IQWiG Reports – Commission No. A20-34

Avelumab (metastatic Merkel cell carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Avelumab (metastasiertes Merkelzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2020). Please note: This document was translated by an external translator and 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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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

Medical and scientific advice

Due to the corona pandemic, no external experts were involved.

IQWiG employees involved in the dossier assessment

- Christina Braun
- Gertrud Egger
- Reza Fathollah-Nejad
- Klaus Gossens
- Katharina Hirsch
- Ulrike Lampert
- Sonja Schiller
- Volker Vervölgyi

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug avelumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 March 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of avelumab in comparison with the appropriate comparator therapy (ACT) in patients with metastatic Merkel cell carcinoma.

The specification of the ACT by the G-BA resulted in the research question presented in Table 2 below.

Table 2: Research questions of the benefit assessment of avelumab

Therapeutic indication	**ACT[a]**
Adults with metastatic Merkel cell carcinoma	Therapy upon the physician's discretion[b]
a. Presentation of ACT specified by the G-BA. b. Currently, avelumab is the only drug approved for metastatic Merkel cell carcinoma. The G-BA deems the off-label use of pembrolizumab or nivolumab an adequate implementation of the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The pharmaceutical company (hereinafter "company") designates a therapy upon the physician's discretion as the ACT and thereby follows the G-BA's specification. In the further discussion, the company chooses pembrolizumab as the implementation of the ACT, arguing that more evidence is available on this drug. This choice is adequate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

JAVELIN Merkel 200 study unsuitable for deriving an added benefit

No studies relevant for the present benefit assessment were found. Due to a lack of suitable comparative data, the 1-arm JAVELIN Merkel 200 study conducted by the company is unsuitable for assessing an added benefit of avelumab in comparison with the ACT in patients

with metastatic Merkel cell carcinoma. Therefore, no suitable data are available for the present benefit assessment. Consequently, there is no hint of added benefit of avelumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, the probability and extent of added benefit of the drug avelumab in comparison with the ACT are assessed as follows:

No suitable data are available for the assessment of the added benefit of avelumab. In adults with metastatic Merkel cell carcinoma, an added benefit of avelumab in comparison with the ACT is not proven.

Table 3 presents a summary of the probability and extent of added benefit of avelumab.

Table 3: Avelumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with metastatic Merkel cell carcinoma	Therapy upon the physician's discretion[b]	Added benefit not proven

a. Presentation of ACT specified by the G-BA.
b. Currently, avelumab is the only drug approved for metastatic Merkel cell carcinoma. The G-BA deems the off-label use of pembrolizumab or nivolumab an adequate implementation of the ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in the context of the market launch in 2018. Therein, the G-BA defined 2 subpopulations and found a non-quantifiable added benefit of avelumab both for patients without prior chemotherapy and for patients with at least 1 prior chemotherapy in the metastatic stage. However, in that assessment, the added benefit was considered to be proven by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report is to assess the added benefit of avelumab in comparison with the ACT in patients with metastatic Merkel cell carcinoma.

The specification of the ACT by the G-BA resulted in the research question presented in Table 4 below.

Table 4: Research questions of the benefit assessment of avelumab

Therapeutic indication	**ACT[a]**
Adults with metastatic Merkel cell carcinoma	Therapy upon the physician's discretion[b]
a. Presentation of ACT specified by the G-BA. b. Currently, avelumab is the only drug approved for metastatic Merkel cell carcinoma. The G-BA deems the off-label use of pembrolizumab or nivolumab an adequate implementation of the ACT [3]. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company designates therapy upon the physician's discretion as the ACT and thereby follows the G-BA's specification. In the further discussion, the company chooses pembrolizumab as the implementation of the ACT, arguing that more evidence is available on this drug. This choice is adequate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on avelumab (as of 14 January 2020)
- Bibliographic literature search on avelumab (most recent search on 14 January 2020)
- Search in trial registries / study results databases on avelumab (most recent search on 14 January 2020)
- Search on the G-BA website on avelumab (most recent search on 14 January 2020)
- Bibliographic literature search on the ACT (most recent search on 14 January 2020)
- Search in trial registries or results databases on the ACT (most recent search on 14 January 2020)
- Search on the G-BA website on the ACT (most recent search on 14 January 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on avelumab (most recent search on 7 April 2020)

- Search in trial registries on the ACT (most recent search on 7 April 2020)

Concurring with the company, the check of completeness of the study pool did not reveal any direct comparative randomized controlled trials with avelumab in comparison with the ACT.

In the absence of any comparative studies on avelumab in the therapeutic indication, the company presented the data from the ongoing 1-arm approval study JAVELIN Merkel 200 [4,5] and used it for its benefit assessment.

The results presented by the company are unsuitable for deriving an added benefit of avelumab. The reasons are explained below.

Study used by the company (JAVELIN Merkel 200)

The JAVELIN Merkel 200 study is an ongoing, 1-arm, open-label, multicentric phase II study. This study is the basis for the approval of avelumab as an orphan drug for treating metastatic Merkel cell carcinoma. The study has 2 parts. The two study parts differ in the characteristics of the included study participants: Patients who had already received ≥ 1 chemotherapy for metastatic Merkel cell carcinoma were included in study Part A, while those without prior systemic chemotherapy for metastatic disease were included in study Part B. Part A of the JAVELIN Merkel 200 study included 88 patients, while Part B included 116 patients.

In both study arms, patients received 10 mg avelumab per kg of body weight administered as an intravenous infusion over 60 minutes every 2 weeks. Avelumab was approved at a fixed dose of 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks [6]. Both dosing regimen result in a similar exposure to avelumab [7]. In 2016, in an effort to simplify the dosing regimen, the European Medicines Agency (EMA) changed the approval from weight-based dosing to a fixed-dose regimen [7]. Hence, avelumab treatment in the JAVELIN Merkel 200 study was in compliance with approval [6-8].

The primary outcome of the JAVELIN Merkel 200 study was best overall response in Part A and sustained response rate (sustained for ≥ 6 months) in Part B. Both outcomes were recorded using imaging procedures and assessed with the RECIST criteria (version 1.1).

The company used both parts of the JAVELIN Merkel 200 study for assessing an added benefit of avelumab. It did not present any comparative data regarding the ACT.

JAVELIN Merkel 200 study unsuitable for deriving an added benefit

The JAVELIN Merkel 200 study is unsuitable for deriving an added benefit. The reason is explained below:

In the present therapeutic indication, the 1-arm JAVELIN Merkel 200 study used by the company is generally suitable only for comparing individual arms from various studies. For the ACT, however, the company does not identify any suitable data. While the company found 2 publications on the 1-arm KEYNOTE-017 study, which included previously treatment-naive

patients with metastatic Merkel cell carcinoma and treated them with pembrolizumab [9,10], it reports that these publications lack data on the patient characteristics of extent of metastasis (number and type of affected organs), time since diagnosis of metastatic stage, presence of tumour-infiltrating lymphocytes, and prior therapies. The company argues that, for this reason, it is impossible to conclusively assess the comparability of the study populations. Therefore, the company foregoes the presentation of comparative data on the ACT on the basis of the KEYNOTE-017 study and describes only the results of the JAVELIN Merkel 200 study on avelumab.

The company's approach of excluding the KEYNOTE-017 study from the present benefit assessment is adequate since, due to the lack of information on the study population, the comparability of patient characteristics cannot be assessed. Irrespective thereof, any effects seen when comparing the two 1-arm studies would not be large enough to rule out an explanation based solely on systematic bias (see Module 4 A, Section 4.3.2.3.3 as well as Nghiem 2019 [9]). The company further asserts that, with regard to the direction of effect, disadvantages rather than advantages of avelumab in comparison with pembrolizumab tended to be shown for patient-relevant outcomes.

In summary, due to the lack of suitable comparative data, the JAVELIN Merkel 200 study is unsuitable for assessing an added benefit of avelumab in comparison with the ACT in patients with metastatic Merkel cell carcinoma. Therefore, no suitable data are available for the present benefit assessment.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of avelumab in comparison with the ACT. Consequently, there is no hint of added benefit of avelumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of avelumab. In adults with metastatic Merkel cell carcinoma, an added benefit of avelumab in comparison with the ACT is not proven.

Table 5 presents a summary of the result of the benefit assessment of avelumab in comparison with the ACT.

Table 5: Avelumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with metastatic Merkel cell carcinoma	Therapy upon the physician's discretion[b]	Added benefit not proven

a. Presentation of ACT specified by the G-BA.
b. Currently, avelumab is the only drug approved for metastatic Merkel cell carcinoma. The G-BA deems the off-label use of pembrolizumab or nivolumab an adequate implementation of the ACT [3].

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The above-described assessment deviates from that of the company, which derives a non-quantifiable added benefit of avelumab on the basis of the 1-arm study JAVELIN Merkel 200.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in the context of the market launch in 2018. Therein, the G-BA defined 2 subpopulations and found a non-quantifiable added benefit of avelumab both for patients without prior chemotherapy and for patients with at least 1 prior chemotherapy in the metastatic stage. However, in that assessment, the added benefit was considered to be proven by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Avelumab (Bewertung nach Aufhebung des Orphan Drug-Status: metastasiertes Merkelzellkarzinom); zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/540/#zweckmaessige-vergleichstherapie].

4. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016; 17(10): 1374-1385.

5. D'Angelo SP, Russell J, Lebbe C, Chmielowski B, Gambichler T, Grob JJ et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. JAMA Oncol 2018; 4(9): e180077.

6. Merck. Bavencio 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 09.2019 [Accessed: 31.03.2020]. URL: https://www.fachinfo.de/.

7. European Medicines Agency. Bavencio-H-C-004338-II-0009-G: EPAR; Assessment Report; variation [online]. 2019 [Accessed: 11.02.2020]. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/bavencio.

8. European Medicines Agency. Bavencio: European public assessment report [online]. 20.07.2017 [Accessed: 20.05.2020]. URL: https://www.ema.europa.eu/documents/assessment-report/bavencio-epar-public-assessment-report_en.pdf.

9. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019; 37(9): 693-702.

10. Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med 2016; 374(26): 2542-2552.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-34-avelumab-metastatic-merkel-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.13063.html.