IQWiG Reports – Commission No. A20-41

Avelumab (renal cell carcinoma) –

Addendum to Commission A19-95[1]

Addendum

Commission: A20-41
Version: 1.0
Status: 23 April 2020

[1] Translation of addendum A20-41 *Avelumab (Nierenzellkarzinom) – Addendum zum Auftrag A19-95* (Version 1.0; Status: 23 April 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
Avelumab (renal cell carcinoma) – Addendum to Commission A19-95

Commissioning agency
Federal Joint Committee

Commission awarded on
6 April 2020

Internal Commission No.
A20-41

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Ulrike Seay
- Anke Schulz
- Volker Vervölgyi

Keywords: Avelumab, Axitinib, Carcinoma - Renal Cell, Benefit Assessment, NCT02684006

Table of contents

Page

List of tables

Page

List of abbreviations

Abbreviation	Meaning
CI	confidence interval
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)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
VAS	visual analogue scale

1 Background

On 6 April 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-95 (Avelumab – Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of avelumab in combination with axitinib (hereinafter referred to as "avelumab + axitinib") in treatment-naive adult patients with advanced renal cell carcinoma, the pharmaceutical company (hereinafter referred to as "the company") presented the study Javelin Renal 101 in its dossier [2]. In doing so, it presented analyses for two subpopulations, corresponding to the 2 research questions of the benefit assessment; on the one hand for the patient population with favourable and intermediate risk profile (International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] score 0 to 2) (research question 1), on the other for the subpopulation with poor risk profile (IMDC score ≥ 3) (research question 2). The analyses of these two subpopulations were used for the benefit assessment.

With its comments [3], the company submitted further analyses of the patient-reported outcomes "Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS)" and "visual analogue scale of the European Quality of Life-5 Dimensions [EQ-5D VAS]". After the oral hearing [4], the GBA commissioned IQWiG with the assessment of the analyses subsequently submitted.

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 benefit assessment [1] included the outcomes "symptoms", measured using the FKSI-DRS instrument, and "health status", measured using the "EQ-5D VAS" instrument, for both research questions.

Concurring with the company, the risk of bias of these two patient-reported outcomes was rated as high. This was due to the open-label study design. Moreover, more than 10% of the patients were completely missing in the mixed-effects model repeated measures (MMRM) analyses of the FKSI-DRS (both subpopulations), and the EQ-5D VAS (subpopulation 1 [favourable and intermediate risk profile]). In contrast with the original planning in the study Javelin Renal 101, the MMRM analyses only considered values recorded under treatment.

In subpopulation 2 (poor risk profile), the difference between the proportion of patients from both arms who were completely missing in the MMRM analysis of the EQ-5D VAS was above 15%. Therefore, the data were not used to derive a conclusion on the benefit.

Further details can be found in dossier assessment A19-95 of avelumab [1].

With its comments [3], the company presented further analyses of the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)". All available documentation times also after treatment discontinuation were considered in the analyses. Thus, a larger proportion of patients was considered in both study arms.

Results

Proportion of patients considered in the subsequently submitted analyses on FKSI-DRS and EQ-5D VAS

In subpopulation 1 (favourable and intermediate risk profile), 92% of the randomized patients in each study arm were considered in the analyses for both outcomes. In subpopulation 2 (poor risk profile), these were 90% of the randomized patients in the intervention arm and 83% in the control arm (FKSI-DRS); for EQ-5D VAS, these were 90% of the randomized patients in the intervention arm and 80% in the control arm.

Risk of bias

The risk of bias for the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)" was still rated as high in both study populations. For both outcomes, this was due to the subjective recording of outcomes at open-label study design. Moreover, more than 10% of the patients in subpopulation 2 (poor risk profile) were not considered in the analysis.

Results

Research question 1: patients with favourable and intermediate risk profile

Table 1 shows the results of the analyses on FKSI-DRS and EQ-5D VAS in patients with favourable and intermediate risk profile.

Table 1: Results (morbidity, continuous) – randomized controlled trial (RCT), direct comparison: avelumab + axitinib vs. sunitinib (research question 1: patients with favourable and intermediate risk profile)

Study Outcome category Outcome	Avelumab + axitinib			Sunitinib			Avelumab + axitinib vs. sunitinib
	N	Values at start of study mean (SD)	Change mean[a] [95% CI]	N	Values at start of study mean (SD)	Change mean[a] [95% CI]	MD [95% CI][b]; p-value
Javelin Renal 101							
Morbidity							
Symptoms (FKSI-DRS)	334	ND	−1.33 [−1.65; −1.01]	342	ND	−1.22 [−1.55; −0.88]	−0.11 [−0.57; 0.35] 0.643
Health status (EQ-5D VAS)	336	ND	−1.17 [−2.39; 0.04]	343	ND	−1.53 [−2.80; −0.27]	0.36 [−1.40; 2.11] 0.689

a. Least-square mean [95% CI]; positive values mean an improvement; positive effects indicate an advantage for "intervention".
b. MMRM; stratification factors of the randomization are not included in the model. No information is available on whether the changes per treatment group and the MD refer to the changes averaged over the entire course of the study versus the start of the study or to changes compared to the start of the study.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; 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

Symptoms (FKSI-DRS) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcomes "symptoms" (FKSI-DRS) and "health status" (EQ-5D VAS). This resulted in no hint of an added benefit of avelumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Research question 2: patients with poor risk profile

Table 2 shows the results of the analyses on FKSI-DRS and EQ-5D VAS for patients with poor risk profile.

Table 2: Results (morbidity, continuous) – RCT, direct comparison: avelumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile)

Study Outcome category Outcome	Avelumab + axitinib			Sunitinib			Avelumab + axitinib vs. sunitinib
	N	Values at start of study mean (SD)	Change mean[a, b] [95% CI]	N	Values at start of study mean (SD)	Change mean[a, b] [95% CI]	MD [95% CI][b]; p-value
Javelin Renal 101							
Morbidity							
Symptoms (FKSI-DRS)	65	ND	1.36 [0.09; 2.64]	59	ND	−0.71 [−2.29; 0.87]	2.07 [0.04; 4.10] 0.045 SMD 0.37 [0.01; 0.72] 0.043
Health status (EQ-5D VAS)	65	ND	4.66 [0.48; 8.85]	57	ND	−5.27 [−10.3; −0.19]	9.93 [3.36; 16.50] 0.036 SMD 0.55 [0.19; 91] 0.003

a. Least squares mean; positive values indicated improvement; positive effects mean an advantage for intervention.
b. MMRM; stratification factors of the randomization are not included in the model. No information is available on whether the changes per treatment group and the MD refer to the changes averaged over the entire course of the study versus the start of the study or to changes only at one point in time compared to the start of the study.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MMRM: mixed-effects model repeated measures; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference in the form of Hedges' g; VAS: visual analogue scale

Symptoms (FKSI-DRS) and health status (EQ-5D VAS)

There was a statistically significant difference between the treatment groups in favour of avelumab + axitinib in comparison with sunitinib for the outcomes "symptoms (FKSI-DRS)" and "health status (EQ-5D VAS)". The standardized mean difference (SMD) similar to Hedges' g was considered to assess the relevance of the results. However, the 95% confidence interval of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that these effects are relevant. There was no hint of an added benefit of avelumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of avelumab from dossier assessment A19-95.

The following Table 3 shows the result of the benefit assessment of avelumab under consideration of dossier assessment A19-95 and the present addendum.

Table 3: Avelumab + axitinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile (International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] score 0–2)[b]	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **monotherapy with sunitinib**	Added benefit not proven
Treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile (IMDC score ≥ 3)[b]	Temsirolimus or **sunitinib**	Indication of non-quantifiable 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 Javelin Renal 101 study investigated no patients with ECOG PS > 1, with non-clear cell renal cell carcinoma or active brain metastases (see Section 2.7.4.1 of dossier assessment A19-95 [1]). It remains unclear whether the observed effects can be transferred to patients with these characteristics.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Avelumab (Nierenzellkarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-95 [online]. 27.02.2020 [Accessed: 02.03.2020]. (IQWiG-Berichte; Volume 885). URL: https://www.iqwig.de/download/A19-95_Avelumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Merck Serono, Pfizer Pharma. Avelumab (Bavencio): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 20.11.2019 [Accessed: 12.03.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/508/#dossier.

3. Merck Serono, Pfizer Pharma. Stellungnahme zum IQWiG-Bericht Nr. 885: Avelumab (Nierenzellkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-95. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/508/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35a Abs. 3 S. 2 SGB V; hier: Wirkstoff Avelumab (D-504); stenografisches Wortprotokoll [online]. 06.04.2020 [Accessed: 17.04.2020]. URL: https://www.g-ba.de/downloads/91-1031-508/2020-04-06_Wortprotokoll_Avelumab_D-504.pdf.