs
Lenvatinib + everolimus vs. everolimus										
Study 205	L	L	–[a]	–[a]	–[a]	–[a]	H[b, c, d, g]	H[b, c, d, g]	H[c, d, e, g]	–[d, f]
Cabozantinib vs. everolimus										
METEOR	L	L	–[a]	–[a]	–[a]	–[a]	H[b, d, g]	H[b, d, g]	H[d, e, g]	–[d, f]

a. Indirect comparison cannot be performed (outcome or category not recorded in at least one study).
b. Incomplete observations for potentially informative reasons with different follow-up observations.
c. Within the Cox proportional hazards model, deviating stratification of the primarily planned analysis of the outcome "overall survival".
d. Requirement for the certainty of results to perform an adjusted indirect comparison is not met (see Section 2.4.3).
e. Lack of blinding in subjective decision for treatment discontinuation.
f. The company presented only a choice of specific AEs for the indirect comparison.
g. Overall AE rate without progression of the underlying disease.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

No indirect comparison can be conducted for outcomes that were not recorded in at least one of the 2 studies of the indirect comparison. Hence, the risk of bias was not assessed for these outcomes.

The risk of bias for the outcome "overall survival" was rated as low for both studies. This concurs with the company's assessment. The results of all other outcomes recorded in both studies of the indirect comparison had a high risk of bias. This is justified below.

Study 205

The risk of bias was rated as high for the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3) due to incomplete observations for potentially informative reasons with notable differences in the median times for the observation period for the third data cut-off of 31 July 2015 (lenvatinib + everolimus: 8.8 months versus everolimus: 5.3 months). The results for the outcome "discontinuation due to AEs" also had a high risk of bias due to the lack of blinding

in subjective recording of outcomes. This deviates from the assessment of the company, which assessed the risk of bias for the outcomes on side effects as low.

METEOR

The risk of bias was rated as high for the results of the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3). With notable differences in the median times of treatment duration for the data cut-off on 2 October 2016 (cabozantinib: 8.3 months versus everolimus: 4.4 months), different observation periods between the treatment arms and associated incomplete observations for potentially informative reasons can also be assumed. The results for the outcome "discontinuation due to AEs" also had a high risk of bias due to the lack of blinding in subjective recording of outcomes. This deviates from the assessment of the company, which assessed the risk of bias of the results for the side effect outcomes as low.

Impact of the risk of bias on the indirect comparison

The risk of bias of the results for the side effect outcomes was high in both studies. This means that the requirement for the certainty of results for conducting an adjusted indirect comparison was not met for the following outcomes: SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs. No indirect comparison was therefore conducted for these outcomes.

2.4.3 Results

Table 14 summarizes the results of the comparison of lenvatinib + everolimus with cabozantinib in patients with advanced renal cell carcinoma after one prior VEGF-targeted therapy. Where necessary, the data from the company's dossier are supplemented by calculations conducted by the Institute and data from the dossier assessments A16-63, A16-69, A17-56 and A18-18. Kaplan-Meier curves on the presented event time analyses can be found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Lenvatinib + everolimus or cabozantinib** **N**	**Lenvatinib + everolimus or cabozantinib** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Everolimus** **N**	**Everolimus** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
Mortality					
Overall survival					
Lenvatinib + everolimus vs. everolimus					
Study 205 (data cut-off 31 July 2015)	51	25.5 [16.4; 32.1] 32 (62.7)	50	15.4 [11.8; 20.6] 37 (74.0)	0.59 [0.36; 0.97]; 0.036[a]
Cabozantinib vs. everolimus					
METEOR (data cut-off: 2 October 2016)	330	21.4 [18.6; 23.5] 198 (60.0)	328	17.1 [14.9; 18.9] 232 (70.7)	0.70 [0.58; 0.85]; < 0.001[b]
Indirect comparison using a common comparator[c]:					
Lenvatinib + everolimus vs. cabozantinib					0.84 [0.50; 1.43]; ND
Morbidity					
Symptoms (FKSI-DRS)	Recorded only in the METEOR study				
Health status (EQ-5D VAS)	Recorded only in the METEOR study				
Skeletal-related events	Recorded only in the METEOR study				
Health-related quality of life	Not recorded in either study				
Side effects					
AEs (supplementary information)					
Lenvatinib + everolimus vs. everolimus					
Study 205 (data cut-off 31 July 2015)	51	0.1 [0.1; 0.2][d] 51 (100)	50	0.3 [0.2; 0.3][d] 50 (100)	–
Cabozantinib vs. everolimus					
METEOR (data cut-off: 2 October 2016)	331	ND 331 (100)[e]	322	ND 321 (100)[e]	–

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Lenvatinib + everolimus or cabozantinib** **N**	**Lenvatinib + everolimus or cabozantinib** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Everolimus** **N**	**Everolimus** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Group difference** **HR [95% CI]; p-value**
SAEs					
Lenvatinib + everolimus vs. everolimus					
Study 205 (data cut-off 31 July 2015)	51	11.9 [2.1; 19.4] [d] 30 (58.8)	50	7.6 [5.7; NA][d] 21 (42.0)	1.18 [0.66; 2.10][f]; ND
Cabozantinib vs. everolimus					
METEOR (data cut-off 2 October 2016)[e]	331	12.9 [10.4; 18.2] 154 (47)	322	11.1 [7.5; 14.1] 144 (45)	0.80 [0.63; 1.00]; 0.052[b]
Indirect comparison using a common comparator[c]:					
Lenvatinib + everolimus vs. cabozantinib					-[g]
Severe AEs (CTCAE grade ≥ 3)					
Lenvatinib + everolimus vs. everolimus					
Study 205 (data cut-off 31 July 2015)	51	1.6 [0.9; 4.1] [d] 39 (76.5)	50	5.8 [1.9; NA][d] 27 (54.0)	1.59 [0.96; 2.62][f]; ND
Cabozantinib vs. everolimus					
METEOR (data cut-off 2 October 2016)[e]	331	2.2 [1.7; 2.8] 264 (80)	322	3.6 [2.8; 4.6] 219 (68)	1.23 [1.03; 1.47]; 0.023[b]
Indirect comparison using a common comparator[c]:					
Lenvatinib + everolimus vs. cabozantinib					-[g]
Discontinuation due to AEs					
Lenvatinib + everolimus vs. everolimus					
Study 205 (data cut-off 31 July 2015)	51	NA [24.4; NA][d] 13 (25.5)	50	NA [13.5; NA][d] 6 (12.0)	1.64 [0.62; 4.37][f]; ND
Cabozantinib vs. everolimus					
METEOR (data cut-off 2 October 2016)[e]	331	NA [27.5; NC] 88 (27)	322	26.2 [19.4; NC] 87 (27)	0.72 [0.54; 0.98]; 0.036[h]
Indirect comparison using a common comparator[c]:					
Lenvatinib + everolimus vs. cabozantinib					-[g]
Specific AEs			No usable data[j]		

Table 14: Results (mortality, morbidity, side effects) – RCT, indirect comparison: lenvatinib + everolimus vs. cabozantinib (multipage table)

Outcome category Outcome	Lenvatinib + everolimus or cabozantinib		Everolimus		Group difference
Comparison Study	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
a. HR, 95% CI and p-value from Cox proportional hazards model stratified by haemoglobin and corrected serum calcium. b. HR and 95% CI from Cox proportional hazards model, p-value from log-rank test; analyses stratified by number of prior VEGF-targeted TKI therapies and number of MSKCC risk factors. c. Indirect comparison according to Bucher [3]. d. Institute's calculation (days in months). e. Deviating from the presentation of the company in the dossier, the events are presented without progression of the underlying disease. f. HR and 95% CI from unstratified Cox proportional hazards model. g. No presentation of effect estimations, as no hint, e.g. of an added benefit, is derived due to the outcome-specific high risk of bias in at least one of the studies of the indirect comparison and the resulting insufficient certainty of results of the indirect comparison (see Section 2.4.3). h. Underlying model not specified. i. The company presented only a choice of specific AEs for the indirect comparison. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale; VEGF: vascular endothelial growth factor; vs.: versus					

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of lenvatinib + everolimus versus cabozantinib, the consistency assumption could not be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

In addition, the risk of bias of the results in the respective study from the indirect comparison was high for all outcomes except the outcome "overall survival". The certainty of results of the results from the indirect comparisons is therefore not sufficient. Therefore, no indirect comparison was performed for these outcomes, and, on principle, no hint of an added benefit was derived.

This assessment does not concur with that of the company, which conducted indirect comparisons for all included outcomes and derived a hint for each of them.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

No patient-relevant outcomes of the category of morbidity were recorded in study 205. This resulted in no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib for the outcome category of morbidity; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which used results for the outcomes "PFS" and "objective response rate" for the derivation of the added benefit, but did not derive any added benefit from them.

Health-related quality of life

There were no data for an indirect comparison for the outcome "health-related quality of life", as this outcome was not recorded in the studies 205 and METEOR.

Hence, there was no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Due to insufficient certainty of results in both studies, no indirect comparison was calculated for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs".

Hence, there was no hint of greater or lesser harm from lenvatinib + everolimus in comparison with cabozantinib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

No subgroup analyses for the indirect comparison are available for the present benefit assessment of lenvatinib + everolimus.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, 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 the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Table 15: Extent of added benefit at outcome level: lenvatinib + everolimus vs. cabozantinib

Outcome category **Outcome**	**Lenvatinib + everolimus vs. cabozantinib** **Median time to event [months]** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	25.5 vs. 21.4 HR 0.84 [0.50; 1.43]; ND	Lesser benefit/added benefit not proven
Morbidity		
Skeletal-related events	No sufficient data[c]	Lesser benefit/added benefit not proven
Symptoms (FKSI-DRS)	No sufficient data[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No sufficient data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
Not recorded		
Side effects		
SAEs	No usable data[d]	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	No usable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[d]	Greater/lesser harm not proven
Specific AEs	No usable data[d, e]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. This outcome was not recorded in study 205.
d. No indirect comparison is presented due to an insufficient certainty of results (see Section 2.4.3).
e. The company presented only a choice of specific AEs for the indirect comparison.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of lenvatinib + everolimus in comparison with cabozantinib

Positive effects	**Negative effects**
–	–
No usable data are available for the outcomes on morbidity, health-related quality of life and side effects.	

Overall, based on the adjusted indirect comparison using the common comparator everolimus, there are neither positive nor negative effects of lenvatinib + everolimus in comparison with cabozantinib.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival". There is no hint of an added benefit of lenvatinib + everolimus for this outcome, as the indirect comparison showed no statistically significant difference. Outcomes on morbidity and health-related quality of life were not recorded on at least one side of the indirect comparison. No usable data for an indirect comparison are available for the outcome category of side effects, as the certainty of results was not sufficient for an indirect comparison.

In summary, there is no hint of an added benefit of lenvatinib + everolimus in comparison with cabozantinib for adult patients with advanced renal cell carcinoma following one prior VEGF-targeted therapy.

The result of the assessment of the added benefit of lenvatinib + everolimus in comparison with the ACT is summarized in Table 17.

Table 17: Lenvatinib + everolimus – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients[b] with advanced renal cell carcinoma following one prior VEGF-targeted therapy	**Cabozantinib** or nivolumab	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Only patients with clear-cell renal cell carcinoma with an ECOG PS of 0 or 1 were included in the studies 205 and METEOR (except for one patient in study 205). It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with non-clear cell renal cell carcinoma.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The assessment described above concurs with that of the company.

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

Supplementary information on the implementation of the conditions of the limitation

The G-BA stated the following in its justification of the decision on lenvatinib in combination with everolimus from 16 March 2017 [37]:

For the reassessment after expiry of the decision, data in comparison with the appropriate comparator therapy have to be recorded on the basis of comparative clinical studies. Data on all patient-relevant outcomes – mortality, morbidity, health-related quality of life and side effects – are to be presented that, covering an adequate sample size, guarantee a sufficiently high statistical power of the study and that, in comparison with the evidence on the added benefit of lenvatinib presented to date, also allow drawing conclusions on disease-specific morbidity, health-related quality of life and more reliable conclusions on side effects in addition to mortality. It is also desirable that the study population also includes patients with brain metastases and that it sufficiently corresponds to the actual German health care setting by also including patients with an ECOG PS of 2 or higher.

The company did not fully meet these requirements in the present dossier.

The company did not present any new data in the form of an RCT of direct comparison. Instead, it carried out an indirect adjusted comparison. For this purpose, it chose the treatment arm lenvatinib + everolimus of study 205, which was already presented in the first assessment, and compared it with the treatment arm cabozantinib of the METEOR study using the common comparator everolimus. It thus followed the update of the ACT specified by the G-BA.

However, conclusions on disease-specific morbidity, health-related quality of life and more reliable conclusions on side effects still cannot be drawn adequately. No data of study 205 are available for patient-relevant outcomes of morbidity and health-related quality of life. An indirect comparison is therefore not possible for these categories. For the outcomes on side effects, the risk of bias in the respective study from the indirect comparison was high, so that the certainty of results of the results from the indirect comparisons is not sufficient. The low number of patients in study 205 and the associated low power to identify statistically significant effects should also be noted, which generally means that both positive and negative effects can remain undetected. Conducting an indirect comparison tends to lead to an additional reduction of this low power. As patients with brain metastases or an ECOG PS of 2 or higher were not allowed to participate in study 205, it is still not possible to draw conclusions on the added benefit for these patients.

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Please see full dossier assessment for full reference list.

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

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