Pembrolizumab (endometrial cancer, first-line treatment)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Pembrolizumab (Endometriumkarzinom, Erstlinientherapie) – Nutzenbewertung gemäß § 35a SGB V*. 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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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 of persons concerned was received within 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 deficiency
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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	high-frequency microsatellite instability
pMMR	mismatch repair proficiency
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
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 (in combination with carboplatin and paclitaxel). 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 14 November 2024.

Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer for whom systemic therapy is an option.

Table 2: Research questions of the benefit assessment of pembrolizumab in combination with carboplatin and paclitaxel

Research question	Therapeutic indication	ACT[a]
1	First-line treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy[b]	Dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy
2	First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer and who are candidates for systemic therapy[b]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab with olaparib

a. Presented is the respective ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; pMMR: mismatch repair proficiency

On 26 November 2024, the G-BA adjusted the ACT after submission of the dossier by the company (14 November 2024). The ACT previously defined by the G-BA (consented on 8 November 2022) was a systemic chemotherapy of physician's choice, which referred to the entire patient population in the present therapeutic indication in only one research question.

The company stated that it would follow the originally defined ACT of the G-BA and chose cisplatin in combination with paclitaxel as the ACT. Accordingly, the company only addresses one research question in the dossier and does not divide the patient population into patients with mismatch repair deficiency (dMMR) or high-frequency microsatellite instability (MSI-H)

endometrial cancer (research question 1) and patients with mismatch repair proficiency (pMMR) endometrial cancer (research question 2). The present assessment is carried out in comparison with the G-BA's current ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit.

Results

The check for completeness of the study pool revealed no relevant studies on the comparison of pembrolizumab in combination with carboplatin and paclitaxel versus the ACT specified by the G-BA, neither for research question 1 nor for research question 2.

The KEYNOTE 868 study included by the company is not suitable for the assessment of the added benefit of pembrolizumab in combination with carboplatin and paclitaxel in both research questions, as the ACT of the G-BA was not implemented. This is justified below.

Evidence presented by the company – KEYNOTE 868 study

The KEYNOTE 868 study is an ongoing double-blind RCT comparing pembrolizumab in combination with carboplatin and paclitaxel with placebo in combination with carboplatin and paclitaxel.

The study included adult patients with a histologically confirmed diagnosis of advanced endometrial cancer (stage III, IVA or IVB) or recurrent endometrial cancer of all histologies (except carcinosarcoma) and regardless of MMR status. Patients were not allowed to have received any previous systemic therapy for the treatment of the endometrial cancer; previous chemotherapy was only permitted in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if the chemotherapy-free interval prior to randomization was at least 12 months. Hormonal therapy for the treatment of endometrial cancer had to be completed at least 3 weeks before randomization, radiotherapy at least 4 weeks before randomization. Further inclusion criteria were an immunohistochemical determination of the MMR status and an Eastern Cooperative Oncology Group-Performance Status (ECOG PS) of ≤ 2.

A total of 819 patients with endometrial cancer were randomized in a 1:1 ratio stratified by the characteristics presence of dMMR (yes vs. no), ECOG PS (0 or 1 vs. 2) and prior chemotherapy (yes vs. no). Module 4 A of the dossier shows that 223 (27%) patients had dMMR and 586 (72%) patients had pMMR. In 10 (1%) patients, the MMR status was missing or could not be determined.

After randomization, the KEYNOTE 868 study was divided into a combination phase, a maintenance phase and a 5-year follow-up. In the combination phase, patients received

carboplatin and paclitaxel in combination with pembrolizumab or placebo for 6 cycles. In the subsequent maintenance phase, pembrolizumab or placebo was administered for up to 14 further cycles. Patients with stable disease or with a partial response according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, and measurable disease at the end of cycle 6 were allowed to continue treatment with carboplatin and paclitaxel (in combination with pembrolizumab or placebo) for up to 10 cycles at the investigator's discretion.

Patients were treated until disease progression, the occurrence of unacceptable toxicity, withdrawal of consent, treatment discontinuation due to a decision by the physician or up to a maximum of 20 cycles (corresponds to up to approx. 24 months).

ACT specified by the G-BA not implemented

In the first-line treatment of patients with primary advanced or recurrent dMMR or MSI-H (research question 1) endometrial cancer, the G-BA defined dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy, as an ACT. For patients with pMMR (research question 2), the G-BA determined durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab in combination with olaparib, as ACT. None of the two treatment regimens was investigated in the control arm of KEYNOTE 868. As the ACT has thus not been implemented for either of the 2 research questions, the KEYNOTE 868 study is not suitable for the assessment of the added benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with the G-BA's ACT in both research questions.

Results on added benefit

As no suitable data are available for either research question of the benefit assessment, there is no hint of added benefit of pembrolizumab in combination with carboplatin and paclitaxel 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 in combination with carboplatin and paclitaxel versus the ACT.

[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].

Table 3: Pembrolizumab in combination with carboplatin and paclitaxel – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	First-line treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy[b]	Dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy	Added benefit not proven
2	First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer and who are candidates for systemic therapy[b]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab with olaparib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; pMMR: mismatch repair proficiency

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with the ACT for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer for whom systemic therapy is an option.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab in combination with carboplatin and paclitaxel

Research question	Therapeutic indication	ACT[a]
1	First-line treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy[b]	Dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy
2	First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer and who are candidates for systemic therapy[b]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab with olaparib

a. Presented is the respective ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; pMMR: mismatch repair proficiency

On 26 November 2024, the G-BA adjusted the ACT after submission of the dossier by the company (14 November 2024) as shown in Table 4. The ACT previously defined by the G-BA (consented on 8 November 2022) was a systemic chemotherapy of physician's choice, which referred to the entire patient population in the present therapeutic indication in only one research question.

The company stated that it would follow the originally defined ACT of the G-BA and chose cisplatin in combination with paclitaxel as the ACT. Accordingly, the company only addresses one research question in the dossier and does not divide the patient population into patients with dMMR or MSI-H endometrial cancer (research question 1) and patients with pMMR endometrial cancer (research question 2). The present assessment was carried out in comparison with the current ACT specified by the G-BA (see Table 4).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

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: 25 September 2024)
- bibliographical literature search on pembrolizumab (last search on 4 September 2024)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 04 September 2024)
- search on the G-BA website for pembrolizumab (last search on 4 September 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 25 November 2024); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies on the comparison of pembrolizumab in combination with carboplatin and paclitaxel versus the ACT specified by the G-BA, neither for research question 1 nor for research question 2.

This deviates from the assessment of the company, whose information retrieval identified the KEYNOTE 868 study [3] and included it in its study pool.

The KEYNOTE 868 study included by the company is not suitable for the assessment of the added benefit of pembrolizumab in combination with carboplatin and paclitaxel in both research questions, as the ACT of the G-BA was not implemented. This is justified below.

Evidence presented by the company – KEYNOTE 868 study

The KEYNOTE 868 study is an ongoing double-blind RCT comparing pembrolizumab in combination with carboplatin and paclitaxel with placebo in combination with carboplatin and paclitaxel. The study included adult patients with a histologically confirmed diagnosis of advanced endometrial cancer (stage III, IVA or IVB) or recurrent endometrial cancer of all histologies (except carcinosarcoma) and regardless of MMR status. Patients were not allowed to have received any previous systemic therapy for the treatment of the endometrial cancer; previous chemotherapy was only permitted in the adjuvant setting. Patients who had received prior adjuvant chemotherapy (alone or as combined radiochemotherapy) were eligible if the chemotherapy-free interval prior to randomization was at least 12 months. Hormonal therapy for the treatment of endometrial cancer had to be completed at least 3 weeks before randomization, radiotherapy at least 4 weeks before randomization. Further inclusion criteria were an immunohistochemical determination of the MMR status and an ECOG PS of ≤ 2.

A total of 819 patients with endometrial cancer were randomized in a 1:1 ratio stratified by the characteristics presence of dMMR (yes vs. no), ECOG PS (0 or 1 vs. 2) and prior chemotherapy (yes vs. no). Module 4 A of the dossier shows that 223 (27%) patients had dMMR and 586 (72%) patients had pMMR. In 10 (1%) patients, the MMR status was missing or could not be determined.

After randomization, the KEYNOTE 868 study was divided into a combination phase, a maintenance phase and a 5-year follow-up. In the combination phase, patients received carboplatin and paclitaxel in combination with pembrolizumab or placebo for 6 cycles. In the subsequent maintenance phase, pembrolizumab or placebo was administered for up to 14 further cycles. Patients with stable disease or with a partial response according to RECIST, version 1.1, and measurable disease at the end of cycle 6 were allowed to continue treatment with carboplatin and paclitaxel (in combination with pembrolizumab or placebo) for up to 10 cycles at the investigator's discretion.

Patients were treated until disease progression, the occurrence of unacceptable toxicity, withdrawal of consent, treatment discontinuation due to a decision by the physician or up to a maximum of 20 cycles (corresponds to up to approx. 24 months).

Primary outcome of the KEYNOTE 868 study was progression-free survival (PFS); secondary outcomes included overall survival as well as outcomes on morbidity, health-related quality of life and side effects.

ACT specified by the G-BA not implemented

In the first-line treatment of patients with primary advanced or recurrent dMMR or MSI-H (research question 1) endometrial cancer, the G-BA defined dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy, as an ACT. For patients with pMMR (research question 2), the G-BA determined durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab in combination with olaparib, as ACT. None of the two treatment regimens was investigated in the control arm of the KEYNOTE 868 study. As the ACT has thus not been implemented for either of the 2 research questions, the KEYNOTE 868 study is not suitable for the assessment of the added benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with the G-BA's ACT in both research questions.

I 4 Results on added benefit

There are no suitable data available for the assessment of the added benefit of pembrolizumab in combination with carboplatin and paclitaxel compared with the ACT for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer for whom systemic therapy is an option. There is no hint of added benefit of pembrolizumab in combination with carboplatin and paclitaxel comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of pembrolizumab in combination with carboplatin and paclitaxel versus the ACT.

Table 5: Pembrolizumab in combination with carboplatin and paclitaxel – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	First-line treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy[b]	Dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy	Added benefit not proven
2	First-line treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer and who are candidates for systemic therapy[b]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab with olaparib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; pMMR: mismatch repair proficiency

The assessment described above departs from that by the company, which derived a hint of non-quantifiable, but at least minor added benefit for the total population of the present therapeutic indication.

The G-BA decides on the added benefit.

I 6 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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