IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Cabozantinib (renal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Cabozantinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 January 2017). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSKCC	Memorial Sloan Kettering Cancer Center
PFS	progression-free survival
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 cabozantinib. 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 31 October 2016.

Research question

The aim of the present report was to assess the added benefit of cabozantinib in comparison with the appropriate comparator therapy (ACT) in adults with advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of cabozantinib

Research question	**Therapeutic indication**	**ACT**[a]
1	Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy	Nivolumab[b] or **everolimus**

a: Presentation of the ACT specified by the G-BA.
b: Nivolumab was added in the course of the dossier assessment.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

In the course of the dossier assessment, the G-BA adjusted the ACT for the benefit assessment of cabozantinib in patients with advanced renal cell carcinoma following prior VEGF-targeted therapy (discussion in the G-BA's pharmaceuticals subcommittee on 20 December 2016). The comparator therapy originally specified (everolimus) was expanded (nivolumab or everolimus). The dossier submitted by the company contained the description of the added benefit of cabozantinib in comparison with everolimus, the original ACT. These documents were still relevant because everolimus was also part of the adjusted ACT. The present assessment of cabozantinib was conducted in comparison with everolimus.

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 characteristics

The study pool for the benefit assessment of cabozantinib in comparison with everolimus consisted of the study METEOR. This 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). The patients had radiographic tumour progression within 6 months during or after their last dose of the most recent VEGF-targeted 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).

Treatment with cabozantinib or everolimus 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; treatment switching from the comparator intervention everolimus to the experimental intervention cabozantinib was not permitted, however.

Primary outcome of the study was progression-free survival (PFS); relevant secondary outcomes were overall survival, morbidity and side effects. Only overall survival was recorded until the end of the study participation.

The analysis of the primary outcome “PFS” was planned after 259 events. The data cut-off for the primary outcome was conducted on 22 May 2015. In consultation with the European Medicines Agency (EMA), a second interim data cut-off was prospectively planned for overall survival. This was conducted on 31 December 2015.

The METEOR study is still ongoing. The final analysis of overall survival was planned after 408 events. According to the information provided by the company in Module 4 A, the final results for overall survival and side effects are expected for 2017.

Risk of bias

The risk of bias at study level for the METEOR study was rated as low. At outcome level, the risk of bias was rated as low for overall survival and as high for the outcome “health status” (category “morbidity”).

Results

Mortality

A statistically significant advantage of cabozantinib was shown for the outcome “overall survival” for the decisive second data cut-off on 31 December 2015. This resulted in an indication of an added benefit of cabozantinib in comparison with everolimus.

Morbidity

- Skeletal-related events

There were no usable data for the outcome "skeletal-related events". There were no survival time analyses, which are required because of the different observation periods in the treatment groups. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

- Symptoms (FKSI-DRS)

There were no usable data for the outcome "symptoms" (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]) because the version of the questionnaire used in the study is not validated. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

- Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]). Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not investigated in the METEOR study. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven.

Side effects

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

There were no usable data for the outcomes "serious adverse events (SAEs)", "discontinuation due to adverse events (AEs)" and "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) because the analyses contain progressions of the underlying disease to a relevant degree. Hence there was no hint of lesser or greater harm of cabozantinib in comparison with everolimus for these outcomes; lesser or greater harm is therefore not proven.

- Specific adverse events

There were no usable data for the outcome "specific AEs". There were no survival time analyses, which are required because of the different observation periods in the treatment groups. Hence there was no hint of lesser or greater harm of cabozantinib in comparison with everolimus for this outcome; lesser or greater harm is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug cabozantinib compared with the ACT is assessed as follows:

From the METEOR study, complete analyses were only available for mortality. In the category "morbidity", a conclusion is only possible for the outcome "health status"; no usable analyses were available for further patient-relevant outcomes recorded in the study. Health-related quality of life was not recorded in the study. No usable analyses were available for side effects.

In the overall consideration, on the positive side, there is an indication of an added benefit with the extent "major" in the category "mortality". Due to the missing data in the categories "morbidity", "health-related quality of life" and particularly also on side effects, a balancing of positive and negative effects is not possible. In principle, it is not assumed that the presumably existing negative effects raise doubts about the survival advantage of cabozantinib.

In summary, there is an indication of a non-quantifiable added benefit of cabozantinib in comparison with the ACT everolimus for patients with advanced renal cell carcinoma who have been treated with at least one prior VEGF-targeted therapy.

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

Table 3: Cabozantinib – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Extent and probability of added benefit**
Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy	Nivolumab[b] or **everolimus**	Indication of a non-quantifiable added benefit
a: Presentation of the ACT specified by the G-BA. b: Nivolumab was added in the course of the dossier assessment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor		

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

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of cabozantinib in comparison with the ACT in adults with advanced renal cell carcinoma following prior VEGF-targeted therapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cabozantinib

Research question	**Therapeutic indication**	**ACT**[a]
1	Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy	Nivolumab[b] or **everolimus**

a: Presentation of the ACT specified by the G-BA.
b: Nivolumab was added in the course of the dossier assessment.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

In the course of the dossier assessment, the G-BA adjusted the ACT for the benefit assessment of cabozantinib in patients with advanced renal cell carcinoma following prior VEGF-targeted therapy (discussion in the G-BA's pharmaceuticals subcommittee on 20 December 2016). The comparator therapy originally specified (everolimus) was expanded (nivolumab or everolimus). The dossier submitted by the company contained the description of the added benefit of cabozantinib in comparison with everolimus, the original ACT. These documents were still relevant because everolimus was also part of the adjusted ACT. The present assessment of cabozantinib was conducted in comparison with everolimus.

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 cabozantinib (status: 15 August 2016)
- bibliographical literature search on cabozantinib (last search on 12 August 2016)
- search in trial registries for studies on cabozantinib (last search on 12 August 2016)

To check the completeness of the study pool:

- search in trial registries for studies on cabozantinib (last search on 16 October 2016)

No additional relevant study was identified from the check.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: cabozantinib vs. everolimus

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NCT01865747 (METEOR[b])	Yes	Yes	No

a: Exelixis sponsors the study and has transferred the approval and marketing rights for Europe to the company Ipsen Pharma responsible for the dossier.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of cabozantinib in comparison with everolimus consisted of the METEOR study and concurred with that of the company.

Section 2.6 contains a reference list for the study included.

In addition to the analyses presented by the company in Module 4 A, the company's dossier contained additional data in the publication Choueiri 2016 [3]. If relevant, these were used for the benefit assessment (see also Section 2.3.2).

2.3.2 Study characteristics

Characteristics of the study and of the interventions

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

Table 6: Characteristics of the study included – direct comparison: cabozantinib vs. everolimus

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
METEOR	RCT, open-label, parallel	▪ Patients (≥ 18 years) with advanced, metastatic and clear-cell renal cell carcinoma who have received at least one prior VEGF-targeted TKI therapy[b] ▪ radiographic tumour progression within 6 months during or after their last dose of the most recent VEGF-targeted TKI therapy ▪ Karnofsky performance status ≥ 70%	Cabozantinib (N = 330) everolimus (N = 328)	▪ Screening: at most 28 days prior to randomization ▪ Treatment: as long as there is a clinical benefit under treatment and no unacceptable toxicity occurs or subsequent systemic antineoplastic treatment is necessary ▪ 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–ongoing[d]	Primary: progression-free survival Secondary: overall survival, morbidity, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b. Randomization stratified by the following factors: number of prior VEGF-targeted TKI treatments (1 vs. ≥ 2) and number of MSKCC risk factors (0 vs. 1 vs. 2–3; according to eCRF).
c: Outcome-specific information is provided in Table 8.
d: The study is ongoing; the first (planned) interim analysis was conducted on 22 May 2015; the second interim analysis (originally unplanned, but added in the third version of the SAP as prospectively planned) was conducted on 31 December 2015. The planned final analysis of the outcome "overall survival" is planned after occurrence of a total of 408 deaths, which was not yet achieved at the time point of the second interim analysis.

AE: adverse event; eCRF: electronic case report form; max: maximum; min: minimum; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of randomized patients; RCT: randomized controlled trial; SAP statistical analysis plan; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: cabozantinib vs. everolimus

Study	Cabozantinib	Everolimus
METEOR	60 mg cabozantinib, once/day, orally (patients were not allowed to eat for at least 2 hours before and 1 hour after treatment)	10 mg everolimus, once/day, orally (patients were not allowed to eat for at least 2 hours before and 1 hour after treatment)
	Dose reduction and interruption in case of unacceptable toxicity was possible at any time: ▪ first dose reduction[a]: from 60 mg to 40 mg ▪ second dose reduction[a]: from 40 mg to 20 mg ▪ treatment discontinuation in case of dose interruptions ≥ 6 weeks due to AEs; dose interruptions ≥ 6 weeks for other reasons (e.g. surgery) were allowed[b]	Dose reduction and interruption was possible in case of severe or intolerable adverse reactions: ▪ dose reduction: by about 50% of the prior dose[c] treatment discontinuation in case of dose interruptions ≥ 6 weeks due to AEs; dose interruptions ≥ 6 weeks for other reasons (e.g. surgery) were allowed[d]
	Pretreatment ▪ at least one prior VEGF-targeted TKI therapy (e.g. sorafenib, sunitinib, axitinib, pazopanib or tivozanib) ▪ Further pretreatments with other antineoplastic therapies, including cytokines (e.g. interleukin 2, interferon alpha), monoclonal antibodies (VEGF-, PD-1- or PD-L1/L2[2]-targeted therapies) and cytotoxic chemotherapies were allowed without restriction to 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. with bisphosphonates and the receptor activator of nuclear factor kappa-B ligand [RANK-L] inhibitor denosumab) was allowed if this had been initiated before randomization. **Restricted concomitant treatment** The following treatments were to be avoided: ▪ local antineoplastic treatments (e.g. palliative radiation or surgery) until the day of the last tumour assessment with imaging techniques **Non-permitted concomitant treatment** ▪ concomitant further systemic antineoplastic treatments	

a: In compliance with the requirements of the SPC [4].
b: According to the SPC [4], dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities.
c: According to the SPC [5], 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).
d: According to the SPC [5], dose interruptions are allowed in case of serious and/or unacceptable suspected side effects.
e: 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%.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; mTOR: mechanistic target of rapamycin; PD-1: programmed cell death 1; PD-L: programmed death ligand; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

The METEOR was a randomized, open-label, active-controlled approval study on the comparison of cabozantinib and everolimus. It was a multicentre study conducted in 173 study centres in 26 countries.

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.

The patients had radiographic tumour progression within 6 months during or after their last dose of the most recent VEGF-targeted therapy. In addition, the patients had to be in good general condition (Karnofsky index of ≥ 70%).

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

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

Randomization was stratified by the following factors: number of prior VEGF-targeted TKI treatments (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 Summaries of Product Characteristics (SPCs) [4,5].

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.

Treatment with cabozantinib or everolimus 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; treatment switching from the comparator intervention everolimus to the experimental intervention cabozantinib was not permitted, however. At the time point of the second data cut-off (31 December 2015), 187 (57%) patients in the cabozantinib arm and 208 (63%) patients in the everolimus arm were already receiving subsequent antineoplastic therapy. The most common subsequent treatments

in the cabozantinib arm were everolimus (29%), axitinib (17%) and sunitinib (5.2%). In comparison, the subsequent treatments in the everolimus were distributed between axitinib (27%), sunitinib (10%) and sorafenib (9.5%).

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

Analysis and data cut-offs

The analysis of the primary outcome "PFS" was planned after 259 events. The data cut-off for the primary outcome was conducted on 22 May 2015. At this time point, a first interim analysis was prespecified for the outcome "overall survival"; no interim analyses were planned for the other outcomes.

In consultation with the EMA, a second interim data cut-off was prospectively planned for overall survival. This was conducted on 31 December 2015.

In Module 4 A, the company presented analyses for all outcomes based on the first data cut-off from 22 May 2015. It presented also analyses based on the second data cut-off from 31 December 2015 only for the outcome "overall survival" in Module 4 A.

In addition the company's dossier contained further analyses on the second data cut-off from 31 December 2015 in the publication Choueiri 2016 [3], which the company did not present in Module 4 A without justification (see Section 2.7.2.3.2 of the full dossier assessment). If relevant, these were used for the benefit assessment.

The METEOR study is still ongoing. The final analysis of overall survival was planned after 408 events. According to the information provided by the company in Module 4 A, the final results for overall survival and side effects are expected for 2017.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome category Outcome	Planned follow-up
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 final analysis of overall survival
Morbidity	
Health status (EQ-5D VAS) and symptoms (FKSI-DRS)	▪ Every 4 weeks until week 25, then every 8 weeks until the day of the last tumour assessment using imaging techniques[a]
Skeletal-related events	▪ Continuously until the day of the last tumour assessment using imaging techniques[a]
Health-related quality of life	▪ Not recorded in the study
Side effects	
All outcomes in the category "side effects"	▪ Continuously at least every 2 weeks until week 9, then every 4 weeks until 30 (+ 14) days after permanent treatment discontinuation

a: The last tumour assessment using imaging techniques was planned 8 weeks (or 12 weeks for patients with treatment duration > 1 year) after determination of radiographic progression or, in case of treatment beyond radiographic progression, in case of treatment discontinuation.

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; VAS: visual analogue scale; vs.: versus

Only overall survival was recorded until the end of the study participation.

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment (plus 30 [+ 14] days). The outcomes on morbidity were recorded until the day of the last tumour assessment using imaging techniques. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to also record the outcomes on side effects and morbidity over the total period of time, as was the case for survival.

Patient characteristics

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

Table 9: Characteristics of the study population – RCT, direct comparison: cabozantinib vs. everolimus

Study **Characteristics** **Category**	**Cabozantinib**	**Everolimus**
METEOR	N[a] = 330	N[a] = 328
Age [years], mean (SD)	62 (10)	61 (11)
Sex [F/M], %	23/77	26/73
Ethnicity, n (%)		
White	269 (82)	263 (80)
Non-white	46 (14)	42 (13)
No data	15 (4.5[b])	23 (7)
Region, n (%)		
Europe	167 (51)	153 (47)
North America	118 (36)	122 (37)
Asia-Pacific	39 (12)	47 (14)
South America	6 (1.8)	6 (1.8)
Number of prior VEGF-targeted TKI therapies, n (%)		
1	235 (71)	229 (70)
2	84 (25)	91 (28)
≥ 3	11 (3.3)	8 (2.4)
Number of prior VEGF-targeted TKI therapies, median [min; max]	1.0 [1; 3]	1.0 [1; 4]
Number of prior systemic antineoplastic therapies, median [min; max]	1.0 [1; 6]	1.0 [1; 7]
Time between first diagnosis and randomization [years], median [min; max]	2.8 [0; 30]	2.5 [0; 33]
Time from radiographic progression between initiation of prior VEGF-targeted TKI therapy and randomization [months], median [min; max]	1.02 [0.1; 39.7]	1.25 [0.1; 45.0]
Disease stage		
Stage IV	272 (82)	287 (88)
Stage III	34 (10)	24 (7.3)
Unknown or missing	24 (7.3)	17 (5.2[b])
Number of organs with metastases, n (%)		
1	59 (18)	56 (17)
2	101 (31)	77 (23)
≥ 3	168 (51)	190 (58)
No data	2 (0.6)	5 (1.5)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: cabozantinib vs. everolimus (continued)

Study **Characteristics** **Category**	**Cabozantinib**	**Everolimus**
METEOR	N[a] = 330	N[a] = 328
MSKCC score at the start of the study, n (%)		
Favourable (0)	150 (45)	150 (46)
Intermediate (1))	139 (42)	135 (41)
Poor (2–3)	41 (12)	43 (13)
Heng criterion (number of risk factors), n (%)		
Low risk (0)	66 (20)	62 (19)
Intermediate risk (1-2)	210 (64)	214 (65)
High risk (3-6)	54 (16)	52 (16)
ECOG PS calculated from Karnofsky status		
0	226 (68)	216 (66)
1	104 (32)	112 (34[b])
≥ 2	0 (0)	0 (0)
Smoker, n (%)		
Never	136 (41)	149 (45)
Former	155 (47)	143 (44)
Current	37 (11)	33 (10)
Unknown	2 (0.6)	3 (0.9)
Treatment discontinuation[c], n (%)	256 (78)[d]	303 (92)[d]
Study discontinuation[c], n (%)	10 (3.0)[b,e]	18 (5.5)[b,e]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Second data cut-off (31 December 2015)
d: Mainly due to disease progression (cabozantinib: n = 159; everolimus: n = 190).
e: Including withdrawal of informed consent (cabozantinib: n = 8; everolimus: n = 14), lost to follow-up (cabozantinib: n = 1; everolimus: n = 4) and other reasons (cabozantinib: n = 1; everolimus: n = 0).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; max: maximum; min: minimum; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

The demographic and disease-specific patient characteristics were sufficiently comparable between the 2 study arms.

The mean age of the patients was about 60 years; most of them were male and white. The majority of the patients were in disease stage IV; in about half of them 3 or more organs had metastases. About 40% of the patients had an intermediate MSKCC score; about 65% of the population were rated as patients with intermediate risk according to the Heng criterion. The

Eastern Cooperative Oncology Group Performance Status (ECOG PS) was mostly 0. The majority of the patients had been pretreated with one single VEGF-targeted TKI therapy.

At the time point of the second data cut-off (31 December 2015), 256 (78%) patients in the cabozantinib arm and 303 (92%) patients in the everolimus arm had discontinued the study treatment. The treatment discontinuations in both arms were largely due to disease progression (48% of the discontinuations in the cabozantinib arm and 58% of the discontinuations in the everolimus arm).

Course of the study

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

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

Study **Time point** **Duration of the study phase** **Outcome category**	**Cabozantinib**	**Everolimus**
METEOR		
First data cut-off 22 May 2015		
Treatment duration [months][a]	N = 331[b]	N = 322
Median [min; max]	7.4 [0.3; 20.5]	4.4 [0.2; 18.9]
Mean (SD)	7.6 (3.9)	5.5 (3.9)
Observation period [months]		
Mortality	ND	
Morbidity	ND	
Health-related quality of life	No patient-relevant outcomes of this category recorded	
Side effects	ND	
Second data cut-off 31 December 2015[c]		
Treatment duration [months]	N = 331[b]	N = 322
Median [Q1; Q3]	8.3 [4.2; 14.6]	4.4 [1.9; 8.6]
Observation period [months]	N = 330	N = 328
Mortality: overall survival		
Median [Q1; Q3]	18.7 [16.1; 21.1]	18.8 [16.0; 21.2]

a: Institute's calculation from weeks.
b: One patient randomized to everolimus received treatment with cabozantinib.
c: No usable data for overall survival were available for this data cut-off.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

At the time point of the second data cut-off (31 December 2015), 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). The median observation period for the time point "overall survival" was 18.7 months in the cabozantinib arm and 18.8 months in the everolimus arm.

No information on observation period was available for the outcomes of the categories "morbidity" and "side effects". The observation period can differ between the individual outcomes because of the different criteria for follow-up (see Table 8).

The observation period for side effects can be estimated on the basis of the data on median treatment duration because AEs were predefined to be recorded up to 30 (+ 14) days after the last study medication. Under the assumption that all patients exhausted the specified follow-up period, the resulting median observation period was approximately 9.3 months in the cabozantinib arm versus approximately 5.4 months in the everolimus arm.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: cabozantinib vs. everolimus

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

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

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

- Mortality
  - overall survival
- Morbidity
  - skeletal-related events
  - symptoms (FKSI-DRS)
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
- if applicable, further specific AEs

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

The analyses on side effects presented by the company to an important degree included events constituting progression of the underlying disease; according to the study protocol, these had to be recorded as AEs. For this reason, the available analyses of AEs cannot be used for the assessment of side effects. An analysis without recording of the disease progression would be required for a meaningful assessment. This was to be based on the data recorded at the second data cut-off (31 December 2015) (see Section 2.7.2.4.3 of the full dossier assessment).

Due to the differences in observation periods, the analyses on the basis of naive proportions cannot be interpreted for the outcomes “skeletal-related event”, “SAEs”, “severe AEs” (CTCAE grade ≥ 3) and “specific AEs”. Survival time analyses and the provision of hazard ratios (HRs) are required for a meaningful analysis.

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

Table 12: Matrix of outcomes – RCT, direct comparison: cabozantinib vs. everolimus

Study	Outcomes							
	Overall survival	Health status (EQ-5D VAS)	Skeletal-related events	Symptoms (FKSI-DRS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
METEOR	Yes	Yes	No[a]	No[b]	No[c]	No[d]	No[d]	No[d]

a: No usable data available because no survival time analyses were conducted because of different observation periods in the treatment arms.
b: No usable data available because the version of the questionnaire used in the study is not validated.
c: No patient-relevant outcomes of this category recorded.
d: No usable data available because the progression of the underlying disease was also recorded (or because, for the discontinuation due to AEs, it was not clear for the analysis without progression which AEs were rated as progression of the underlying disease and were therefore not included in the analysis); see Section 2.7.2.4.3 of the full dossier assessment for further reasons.

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

2.4.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: cabozantinib vs. everolimus

Study	Study level	Outcomes							
		Overall survival	Health status (EQ-5D VAS)	Skeletal-related events	Symptoms (FKSI-DRS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)
METEOR	L	L	H[a]	–[b]	–[b]	–[c]	–[b]	–[b]	–[b]

a: Lack of blinding in subjective recording of outcomes; large proportion of potentially informative censoring.
b: No usable data; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
c: No patient-relevant outcomes of this category recorded.

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

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

For the outcome "health status" (EQ-5D VAS), the risk of bias was rated as high due to lack of blinding in subjective recording of outcomes and potentially informative censoring (see Section 2.7.2.4.2 of the full dossier assessment). The company also rated the risk of bias as high for this outcome.

No usable data were available for the outcomes "skeletal-related events", "symptoms" (FKSI-DRS) and "side effects". Health-related quality of life was not recorded in the METEOR study.

2.4.3 Results

Table 14 and Table 15 summarize the results of the comparison of cabozantinib with everolimus in patients with advanced renal cell carcinoma after prior VEGF-targeted therapy. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. The available Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment. The common AEs are presented in Appendix B.

Table 14: Results – RCT, direct comparison: cabozantinib vs. everolimus

Study **Outcome category**	**Cabozantinib**		**Everolimus**		**Cabozantinib vs. everolimus**
Time point **Outcome**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
METEOR					
Mortality					
First data cut-off (22 May 2015, additional information)					
Overall survival	*330*	*18.2 [16.1; NC]* *89 (27)*	*328*	*NC [13.9; NC]* *113 (34)*	*0.68 [0.51; 0.90]; 0.006*
Second data cut-off (31 Dec 2015)					
Overall survival	330	21.4 [18.7; NC] 140 (42)	328	16.5 [14.7; 18.8] 180 (55)	0.67 [0.53; 0.83]; < 0.001
Morbidity (first and second data cut-off)					
Skeletal-related events	No usable data[b]				
Symptoms (FKSI-DRS)	No usable data[c]				
Health-related quality of life	No patient-relevant outcomes of this category recorded				
Side effects (first and second data cut-off)					
AEs (supplementary information)	No usable data[b]				
SAEs	No usable data[d]				
Severe AEs (CTCAE grade ≥ 3)	No usable data[d]				
Discontinuation due to AEs	No usable data[e]				

a: Stratified by number of prior VEGF-targeted TKI therapies and number of MSKCC risk factors.
b: Analysis of the number of patients with event not interpretable due to the differences in observation periods between the treatment arms.
c: Only data on 9 individual items of the FKSI-DRS are available.
d: The analyses presented (survival time analyses [first data cut-off] or number of patients with event [second data cut-off]) include a large proportion of events due to progression of the underlying disease and are therefore not interpretable for a conclusion on the extent of side effects. In addition, the analyses on the second data cut-off are not interpretable due to differences in observation periods between the treatment arms.
e: The dossier contains analyses on the number of patients with event for the outcome "discontinuation due to AEs" for both data cut-offs. Events caused by progression of the underlying disease were not included in these analyses. These analyses are not interpretable because it is not clear which events were rated as progression of the underlying disease.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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 patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

Table 15: Results (morbidity) – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome category Outcome Time point	Cabozantinib			Everolimus			Cabozantinib vs. everolimus
	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	Mean (SD); p-value[b]
METEOR							
Morbidity							
Health status (EQ-5D VAS)							
First data cut-off (22 May 2015)	317	73.6 (18.62)	-1.32 (17.28)	304	74.1 (17.50)	-1.27 (16.16)	-0.05 (16.81); 0.921
Second data cut-off (31 Dec 2015)	No results available						

a: Number of patients considered in the analysis for the calculation of the effect estimate. The values at the start of the study may be based on other patient numbers.
b: MMRM analysis of the ITT population, adjusted for baseline value, number of prior VEGF-targeted TKI therapies and number of MSKCC risk factors.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; MMRM: mixed-effects model repeated measures; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale; VEGF: vascular endothelial growth factor; vs.: versus

Based on the data presented by the company on the METEOR study, due to the high risk, of bias at most indications, e.g. of an added benefit, can be determined for overall survival, and at most hints for health status.

Mortality

Overall survival

A statistically significant advantage of cabozantinib was shown for the outcome "overall survival" for the decisive second data cut-off on 31 December 2015. This resulted in an indication of an added benefit of cabozantinib in comparison with everolimus.

This concurs with the company's assessment.

Morbidity

Skeletal-related events

There were no usable data for the outcome "skeletal-related events". There were no survival time analyses, which are required because of the different observation periods in the treatment groups. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented no data on skeletal-related events in Module 4 A of the dossier and did not use the outcome "skeletal-related events" for the derivation of the added benefit.

Symptoms (FKSI-DRS)

There were no usable data for the outcome "symptoms" (FKSI-DRS) because the version of the questionnaire used in the study is not validated (see Section 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which used the outcome "FKSI-19" for the derivation of the added benefit in the category "health-related quality of life", however.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status" (EQ-5D VAS). Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

Health-related quality of life was not investigated in the METEOR study. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

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

There were no usable data for the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade ≥ 3) because the analyses contain progressions of the underlying disease to a relevant degree. Hence there was no hint of lesser or greater harm of cabozantinib in comparison with everolimus for these outcomes; lesser or greater harm is therefore not proven. This deviates from the assessment of the company, which derived an indication of an added benefit of cabozantinib for SAEs and discontinuation due to AEs and an indication of greater harm from cabozantinib for severe AEs.

Specific adverse events

There were no usable data for the outcome "specific AEs". There were no survival time analyses, which are required because of the different observation periods in the treatment groups. Hence there was no hint of lesser or greater harm of cabozantinib in comparison with everolimus for this outcome; lesser or greater harm is therefore not proven.

This deviates from the assessment of the company, which did not use specific AEs for the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

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

- sex (men/women)
- age (< 65/≥ 65 years)
- region (Asia-Pacific/Europe/South America/North America)
- number of prior VEGF-targeted TKI therapies (1/≥ 2)
- number of organs with metastases (1/2/≥ 3)
- number of MSKCC risk factors (according to eCRF) (0/1/≥ 2)

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Subgroup analyses were only available for the outcome “overall survival”, but they showed no indication or proof of an effect modification.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 showed an indication of an added benefit of cabozantinib in comparison with everolimus for the outcome “overall survival”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: cabozantinib vs. everolimus

Outcome category **Outcome**	**Cabozantinib vs. everolimus** **Median time to event or mean value** **Effect estimate [95% CI] or (SD); p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 21.4 vs. 16.5 months HR: 0.67 [0.53; 0.83] p < 0.001 probability: “indication”	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
Morbidity		
Skeletal-related events	No usable data	Lesser benefit/added benefit not proven
Symptoms (FKSI-DRS)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean value: −1.32 vs. −1.27 MD: −0.05 (16.81) p = 0.921	Lesser benefit/added benefit not proven
Health-related quality of life		
No patient-relevant outcomes of this category recorded		
Side effects		
SAEs	No usable data	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	No usable data	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
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; HR: hazard ratio; MD: mean difference; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of cabozantinib in comparison with everolimus

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "major"	–
No usable data are available on side effects; no patient-relevant outcomes for health-related quality of life were recorded in the study included.	

From the METEOR study, complete analyses were only available for mortality. In the category "morbidity", a conclusion is only possible for the outcome "health status"; no usable analyses were available for further patient-relevant outcomes recorded in the study. Health-related quality of life was not recorded in the study. No usable analyses were available for side effects.

In the overall consideration, on the positive side, there is an indication of an added benefit with the extent "major" in the category "mortality". Due to the missing data in the categories "morbidity", "health-related quality of life" and particularly also on side effects, a balancing of positive and negative effects is not possible. In principle, it is not assumed that the presumably existing negative effects (see Appendix B of the full dossier assessment) raise doubts about the survival advantage of cabozantinib.

In summary, there is an indication of a non-quantifiable added benefit of cabozantinib in comparison with the ACT everolimus for patients with advanced renal cell carcinoma who have been treated with at least one prior VEGF-targeted therapy. The result of the assessment of the added benefit of cabozantinib in comparison with the ACT is summarized in Table 18.

Table 18: Cabozantinib – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy	Nivolumab[b] or **everolimus**	Indication of a non-quantifiable added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. b: Nivolumab was added in the course of the dossier assessment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor		

This deviates from the company's approach, which claimed a major added benefit.

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

2.6 List of included studies

Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373(19): 1814-1823.

Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016; 17(7): 917-927.

Exelixis. Eine randomisierte, kontrollierte Studie der Phase 3 zu Cabozantinib (XL184) gegenüber Everolimus bei Patienten mit metastasierendem Nierenzellkarzinom, das nach vorheriger Therapie mit VEGFR-Tyrosinkinasehemmer fortgeschritten ist [online]. In: Deutsches Register Klinischer Studien. 14.07.2016 [Accessed: 21.11.2016]. URL: http://www.drks.de/DRKS00005393.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy [online]. In: EU Clinical Trials Register. [Accessed: 21.11.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001010-14.

Exelixis. A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR): full text view [online]. In: ClinicalTrials.gov. 14.07.2016 [Accessed: 21.11.2016]. URL: https://clinicaltrials.gov/show/NCT01865747.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy: study XL184-308; clinical study protocol [unpublished]. 2014.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy: study XL184-308; clinical study report [unpublished]. 2015.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy: study XL184-308; statistical analysis plan [unpublished]. 2015.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy: study XL184-308; clinical study report addendum [unpublished]. 2016.

Exelixis. A phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy: study XL184-308; Zusatzanalysen [unpublished]. 2016.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

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

3. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016; 17(7): 917-927.

4. *Ipsen Pharma Gmb H. Fachinformation Cabozantinib (CABOMETYXTM), Stand: September 2016. [online] 2016.

5. *Novartis Pharma Gmb H. Fachinformation Everolimus (Afinitor®). Stand: Mai 2016. [online] 2016. URL: www.fachinfo.de.

Citations marked with * are unedited citations provided by the company.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-69-cabozantinib-renal-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.7687.html.