IQWiG Reports – Commission No. A22-78

Pembrolizumab (MSI-H or dMMR small intestine 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 (Dünndarmkarzinom 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
AGEO	Association des Gastroentérologues Oncologues (Association of Gastrointestinal Oncologists)
dMMR	mismatch repair deficient
FOLFIRI	5-fluorouracil + folinic acid + irinotecan
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 adults with unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) small intestine cancer who have disease progression on or following at least 1 prior therapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	ACT[a]
Adults with unresectable or metastatic MSI-H or dMMR small intestine 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. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: FOLFIRI, irinotecan, nab-paclitaxel, nivolumab ± ipilimumab as well as BSC alone. BSC 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.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

The company followed the G-BA's specification on the ACT.

The assessment is 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 27 patients with MSI-H small intestine cancer.

On the ACT side, the company included the Zaanan 2011 study. In this retrospective study, 28 patients were investigated who had received second-line therapy with 5-fluorouracil +

folinic acid + irinotecan (FOLFIRI). No information is available on the study population's MSI-H or dMMR status.

For the benefit assessment, the company submitted a comparison of individual arms from the KEYNOTE 158 and Zaanan 2011 studies.

Comparison of individual arms from the KEYNOTE 158 and Zaanan 2011 studies is unsuitable for the benefit assessment

The analyses on the comparison of individual arms of different studies presented by the company are not suitable for the benefit assessment. This is due, firstly, to the Zanaan 2011 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 is to be assessed in patients with MSI-H or dMMR small intestine cancer. The Zaanan 2011 study provides no information on the investigated patients' approval-justifying and potentially prognostic criterion of dMMR or MSI-H tumour status, and presumably, only a small proportion of Zaanan 2011 participants exhibited this characteristic. Furthermore, FOLFIRI does not represent all treatment options of physician's choice. Since the therapy of Zaanan 2011 participants was selected more than 10 years ago, when relevant comparator options such as nivolumab were not yet available, it is unclear whether FOLFIRI is currently the suitable ACT option for all patients. The company likewise failed to submit data on KEYNOTE 158 participants to show that FOLFIRI is a suitable option for these patients in line with treatment of physician's choice. Overall, on the basis of the available information, the ACT cannot be deemed implemented in the presented comparisons. Additionally, performing comparisons of individual arms from different studies fails to 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 small intestine cancer who have disease progression on or following at least 1 prior therapy

Results on added benefit

Because 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 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
Adults with unresectable or metastatic MSI-H or dMMR small intestine 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. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: FOLFIRI, irinotecan, nab-paclitaxel, nivolumab ± ipilimumab as well as BSC alone. BSC 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.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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 adults with unresectable or metastatic MSI-H or dMMR small intestine cancer who have disease progression on or following at least 1 prior therapy.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Adults with unresectable or metastatic MSI-H or dMMR small intestine 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. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: FOLFIRI, irinotecan, nab-paclitaxel, nivolumab ± ipilimumab as well as BSC alone. BSC 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.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

The company followed the G-BA's specification on the ACT.

The assessment is 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 3 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 18 May 2022)
- search on the G-BA website for pembrolizumab (last search on 18 May 2022)
- bibliographical literature search on the ACT (last search on 3 May 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 3 May 2022)
- search on the G-BA website for the ACT (last search on 18 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

Concurring with the company, the check of completeness of the study pool found no randomized controlled trials (RCTs) for the direct comparison of pembrolizumab versus the ACT specified by the G-BA.

Not having identified any RCTs for a direct comparison, the company conducted an 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 between individual arms from the KEYNOTE 158 and Zaanan 2011 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. It is inappropriate to disregard the dMMR/MSI-H status during the study selection because, according to the research question for this benefit assessment, the added benefit of pembrolizumab versus the ACT is assessed is patients with dMMR or MSI-H endometrial carcinoma. 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. In particular, this is due to the company disregarding best supportive care (BSC) as an ACT option both in the bibliographic search and in the search in study registries.

The check of the study pool's completeness on the intervention side identified no relevant study other than KEYNOTE 158. A check of 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 Summary of Product Characteristics [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 27 patients with small intestine 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 no potentially relevant patients with small intestine cancer [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), both of which were 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, this data cut-off was implemented for the predefined final analysis on 12 January 2022, but no corresponding study report is available at this time.

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

Study with the ACT: Zaanan 2011 (AGEO)

The Zaanan 2011 study is a retrospective study by the Association des Gastroentérologues Oncologues (AGEO) study group. This study group had previously already resorted to patient files to investigate 93 patients with locally advanced or metastatic adenocarcinoma of the small intestine who had received first-line chemotherapy with 5-fluorouracil and leucovorin alone or in combination with irinotecan, cisplatin, or oxaliplatin between November 1996 and February 2008 [7]. A total of 51 of these patients received second-line chemotherapy. The Zaanan 2011 study investigated a subpopulation of these patients who had received second-line FOLFIRI. No information is available on the study population's MSI-H or dMMR status. The goal of the study was to assess the efficacy and tolerability of second-line FOLFIRI therapy in patients with advanced adenocarcinoma of the small intestine. For the comparison of individual arms on the comparator side, the company used the data of the total population (28 patients) receiving FOLFIRI therapy from the Zaanan 2011 study. The company's Module 4D refers to this study as AGEO.

Comparison of individual arms from the KEYNOTE 158 and Zaanan 2011 studies is unsuitable for the benefit assessment

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 small intestine cancer. The research question excludes patients whose tumours are neither dMMR nor MSI-H. The Zaanan 2011 study provides no information on the approval-justifying and potentially prognostic criterion of the investigated patients' dMMR or MSI-H tumour status. Given that only about 5% to 33% of small intestine cancer tumours are MSI-H/dMMR (see Sections II.1.3.1 and II.1.3.2 of the full dossier assessment), a similarly low percentage of Zaanan 2011 participants' tumours presumably exhibited this characteristic. Hence, the Zaanan 2011 study's total population does not reflect this benefit assessment's research question and is unsuitable for deriving added benefit.

Implementation of the appropriate comparator therapy

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

- FOLFIRI
- irinotecan
- nab-paclitaxel
- nivolumab + ipilimumab
- BSC

The Zaanan 2011 study provides data on patients who received second-line FOLFIRI therapy before 2011. However, this is only one of the identified ACT options. Since Zaanan 2011

participants' therapy was selected more than 10 years ago, it is unclear whether FOLFIRI currently represents the suitable ACT option for all patients. This question is raised particularly by the fact that nivolumab was not yet available at that time.

The company likewise failed to submit data on KEYNOTE 158 participants to show that for these patients, FOLFIRI is a suitable option in terms of treatment of physician's choice. The current guideline on adenocarcinoma of the small intestine [8] lists FOLFIRI alongside several other treatment options, without assigning particular importance to any of them.

Overall, on the basis of the available information, the ACT cannot be deemed implemented in the presented comparisons.

Method of the comparison of individual arms of 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 Zaanan 2011 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) an adjustment for potentially relevant effect modifiers or prognostic factors. Due to the absence of randomization, these comparisons are subject to inherent uncertainty and fail to represent an adequate method for an indirect comparison [1].

Summary

The Zaanan 2011 study's total population departs from the benefit assessment's research question because it provided no information on MSI-H or dMMR. Likewise, the Zaanan 2011 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 small intestine 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 small intestine 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 has 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 small intestine 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 small intestine 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. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: FOLFIRI, irinotecan, nab-paclitaxel, nivolumab ± ipilimumab as well as BSC alone. BSC 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.

ACT: appropriate comparator therapy; BSC: best supportive care; dMMR: mismatch repair deficient; FOLFIRI: 5-fluorouracil + folinic acid + irinotecan; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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 Zaanan 2011 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.

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