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Cabozantinib (renal cell carcinoma) –

Addendum to Commission A17-56[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GRCS	Global Rating of Change Scale
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
SGB	Sozialgesetzbuch (Social Code Book)
VEGF	vascular endothelial growth factor

1 Background

On 19 February 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-56 (Cabozantinib – Benefit assessment according to §35a Social Code Book V [SGB V]) [1].

In Module 4 of its dossier on cabozantinib [2], the pharmaceutical company (hereinafter referred to as "the company") presented the METEOR study for the therapeutic indication of advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy.

The METEOR study was used for the benefit assessment. However, the responder analyses for the morbidity outcome "symptoms" presented by the company, represented by the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS), was not included in the benefit assessment, as it was not considered sufficiently validated.

After the oral hearing [3], the G-BA commissioned IQWiG with the methodological evaluation of the responder analyses of the FKSI-DRS and the FKSI-15 presented by the company. Moreover, the outcome "discontinuation due to adverse events" (AEs) should be assessed.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

For the METEOR study, the company presented several analyses of the FKSI-DRS in its dossier on cabozantinib. Besides analyses on the basis of mean differences, these were responder analyses. The mean differences were used for the benefit assessment [1], since the response criteria used by the company were not considered sufficiently validated. This assessment is explained in the following Section 2.1. Section 2.2 addresses the assessment of the outcome "discontinuation due to adverse events", which was also requested.

2.1 Methodological evaluation of the responder analyses presented by the company

In its dossier on cabozantinib, the company presented responder analyses for the time to deterioration for the FKSI-DRS. These analyses were not prespecified in the METEOR study. The company used a minimally important difference (MID) of 3 points as response criterion for the analysis of the time to deterioration; as additional information, it presented analyses on the basis of a MID of 4 points. To demonstrate the validity of its response criteria, the company refers to the work of Cella 2007 [4]. However, this piece of work is not suitable to demonstrate the validity of a MID for the FKSI-DRS.

The validation study included 141 patients with renal cancer. There was no intervention during the observation period. The patients were recruited among the members of a patient organization. Their mean age was about 60 years; almost all of them were white. More than 80% of the patients assessed themselves as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The publication provides inconsistent data on prior therapies and on the proportion of patients who received a therapy at study inclusion (according to Table 1 of the work, 66% of the patients did not receive a therapy at study inclusion and about one third of the patients had been pretreated with a chemotherapy or a radiotherapy respectively; according to the running text, in contrast, 66% received a therapy at study inclusion and two thirds had been pretreated with a chemotherapy or a radiotherapy respectively). Independent of these uncertainties, the population was heterogeneous with regard to the prior therapies and the therapy during the observation. Information on the severity of the disease is missing.

The patients were interviewed at 3 time points, at study entry (time point 1), 3 to 7 days after the start of the study (time point 2) and 2 to 3 months after the start of the study (time point 3). At study entry as well as at time points 2 and 3, the patients answered the FKSI-15. At the start of the study, they provided a self-reported current health status based on the ECOG-PS. At time point 3 (2 to 3 months after the start of the study), they additionally answered a Global Rating of Change Scale (GRCS) (the wording of these questions is missing). In the GRCS, the patients assessed the change of their own health status on a scale from 7 (much better) to −7 (much worse).

The questions of the FKSI-15 that are relevant for this symptom scale were used to investigate the MID for FKSI-DRS.

The authors used several measures to assess the MID. These measures included the difference of the mean FKSI-DRS in patients with ECOG-PS 0, 1 or 2 at the start of the study (anchor-based, cross-sectional study), the difference of the mean FKSI-DRS in patients without change or with improvement or deterioration on the GRCS at time point 3 compared with the start of the study (anchor-based, longitudinal study) as well as assessments on the MID based on distribution.

In the current discussion, the determination of a MID by means of anchor-based procedures from longitudinal studies is particularly important, as these procedures provide a direct reflection of the changes perceived by the patients [5-8].

In the present validation study for the FKSI-DRS, the patients were largely stable with regard to their health status. At time point 3, for instance, only 13 of the 141 patients included assessed their health status as deteriorated, and 10 as improved. The very similar mean values of the FKSI-DRS at the start of the study (29.1, SD = 5.4), time point 2 (29.5, SD = 4.7) and time point 3 (29.2, SD = 5.3) also point to the stable health status of the study population. The derivation of an anchor-based MID for a change in symptoms from such a stable population is questionable.

The work does not provide information on the extent of the change of the anchor assessed by the patients who reported a deterioration of their health status (N = 13 [9.2%] of 141 patients included). Due to the small number of patients with changes, the authors summarized all patients in this group for the calculation of the mean change of the FKSI-DRS and did not restrict the analysis to those with minor changes of the anchor, which is in contrary to the usual approach. Which change of the FKSI-DRS corresponds to a minor change of the GRCS can thus not be derived from the data. Altogether, a MID for the FKSI-DRS cannot be derived from the presented validation study.

In its dossier, the company also presented responder analysis of the FKSI-15 and also cited the Cella 2007 study as evidence of the validity of the chosen MIDs of 4 or 5 points [4]. However, the MID of the FKSI-15 was not investigated in the Cella 2007 study. The basis on which the company defined these response criteria remains unclear. Moreover, these responder analyses were not prespecified in the METEOR study. The presented response criteria were assessed as non validated.

The responder analyses on FKSI-DRS and FKSI-15 are provided in Appendix A as supplementary information.

2.2 Results on side effects

The company's analyses for the final data cut-off at 2 October 2016 on the outcome "discontinuation due to adverse events" were inconsistent and were thus not used for dossier assessment A17-56 [1]. The company corrected its data with its comment [9]. Table 1 shows the result for the outcome "discontinuation due to adverse events".

Table 1: Results (side effects) – RCT, direct comparison: cabozantinib vs. everolimus (third data cut-off: 2 October 2016)

Study Outcome category Outcome	Cabozantinib		Everolimus		Cabozantinib vs. everolimus
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
METEOR study					
Side effects					
Discontinuation due to AEs[a]	331	88 (27)	332	87 (27)	1.01 [0.79; 1.31]; 0.944[b]

a: Without events rated as progression of the underlying disease (the following PTs are not contained in the analysis: lymphangiosis carcinomatosa, neoplasm malignant, bone metastases, metastases to central nervous system, metastases to ovary, metastases to pelvis, spinal metastases, metastases to testicle, peritoneal metastases, metastatic pain, metastatic renal cell carcinoma, renal cancer, renal cell carcinoma, renal cancer metastatic, tumour associated fever, tumour pain and tumour thrombosis).
b: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [10]).
AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; CSZ: convexity, symmetry, z score; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Discontinuation due to AEs

There was no statistically significant difference between the study arms 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.

2.3 Summary

The present addendum does not entail a change in the conclusions on the added benefit of cabozantinib.

The G-BA decides on the added benefit.

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

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Appendix A – Supplementary presented results of the METEOR study

Table 2: Results (morbidity) – RCT, direct comparison: cabozantinib vs. everolimus (third data cut-off: 2 October 2016)

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
Meteor study					
Morbidity					
FKSI-DRS time to deterioration					
3 points	318	5.6 [3.9; 9.3] 183 (58)	297	2.8 [2.8; 3.7] 196 (66)	0.67 [0.55; 0.83]; < 0.001
4 points	318	5.6 [4.1; 11.2] 172 (54)	297	3.8 [3.0; 5.6] 176 (59)	0.77 [0.62; 0.95]; 0.016
FKSI-15 time to deterioration					
4 points	318	3.7 [2.8; 4.6] 205 (64)	297	2.8 [1.9; 3.7] 202 (68)	0.80 [0.66; 0.98]; 0.027
5 points	318	3.7 [2.8; 5.6] 195 (61)	297	3.7 [2.7; 4.6] 189 (64)	0.84 [0.69; 1.03]; 0.093

CI: confidence interval; DRS: Disease Related Symptoms; FKSI: Functional Assessment of Cancer Therapy – Kidney Symptom Index; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus