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Pembrolizumab (MSI-H or dMMR biliary cancer) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (biliäres Karzinom mit MSI-H oder dMMR) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 October 2022). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ASC	active symptom control
BSC	best supportive care
dMMR	mismatch repair deficient
FGFR2	fibroblast growth factor receptor 2
FOLFOX	folinic acid, 5-fluorouracil, oxaliplatin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSI-H	microsatellite instability high
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 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 assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 25 July 2022.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) biliary cancer who have disease progression on or following at least 1 prior therapy

The research question presented in Table 2 is derived from the G-BA's specification of the ACT.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Adults with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy	Treatment of physician's choice[b]
a. Presented is the ACT specified by the G-BA. b. The following drug therapies are deemed suitable comparators in the context of a clinical trial: a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), pemigatinib (only for patients with FGFR2 fusion or rearrangement), BSC. BSC is defined as the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high	

Since best supportive care (BSC) was identified as the ACT in the original consultation request, the company chose BSC as the ACT. The company additionally reports operationalizing BSC as active symptom control (ASC) in combination with systemic antineoplastic therapy.

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

Study pool and study design

For pembrolizumab, the company included the single-arm KEYNOTE 158 study, which administered pembrolizumab to treatment-experienced patients with advanced (metastatic and/or unresectable) solid tumours. The company formed a subpopulation of 22 patients with biliary cancer and MSI-H.

On the ACT side, the company included the ABC-06 study. The ABC-06 study is an open-label randomized controlled trial (RCT) which allocated adult patients with unresectable or metastatic biliary cancer who had previously received cisplatin and gemcitabine first-line therapy to the study arms of ASC or ASC in combination with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX). No information is available on the study population's MSI-H or dMMR status. The company used only the ASC + FOLFOX arm (81 patients) for the indirect comparison.

For the benefit assessment, the company submitted a comparison of individual arms from the KEYNOTE 158 and ABC-06 studies.

Unsuitable comparison of individual arms from the KEYNOTE 158 and ABC-06 studies

The analyses presented by the company which compared individual arms from different studies are unsuitable for the benefit assessment. This is due, firstly, to the ABC-06 study's overall population not reflecting this benefit assessment's research question. According to this benefit assessment's research question, the added benefit of pembrolizumab in comparison with the ACT must be assessed in patients with biliary cancer with MSI-H or dMMR tumours. The ABC-06 study provides no information on the investigated patients' approval-justifying and potentially prognostic criterion of MSI-H or dMMR tumour status, and presumably, only a small proportion of ABC-06 participants' tumours exhibited this characteristic. Furthermore, ASC + FOLFOX does not represent all treatment options according to physician's choice. It is unclear whether participants in the ASC + FOLFOX arm would have received this therapy as treatment according to physician's choice. In addition, no information is available on ABC-06 and KEYNOTE 158 participants' fibroblast growth factor receptor 2 (FGFR2) status. Hence, the relevance of the treatment option of pemigatinib is unclear both for the ABC-06 study population and for the KEYNOTE 158 study's relevant subpopulation. Overall, on the basis of the available information, the ACT cannot be deemed implemented in the presented comparisons. Additionally, comparing different studies' individual arms does not represent an adequate method for an indirect comparison.

Overall, the data submitted by the company are unsuitable for assessing the benefit of pembrolizumab versus the ACT in patients with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy

Results on added benefit

Since no usable data are available for the benefit assessment, there is no hint of an added benefit of pembrolizumab 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]

Table 3 summarizes the probability and extent of added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The following drug therapies are deemed suitable comparators in the context of a clinical trial: a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), pemigatinib (only for patients with FGFR2 fusion or rearrangement), BSC. BSC is defined as the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability

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].

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy

The research question presented in Table 4 is derived from the G-BA's specification of the ACT.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Adults with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy	Treatment of physician's choice[b]
a. Presented is the ACT specified by the G-BA. b. The following drug therapies are deemed suitable comparators in the context of a clinical trial: a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), pemigatinib (only for patients with FGFR2 fusion or rearrangement), BSC. BSC is defined as the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability	

Since BSC was identified as the ACT in the original consultation request, the company chose BSC as the ACT. The company additionally reports operationalizing BSC as ASC in combination with systemic antineoplastic therapy. The company did not discuss the G-BA's current specification of the ACT. Section I 3 below describes the extent to which this approach affects the company's information retrieval and study pool. This assessment was conducted on the basis of the ACT specified by the G-BA.

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

I 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 pembrolizumab (status: 1 June 2022)
- bibliographical literature search on pembrolizumab (last search on 2 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 5 May 2022)
- search on the G-BA website for pembrolizumab (last search on 10 May 2022)
- bibliographical literature search on the ACT (last search on 2 May 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 2 May 2022)
- Search on the G-BA website for the ACT (most recent search on 10 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 18 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool found no RCT for the direct comparison of pembrolizumab in comparison with the ACT specified by the G-BA. In terms of RCTs, the restriction applied by the company to studies with BSC as the comparator therapy is therefore of no consequence for the completeness of the study pool.

Because it identified no RCTs for a direct comparison, the company conducted information retrieval for further studies.

On the intervention side, the company identified only the single-arm KEYNOTE 158 study [3]; this rendered impossible any adjusted indirect comparison using the common comparator of pembrolizumab versus the ACT. The company therefore presented comparisons of individual arms from the KEYNOTE 158 and ABC 06 studies [4].

Regarding the patient population, the company reports, for the information retrieval on other investigations, that it disregarded dMMR/MSI-H status in its study selection if it found no suitable study taking into account the dMMR/MSI-H status. Disregarding dMMR/MSI-H status in the study selection is inappropriate because this benefit assessment’s research question specifies for the added benefit of pembrolizumab versus the ACT to be assessed in patients with dMMR or MSI-H biliary cancer. The research question excludes patients whose tumour is neither dMMR nor MSI-H.

Furthermore, the company reports that where several studies of different evidence levels were found to be relevant, the company took into account only the studies of the highest evidence level and excluded all others via the criterion of study type. When comparing individual arms from different studies, however, this approach is inadequate. For instance, in the comparison of individual arms, single-arm studies are potentially of equal relevance as individual arms from RCTs. It is unclear whether the company's approach resulted in the exclusion of potentially relevant studies.

The company's information retrieval for the ACT is unsuitable for ensuring the completeness of the search results. This is due, in particular, to the following reason: The company uses only broad categories with very general search terms ("active symptom control"), researching solely BSC both in the bibliographic search as well as in the search of study registries. What would have been necessary, for instance, is an additional search for specific interventions used as BSC in the therapeutic indication in question. In addition, by selecting only the ACT of BSC (operationalized as ASC + systemic antineoplastic therapy), the company disregarded the other ACT options (FOLFOX and pemigatinib) in its information retrieval.

The check of the study pool's completeness on the intervention side identified no relevant study other than KEYNOTE 158. The study pool's completeness on the ACT side was skipped because, for patients in this therapeutic indication, the data submitted by the company are generally unsuitable for drawing any conclusions on the added benefit of pembrolizumab in comparison with the ACT. This is explained below.

Study pool of the company

Study with pembrolizumab: KEYNOTE 158

The KEYNOTE 158 study is an ongoing, single-arm study enrolling pretreated patients with advanced (metastatic and/or unresectable) solid tumours. Study participants receive pembrolizumab as per the SPC [5]. The following cohorts are potentially relevant for this benefit assessment:

- Cohort K: Any advanced tumour (except colorectal carcinoma) with MSI-H
- Cohort L: Any advanced tumour with dMMR/MSI-H in Chinese patients

The company formed a subpopulation of 22 patients with biliary cancer from Cohort K, while not providing any information on potentially relevant patients from Cohort L. However, information from the marketing authorization documents suggests that at the time of the benefit assessment, Cohort L included only 1 potentially relevant patient [6].

The company's dossier used results from the data cut-offs of 5 October 2020 (interim analysis XI) and 15 October 2021 (interim analysis XIII), which were both implemented for the submission of marketing authorization documents for colorectal cancer. No study report is available on the later data cut-off from 15 October 2021. According to the company, the data

cut-off was implemented for the predefined final analysis on 12 January 2022, but no corresponding study report is available at this time.

The primary outcome of the study was objective response rate. Additionally, outcomes were surveyed on mortality, morbidity, health-related quality of life, and side effects.

Study with the ACT: ABC-06

The ABC-06 study is an open-label RCT allocating adult patients with unresectable or metastatic biliary cancer who had already received cisplatin and gemcitabine first-line therapy to the study arms of ASC or ASC in combination with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX). No information is available on the study population's MSI-H or dMMR status. The study's primary outcome was overall survival. For the indirect comparison, the company used only the ASC + FOLFOX arm (81 patients).

Unsuitable comparison of individual arms from the KEYNOTE 158 and ABC-06 studies

Comparator side fails to reflect the research question's population

According to this benefit assessment's research question, the added benefit of pembrolizumab in comparison with the ACT is to be assessed in patients with MSI-H or dMMR biliary cancer. Patients whose tumours are neither MSI-H nor dMMR, in contrast, have been excluded from the research question. The ABC-06 study provides no information on the approval-justifying and potentially prognostic criterion of investigated patients' MSI-H or dMMR tumour status. Given that only about 4.2% to 8.3% of biliary cancer tumours are MSI-H/dMMR (see Sections II.1.3.1 and II.1.3.2 of the full benefit assessment), a similarly low percentage of ABC-06 participants' tumours presumably exhibited this characteristic. Hence, the ABC-06 study's total population does not reflect this benefit assessment's research question and is unsuitable for deriving added benefit.

Implementation of the ACT

The G-BA specified the ACT as treatment according to physician's choice, which is deemed to include the following treatment options as suitable comparators:

- FOLFOX
- pemigatinib (only for patients with FGFR2 fusion or rearrangement)
- BSC

The ABC-06 study administered ASC + FOLFOX or ASC alone to patients as randomized. It is unclear whether for all patients in the ASC + FOLFOX arm, this therapy also represents the ACT of treatment of physician's choice. In particular, no information is available on the patients' FGFR2 status; therefore, the relevance of the pemigatinib treatment option remains unclear for the ABC-06 study population.

The company likewise failed to submit data on KEYNOTE 158 participants to show that ASC + FOLFOX is a suitable option for these patients in line with treatment according to physician's choice. The company argues that FOLFOX is the standard treatment in the present therapeutic indication. The S3 guideline describes FOLFOX as an important option for second-line therapy, particularly based on the results of the ABC-06 study. However, the guidelines also discuss (a) other treatment options and (b) the importance of both the tumour's molecular characterization and targeted treatment options [7]. Since no information is available on patients' FGFR2 status, the relevance of the treatment option of pemigatinib in particular is unclear for the KEYNOTE 158 study's relevant subpopulation.

Methods used to compare individual arms from different studies

For the outcomes of all-cause mortality and objective response rate, the company submitted comparisons of individual arms from the KEYNOTE 158 and ABC-06 studies. For the outcomes of progression-free survival and severe adverse events, the company descriptively compared the results of the 2 studies, but it did not calculate an effect. The company presented the KEYNOTE 158 study's results on morbidity and health-related quality of life as supplementary information but did not derive any added benefit therefrom.

The comparisons of individual arms presented by the company represent comparisons lacking (a) a common comparator, (b) individual patient data on the comparator side, and (c) adjustment for potentially relevant effect modifiers or prognostic factors. Due to the lack of randomization, these comparisons are subject to inherent uncertainty and fail to represent an adequate method for an indirect comparison [1].

Summary

The ABC-06 study's total population departs from the benefit assessment's research question because the criterion of MSI-H or dMMR was disregarded. Likewise, the ABC-06 study inadequately represents the ACT. Additionally, comparing different studies' individual arms does not represent an adequate method for an indirect comparison. Overall, the data submitted by the company are unsuitable for assessing the benefit of pembrolizumab versus the ACT in patients with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy

I 4 Results on added benefit

No suitable data are available to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy. This results in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The company presented no suitable data to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy; hence, there is no proof of added benefit of pembrolizumab for these patients.

Table 5 summarizes the result of the assessment of added benefit of pembrolizumab in comparison with the ACT.

Table 5: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with unresectable or metastatic MSI-H or dMMR biliary cancer who have disease progression on or following at least 1 prior therapy	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The following drug therapies are deemed suitable comparators in the context of a clinical trial: a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), pemigatinib (only for patients with FGFR2 fusion or rearrangement), BSC. BSC is defined as the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficiency; FGFR2: fibroblast growth factor receptor 2; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability

The above assessment departs from that by the company, which overall derived a hint of non-quantifiable added benefit on the basis of the submitted comparisons of individual arms from the KEYNOTE 158 and ABC-06 studies.

The G-BA decides on the added benefit.

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 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T 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. https://dx.doi.org/10.1002/bimj.201300274.

3. Maio M, Ascierto PA, Manzyuk L et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022. https://dx.doi.org/10.1016/j.annonc.2022.05.519.

4. Lamarca A, Palmer DH, Wasan HS et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 2021; 22(5): 690-701. https://dx.doi.org/10.1016/S1470-2045(21)00027-9.

5. MSD. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2022 [Accessed: 24.08.2022]. URL: https://www.fachinfo.de.

6. European Medicines Agency. Keytruda; Assessment report [online]. 2022 [Accessed: 24.08.2022]. URL: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0109-epar-assessment-report-variation_en.pdf.

7. Leitlinienprogramm Onkologie. Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome; Langversion 3.0 [online]. 2022 [Accessed: 08.09.2022]. URL: https://www.leitlinienprogramm-onkologie.de/leitlinien/hcc-und-biliaere-karzinome/.

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