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Pembrolizumab (urothelial carcinoma first-line treatment) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab (Urothelkarzinom Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse)* (Version 1.0; Status: 27 March 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CPS	combined positive score
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
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 pembrolizumab. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier on the drug to be evaluated as monotherapy in the first-line treatment of locally advanced or metastatic urothelial carcinoma in the originally approved therapeutic indication on 11 September 2017 for the early benefit assessment. On 2 August 2018, the G-BA now requested a new benefit assessment because of new scientific findings. This was based on the European Commission's decision of 6 July 2018 to restrict the approval, because an ongoing clinical study on pembrolizumab showed reduced survival in the first-line treatment of urothelial carcinoma in adults with low programmed cell death ligand 1 (PD-L1) expression. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 21 December 2018.

Research question

The aim of the present report was to assess the added benefit of pembrolizumab as monotherapy in comparison with chemotherapy specified by the physician as appropriate comparator therapy (ACT) for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

For the benefit assessment of pembrolizumab, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

As in the dossier on the originally approved therapeutic indication of the first-line treatment (corresponding dossier assessment A17-46), the company specified carboplatin + gemcitabine as the only relevant comparator therapy for the present research question. The company's choice of the ACT has no consequence for the present benefit assessment, because the presented data are not suitable for the assessment of an added benefit of pembrolizumab.

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

Results

As already done in the dossier of 11 September 2017, the company presented a comparison of individual arms from different studies, which was based on the still incomplete data situation, in its current dossier. The studies on carboplatin + gemcitabine identified by the company provided only few data on patient-relevant outcomes. The data situation is still unsuitable to derive an added benefit of pembrolizumab in comparison with the ACT in the therapeutic indication to be assessed. The preliminary results of the ongoing randomized controlled trial (RCT) KEYNOTE 361, which led to the restriction of the originally approved therapeutic indication, confirm this assessment. Informative results of the above RCT on all patient-relevant outcomes must be awaited for the benefit assessment.

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

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

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1		

The G-BA decides on the added benefit.

[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 the present report was to assess the added benefit of pembrolizumab as monotherapy in comparison with chemotherapy specified by the physician as ACT for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10.

For the benefit assessment of pembrolizumab, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT[a]**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

As in the dossier on the originally approved therapeutic indication of the first-line treatment [3] (corresponding dossier assessment A17-46 [4]), the company specified carboplatin + gemcitabine as the only relevant comparator therapy for the present research question. The company's choice of the ACT has no consequence for the present benefit assessment, because the presented data are not suitable for the assessment of an added benefit of pembrolizumab (see also Section 2.3).

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 lists on pembrolizumab (status: 1 November 2018)
- bibliographical literature search on pembrolizumab (last search on 5 October 2018)
- search in trial registries for studies on pembrolizumab (last search on 2 October 2018)
- bibliographical literature search on the ACT (last search on 5 October 2018)
- search in trial registries for studies on the ACT (last search on 2 October 2018)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 7 January 2019)

The check of the completeness of the study pool produced no suitable data for the assessment of the added benefit of pembrolizumab for the present research question.

The company presented a comparison of individual arms from different studies. However, this comparison was unsuitable to derive an added benefit of pembrolizumab in comparison with the ACT. This is explained below.

Study pool of the company

As in its dossier on the originally approved therapeutic indication of the first-line treatment, the company used no RCT on the direct comparison of pembrolizumab with the ACT for the current therapeutic indication. It claimed not to have identified any relevant RCTs. In its search, the company found an RCT in the current therapeutic indication, but excluded this RCT due to an unavailable results report (see information on the KEYNOTE 361 study below [5]). It therefore presented a comparison of individual arms from different studies on pembrolizumab versus carboplatin + gemcitabine.

The studies submitted by the company were the same as those submitted in its dossier of 11 September 2017. For pembrolizumab, this was the single-arm KEYNOTE 052 study [6,7]. For carboplatin + gemcitabine, these were the following 6 studies: Bellmunt 2001 [8], Carles 2000 [9], Linardou 2004 [10], De Santis 2012 [11,12], Sella 2012 [13], and Kim 2015 [14]. With the exception of De Santis 2012 (RCT) and Kim 2015 (retrospective comparator study), these were single-arm studies.

Detailed information on the characteristics of the studies mentioned above and information on the interventions can be found in the dossier assessment on the originally approved therapeutic indication of the first-line treatment (see Section 2.3.1 and Appendix A of dossier assessment A17-46 [4]). In accordance with the restriction of the therapeutic indication, in the current dossier, the company now presented data for patients whose tumours express PD-L1 with a CPS ≥ 10 for the study with pembrolizumab (KEYNOTE 052). A total of 370 patients were included in the study, of whom 110 patients had a tumour that expressed PD-L1 with a CPS ≥ 10 (relevant population for the present benefit assessment). According to the company, no data on PD-L1 expression were available for the studies with carboplatin + gemcitabine, so that it used the total population of the studies in each case.

Assessment of the evidence presented by the company

Lack of suitability of the data presented by the company for the derivation of an added benefit

For the outcome "overall survival", the company presented results on 3 data cut-offs (last data cut-off: 30 November 2017) for the KEYNOTE 052 study. Analogous to its procedure in the dossier of 11 September 2017, the company presented a comparison from the individual arms of the studies on pembrolizumab with those on carboplatin + gemcitabine. In addition, the

company performed a matching-adjusted indirect comparison (MAIC) for the current benefit assessment.

Irrespective of the fact that the company now also submitted a MAIC, the general criticism of the data situation for the derivation of the added benefit already described in dossier assessment A17-46 remains. Thus, the comparisons carried out by the company were based on the same incomplete data situation as described in detail in dossier assessment A17-46. The studies on carboplatin + gemcitabine identified by the company provided only few data on patient-relevant outcomes. The median overall survival in the population relevant for the present benefit assessment was 18.5 months in the KEYNOTE 052 study and 7.2 to 10 months in the comparator studies on carboplatin + gemcitabine. The effects presented by the company were not large enough to be able to exclude with sufficient certainty that differences were caused by bias alone. The data of an ongoing RCT in particular confirmed the assessment that the data presented by the company were unsuitable for the derivation of an added benefit.

New findings from an RCT in the therapeutic indication support the assessment on the lack of suitability of the data presented by the company

The KEYNOTE 361 study sponsored by the company is an ongoing RCT [5,15]. Among other aspects, the study investigates adult patients with advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. The study also compares pembrolizumab with carboplatin + gemcitabine. Preliminary data show reduced survival under pembrolizumab in comparison with carboplatin + gemcitabine in the first-line treatment for patients whose tumours express PD-L1 with a CPS < 10 [16]. Based on these preliminary data and following a recommendation by the European Medicines Agency (EMA), the European Commission restricted the approved therapeutic indication to patients whose tumours express PD-L1 with a CPS ≥ 10.

The preliminary data of the ongoing RCT KEYNOTE 361, which led to the restriction of the approval, confirm the assessment that the data presented by the company in its dossier were unsuitable for the derivation of the added benefit. The company cited the KEYNOTE 361 study in its study list in Module 4 A and enclosed the study protocol in Module 5. It did not elaborate further on the interim results on which a restriction of the approval was based – not even in Section 4.5.1 of Module 4 A, in which it justified the data it presented (see Section 2.7.9.2 of the full dossier assessment). In addition, the company did not provide any information as to when the first evaluations for the KEYNOTE 361 study are to be expected. According to the ClinicalTrials.gov registry, the estimated final data collection date for the primary outcome is already in June 2019, and the trial is planned to run until the end of May 2020 [5]. Informative results of the above RCT on all patient-relevant outcomes must be awaited for the benefit assessment.

Summary

As already done in the dossier of 11 September 2017, the company presented a comparison of individual arms from different studies in its current dossier. The data situation is still unsuitable

to derive an added benefit of pembrolizumab in comparison with the ACT in the therapeutic indication to be assessed. The preliminary results from the RCT KEYNOTE 361 confirm this assessment.

2.4 Results on added benefit

The company presented no suitable data for the derivation of an added benefit of pembrolizumab as monotherapy in the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 5.

Table 5: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10	Chemotherapy specified by the physician	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the data provided.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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.

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