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Cabozantinib (hepatocellular carcinoma) –

Addendum to Commission A18-85[1]

Addendum

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[1] Translation of addendum A19-38 *Cabozantinib (hepatozelluläres Karzinom) – Addendum zum Auftrag A18-85* (Version 1.0; Status: 15 May 2019). 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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Abbreviation	Meaning
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
VAS	visual analogue scale

1 Background

On 24 April 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-85 (Cabozantinib – Benefit assessment according to §35a Social Code Book V) [1].

The G-BA's commission comprised the following assessment:

- assessment of the responder analyses on the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)

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

The CELESTIAL study included for the benefit assessment recorded health status using the EQ-5D by means of a VAS.

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented mixed-effects model repeated measures (MMRM) analyses, which had been planned a priori according to the study protocol, for the EQ-5D VAS. In addition, the company presented event time analyses on patients with definitive deterioration by ≥ 7 or ≥ 10 points on the VAS in comparison with baseline. The company did not show the validity of these response criteria in the dossier. It stated in its comments that the validity of the response criteria had been shown in the publication by Pickard 2007 [3].

As described in dossier assessment A18-85 [1], the MMRM analyses is the analysis suitable for the assessment because the validity has not been shown for the response criteria used by the company. The publication by Pickard 2007 cited by the company in the comments is also unsuitable to show the validity. A more in-depth discussion on the validity of these response criteria can be found in benefit assessment A18-33 [4].

Unclear operationalization of the response criterion "definitive deterioration"

In Module 4 of its dossier [2], the company operationalized the time to definitive deterioration of health status as a deterioration by at least 7 mm or 10 mm on the EQ-5D VAS without subsequent improvement to the baseline value. Contrary to this, the source document [5] submitted by the company contains the information "time to first deterioration" both in the tables and in the Kaplan-Meier curves. It is therefore unclear whether the analyses presented by the company refer to singular or permanent deterioration.

Risk of bias

Regardless of the unclear operationalization, the responder analyses presented by the company are potentially highly biased, since no completed questionnaire was available for a relevant proportion (> 10%) of the patients at the first documentation time after the start of the study. As already described in the dossier assessment [1], the EQ-5D VAS was only planned to be recorded up to 8 weeks after disease progression or treatment discontinuation. With regard to all patients who were in the study at the time, there was an early sharp decline in the response rate, which showed increasing difference between the treatment arms. Due to these decreasing response rates and the operationalization of definitive deterioration considered by the company, there was therefore an additional aspect of bias. The data on the response to the questionnaires showed that the proportion of patients with available documentation was lower in the control arm than in the intervention arm at all time points after the start of the study. Fewer follow-up recordings were therefore available in the control arm due to the earlier discontinuation. As a result, it may have been more likely for singular or temporary deteriorations to be wrongly recorded as permanent deteriorations in the control arm than in the intervention arm. The

responder analyses (irrespective of the response criteria) were not interpretable for these reasons.

The responder analyses on the EQ-5D VAS are presented as additional information in Appendix A, the corresponding Kaplan-Meier curves can be found in Appendix B.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Cabozantinib (hepatozelluläres Karzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-85 [online]. 13.03.2019 [Accessed: 01.04.2019]. (IQWiG-Berichte; Volume 739). URL: https://www.iqwig.de/download/A18-85_Cabozantinib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Ipsen Pharma GmbH. Cabozantinib-L-malat (Cabometyx): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 10.12.2018. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/422/#tab/dossier.

3. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007; 5: 70.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Bosutinib (chronische myeloische Leukämie): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-33 [online]. 29.08.2018 [Accessed: 05.09.2018]. (IQWiG-Berichte; Volume 660). URL: https://www.iqwig.de/download/A18-33_Bosutinib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

5. Ipsen Pharma. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; Zusatzanalysen [unpublished]. 2018.

Appendix A – Supplementary presentation of the responder analyses of the EQ-5D VAS

Table 1: Results (health status) – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study Outcome category Outcome	Cabozantinib + BSC		Placebo + BSC		Cabozantinib + BSC vs. placebo + BSC
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
CELESTIAL					
Morbidity					
EQ-5D VAS (time to deterioration[b, c])					
7 points	506	5.55 [4.63; 7.39] 247 (49)	260	4.63 [3.75; 7.52] 102 (39)	0.98 [0.77; 1.24]; 0.789
10 points	506	5.59 [4.63; 7.39] 245 (48)	260	5.55 [3.78; 9.56] 98 (38)	1.01 [0.79; 1.28]; 0.981

a: HR and CI: stratified Cox regression model; p-value: stratified log-rank test; stratification factors: aetiology of disease (HBV [with or without HCV], HCV [without HBV], other), geographical region (Asia, other), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no).
b: Contradictory information on operationalization: Defined as deterioration by at least 7 mm or 10 mm without subsequent improvement to baseline value according to information provided by the company in Module 4; defined as time to first deterioration according to information in the source document.
c: Data cut-off 1 December 2017.

CI: confidence interval; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Appendix B – Graphic display of the event time analyses presented in the addendum (Kaplan-Meier curves)

Note on Figure 1 and Figure 2: According to the information provided by the company in Module 4 of the dossier, the presented analyses are the time to definitive deterioration. In contrast, the corresponding Kaplan-Meier curves presented by the company as well as the source documents refer to these analyses as time to first deterioration.

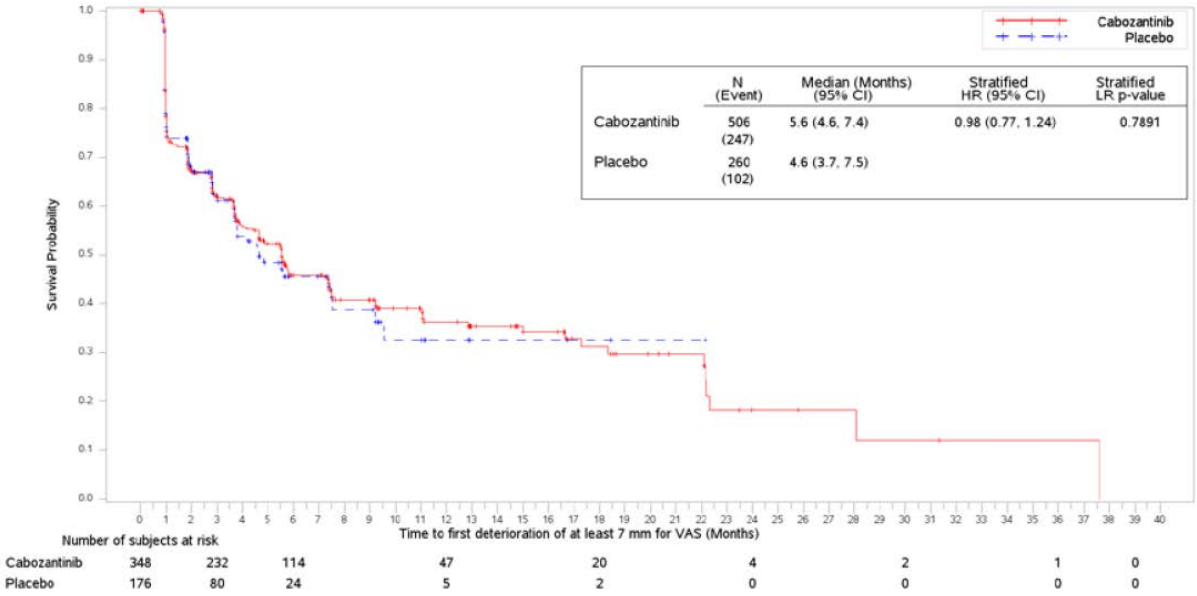

Figure 1: Kaplan-Meier curves on health status (EQ-5D VAS), time to deterioration by ≥ 7 points

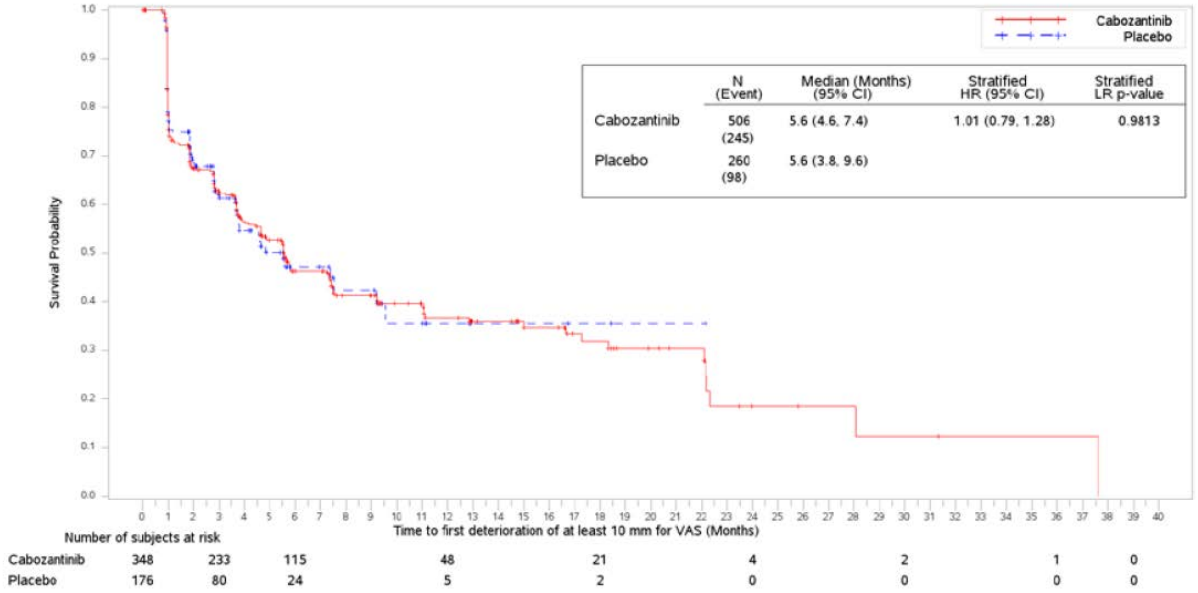

Figure 2: Kaplan-Meier curves on health status (EQ-5D VAS), time to deterioration by ≥ 10 points