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Cabozantinib (renal cell carcinoma) –

Addendum to Commission A16-69[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
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
SGB	Sozialgesetzbuch (Social Code Book)
SOC	Summary of Product Characteristics
VEGF	vascular endothelial growth factor

1 Background

On 7 March 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-69 (Cabozantinib – Benefit assessment according to §35a Social Code Book V [1]).

In Module 4 A 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. In Module 4 A of the dossier, the company presented analyses based on the first data cut-off from 22 May 2015. However, there were no usable data for the outcomes "skeletal-related events", "symptoms" and on side effects. Module 4 A additionally contained analyses based on the second data cut-off from 31 December 2015 for the outcome "overall survival". The company presented no analyses on adverse events (AEs) on this second data cut-off in Module 4 of the dossier, although analyses on these outcomes had been published in a journal [3].

In its written comments to the dossier assessment [4] and after the oral hearing, the company sent supplementary information, which went beyond the information provided in the dossier on cabozantinib [2], to prove the added benefit. The G-BA therefore commissioned IQWiG with further assessments.

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

2 Assessment

With its comment and after the oral hearing, the company submitted further analyses of the METEOR study. These were the following documents and analyses:

- Presented with the comment (of 22 February 2017) on the dossier assessment:
  - analyses of the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) and of the FKSI-15 for the first data cut-off on 22 May 2015
  - analyses (survival time analyses) for skeletal-related events for the first data cut-off on 22 May 2015
  - analyses (survival time analyses) of the overall AE rates without progression events and of the specific AEs (System Organ Class [SOC] and Preferred Term [PT]) selected by IQWiG on the basis of the first data cut-off for the second data cut-off on 31 December 2015
  - analyses of overall survival for the third data cut-off on 2 October 2016
- Presented after the oral hearing (on 7 March 2017) on the dossier assessment:
  - overview of the subsequent therapies for the third data cut-off on 2 October 2016
  - analyses (survival time analyses) of the overall AE rates without progression events and of the specific AEs (SOC and PT) selected by IQWiG on the basis of the first data cut-off for the third data cut-off on 2 October 2016
  - addendum to the clinical study report (CSR) (of 14 February 2017) of the METEOR study for the third data cut-off on 2 October 2016 (the document was incomplete, see below)

With the comment, the company supplemented analyses for the symptom questionnaire and the skeletal-related events resulting from IQWiG's dossier assessment. The analyses of skeletal-related events were incomplete, however, because there was no analysis of the individual components for the composite outcome. In addition, the company for the first time presented analyses of AEs for the second data cut-off on 31 December 2015. The dossier had contained no information on AEs for this data cut-off. The company only presented survival time analyses on overall rates and on specific AEs selected on the basis of the first data cut-off. There was still no presentation of all AEs, serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuations due to AEs by SOC and PT. It could therefore not be investigated whether the identification of specific AEs conducted on the basis of AEs of the first data cut-off was still relevant. In addition, the company for the first time presented results on overall survival for the third data cut-off on 2 October 2016.

After the oral hearing, the company supplemented the data once more. It submitted the overview of subsequent therapies after progression requested in the oral hearing. In addition, it presented analyses on AEs for the third data cut-off and an addendum to the CSR for the third data cut-off. The addendum to the CSR of 14 February 2017 had already been available at the time point of the company's comment. It therefore remained unclear why it had not been submitted already with the comment. In addition, the addendum to the CSR was incomplete. The appendix contained no result tables (section 14 of the addendum). The table of contents of section 14 showed that this section also contained results on skeletal-related events, which were missing due to the incomplete report, however. The fact that analyses on skeletal-related events were conducted at the third data cut-off complied with the study protocol. It remained unclear why, even on enquiry, the company stated in the oral hearing that this patient-relevant outcome had no longer been recorded after the first data cut-off. Irrespective of this uncertainty, the data were not available for the benefit assessment.

In summary, at no time point did the company submit complete documents. This also applies to the data subsequently submitted in the commenting procedure and after the oral hearing. The data subsequently submitted did therefore not change the conclusion on the added benefit. The results submitted are presented in table format in Appendix A, Appendix B and Appendix C.

3 References

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2. Ipsen Pharma. Cabozantinib-L-malat (CABOMETYX): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; Behandlung des fortgeschrittenen Nierenzellkarzinoms bei Erwachsenen nach vorangegangener zielgerichteter Therapie gegen VEGF (vaskulärer endothelialer Wachstumsfaktor); medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 28.10.2016 [Accessed: 09.03.2017]. URL: https://www.g-ba.de/downloads/92-975-1730/2016-10-28_Modul4A_Cabozantinib.pdf.

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4. Ipsen Pharma. Stellungnahme zum IQWiG-Bericht Nr. 478: Cabozantinib (Nierenzellkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-69. 2017: [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/267/tab/beschluesse in the document "Zusammenfassende Dokumentation"].

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Appendix A – Results of the METEOR study

Table 1: Results (mortality and side effects) – RCT, direct comparison: cabozantinib vs. everolimus

Study Outcome category Time point Outcome	Cabozantinib N	Cabozantinib Median survival time in months [95% CI] Patients with event n (%)	Everolimus N	Everolimus Median survival time in months [95% CI] Patients with event n (%)	Cabozantinib vs. everolimus HR [95% CI]; p-value[a]
METEOR					
Mortality					
Third data cut-off: 2 Oct 2016					
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					
First data cut-off: 22 May 2015					
Skeletal-related events	330	NA [NC; NC] 38 (11.5)	328	NA [NC; NC] 46 (14.0)	0.77 [0.50; 1.19]; 0.233
Pathological fractures	No data available				
Spinal cord compression	No data available				
Surgical bone procedure	No data available				
Bone radiation	No data available				
Third data cut-off: 2 Oct 2016	No data available				
Side effects					
Third data cut-off: 2 Oct 2016					
SAEs[b]	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)[b]	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[b, c]	331	NA [29.4; NC] 59 (18)	322	NA [26.2; NC] 50 (16)	0.85 [0.58; 1.25]; 0.404
SOC blood and lymphatic system disorders	331	36.8 [NC; NC] 90 (27)	322	8.2 [5.5; 18.1] 142 (44)	0.38 [0.29; 0.50]; < 0.001
SOC gastrointestinal disorders	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
SOC vascular disorders	331	12.8 [6.1; NC] 157 (47)	322	NA [NC; NC] 53 (16)	3.23 [2.36; 4.41]; < 0.001
PT anaemia	331	NA [NC; NC] 67 (20)[d]	322	11.1 [7.5; 19.9] 130 (40)[d]	0.29 [0.22; 0.40]; < 0.001

(continued)

Table 1: Results (mortality and side effects) – RCT, direct comparison: cabozantinib vs. everolimus (continued)

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]
PT diarrhoea	331	1.5 [1.4; 1.8] 249 (75)[e]	322	22.7 [17.9; NC] 95 (30)[e]	3.85 [3.02; 4.90]; < 0.001
PT hypertension	331	NA [NC; NC] 123 (37)[f]	322	NA [NC; NC] 26 (8)[f]	5.29 [3.46; 8.09]; < 0.001
PT palmar-plantar erythrodysaesthesia syndrome	331	27.2 [12.2; NC] 145 (44)[g]	322	NA [NC; NC] 19 (6)[g]	9.03 [5.59; 14.58]; < 0.001

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: Overall AE rate 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).
c: Analysis of patients with event results in qualitatively identical results: RR [95% CI]; p-value: 1.15 [0.81; 1.62]; 0.531; Institute's calculation of RR. CI (asymptotic) and p-value (unconditional exact test (CSZ method according to [5])).
d: Proportion of patients with severe AEs (CTCAE ≥ 3]: cabozantinib arm 22 (6.6); everolimus arm 55 (17).
e: Proportion of patients with severe AEs (CTCAE ≥ 3]: cabozantinib arm 44 (13); everolimus arm 8 (2.5).
f: Proportion of patients with severe AEs (CTCAE ≥ 3]: cabozantinib arm 51 (15); everolimus arm 12 (3.7).
g: Proportion of patients with severe AEs (CTCAE ≥ 3]: cabozantinib arm 28 (8.5); everolimus arm 3 (0.9).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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; vs.: versus

Table 2: Results (morbidity) – RCT, direct comparison: cabozantinib vs. everolimus

Study **Outcome category**	**Cabozantinib**			**Everolimus**			**Cabozantinib vs. everolimus**
Time point **Outcome**	**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[b]**
METEOR							
Morbidity (symptoms)							
First data cut-off: 22 May 2015							
FKSI-DRS[c] (total score)	323	ND	−0.52 (4.74)	303	ND	−0.93 (4.67)	0.41 [ND]; 0.006 Hedges' g[d] (*0.09 [−0.07; 0.25] 0.254)*
Supplementary information:							
FKSI-15[c] (total score)	*324*	*ND*	*−1.53 (7.63)*	*310*	*ND*	*−1.55 (7.89)*	*0.01 [ND]; 0.956*
Third data cut-off: 2 Oct 2016	No data 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, study visit, number of prior VEGF-targeted TKI therapies and number of MSKCC risk factors.
c: Negative changes indicate deterioration.
d: Calculation of Hedges' g not plausible. Based on information provided by the company in its comment [4]. Institute's calculation not possible on the basis of the available information.

CI: confidence interval; FKSI: Functional Assessment of Cancer Therapy; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; ITT: intention to treat; MMRM: mixed-effects model repeated measures; MSKCC: Memorial Sloan Kettering Cancer Center; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; vs.: versus

Appendix B – Kaplan-Meier curve on overall survival from the METEOR study

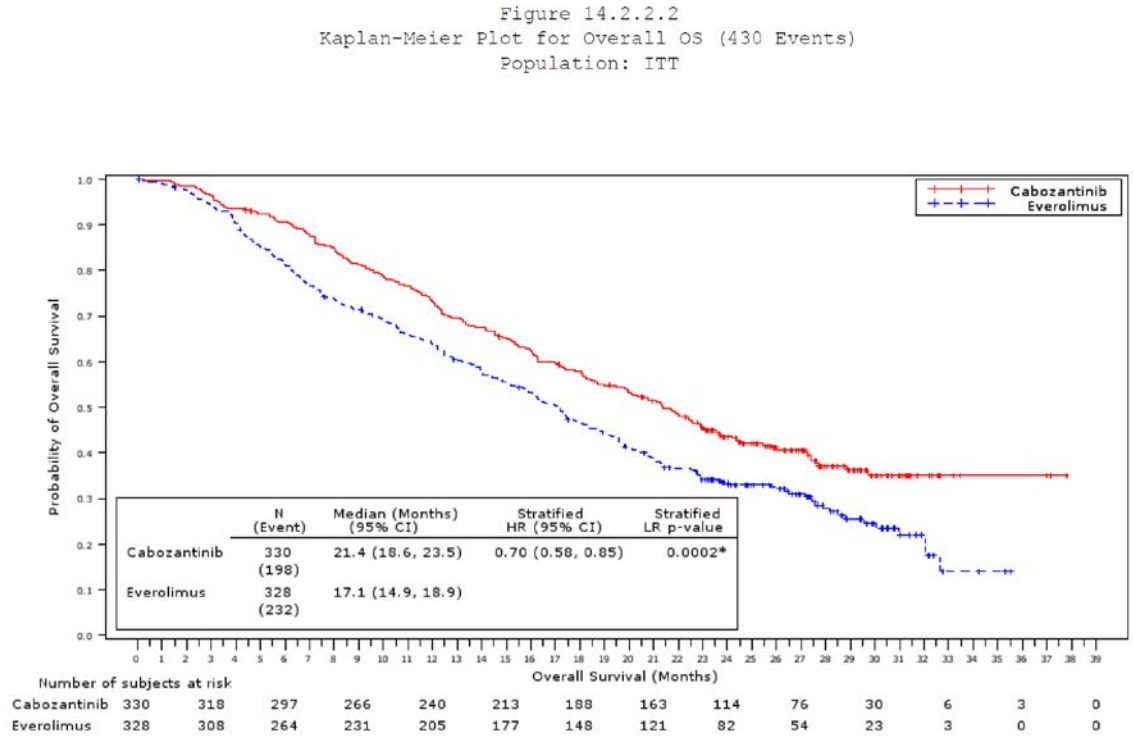

Figure 1: Kaplan-Meier on overall survival from the METEOR study at the third data cut-off on 2 October 2016

Appendix C – Overview of subsequent therapies in the METEOR study

Table 3: Tumour therapies after completion of treatment with the study medication (post-progression therapy) – RCT, direct comparison: cabozantinib vs. everolimus

Study (time point) Tumour therapy	Patients with event n (%)[a]	
	Cabozantinib N = 330	Everolimus N = 328
METEOR (data cut-off: 2 October 2016)		
Number of patients with at least one systemic tumour therapy after completion of the study medication	187 (57)	205[b] (63)
VEGFR-TKI therapies	90 (27)	165 (50)
Axitinib	67 (20)	97 (30)
Sunitinib	18 (5.5)	36 (11)
Sorafenib	13 (3.9)	33 (10)
Pazopanib	5 (1.5)	23 (7)
Cabozantinib	2 (0.6)	14 (4.3)
Lenvatinib	1 (0.3)	0 (0)
Other systemic tumour therapies		
Everolimus	109 (33)	16 (4.9)
Bevacizumab	9 (2.7)	11 (3.4)
interferon alpha/peginterferon	7 (2.1)	8 (2.4)
Temsirolimus	5 (1.5)	4 (1.2)
Interleukin (interleukin 2)	0 (0)	4 (1.2)
PD-1/PD-L1-targeted therapies	45 (14)	51 (16)
Nivolumab	43 (13.0[c])	48 (14.6[c])
Atezolizumab	2 (0.6[c])	1 (0.3[c])
AMP-514	0 (0)	2 (0.6[c])
MK-3475/pembrolizumab	1 (0.3[c])	0 (0)
Chemotherapy	11 (3.3)	14 (4.3)

a: The patients could have received more than 1 systemic tumour therapy.
b: Citing 208 patients, the company provided deviating information on the second data cut-off from 31 December 2015.
c: Institute's calculation.
n: number of patients with (at least one) event; N: number of analysed patients; PD-1: programmed cell death 1; PD-L: programmed death ligand; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor; vs.: versus