IQWiG Reports – Commission No. A20-03

Ramucirumab (hepatocellular carcinoma) –

Addendum to Commission A19-73[1]

Addendum

Commission: A20-03
Version: 1.0
Status: 30 January 2020

[1] Translation of addendum A20-03 *Ramucirumab (hepatozelluläres Karzinom) – Addendum zum Auftrag A19-73* (Version 1.0; Status: 30 January 2020). 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

Ramucirumab (hepatocellular carcinoma) – Addendum to Commission A19-73

Commissioning agency

Federal Joint Committee

Commission awarded on

6 January 2020

Internal Commission No.

A20-03

Address of publisher

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Keywords: Ramucirumab, Carcinoma – Hepatocellular, Benefit Assessment, NCT01140347, NCT02435433

Table of contents

Page

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AFP	alpha fetoprotein
BSC	best supportive care
FACT	Functional Assessment of Cancer Therapy
FHSI-8	FACT Hepatobiliary Symptom Index-8
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial

1 Background

On 6 January 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-73 (Ramucirumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trials (RCTs) REACH und REACH-2 for the benefit assessment of ramucirumab in patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/mL and who have been previously treated with sorafenib. These 2 RCTs were included in the benefit assessment of ramucirumab [1].

In its dossier, the company presented event time analyses for the time to deterioration of symptoms for the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) questionnaire. These were not used for the assessment, as the chosen response criteria (deterioration by ≥ 3 points and sensitivity analyses for ≥ 2 and ≥ 4 points) are not sufficiently validated [1]. With its comments [3], the company presented a meta-analysis of the studies REACH and REACH-2 for the response criterion of deterioration by ≥ 5 points for the FHSI-8. After the oral hearing [4], the company subsequently submitted further analyses regarding the response criterion of ≥ 5 points [5].

The G-BA commissioned IQWiG to assess the analyses subsequently submitted on the FHSI-8 with a response criterion of ≥ 5 points and to assess the information subsequently submitted by the company on the data missing from the analysis, particularly with regard to the REACH study.

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

After the oral hearing [4], the company subsequently submitted further event time analyses on the FHSI-8 for the response criterion of ≥ 5 points (time to deterioration) [5].

These are, on the one hand, event time analyses based on the individual studies REACH and REACH-2 and, on the other, a meta-analysis of both studies. In addition, the company submitted information on the proportion of patients for whom data on the FHSI-8 were available both for the start of the study and for at least one subsequent recording, both for each of the studies REACH and REACH-2.

Results

Proportion of patients considered in the analysis on the FHSI-8

In the event time analyses presented by the company on the time to deterioration by ≥ 5 points based on the FHSI-8, patients who only had a baseline value but not a subsequent value in the course of the study were censored on day 1. Patients for whom no baseline value was available were also censored on day 1. These patients were therefore de facto not included in the analysis. The company's dossier contained discrepant information regarding the proportion of these patients, with the possibility that the proportion was over 30%.

In the documents subsequently submitted after the oral hearing, the company stated for how many patients data from the beginning of the study and from at least one subsequent recording were available for the FHSI-8. According to this information, 214 (85.6%) patients in the subpopulation with AFP ≥ 400 ng/mL of the REACH study had baseline values as well as data on subsequent recordings (104 [87.4%] in the ramucirumab + best supportive care [BSC] arm, and 110 [84.0%] in the placebo + BSC arm). In the REACH-2 study, 255 (87.3%) of the patients had both values at baseline and for at least one subsequent recording (178 [90.4%] in the ramucirumab + BSC arm and 77 [81.1%] in the placebo + BSC arm). Thus, a sufficient number of patients from each study was included in the event time analysis on the FHSI-8, which can therefore be used.

Risk of bias

The risk of bias for the results of the event time analyses on the FHSI-8 total score was rated as high for both studies. On the one hand, this was due to the large proportion of patients who did not have at least one value at baseline and one subsequent recording (difference between the treatment arms of > 10% or > 5 percentage points [REACH-2], see above). On the other, the high risk of bias was due to incomplete observations for potentially informative reasons. The outcome was only recorded until 7 days after the end of treatment. Hence, the observation period was driven by the reasons for treatment discontinuation, which differed notably between the treatment arms (for more detailed reasons, see dossier assessment A19-73 [1]).

Results

Table 1 shows the results of the responder analyses on the FHSI-8.

Table 1: Results (symptoms) – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC

Outcome category Outcome Study	Ramucirumab + BSC N	Ramucirumab + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Ramucirumab + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
Morbidity					
Symptoms (FHSI-8, total score)					
≥ 5 points[b]					
REACH (AFP ≥ 400 ng/mL)	119	7.13 [4.17; 21.65] 32 (26.9)	131	2.83 [1.84; 9.03] 46 (35.1)	0.57 [0.36; 0.90]; 0.014
REACH-2	197	6.97 [4.67; 9.76] 72 (36.5)	95	3.02 [2.79; 6.93] 31 (32.6)	0.65 [0.42; 1.01]; 0.056
Total[c]					0.61 [0.45; 0.84]; 0.002

a: HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test; for pooled analysis stratified by study.
b: Time to first deterioration; defined as decrease of the score by ≥ 5 points compared with baseline.
c: IPD meta-analysis.
AFP: alpha fetoprotein; BSC: best supportive care; CI: confidence interval; FACT: Functional Assessment of Cancer Therapy; FHSI-8: FACT Hepatobiliary Symptom Index-8; HR: hazard ratio; IPD: individual patient data; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

Symptoms (FHSI-8)

The meta-analysis showed a statistically significant difference between the treatment groups in favour of ramucirumab + BSC in comparison with placebo + BSC for the outcome "symptoms measured with the FHSI-8".

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the extent of the conclusion on the added benefit of ramucirumab from dossier assessment A19-73. This was particularly due to the fact that there was proof of a major added benefit of ramucirumab + BSC versus BSC for the outcome "overall survival". The data subsequently submitted now also showed an advantage for symptoms.

The following Table 2 shows the result of the benefit assessment of ramucirumab under consideration of dossier assessment A19-73 and the present addendum.

Table 2: Ramucirumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein of ≥ 400 ng/mL and who have been previously treated with sorafenib	**Best supportive care[b]** or cabozantinib	Proof of considerable added benefit[c]

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: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c: The studies REACH and REACH-2 only included patients with an ECOG PS of 0 or 1 and with Child Pugh class A. It therefore remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or Child-Pugh class B or C.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma

The G-BA decides on the added benefit.

3 References

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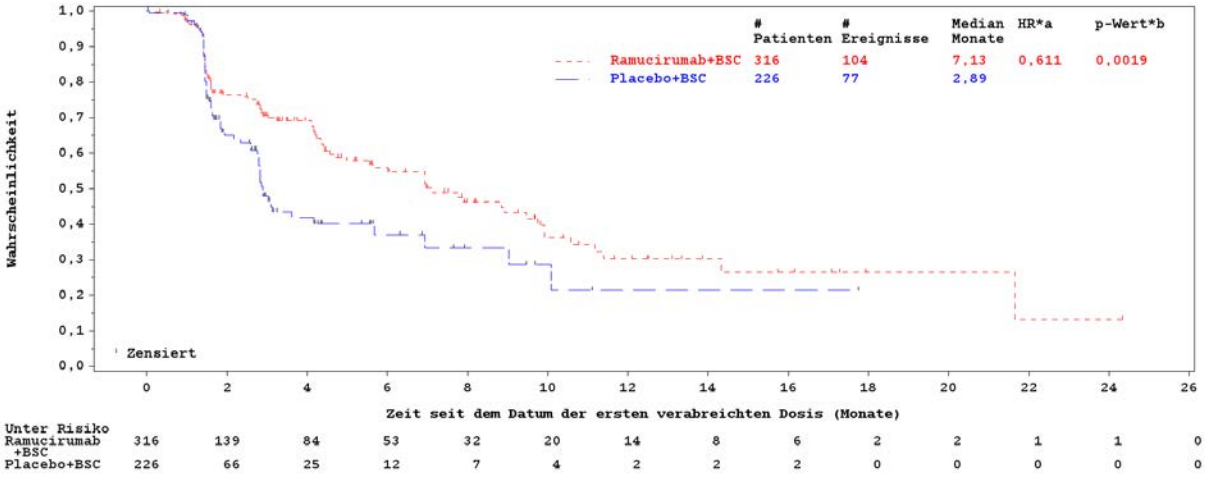
2. Lilly Deutschland. Ramucirumab (Cyramza): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 28.08.2019 [Accessed: 09.12.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/480/#dossier.

3. Lilly Deurschland. Stellungnahme zum IQWiG-Bericht Nr. 839: Ramucirumab (hepatozelluläres Karzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-73. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/480/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Gemeinsamer Bundesausschuss. Wirkstoff: Ramucirumab; mündliche Anhörung gemäß § 35a Abs. 3 S. 2 SGB V; stenografisches Wortprotokoll [online]. 06.01.2020 [Accessed: 15.01.2020]. URL: https://www.g-ba.de/downloads/91-1031-480/2020-01-06_Wortprotokoll_Ramucirumab-D474.pdf.

5. Lilly Deutschland. Nachgereichte Unterlagen zur Stellungnahme zum IQWiG-Bericht Nr. 839: Ramucirumab (hepatozelluläres Karzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-73. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/480/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Kaplan-Meier curve



Wahrscheinlichkeit – Probability; Zeit seit dem Datum der ersten verabreichten Dosis (Monate) – Time since date of administration of first dose (months); Unter Risiko – At risk; Patienten – Patients; Ereignisse – Events; Median Monate – Median months; p-Wert – p-value; Zensiert - Censored

Figure 1: Kaplan-Meier curve for the outcome "FHSI-8 (time to deterioration by ≥ 5 points)" from the meta-analysis of the studies REACH und REACH-2