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Pembrolizumab (MSI-H or dMMR endometrial carcinoma) –

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 (Endometriumkarzinom 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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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
dMMR	mismatch repair deficient
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)
SPC	Summary of Product Characteristics

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 this report is to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) for adult patients with advanced or recurrent microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation.

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]
Adult patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation	Treatment of physician's choice[b]

a. Presented is the ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in a clinical trial in connection with treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include repeat platinum-based treatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), or BSC alone. 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; 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 94 patients with

MSI-H endometrial carcinoma and disease progression on or following prior treatment with a platinum-based therapy

On the ACT side, the company included the randomized controlled trial (RCT) KEYNOTE 775, which enrolled adult patients with advanced or recurrent endometrial carcinoma and disease progression following prior systemic, platinum-based chemotherapy. Patients received either pembrolizumab + lenvatinib or treatment of physician's choice, selecting from doxorubicin or paclitaxel. For the indirect comparison, the company used the subpopulation of patients with dMMR in the doxorubicin or paclitaxel arm (N = 65).

For the benefit assessment, the company submitted a comparison of individual arms from the KEYNOTE 158 and KEYNOTE 775 studies.

The company's study pool is incomplete because, on the intervention side, it included only the KEYNOTE 158 study, disregarding the NCT02899793 study, which enrolled 24 patients with dMMR and/or MSI-H endometrial carcinoma and recurrence or progression following at least 1 prior chemotherapy who were treated with pembrolizumab.

Comparisons of individual arms from the KEYNOTE 158 and KEYNOTE 775 studies are unsuitable for the benefit assessment

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 KEYNOTE 775 study, which the company used on the comparator side, offering the 2 treatment options of doxorubicin or paclitaxel and thereby not adequately reflecting the ACT. Based on the available data, it cannot be conclusively determined whether these 2 treatment options represent treatment of physician's choice for the relevant subpopulation of the KEYNOTE 775 study. Additionally, comparing different studies' individual arms does not represent an adequate method for an indirect comparison.

Overall, the data presented by the company are unsuitable for the benefit assessment of pembrolizumab in comparison with the ACT for patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy at any stage of disease and who are not candidates for curative surgery or radiation.

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 added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in a clinical trial in connection with treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include repeat platinum-based treatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), or BSC alone. 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; 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 this report is to assess the added benefit of pembrolizumab in comparison with the ACT for adult patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation.

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]
Adult patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation	Treatment of physician's choice[b]

a. Presented is the ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in a clinical trial in connection with treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include repeat platinum-based treatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), or BSC alone. 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; 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 10 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 3 May 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 10 May 2022)
- search on the G-BA website for the ACT (last 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

Concurring with the company, the check of completeness of the study pool found no 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. On the comparator side, the company found the KEYNOTE 775 study [4] and presents comparisons of individual arms of the KEYNOTE 158 and KEYNOTE 775 studies.

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 to be assessed in patients with dMMR or MSI-H endometrial carcinoma. The research question excludes patients whose tumour is neither dMMR nor MSI-H. In the present benefit assessment, the company's approach remains without consequence because it used studies and subpopulations taking into account dMMR/MSI-H status.

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 comparisons 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 information retrieval for the ACT is unsuitable for ensuring the completeness of the search results. The reasons are as follows: To identify relevant other investigations, the company conducted bibliographic searches and searches in study registries on the ACT. In the process, the company tightly restricted the searches by linking search blocks on the indication and on dMMR/MSI-H status. This approach fails to ensure that all studies pertaining to the therapeutic indication and being of potential relevance for the benefit assessment are found. For instance, the registry entry on the NCT02899793 study [5] was missed with this approach, and the same applies to the publications on the KEYNOTE 775 study in bibliographic databases. The company reports that these publications were found by a scoping search, but further information on the detailed procedure is missing.

The check of the study pool's completeness on the intervention side identified the KEYNOTE 158 study as well as the NCT02899793 study (see section below). The study pool's completeness on the ACT side was skipped because, for patients with 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 (SPC) [6]. The following cohorts are potentially relevant for this benefit assessment:

- Cohort D: endometrial carcinoma
- 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 94 patients with MSI-H endometrial carcinoma and progression of disease on or following prior treatment with a platinum-based therapy from Cohorts D and 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 few if any potentially relevant patients [7].

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, 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.

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: KEYNOTE 775

The KEYNOTE 775 study is a randomized, active control, open-label study comparing pembrolizumab + lenvatinib versus treatment of physician's choice, selecting from doxorubicin and paclitaxel. The study included adult patients with advanced or recurrent endometrial carcinoma and disease progression following prior systemic, platinum-based chemotherapy. For the indirect comparison, the company used the subpopulation of patients with dMMR in the doxorubicin or paclitaxel arm (N = 65). The data used by the company are from the Makker 2022 publication [4] and the congress contribution Makker 2021 [8], which is not publicly available.

Incomplete study pool of the company

The check of the study pool's completeness on the intervention side identified the KEYNOTE 158 study as well as the NCT02899793 study [5]. The company excluded the NCT02899793 study, reasoning that the population criterion was not met. The total population of the NCT02899793 study consists of 24 patients with dMMR and/or MSI-H endometrial carcinoma and recurrence or progression following at least 1 prior chemotherapy. The patients received pembrolizumab in line with the SPC [6]. All patients had previously received platinum-based therapy. Therefore, excluding this study is not reasonable.

Comparison of individual arms from the KEYNOTE 158 and KEYNOTE 775 studies is unsuitable for the benefit assessment

Implementation of the ACT

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

- Endocrine therapy:
  - medroxyprogesterone acetate
  - megestrol acetate
- Systemic chemotherapy, potentially including repeat platinum-based treatment:
  - cisplatin (monotherapy or in combination with doxorubicin)
  - doxorubicin (monotherapy or in combination with cisplatin)

- carboplatin in combination with paclitaxel
- paclitaxel (monotherapy)

- Best supportive care (BSC)

As part of dossier assessment A21-164 [9], the KEYNOTE 775 study was used for the direct comparison of pembrolizumab + lenvatinib in comparison with treatment of physician's choice for patients for whom doxorubicin or paclitaxel is the suitable treatment of physician's choice. For this purpose, a review was conducted to determine the extent to which ACT options other than doxorubicin and paclitaxel represent suitable treatments of physician's choice for the included patients. The present dossier assessment should therefore include a corresponding check for the employed KEYNOTE 775 subpopulation, which represents a small group, at only 16% of the control arm. However, insufficient information is available to perform such a check. Because no information on the platinum-free interval is available, it is unclear, in particular, whether repeat platinum-based therapy represents an option for patients. The implementation of the ACT, i.e. treatment of physician's choice, cannot be conclusively evaluated based on the data presented by the company on the KEYNOTE 775 subpopulation.

Methods used to compare individual arms from different studies

For the outcomes of all-cause mortality and objective response rate, the company submitted an indirect comparison of individual arms from the KEYNOTE 158 and KEYNOTE 775 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 naive 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]. In addition, in the present scenario of indirect comparison without a common comparator, the identified effects might potentially result solely from systematic bias due to confounders.

Summary

The company's study pool is incomplete, and no data are available to show that the KEYNOTE 775 study adequately reflects the ACT. Additionally, performing comparisons of individual arms from different studies fails to represent an adequate method for an indirect comparison. Overall, the data presented by the company are unsuitable for the benefit assessment of pembrolizumab in comparison with the ACT for patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy at any stage of disease and who are not candidates for curative surgery or radiation.

I 4 Results on added benefit

Overall, the data presented by the company for the benefit assessment of pembrolizumab in comparison with the ACT for patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation. 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 advanced or recurrent MSI-H or dMMR small endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation; 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**
Adult patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-based therapy at any stage of disease and who are not candidates for curative surgery or radiation	Treatment of physician's choice[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in a clinical trial in connection with treatment of physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include repeat platinum-based treatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), or BSC alone. 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; 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 KEYNOTE 775 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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