IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-56

Cabozantinib (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 2.6 of the dossier assessment *Cabozantinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 11 January 2018). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Cabozantinib (renal cell carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
16 October 2018

Internal Commission No.:
A17-56

Address of publisher:
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Keywords: cabozantinib, carcinoma – renal cell, benefit assessment, NCT01865747

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[2] 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
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EQ-5D	European Quality of Life-5 Dimensions
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)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 16 October 2017.

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 or **everolimus**

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**.

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

The company followed the G-BA's specification of the ACT and chose everolimus from the options presented. The assessment was conducted in comparison with the ACT specified by the G-BA. 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. The presented METEOR study had already been presented for the first assessment of cabozantinib in the therapeutic indication of renal cell carcinoma.

The final analysis of overall survival in the METEOR study was planned after 408 events and was reached with the data cut-off from 2 October 2016.

Risk of bias

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

The risk of bias for the outcome "overall survival" was rated as low. The risk of bias was rated as high for the following outcomes: symptoms (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]), health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), skeletal-related events, serious adverse events (SAEs), severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and specific AEs.

Results

Mortality

There was a statistically significant advantage of cabozantinib compared with everolimus for the outcome "overall survival". This resulted in an indication of an added benefit of cabozantinib in comparison with everolimus.

Morbidity

- Skeletal-related events

No statistically significant difference between the treatment arms was shown for the outcome "skeletal-related events" for the composite outcome or for the individual components. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven.

- Symptoms (FKSI-DRS)

A statistically significant difference in favour of cabozantinib in comparison with everolimus was shown for the outcome "symptoms" (FKSI-DRS). However, the 95% confidence interval (CI) of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; 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" (EQ-5D VAS). However, there was proof of an effect modification by the characteristic "region" for this outcome. There was no statistically significant difference between the treatment arms for patients from the region of Europe. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; 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

There was no statistically significant difference between the treatment arms for the outcome "SAEs". Hence there was no hint of greater or lesser harm from cabozantinib; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events

There were no usable data for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from cabozantinib; greater or lesser harm is therefore not proven.

- Severe adverse events (CTCAE grade ≥ 3)

There was a statistically significant difference to the disadvantage of cabozantinib in comparison with everolimus for the outcome "severe AEs (CTCAE grade ≥ 3)".

In addition, there was proof of an effect modification by the characteristic "region" for this outcome. There was a statistically significant disadvantage of cabozantinib compared with everolimus for patients of the region of Europe. This resulted in a hint of greater harm from cabozantinib in comparison with everolimus.

- Specific adverse events

A statistically significant advantage of cabozantinib in comparison with everolimus was shown for each of the outcomes "anaemia" and "pneumonitis". Under consideration of the high risk of bias, this resulted in a hint of lesser harm of cabozantinib in comparison with everolimus in each case.

A statistically significant disadvantage of cabozantinib in comparison with everolimus was shown for each of the outcomes "diarrhoea", "hypertension", and "palmar-plantar erythrodysaesthesia syndrome". Under consideration of the high risk of bias, this resulted in a hint of greater harm of cabozantinib in comparison with everolimus in each case.

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

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

The overall assessment of the data showed both positive and negative effects with different certainty of results (indication or hint) for cabozantinib in comparison with everolimus. An indication of a considerable added benefit was shown for the outcome "overall survival". This was accompanied by a hint of considerably greater harm regarding serious/severe side effects (severe AEs [CTCAE grade ≥ 3]). In addition, there were several hints both of greater and of lesser harm from cabozantinib in the category of non-serious/non-severe side effects. Due to the greater harm in serious/severe side effects, the extent of the added benefit was downgraded from considerable to minor in the overall assessment.

In summary, there is an indication of a minor added benefit of cabozantinib in comparison with everolimus for patients with advanced renal cell carcinoma following prior VEGF-targeted therapy.

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

Table 3: Cabozantinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy[b]	Nivolumab or **everolimus**	Indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The relevant study only included patients with clear-cell metastatic renal cell carcinoma with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, with non-clear cell renal cell carcinoma, or without metastases.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

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

[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].

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

The company followed the G-BA's specification of the ACT and chose everolimus from the options presented. The assessment was conducted in comparison with the ACT specified by the G-BA. 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: 17 July 2017)
- bibliographical literature search on cabozantinib (last search on 19 July 2017)
- search in trial registries for studies on cabozantinib (last search on 17 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on cabozantinib (last search on 3 November 2017)

The check identified no additional relevant study.

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 RCT METEOR and concurred with that of the company. The company had already presented the METEOR study for the first assessment of cabozantinib (A16-69) [3]; hence hereinafter this assessment is referred to if appropriate.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

The presented METEOR study had already been presented for the first assessment of cabozantinib in the therapeutic indication of renal cell carcinoma. Detailed characteristics of the study and of the interventions as well as information on the planned duration of follow-up can be found in dossier assessment A16-69 [3].

The final analysis of overall survival in the METEOR study was planned after 408 events and was reached with the data cut-off from 2 October 2016. Due to the follow-up observation period, the METEOR study is ongoing. The results of the data cut-off from 2 October 2016 were used for the benefit assessment.

Patient characteristics

Table 6 shows the characteristics of the patients in the study included.

Table 6: 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)	23 (7[b])
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 6: 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 (34.1[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 (%)	294 (89)[d]	320 (98)[d]
Study discontinuation[c], n (%)	17 (5.2)[b, e]	25 (7.6)[b, e]

a: Number of randomized patients. Data that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Third data cut-off (2 October 2016).
d: Mainly due to disease progression (cabozantinib: n = 183; everolimus: n = 197).
e: Including withdrawal of informed consent (cabozantinib: n = 10; everolimus: n = 18), lost to follow-up (cabozantinib: n = 4; everolimus: n = 5), and other reasons (cabozantinib: n = 3; everolimus: n = 2).

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.

At the time point of the final data cut-off (2 October 2016), 294 patients in the cabozantinib arm and 320 patients in the everolimus arm had discontinued the study treatment. In both arms, the main reason for treatment discontinuation was disease progression (in each arm, about 62% of all discontinuations).

Table 7 shows the median treatment duration of the patients and the observation period for individual outcomes.

Table 7: 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	N = 331[a]	N = 322[a]
Third data cut-off (2 October 2016)		
Treatment duration [months][b]		
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	No patient-relevant outcomes of this category recorded	
Side effects	ND	

a: One patient randomized to everolimus received treatment with cabozantinib.
b: Institute's calculation from weeks.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

At the time point of the final data cut-off (2 October 2016), 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 observation period was available for the outcomes of the categories "overall survival", "morbidity" and "side effects". The observation period can differ between the individual outcomes because of the different criteria for follow-up (see dossier assessment A16-69 [3]). This particularly applies to the observation periods for the outcomes on side effects because they were only recorded for the time period of treatment (plus 30 [+ 14] days).

Table 8 shows the risk of bias at study level.

Table 8: 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 with the outcome-specific risk of bias in Section 2.4.

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).

According to the study protocol, progression events were also to be recorded as AEs in the METEOR study. These constituted an important proportion of the AEs. The company presented survival time analyses without recording of progression events; these were used for the benefit assessment (see also Section 2.7.2.4.3 of the full dossier assessment).

Table 9 shows for which outcomes data were available in the studies included.

Table 9: Matrix of outcomes – RCT, direct comparison: cabozantinib vs. everolimus

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

a: Composite outcome consisting of the following individual components: pathological fractures, spinal cord compression, surgery to bone or radiation therapy to bone.
b: Overall AE rate without progression events of the underlying disease.
c: The following events are considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC), palmar-plantar erythrodysaesthesia syndrome (PT), gastrointestinal disorders (SOC), diarrhoea (PT), vascular disorders (SOC), hypertension (PT), blood disorders (SOC), anaemia (PT), and pneumonitis (PT).
d: Outcome not recorded.
e: No usable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial: SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 10 describes the risk of bias for the relevant outcomes.

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: cabozantinib vs. everolimus

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

a: Composite outcome consisting of the following individual components: pathological fractures, spinal cord compression, surgery to bone or radiation therapy to bone.
b: Overall AE rate without progression events of the underlying disease.
c: The following events are considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC), palmar-plantar erythrodysaesthesia syndrome (PT), gastrointestinal disorders (SOC), diarrhoea (PT), vascular disorders (SOC), hypertension (PT), blood disorders (SOC), anaemia (PT), and pneumonitis (PT).
d: Unexplained deviation in the statistical analysis in comparison with other outcomes.
e: Large differences in observation periods with potentially informative censoring.
f: Lack of blinding in subjective recording of outcomes.
g: Outcome not recorded.
h: No usable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial: SAE: serious adverse event; SOC: System Organ Class; 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 outcomes "symptoms" (FKSI-DRS) and "health status" (EQ-5D VAS), the risk of bias was rated as high due to lack of blinding in subjective recording of outcomes and due to large differences in observation periods with potentially informative censoring (see Section 2.7.2.4.2 of the full dossier assessment). This concurs with the company's assessment.

The risk of bias was rated as high due to large differences in observation periods with potentially informative censoring for the following outcomes: skeletal-related events, SAEs, severe AEs (CTCAE grade ≥ 3), and specific AEs. There was the additional lack of blinding in subjective recording of outcomes for specific AEs, and an unexplained deviation in the statistical analysis in comparison with other outcomes for the outcome "skeletal-related events" (see Section 2.7.2.4.2 of the full dossier assessment). The company rated the risk of bias for these outcomes as low.

There were no usable data for the outcome “discontinuation due to AEs”. The outcome “health-related quality of life” was not assessed in the METEOR study.

2.4.3 Results

Table 11 and Table 12 summarize the results of the final data cut-off from 2 October 2016 on the comparison of cabozantinib with everolimus in patients with advanced renal cell carcinoma after prior VEGF-targeted therapy. Where necessary, Institute’s own calculations are provided in addition to the data from the company’s dossier. The available Kaplan-Meier curves on the outcomes included are presented in Appendix A, and the common AEs are presented in Appendix B of the full dossier assessment.

Table 11: Results – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome category Outcome	Cabozantinib N	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 (%)	Cabozantinib vs. everolimus HR [95% CI]; p-value[a]
METEOR					
Mortality					
Overall survival	330	21.4 [18.6; 23.5] 198 (60)	328	17.1 [14.9; 18.9] 232 (71)	0.70 [0.58; 0.85]; < 0.001
Morbidity					
Skeletal-related events	330	NA [NC; NC] 57 (17)	328	NA [NC; NC] 50 (15)	0.77 [0.52; 1.13]; 0.175[b]
Pathological fractures	330	NA [NC; NC] 25 (7.6)	328	NA [NC; NC] 13 (4.0)	1.28 [0.65; 2.53]; 0.470[b]
Spinal cord compression	330	NA [NC; NC] 6 (1.8)	328	NA [NC; NC] 8 (2.4)	0.50 [0.17; 1.45]; 0.192[b]
Surgery to bone	330	NA [NC; NC] 18 (5.5)	328	NA [NC; NC] 12 (3.7)	1.00 [0.47; 2.09]; 0.990[b]
Radiation therapy to bone	330	NA [NC; NC] 37 (11)	328	NA [NC; NC] 38 (12)	0.64 [0.41; 1.02]; 0.058[b]
Health-related quality of life	No patient-relevant outcomes of this category recorded				
Side effects					
AEs	331	– 331 (100)	322	– 321 (100)	–
SAEs[c]	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
Severe AEs (CTCAE grade ≥ 3)[c]	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
Discontinuation due to AEs[c]	No usable data[d]				
Blood disorders (SOC)	331	36.8 [NC; NC] 90 (27)	322	8.2 [5.5; 18.1] 142 (44)	0.38 [0.29; 0.50]; < 0.001
Anaemia (PT)	331	NA [NC; NC] 67 (20)[e]	322	11.1 [7.5; 19.9] 130 (40)[e]	0.29 [0.22; 0.40]; < 0.001
Gastrointestinal disorders (SOC)	331	0.6 [0.5; 0.7] 313 (95)	322	0.9 [0.7; 1.3] 250 (78)	1.73 [1.46; 2.05]; < 0.001
Diarrhoea (PT)	331	1.5 [1.4; 1.8] 249 (75)[f]	322	22.7 [17.9; NC] 95 (30)[f]	3.85 [3.02; 4.90]; < 0.001

(continued)

Table 11: Results – RCT, direct comparison: cabozantinib vs. everolimus (continued)

Study Outcome category Outcome	Cabozantinib N	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 (%)	Cabozantinib vs. everolimus HR [95% CI]; p-value[a]
Vascular disorders (SOC)	331	12.8 [6.1; NC] 157 (47)	322	NA [NC; NC] 53 (16)	3.23 [2.36; 4.41]; < 0.001
Hypertension (PT)	331	NA [NC; NC] 123 (37)[g]	322	NA [NC; NC] 26 (8)[g]	5.29 [3.46; 8.09]; < 0.001
Skin and subcutaneous tissue disorders (SOC)	331	1.2 [1.0; 1.5] 247 (75)	322	1.3 [1.0; 1.9] 208 (65)	1.03 [0.86; 1.24]; 0.717
Palmar-plantar erythrodysaesthesia syndrome (PT)	331	27.2 [12.2; NC] 145 (44)[h]	322	NA [NC; NC] 19 (6)[h]	9.03 [5.59; 14.58]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC)	No data				
Pneumonitis (PT)	331	NA [NC; NC] 0 (0)[i]	322	NA [NC; NC] 34 (11)[i]	0.01 [0.00; 0.23][j]; < 0.001
Endocrine disorders (SOC)	No usable data[k]				
Hypothyroidism (PT)	No usable data[k]				

a: HR 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.
b: HR from Cox proportional hazards model, p-value from log-rank test, without stratification.
c: Without progression events of the underlying disease.
d: Discrepant information in the company's dossier and in comparison with addendum A17-10 (see Section 2.7.2.4.3 of the full dossier assessment).
e: Proportion of patients with severe AEs (CTCAE ≥ 3): cabozantinib 22 (6.6); everolimus 55 (17).
f: Proportion of patients with severe AEs (CTCAE ≥ 3): cabozantinib 44 (13); everolimus 8 (2.5).
g: Proportion of patients with severe AEs (CTCAE ≥ 3): cabozantinib 51 (15); everolimus 3 (3.7).
h: Proportion of patients with severe AEs (CTCAE ≥ 3): cabozantinib 28 (8.5); everolimus 3 (0.9).
i: Proportion of patients with severe AEs (CTCAE ≥ 3): cabozantinib 0 (0); everolimus 6 (2).
j: Institute's calculation of RR (with correction factor 0.5 in both study arms) and CI (asymptotic).
k: No survival time analyses were available, only information on the proportion of patients with event.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

Table 12: Results (health status, symptoms) – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome category Outcome	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)	MD [95% CI]; p-value
METEOR							
Morbidity							
Health status (EQ-5D VAS)[c, d]	316	73.6 (18.62)	−2.42 (16.77)	296	74.1 (17.50)	−2.50 (16.02)	0.08 [-0.92; 1.07]; 0.879
Symptoms (FKSI-DRS)[c, d]	318	ND	−1.11 (4.81)	297	ND	−1.54 (4.66)	0.43 [0.15; 0.71]; 0.003 Hedges' g: 0.24 [0.08; 0.40][e]

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.
c: Only values until week 56 were included in the analysis.
d: Negative changes indicate deterioration.
e: Institute's calculation based on effect estimation of the mean difference and of the CI of the MMRM.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Based on the data presented by the company on the METEOR study, at most indications, e.g. of an added benefit, can be determined for overall survival, and, due to the high risk of bias, at most hints can be determined for the outcomes "skeletal-related events", "health status", "FKSI-DRS" and for side effects.

Mortality

Overall survival

There was a statistically significant advantage of cabozantinib compared with everolimus for the outcome "overall survival". 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

No statistically significant difference between the treatment arms was shown for the outcome "skeletal-related events" for the composite outcome or for the individual components. 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.

Symptoms (FKSI-DRS)

A statistically significant difference in favour of cabozantinib in comparison with everolimus was shown for the outcome "symptoms" (FKSI-DRS). However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of added benefit for this outcome.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status" (EQ-5D VAS). However, there was proof of an effect modification by the characteristic "region" for this outcome (see Section 2.4.4). There was no statistically significant difference between the treatment arms for patients from the region of Europe. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven.

This deviates from the approach of the company insofar as the company did not consider effect modifications in the derivation of the added benefit. On the basis of the total population, the company derived no added benefit.

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

There was no statistically significant difference between the treatment arms for the outcome "SAEs". Hence there was no hint of greater or lesser harm from cabozantinib; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit of cabozantinib in comparison with everolimus for this outcome.

Discontinuation due to adverse events

There were no usable data for the outcome "discontinuation due to AEs" (see Section 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of greater or lesser harm from cabozantinib; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived an indication of added benefit for this outcome.

Severe adverse events (CTCAE grade ≥ 3)

There was a statistically significant difference to the disadvantage of cabozantinib in comparison with everolimus for the outcome "severe AEs (CTCAE grade ≥ 3)".

In addition, there was proof of an effect modification by the characteristic "region" for this outcome (see Section 2.4.4). There was a statistically significant disadvantage of cabozantinib compared with everolimus for patients of the region of Europe. This resulted in a hint of greater harm from cabozantinib in comparison with everolimus.

This deviates from the assessment of the company, which did not consider any subgroup results without recording of progression events for this outcome and derived an indication of greater harm based on the analyses on the total population.

Specific adverse events

For the outcome "specific AEs", survival time analyses were only available for those System Organ Classes (SOCs) and Preferred Terms (PTs) that IQWiG had identified as relevant in dossier assessment A16-69 [3]. For the present assessment, only PTs were used for the derivation of the added benefit.

Anaemia and pneumonitis

A statistically significant advantage of cabozantinib in comparison with everolimus was shown for each of the outcomes "anaemia" and "pneumonitis". Under consideration of the high risk of bias, this resulted in a hint of lesser harm of cabozantinib in comparison with everolimus in each case.

Diarrhoea, hypertension, and palmar-plantar erythrodysaesthesia syndrome

A statistically significant disadvantage of cabozantinib in comparison with everolimus was shown for each of the outcomes "diarrhoea", "hypertension", and "palmar-plantar erythrodysaesthesia syndrome". Under consideration of the high risk of bias, this resulted in a hint of greater harm of cabozantinib in comparison with everolimus in each case.

Hypothyroidism

Hypothyroidism (PT within the SOC "endocrine disorders") was identified as further specific AE with notable differences between the treatment groups in proportions of patients with event to the disadvantage of cabozantinib. Since the company presented no survival time analyses for

hypothyroidism and endocrine disorders, this potentially greater harm from cabozantinib cannot be assessed.

This deviates from the assessment of the company, which did not use the 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 in the present benefit 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 Memorial Sloan Kettering Cancer Center (MSKCC) risk factors (according to electronic case report form [eCRF]) (0/1/> 2).

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 13, and Table 14 summarize the subgroup results of cabozantinib in comparison with everolimus. Where necessary, Institute's own calculations are provided in addition to the data from the company's dossier.

Table 13: Subgroups (health status, symptoms) – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome	Cabozantinib			Everolimus			Cabozantinib vs. everolimus
Characteristic Subgroup	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)	MD [95% CI]; p-value
METEOR							
Health status (EQ-5D VAS)[c, e]							
Region							
Pacific-Asia	39	ND	−3.50 (17.04)	44	ND	1.69 (16.96)	−5.19 [−7.69; -2.69]; < 0.001 Hedges' g: −0.89 [−1.34; −0.43][d]
Europe	157	ND	−4.36 (17.27)	139	ND	−3.85 (15.28)	−0.51 [−1.97; 0.95]; 0.489
South America	6	ND	1.07 (13.45)	6	ND	5.16 (16.87)	−4.09 [−11.81; 3.63]; 0.261
North America	114	ND	0.18 (15.92)	107	ND	−2.83 (16.24)	3.01 [1.41; 4.62]; < 0.001 Hedges' g: 0.49 [0.23; 0.76][d]
Total						Interaction:	< 0.001
Symptoms (FKSI-DRS)[c, e]							
Age							
< 65	191	ND	−0.92 (4.99)	175	ND	−1.10 (4.48)	0.19 [−0.17; 0.55]; 0.302
≥ 65	127	ND	−1.39 (4.50)	122	ND	−2.23 (4.85)	0.84 [0.38; 1.30]; < 0.001 Hedges' g: 0.45 [0.201; 0.70][d]
Total						Interaction:	0.028
Region							
Pacific-Asia	39	ND	−0.67 (4.43)	44	ND	−0.79 (5.00)	0.13 [−0.60; 0.85]; 0.73
Europe	162	ND	−1.33 (5.21)	139	ND	−1.41 (4.39)	0.08 [−0.34; 0.50]; 0.713
South America	6	ND	−2.20 (3.84)	6	ND	−3.38 (5.96)	1.18 [−1.10; 3.46]; 0.273
North America	111	ND	−0.91 (4.37)	108	ND	−1.94 (4.73)	1.03 [0.56; 1.49]; < 0.001 Hedges' g: 0.58 [0.31; 0.86][d]
Total						Interaction:	0.011

(continued)

Table 13: Subgroups (health status, symptoms) – RCT, direct comparison: cabozantinib vs. everolimus (continued)

Study Outcome	Cabozantinib			Everolimus			Cabozantinib vs. everolimus
Characteristic Subgroup	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)	MD [95% CI]; p-value
Number of prior VEGF-targeted TKI therapies							
1	225	ND	−1.33 (4.90)	206	ND	−1.54 (4.65)	0.21 [−0.13; 0.55]; 0.216
≥ 2	93	ND	−0.56 (4.52)	91	ND	−1.55 (4.68)	0.99 [0.47; 1.51]; < 0.001 Hedges' g: 0.55 [0.25; 0.84][d]
Total						Interaction:	< 0.001
Number of organs with metastases							
1	56	ND	−1.44 (4.45)	51	ND	−1.00 (4.31)	−0.44 [−1.05; 0.16]; 0.152
2	98	ND	−1.37 (4.98)	70	ND	−1.32 (4.69)	−0.04 [−0.56; 0.47]; 0.865
≥ 3	162	ND	−0.82 (4.83)	171	ND	−1.88 (4.70)	1.06 [0.64; 1.47]; < 0.001 Hedges' g: 0.55 [0.33; 0.77][d]
Total						Interaction:	< 0.001

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.
c: Only values until week 56 were included in the analysis.
d: Institute's calculation based on effect estimation of the mean difference and of the CI of the MMRM.
e: Negative changes indicate deterioration.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale; VEGF: vascular endothelial growth factor; vs.: versus

Table 14: Subgroups (severe AEs [CTCAE grade ≥ 3]) – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome Characteristic Subgroup	Cabozantinib N	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 (%)	Cabozantinib vs. everolimus HR [95% CI][a]	Cabozantinib vs. everolimus p-value[b]
METEOR						
Severe AEs (CTCAE grade ≥ 3)[c]						
Region						
Pacific-Asia	39	5.0 [2.0; 7.1] 29 (74)	47	4.6 [3.6; 7.5] 34 (72)	0.81 [0.49; 1.33]	0.395
Europe	167	1.7 [1.2; 2.3] 143 (86)	151	3.7 [2.8; 5.5] 98 (65)	1.63 [1.26; 2.11]	< 0.001
South America	6	3.4 [0.5; 4.9] 6 (100)	6	1.8 [0.5; 9.2] 5 (83)	0.95 [0.26; 3.49]	0.940
North America	119	2.5 [1.6; 3.7] 86 (72)	118	2.3 [1.6; 3.7] 82 (69)	0.96 [0.71; 1.30]	0.797
Total					Interaction:	0.019[d]

a: HR from Cox proportional hazards model, without stratification.
b: p-value from log-rank test, without stratification.
c: Without progression events of the underlying disease.
d: p-value for interaction test from Cox proportional hazards model, stratified by number of prior VEGF-targeted TKI therapies and number of MSKCC risk factors.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; MSKCC: Memorial Sloan Kettering Cancer Center; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

Health status

EQ-5D VAS

There was proof of an effect modification by the characteristic "region" for the outcome "health status (EQ-5D VAS)". There was a statistically significant difference in favour of cabozantinib compared with everolimus for patients of the region of North America. There was no statistically significant difference between the treatment groups for patients from Europe, Pacific-Asia, and South America. Hence there was no hint of an added benefit of cabozantinib in comparison with everolimus; an added benefit is therefore not proven. In the present constellation, the results from the region of Europe are relevant and were used for the benefit assessment.

This deviates from the approach of the company insofar as the company did not consider effect modifications in the derivation of the added benefit.

Symptoms

FKSI-DRS

For the outcome "symptoms", recorded with the FKSI-DRS, there was proof of an effect modification by the characteristics "age", "region", "number of prior VEGF-targeted TKI therapies", and "number of organs with metastases". The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. The derivation of the added benefit was therefore conducted on the basis of the results on the total population.

This concurs with the assessment of the company insofar as the company did not consider effect modifications in the derivation of the added benefit.

Side effects

Severe adverse events (CTCAE grade ≥ 3)

There was proof of an effect modification by the characteristic "region" for the outcome "severe AEs (CTCAE grade ≥ 3)". There was a statistically significant difference to the disadvantage of cabozantinib compared with everolimus for patients of the region of Europe. Under consideration of the high risk of bias, this resulted in a hint of greater harm of cabozantinib in comparison with everolimus. There was no statistically significant difference between the treatment groups for patients from the regions of Pacific-Asia, South America and North America. Hence there was no hint of greater or lesser harm from cabozantinib; greater or lesser harm is therefore not proven. In the present constellation, the results from the region of Europe are relevant and were used for the benefit assessment.

This deviates from the approach of the company as the company did not consider effect modifications in the derivation of the added benefit and derived an indication of greater harm for this outcome on the basis of the total population.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the 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

Based on the results presented in Section 2.4.3, the extent of the respective added benefit at outcome level is estimated in the following Table 15.

Determination of the outcome category for the outcomes on specific adverse events

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

The specific AEs “anaemia”, “diarrhoea”, “hypertension”, “palmar-plantar erythrodysaesthesia syndrome”, and “pneumonitis” were allocated to the outcome category of non-serious/non-severe side effects as a comparison of the common AEs with SAEs and severe AEs (CTCAE grade ≥ 3) showed that the majority of these events were non-serious or non-severe. This allocation deviates from the company insofar as the company did not allocate specific AEs to any outcome category.

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Cabozantinib vs. everolimus** **Median time to event [months] or mean change from start of study until end of treatment** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 21.4 vs. 17.1 months HR: 0.70 [0.58; 0.85]; p < 0.001 probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ added benefit, extent "considerable"
Morbidity		
Skeletal-related events	Median: NA vs. NA HR: 0.77 [0.52; 1.13] p = 0.175	Lesser benefit/added benefit not proven
Symptoms (FKSI-DRS)	Mean change: −1.11 vs. −1.54 MD: 0.43 [0.15; 0.71]; p = 0.003 Hedges' g: 0.24 [0.08; 0.40][c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS) Region Europe	Mean change: −4.36 vs. −3.85 MD: −0.51 [−1.97; 0.95]; p = 0.489	Lesser benefit/added benefit not proven
Health-related quality of life		
No patient-relevant outcomes of this category recorded		
Side effects		
SAEs	Median: 12.9 vs. 11.1 months HR: 0.80 [0.63; 1.00]; p = 0.052	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3) Region Europe	Median: 1.7 vs. 3.7 months HR: 1.63 [1.26; 2.11]; HR: 0.61 [0.47; 0.79][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Discontinuation due to AEs	No usable data[e]	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: cabozantinib vs. everolimus (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Cabozantinib vs. everolimus** **Median time to event [months] or mean change from start of study until end of treatment** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Anaemia	Median: NA vs. 11.1 months HR: 0.29 [0.22; 0.40]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Diarrhoea	Median: 1.5 vs. 22.7 months HR: 3.85 [3.02; 4.90]; HR: 0.26 [0.20; 0.33][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Hypertension	Median: NA vs. NA HR: 5.29 [3.46; 8.09]; HR: 0.19 [0.12; 0.29][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Palmar-plantar erythrodysaesthesia syndrome	Median: 27.2 vs. NA months HR: 9.03 [5.59; 14.58]; HR: 0.11 [0.07; 0.18][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Pneumonitis	Median: NA vs. NA RR: 0.01 [0.00; 0.23]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Discrepant information in the company's dossier and in comparison with addendum A17-10.
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; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 16: 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: "considerable"	–
–	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): ▫ Europe: hint of greater harm – extent: "considerable"
Non-serious/non-severe side effects ▪ anaemia: hint of lesser harm – extent: "considerable" ▪ pneumonitis: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ diarrhoea: hint of greater harm – extent: "considerable" ▪ hypertension: hint of greater harm – extent: "considerable" ▪ palmar-plantar erythrodysaesthesia syndrome: hint of greater harm – extent "considerable"
No patient-relevant outcomes for health-related quality of life were recorded in the study included. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

The overall assessment of the data showed both positive and negative effects with different certainty of results (indication or hint) for cabozantinib in comparison with everolimus. An indication of a considerable added benefit was shown for the outcome "overall survival". This was accompanied by a hint of considerably greater harm regarding serious/severe side effects (severe AEs [CTCAE grade ≥ 3]). In addition, there were several hints both of greater and of lesser harm from cabozantinib in the category of non-serious/non-severe side effects. Due to the greater harm in serious/severe side effects, the extent of the added benefit was downgraded from considerable to minor in the overall assessment.

In summary, there is an indication of a minor added benefit of cabozantinib in comparison with everolimus for patients with advanced renal cell carcinoma following prior VEGF-targeted therapy.

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

Table 17: Cabozantinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with advanced renal cell carcinoma following prior VEGF-targeted therapy[b]	Nivolumab or **everolimus**	Indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The relevant study only included patients with clear-cell metastatic renal cell carcinoma with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2, with non-clear cell renal cell carcinoma, or without metastases.
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 deviates from that of the company, which derived major added benefit for cabozantinib.

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

2.6 List of included studies

Study METEOR

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. A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR): full text view [online]. In: Clinicaltrials.gov. 18.07.2017 [Accessed: 05.12.2017]. URL: https://clinicaltrials.gov/ct2/show/study/NCT01865747.

Exelixis. A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR): study results [online]. In: Clinicaltrials.gov. 18.07.2017 [Accessed: 05.12.2017]. URL: https://clinicaltrials.gov/ct2/show/results/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 [online]. In: EU Clinical Trials Register. [Accessed: 05.12.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001010-14.

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; statistical analysis plan [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; 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]. 2017.

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 2 [unpublished]. 2017.

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 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-56-cabozantinib-renal-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.7979.html.