IQWiG Reports – Commission No. A21-164

Pembrolizumab (endometrial carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (Endometriumkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 15 June 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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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module 24
ESGO	European Society of Gynaecological Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
MMR	mismatch repair
MMRM	mixed model repeated measurement
PD-1	programmed cell death protein 1
PD-L1	programmed-death-ligand-1
pMMR	proficient mismatch repair
PRO	patient reported outcome
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The 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 December 2021.

Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with lenvatinib (hereinafter referred to as "pembrolizumab + lenvatinib") in comparison with therapy according to physician's choice as the appropriate comparator therapy (ACT) for adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them.

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

Table 2: Research questions of the benefit assessment of pembrolizumab + lenvatinib

Therapeutic indication	**ACT**[a]
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them	Therapy according to 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 connection with therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), and BSC alone. BSC refers to 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; G-BA: Federal Joint Committee

On 7 December 2021, a few days before the dossier was received on 10 December 2021, the G-BA adjusted the ACT as shown in Table 2. As a consequence of this adjustment, paclitaxel monotherapy was added as another treatment option in the comments (see Table 2). The present benefit assessment is based on the adjusted ACT.

The company implemented the ACT in that it designated therapy according to physician's choice as the ACT. However, on the basis of the originally designated ACT and due to its high

therapeutic importance, the company restricted the selection to the treatment option of doxorubicin. This remains without consequence for the identification of relevant studies because the company did not limit its information retrieval to specific treatment options, and the check of completeness of the study pool identified no relevant studies other than the KEYNOTE 775/309 study presented by the company.

However, the company explains that paclitaxel monotherapy (not an ACT option originally included by the G-BA) represents an important treatment option in the therapeutic indication, whereas endocrine therapy and platinum-based retreatment play only a minor role. The company then cites the benefit assessment procedure on dostarlimab, which resulted in the adjustment of the ACT in accordance with Table 2. In the company's view, adding the treatment option of paclitaxel monotherapy leads to the KEYNOTE 775/309 study's total population being relevant for the benefit assessment, rather than only the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment. Due to the ACT having been adjusted only briefly before dossier submission, however, it was reportedly not possible to adapt the dossier, but the results for the total population are presented in Appendix 4G.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit.

Study pool and study design

The benefit assessment uses the randomized, active-control, open-label study KEYNOTE 775/309. This study compared pembrolizumab + lenvatinib with therapy according to investigator's choice, consisting of either doxorubicin or paclitaxel. Therefore, the total population of the study is relevant for the benefit assessment.

The KEYNOTE 775/309 study enrolled adult patients with advanced or recurrent endometrial cancer and disease progression following prior treatment with systemic, platinum-based chemotherapy. However, the approved therapeutic indication also includes patients whose disease progression occurred during prior platinum-based therapy. At study enrolment, patients had to be in good general health corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 and exhibit adequate organ function. A total of 827 patients were enrolled. Based on criteria not further specified, the investigator made a pre-randomization choice between the 2 options (doxorubicin or paclitaxel) to be used for therapy according to investigator's choice in the event the patient was allocated to the comparator arm. Patients were then randomized at a 1:1 ratio to either pembrolizumab + lenvatinib treatment (N = 411) or therapy according to investigator's choice (N = 416, of which N = 307 doxorubicin and N = 109 paclitaxel).

Pembrolizumab and lenvatinib treatment in the intervention arm as well as doxorubicin treatment in the comparator arm were administered largely in compliance with the Summaries of Product Characteristics (SPCs).

Paclitaxel is not approved in the therapeutic indication. The KEYNOTE 775/309 study administered paclitaxel in a 28-day cycle on Days 1, 8, 15 at a dose of 80 mg/m² body surface area (BSA), with a subsequent pause on Day 22. The S3 Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer provides no information on the paclitaxel dosage in the present therapeutic indication. The European guideline issued by the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) discusses weekly paclitaxel administration as second-line therapy for patients with recurrent disease, but without providing any information on dosage. Therefore, it is unclear to what extent the paclitaxel dosage used in the study, which provides for a break on Day 22 of a 28-day cycle, reflects clinical practice in Germany.

Co-primary outcomes of the KEYNOTE 775/309 study were overall survival and progression-free survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and adverse events (AEs).

Implementation of the ACT

Therapy according to investigator's choice selecting from doxorubicin or paclitaxel, as used in the KEYNOTE 775/309 study, is deemed a sufficient implementation of the ACT. For the enrolled patients, ACT options other than doxorubicin and paclitaxel (hormone therapies, platinum-based retreatment, or best supportive care [BSC]) tend to represent treatment options of lesser importance. Hence, the total population of the KEYNOTE 775/309 study is relevant for the benefit assessment. However, the study allows drawing conclusions on the added benefit of pembrolizumab + lenvatinib only for patients for whom doxorubicin or paclitaxel represents the suitable therapy according to physician's choice. In patients for whom a treatment option other than doxorubicin or paclitaxel represents the suitable therapy according to physician's choice, no conclusions on added benefit can be drawn based on the KEYNOTE 775/309 study.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 775/309 study. The outcome-specific risk of bias was rated as low for the results of the outcome of overall survival and as high for the results of all other patient-relevant outcomes for which usable data were available.

Results

Mortality

Overall survival

For the outcome of overall survival, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. This results in an indication of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module 24 [EORTC QLQ-EN24])

Symptoms outcomes were recorded using the EORTC QLQ-C30 and EORTC QLQ-EN24. In each case, the analyses with a mixed model repeated measurement (MMRM) were analysed.

Pain, insomnia (EORTC QLQ-C30), gastrointestinal symptoms, back/pelvis pain (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the EORTC QLQ-C30 pain and insomnia scales or for the EORTC QLQ-EN24 back/pelvis pain scale. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, constipation (EORTC QLQ-C30), urological symptoms (EORTC QLQ-EN24)

For each of the EORTC QLQ-C30 scales of fatigue, nausea and vomiting, and constipation as well as for the EORTC QLQ-EN24 scale of urological symptoms, there is a statistically significant difference in favour of pembrolizumab + lenvatinib. The standardized mean difference (SMD) in the form of Hedges' g was used to check the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of -0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. In each case, this results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven for any of them.

Appetite loss (EORTC QLQ-C30), muscle pain (EORTC QLQ-EN24)

For the EORTC QLQ-C30 scale of appetite loss and the EORTC QLQ-EN24 scale of muscle pain, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range

of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Dyspnoea (EORTC QLQ-C30), lymphoedema, tingling/numbness, taste change (EORTC QLQ-EN24)

For the EORTC QLQ-C30 dyspnoea scale as well as the EORTC QLQ-EN24 scales of lymphoedema, tingling/numbness, and taste change, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For each of them, this results in a hint of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Diarrhoea (EORTC QLQ-C30)

For the EORTC QLQ-C30 diarrhoea scale, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. This results in a hint of lesser benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Sexual/vaginal problems (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual/vaginal problems because only 18.4% of patients were included in the analysis. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Hair loss (EORTC QLQ-EN24)

For the EORTC QLQ-EN24 hair loss scale, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For the outcome of hair loss, the curves of mean change over time from baseline show an immediate increase in symptoms in the comparator group and almost no change in the intervention group. Coupled with the size of the observed effect and the associated 95% CI, this results in an indication of added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Health status (EQ-5D visual analogue scale [VAS])

The MMRM analyses were evaluated for the outcome of health status recorded with the EQ-5D VAS. A statistically significant difference was found in favour of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

Health-related quality of life outcomes were recorded using the EORTC QLQ-C30 and EORTC QLQ-EN24. The MMRM analyses were evaluated in each case.

Global health status, physical functioning, role functioning, cognitive functioning (EORTC QLQ-C30), sexual interest, sexual activity (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was shown for any of the following scales: EORTC QLQ-C30 global health status, physical functioning, role functioning, and cognitive functioning or EORTC QLQ-EN24 sexual interest and sexual activity. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Emotional functioning, social functioning (EORTC QLQ-C30)

For each of the EORTC QLQ-C30 scales of emotional functioning and social functioning, there is a statistically significant difference in favour of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Sexual enjoyment (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual enjoyment because only 18.2% of patients were included in the analysis. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Body image problems (EORTC QLQ-EN24)

For the scale of body image problems, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. This results in a

hint of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Side effects

Serious adverse events (SAEs), discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. For each of them, this results in a hint of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Severe AEs

There was no statistically significant difference between treatment groups for the outcome of severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs and severe AEs, hypertension (severe AEs)

For each of the outcomes of immune-related SAEs and severe AEs as well as hypertension (severe AEs), there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The evaluation of the Kaplan-Meier curves for the outcomes of immune-related SAEs and severe AEs as well as hypertension (severe AEs) shows an immediate decrease in the intervention group curve and an almost event-free, constant course of the comparator group curve. In conjunction with the size of the observed effect and the associated 95% CI, this results in an indication of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel, for each of them.

Bleeding

No usable data were available for the outcome of bleeding. This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Cardiotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of cardiotoxicity (severe AEs). This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Headache (AEs), urinary tract infection (SAEs), gastrointestinal disorders (severe AEs), hepatobiliary disorders (severe AEs), lipase increased (severe AEs), weight decreased (severe AEs), metabolic and nutritional disorders (severe AEs), musculoskeletal and connective tissue disorders (severe AEs), proteinuria (severe AEs), palmar-plantar erythrodysaesthesia syndrome (severe AEs)

For each of the outcomes of headaches (AEs), urinary tract infection (SAEs), gastrointestinal disorders (severe AEs), hepatobiliary disorders (severe AEs), lipase increased (severe AEs), weight decreased (severe AEs), metabolic and nutritional disorders (severe AEs), musculoskeletal and connective tissue disorders (severe AEs), proteinuria (severe AEs), and palmar-plantar erythrodysaesthesia syndrome (severe AEs), there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. For each of them, this results in a hint of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Alopecia (AEs), blood and lymphatic system disorders (severe AEs*)*

For each of the outcomes of alopecia (AEs) and blood and lymphatic system disorders (severe AEs), there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The Kaplan-Meier curves for the outcomes of alopecia (AEs) and blood and lymphatic system disorders (severe AEs) show an immediate decrease in the comparator group curve and an almost event-free, constant course of the intervention group curve. In conjunction with the size of the observed effect and the associated 95% CI, this results in an indication of lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel, for each of them.

Respiratory, thoracic, and mediastinal disorders (severe AEs)

For the outcome of respiratory, thoracic, and mediastinal disorders (severe AEs), there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. This results in a hint of lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

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

On the basis of the results presented, the probability and extent of added benefit of the drug pembrolizumab + lenvatinib compared with the ACT are assessed as follows:

[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).

Overall, both favourable and unfavourable effects were found, with probabilities of hint or indication and showing various extents.

The key aspect for the derivation of added benefit is the indication of major added benefit of pembrolizumab + lenvatinib compared to the ACT which was found for overall survival.

Regarding symptoms and health-related quality of life, favourable effects of pembrolizumab + lenvatinib predominate. Additionally, an indication of lesser harm of major extent was found in the outcome category of serious/severe side effects for the outcome of blood and lymphatic system disorders (severe AEs).

Unfavourable effects, on the other hand, were found particularly in the category of serious/severe side effects, including hints of greater harm of considerable extent for the outcome of SAEs and several specific AEs as well as indications of greater harm of major extent for the outcomes of immune-related SAEs, immune-related severe AEs, and hypertension (severe AEs). The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened follow-up until treatment end (plus 4 cycle lengths or 30 or 120 days).

In summary, there is an indication of considerable added benefit of pembrolizumab + lenvatinib versus the ACT for adult patients with advanced or recurrent endometrial cancer whose disease has progressed on or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them and for whom doxorubicin or paclitaxel is the suitable therapy according to physician's choice.

No added benefit is proven for patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy according to physician's choice.

Table 3 shows a summary of the probability and extent of added benefit of pembrolizumab + lenvatinib.

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 + lenvatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them	Therapy according to physician's choice[b]	Patients for whom doxorubicin or paclitaxel is the suitable therapy according to physician's choice: indication of considerable added benefit[c]
		Patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy according to physician's choice: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in connection with therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), and BSC alone. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. The KEYNOTE 775/309 study included only patients with an ECOG-PS of 0 or 1 and disease progression after prior platinum-based therapy. It remains unclear whether the observed effects can be extrapolated to patients with an ECOG-PS ≥ 2 or to patients with disease progression during prior platinum-based therapy.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on added benefit constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with lenvatinib (hereinafter referred to as "pembrolizumab + lenvatinib") in comparison with the ACT in adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them.

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

Table 4: Research question for the benefit assessment of pembrolizumab + lenvatinib

Therapeutic indication	**ACT[a]**
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them	Therapy according to 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 connection with therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), and BSC alone. BSC refers to 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; G-BA: Federal Joint Committee	

On 7 December 2021, a few days before the dossier was received on 10 December 2021, the G-BA adjusted the ACT as shown in Table 4 [3]. As a consequence of this adjustment, paclitaxel monotherapy was added as another treatment option in the comments (see Table 4). The present benefit assessment is based on the adjusted ACT.

The company implemented the ACT in that it has designated therapy according to physician's choice as the ACT. However, on the basis of the originally designated ACT and due to its high therapeutic importance, the company restricted the selection to the treatment option of doxorubicin. This remains without consequence for the identification of relevant studies because the company did not limit its information retrieval to specific treatment options, and the check of completeness of the study pool (see Section 2.3.1) identified no relevant studies other than the KEYNOTE 775/309 study presented by the company.

However, the company explains that paclitaxel monotherapy (not an ACT option originally included by the G-BA) represents an important treatment option in the therapeutic indication, whereas endocrine therapy and platinum-based retreatment play only a minor role. The company then cites the benefit assessment procedure on dostarlimab [4] which resulted in the adjustment of the ACT according to Table 4. In the company's view, adding the treatment

option of paclitaxel monotherapy leads to the KEYNOTE 775/309 study's total population being relevant for the benefit assessment, rather than only the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment. Due to the ACT having been adjusted only briefly before dossier submission, however, it was reportedly not possible to adapt the dossier, but the results for the total population are presented in Appendix 4G.

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 for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on pembrolizumab + lenvatinib (status: 1 October 2021)
- bibliographical literature search on pembrolizumab + lenvatinib (last search on 1 October 2021)
- search in trial registries / trial results databases for studies on pembrolizumab + lenvatinib (last search on 1 October 2021)
- search on the G-BA website for pembrolizumab + lenvatinib (last search on 1 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on lenvatinib (last search on 20 January 2022); for search strategies, see Appendix A of the full dossier assessment

The search for lenvatinib covers the check for completeness of the study pool regarding the pembrolizumab + lenvatinib combination therapy. The check did not identify any additional relevant study.

2.3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
KEYNOTE 775 / 309	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8-10]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The KEYNOTE 775/309 study was used for the benefit assessment. The study pool concurs with that of the company. The KEYNOTE 775/309 study compared pembrolizumab + lenvatinib with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. Therefore, the study's total population is relevant for the benefit assessment (see Section 2.3.2).

The company further points out that, due the ACT adjustment, the KEYNOTE 775/309 study's total population is relevant for the benefit assessment, rather than only the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment, which is the subpopulation the company used to assess benefit in its dossier based on the originally specified ACT (excluding the treatment option of paclitaxel monotherapy). Due to the ACT having been adjusted only briefly before dossier submission, however, it was reportedly not possible to adapt the dossier, but the results for the total population are presented in Appendix 4G.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used for the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 775 / 309	RCT, open-label, parallel	Adult patients (≥ 18 years) with advanced or recurrent endometrial cancer ▪ whose disease has progressed after prior treatment with systemic, platinum-based chemotherapy[b] ▪ Maximum of 1 prior systemic chemotherapy (except adjuvant or neoadjuvant)[c] ▪ ECOG-PS 0 or 1	Pembrolizumab + lenvatinib (N = 411) Therapy according to physician's choice, selecting from doxorubicin or paclitaxel (N = 416)	Screening: 28 days Treatment: until confirmed disease progression[d], unacceptable toxicity, withdrawal of consent, or until completion of a maximum of 24-month treatment with pembrolizumab[e] or cumulative life-long dose of 500 mg/m² doxorubicin. Follow-up observation[f]: outcome-specific, at the longest until death, withdrawal of consent, loss to follow-up, or end of study	A total of 167 centres in Argentina, Australia, Brazil, Canada, Columbia, France, Germany, Ireland, Israel, Italy, Japan, Korea, Mexico, New Zealand, Poland, Russian Federation, Spain, Taiwan, Turkey, United Kingdom, United States 06/2018 – ongoing Data cut-off: 26 October 2020[g]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

Table 6: Characterization of the included study – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients were to have received a maximum of 2 prior platinum-based chemotherapies, provided that 1 of them was administered in a neoadjuvant or adjuvant setting.
c. There were no limitations on hormone therapy prior to study inclusion.
d. Patients were allowed to continue the study treatment beyond disease progression as defined by RECIST 1.1, provided that the maximum dose of the study drug was not reached, the treating investigator deemed the patient to potentially clinically benefit from the continuation of treatment, and the patient did not exhibit intolerance.
e. Discontinuation of pembrolizumab treatment was an option if patients had achieved confirmed complete response, had received at least 8 cycles of pembrolizumab treatment, and had received at least 2 pembrolizumab treatments after the date the 1st complete response was reported. Patients who met the above criteria or exhibited stable disease, partial response, or complete response and had discontinued the study medication after 35 cycles of pembrolizumab for reasons other than disease progression or intolerance were eligible, in case of disease progression in the further course, for another course of treatment for a maximum of 1 year with pembrolizumab (17 cycles) ± lenvatinib ("second course phrase"). At the present data cut-off of 26 October 2020, only 2 intervention-arm patients from the total population received "second course phase" treatment.
f. Outcome-specific information is provided in Table 8.
g. Prespecified interim analysis.

AE: adverse event; ECOG-PS: Eastern Cooperative of Oncology Group Performance Status; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characterization of the intervention – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study	Intervention	Comparison
KEYNOTE 775 / 309	Pembrolizumab 200 mg i.v., every 3 weeks + Lenvatinib 20 mg orally, once daily	Therapy according to physician's choice: doxorubicin 60 mg/m² BSA i.v., every 3 weeks[a] or paclitaxel 80 mg/m² BSA i. v. on Days 1, 8, and 15, every 28 days[a]
	Dose adjustments ▪ Pembrolizumab: no dose modification allowed; treatment interruption[b]/discontinuation due to toxicity allowed ▪ Lenvatinib: incremental dose reductions possible to 14, 10, or 8 mg daily; treatment interruptions[b]/discontinuations due to toxicity allowed ▪ In case of discontinuation of pembrolizumab or lenvatinib, continued administration of the other drug (lenvatinib or pembrolizumab) was allowed. **Permitted pretreatment** ▪ Maximum of 1 prior systemic chemotherapy (except in an adjuvant or neoadjuvant setting) ▪ Maximum of 2 prior platinum-based chemotherapies so long as 1 of them was administered in a neoadjuvant or adjuvant setting ▪ No restrictions on prior hormone therapies **Non-permitted pretreatment** ▪ Chronic systemic steroid therapy or any other form of immunosuppressant therapy within 7 days prior to study start ▪ Anti-PD-1, anti-PD-L1, or anti-PD-L2 agents and agents targeting VEGF-regulated angiogenesis ▪ T-cell receptor stimulators or coinhibitors (e.g. CTLA-4, OX 40, CD137), if discontinued due to an immune-mediated AE grade ≥ 3 **Permitted concomitant treatment** ▪ Medications for the treatment of complications or AEs, or for symptom alleviation ▪ Anticoagulants ▪ Antihypertensives ▪ Palliative radiotherapy in non-target bone metastases or brain metastases in consultation with the company ▪ Systemic corticosteroids, including for the treatment of immune-mediated AEs[c] **Non-permitted concomitant treatment** ▪ Other antineoplastic therapies such as chemotherapies, hormone therapies, radiotherapies (see above for exceptions), surgical interventions, and immunotherapies	

a. Used in accordance with the SPCs applicable in the respective countries/regions or institutional guidelines.
b. Lenvatinib treatment discontinuation for > 28 days required separate approval by the company. For pembrolizumab, treatment discontinuation due to AEs was allowed for a maximum of 12 weeks.
c. For patients in the intervention arm.

AE: adverse event; BSA: body surface area; CD137: Cluster of Differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EC: endometrial carcinoma; i.v.: intravenous; OX-40: corresponds to Cluster of Differentiation 134; PD-1: programmed cell death protein 1; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

The KEYNOTE 775/309 study is a randomized, active control, open-label study comparing pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin and paclitaxel.

The study included adult patients with advanced or recurrent endometrial cancer and disease progression after systemic, platinum-based chemotherapy. However, the approved therapeutic indication also includes patients whose disease progression occurred during prior platinum-based therapy.

Patients were to have received a maximum of 2 prior platinum-based chemotherapies, provided 1 of them was administered in a neoadjuvant or adjuvant setting. Further, patients were allowed to have received a maximum of 1 prior systemic chemotherapy, excluding neoadjuvant or adjuvant therapies. No restrictions applied to prior hormone therapies. At study enrolment, patients had to be in good general health corresponding to an ECOG-PS of 0 or 1 and exhibit adequate organ function. Patients with active central nervous system metastases were excluded from the study; hence, no data are available for them.

In total, the KEYNOTE 775/309 study enrolled 827 patients. Prior to randomization, the investigator defined, without further specifying the underlying criteria, which of the 2 options (doxorubicin or paclitaxel) was to be used for therapy according to investigator's choice in the event the patient was allocated to the comparator arm. Patients were then randomized at a 1:1 ratio to either pembrolizumab + lenvatinib treatment (N = 411) or therapy according to investigator's choice (N = 416, of which N = 307 doxorubicin and N = 109 paclitaxel). Randomization was initially stratified by mismatch repair (MMR) status (proficient [pMMR] versus deficient [dMMR]). The pMMR stratum was further stratified by ECOG-PS (0 versus 1), geographic region (Europe, United States, Canada, Australia, New Zealand, Israel versus rest of the world), and history of pelvic radiation (yes versus no).

Pembrolizumab and lenvatinib treatment in the intervention arm was largely in compliance with the specifications of the SPCs [11,12]. Deviating from the SPC, treatment with pembrolizumab was limited to a maximum duration of 35 cycles (approx. 24 months). However, according to the SPC, pembrolizumab treatment should be continued until progression of the cancer or the occurrence of unacceptable toxicity [11]. In the KEYNOTE 775/309 study, however, only 3 intervention-arm patients (0.7%) from the total population reached the 35 treatment cycles; therefore, the deviations between the SPC and study protocol regarding treatment duration are negligible.

Doxorubicin treatment in the comparator arm was in compliance with the SPC [13].

Paclitaxel is not approved in the therapeutic indication [14]. The KEYNOTE 775/309 study administered paclitaxel in a 28-day cycle on Days 1, 8, 15 at a dose of 80 mg/m² BSA, with a subsequent pause on Day 22. The S3 Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer provides no information on paclitaxel dosage in the present

therapeutic indication [15]. The European guideline issued by ESGO, ESTRO, and ESP discusses weekly administration of paclitaxel as second-line therapy, without indicating dosage, for patients with recurrent disease [16]. Therefore, it is unclear to what extent the paclitaxel dosage used in the study, which provides for a break on Day 22 of a 28-day cycle, reflects clinical practice in Germany.

In the KEYNOTE 775/309 study, treatment continued until verified disease progression (as defined by Response Evaluation Criteria In Solid Tumors [RECIST] criteria version 1.1), unacceptable toxicity, or withdrawal of consent. Additional discontinuation criteria were completion of a maximum of 24 months of therapy for pembrolizumab and a cumulative lifetime dose of 500 mg/m² BSA for doxorubicin. As per the study protocol amendment dated 15 June 2021, comparator arm patients were allowed to switch to the intervention arm treatment only after the submitted 26 October 2020 data cut-off. Nevertheless, at the submitted data cut-off, 32 comparator-arm patients (7.7%) had already switched to pembrolizumab + lenvatinib treatment (see Section 2.4.2).

Co-primary outcomes of the KEYNOTE 775/309 study were overall survival and progression-free survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

Data cut-offs

The KEYNOTE 775/309 study is still ongoing. The data cut-off presented in Module 4 A, from 26 October 2020, had been prespecified as the 1st interim analysis for overall survival after about 368 deaths among participants with pMMR status, to occur at least 6 months after randomization of the last patient. The final analysis of overall survival is still outstanding and is supposed to occur after about 526 deaths in the study population with pMMR status and at least 18 months after randomization of the last patient. The results from the interim analysis dated 26 October 2020, which were presented by the company, are analysed in the present benefit assessment.

Implementation of the ACT

The G-BA specified the ACT as therapy according to physician's choice, listing the following treatment options as suitable comparators in its comments on the ACT:

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

For the implementation of therapy according to physician's choice, comparisons for the purposes of the benefit assessment are to comprise several of the listed treatment options and appropriately represent therapies commonly used in German healthcare practice.

The comparator therapy in the KEYNOTE 775/309 study is therapy according to physician's choice, selecting from doxorubicin or paclitaxel. In the study, the investigator made a pre-randomization choice of the treatment to be received by the specific patient in case of allocation to the comparator arm, but the employed criteria were not further specified.

Therapy according to investigator's choice, selecting from doxorubicin or paclitaxel, as used in the KEYNOTE 775/309 study, is deemed a sufficient implementation of the ACT. Hence, the total population of the KEYNOTE 775/309 study is relevant for the benefit assessment. The rationale is provided below.

A review was conducted to determine the extent to which ACT options other than doxorubicin and paclitaxel represent suitable therapies according to physician's choice for the included patients.

Because KEYNOTE 775/309 participants are in good general health, as determined by its inclusion criteria (ECOG-PS of 0 or 1 and adequate organ function), the options of BSC alone and hormone therapy are to be deemed of lesser importance. For instance, the S3 Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer [15] describes hormone therapy as a treatment frequently administered to patients with recurrent endometrial cancer who are in reduced general health or of advanced age. However, an uncertainty remains regarding KEYNOTE 775/309 participants' eligibility for hormone therapy. While both hormone receptor status and tumour grading are likely to affect response to hormone therapy, the hormone receptor status was not surveyed, and no information was available on tumour grading at baseline [15,16].

According to the inclusion criteria, all KEYNOTE 775/309 study participants have already received at least 1 platinum-based therapy. As per guidelines, platinum-based retreatment may be an option particularly in patients who have had an extended platinum-free interval (> 12 months) [16,17]. The combination of carboplatin and paclitaxel is described as the standard in first-line therapy of advanced/recurrent endometrial cancer [15,16]. According to the European Public Assessment Report (EPAR) on pembrolizumab and lenvatinib, about 35% of patients received the study medication as first-line treatment of the advanced/metastatic stage [8,9]. However, few of these patients had a platinum-free interval for ≥ 12 months [9]; the median platinum-free interval was 6.2 months in the intervention arm and 5.6 months in the comparator arm [8]. Overall, platinum-based retreatment, including the platinum-based treatment options of the ACT, are therefore rated as treatment options of lesser importance for KEYNOTE 775/309 participants.

Citing the S3 Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer and the European guideline issued by the ESGO, ESTRO, and ESP [15,16], the company's dossier describes doxorubicin and paclitaxel monotherapies as being of high therapeutic importance. With regard to platinum-based re-therapy and endocrine therapy, the company argues that they are of lesser importance, with some of its cited arguments being similar to those above. In its reasoning, the company did not address data on healthcare practice in Germany or on the treatment option of BSC.

Based on the originally specified ACT, which did not include the treatment option of paclitaxel monotherapy, the company assessed added benefit using the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment. However, the company argues that, after the ACT adjustment carried out shortly before dossier submission, the KEYNOTE 775/309 study's total population is the one relevant for the benefit assessment.

Summary

For the total population, therapy according to physician's choice, selecting from doxorubicin or paclitaxel, is overall deemed a sufficient implementation of the ACT in the KEYNOTE 775/309 study despite the uncertainties described regarding potential alternative treatment options and the paclitaxel dosing regimen. However, the study allows drawing conclusions on the added benefit of pembrolizumab + lenvatinib only for patients for whom doxorubicin or paclitaxel represents the suitable therapy according to physician's choice. In patients for whom a treatment option other than doxorubicin or paclitaxel represents the suitable therapy according to physician's choice, no conclusions on added benefit can be drawn based on the KEYNOTE 775/309 study.

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 775 / 309	
Mortality	
Overall survival	Until death or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24) Health status (EQ-5D VAS)	Up to 4 cycle lengths (depending on cycle duration, 21 or 28 days)[a] after the last dose of the study drug
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	Up to 4 cycle lengths (depending on cycle duration, 21 or 28 days)[a] after the last dose of the study drug
Side effects	
AEs, severe AEs[b]	Until 30 days after the last dose of study drug or start of a subsequent cancer therapy
SAEs	Until 120 days after the last dose of study drug or start of a subsequent cancer therapy

a. Patients were not required to complete the questionnaires.
b. Operationalized as CTCAE grade ≥ 3.
c. In case of an AE of CTCAE grade > 1: until improvement to CTCAE grade 0 or 1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the KEYNOTE 775/309 study, only overall survival was recorded until study end. The follow-up periods for the outcomes in the morbidity, health-related quality of life, and side effects categories were systematically shortened because they were recorded only for the time period of treatment with the study medication (plus 4 cycle lengths or plus 30 days or 120 days). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characterization of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Characteristic Category	**Pembrolizumab + lenvatinib N[a] = 411**	**Therapy according to physician's choice (doxorubicin or paclitaxel) N[a] = 416**
KEYNOTE 775 / 309		
Sex [f/m], %	100/0	100/0
Age [years], mean (SD)	63 (9)	64 (9)
Ancestry, n (%)		
White	261 (63.5)	246 (59.1)
Asian	85 (20.7)	92 (22.1)
Black	17 (4.1)	14 (3.4)
Native American or Alaska Native	4 (1.0)	7 (1.7)
Native Hawaiian / Other Pacific Islander	1 (0.2)	0 (0)
Multiple categories	7 (1.7)	13 (3.1)
No data	36 (8.8)	44 (10.6)
ECOG-PS, n (%)		
0	246 (59.9)	241 (57.9)
1	164 (39.9)	175 (42.1)
2	0 (0)	0 (0)
3	1 (0.2)	0 (0)
Disease duration: time since first diagnosis [years], mean (SD)	2.4 (2.4)	2.9 (2.8)
Histological type[b] at first diagnosis, n (%)		
Endometrioid	243 (59.1)[c]	254 (61.1)[c]
Clear-cell	30 (7.3)	17 (4.1)
Serous	103 (25.1)[c]	115 (27.6)[c]
Mucinous	1 (0.2)[c]	1 (0.2)[c]
Mixed	22 (5.4)	16 (3.8)
Other	8 (1.9)[c]	7 (1.7)[c]
Undifferentiated	4 (1.0)	3 (0.7)
Not determined	0 (0)	3 (0.7)
FIGO stage at first diagnosis, n (%)		
Stage I	111 (27.0)[c]	139 (33.4)[c]
Stage II	32 (7.8)	26 (6.3)
Stage III	118 (28.7)[c]	128 (30.8)[c]
Stage IV	150 (36.5)[c]	123 (29.6)[c]
FIGO stage at baseline, n (%)	ND	ND
Metastatic disease, n (%)	ND	ND

Table 9: Characterization of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Characteristic Category	**Pembrolizumab + lenvatinib N[a] = 411**	**Therapy according to physician's choice (doxorubicin or paclitaxel) N[a] = 416**
Recurrent disease	ND	ND
Brain metastases, n (%)	2 (0.5)	2 (0.5)
Bone metastases, n (%)	39 (9.5)	33 (7.9)
Liver metastases, n (%)	101 (24.6)	98 (23.6)
Lung metastases, n (%)	164 (39.9)	152 (36.5)
Intraabdominal metastases[d], n (%)	164 (39.9)	166 (39.9)
Lymph node metastases, n (%)	224 (54.5)	225 (54.1)
MMR status, n (%)		
proficient	346 (84.2)	351 (84.4)
deficient	65 (15.8)	65 (15.6)
Prior systemic therapy[e], n (%)		
neoadjuvant/adjuvant only	144 (35.0)	159 (38.2)
primary therapy	69 (16.8)	43 (10.3)
in advanced/recurrent stage only	114 (27.7)	117 (28.1)
neoadjuvant/adjuvant and in the advanced/recurrent stage	79 (19.2)	92 (22.1)
not applicable	5 (1.2)	5 (1.2)
Number of prior systemic therapies, n (%)		
1	297 (72.3)	277 (66.6)
2	103 (25.1)	126 (30.3)
≥ 3	11 (2.7)	13 (3.1)
Number of prior platinum-based therapies, n (%)		
0	1 (0.2)	0 (0.0)
1	326 (79.3)	315 (75.7)
2	83 (20.2)	101 (24.3)
≥ 3	1 (0.2)	0 (0)
Prior palliative hormone therapy, n (%)	36 (8.8)	44 (10.6)
Prior pelvic radiotherapy, n (%)	174 (42.3)	186 (44.7)
Prior hysterectomy, n (%)	296 (72.0)	329 (79.1)
Treatment discontinuation, n (%)[f]	282 (68.6[c])	285 (68.5[c])
Study discontinuation, n (%)[g]	191 (46.5)	264 (63.5)

Table 9: Characterization of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Characteristic Category	Pembrolizumab + lenvatinib N[a] = 411	Therapy according to physician's choice (doxorubicin or paclitaxel) N[a] = 416

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Endometrioid: endometrioid, endometrioid with squamous differentiation, endometrioid (high grade), endometrioid (low grade); serous: serous, serous (high grade); mucinous: mucinous (low grade), mucinous (high grade); other: other, neuroendocrine.
c. IQWiG calculation.
d. Includes localizations in the large intestine, abdominal cavity, omentum, small intestine, abdominal cavity, and peritoneum.
e. According to information in the study report; information on prior palliative hormone therapy was not taken into account here.
f. Common reasons for treatment discontinuation in the intervention arm vs. control arm: disease progression (45.0% vs. 47.4%), AEs (17.8% vs. 7.9%), and withdrawal of consent (4.4% vs. 7.0%); death was not included as a reason for discontinuing therapy.
g. Common reasons for study discontinuation in the intervention arm vs. control arm were death (44.8% vs. 56.7%) and withdrawal of consent (1.7% vs. 6.3%).

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; f: female; FIGO: International Federation of Gynecology and Obstetrics; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the study population are largely comparable between both treatment arms. Patients' mean age was about 63 years; about 60% were of white ancestry, and about 60% had an endometrioid tumour at the first diagnosis. About 60% of patients had an ECOG-PS of 0.

A total of 79.3% of patients in the intervention arm had received exactly 1 prior platinum-based chemotherapy versus 75.7% in the comparator arm. Two prior platinum-based chemotherapies had been received by 20.2% of patients in the intervention arm and 24.3% in the comparator arm. A total of 35.0% of patients in the intervention arm and 38.2% of patients in the comparator arm received prior systemic therapy only in the neoadjuvant/adjuvant setting.

In each arm, slightly below 69% of patients discontinued treatment. About 47% of patients in the intervention arm and about 64% in the comparator arm discontinued the study, with the majority of study discontinuations being due to deaths.

Information on the course of the study

Table 10 shows patients' mean/median treatment duration and the mean/median follow-up period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + lenvatinib** **N = 411**	**Therapy according to physician's choice (doxorubicin or paclitaxel)** **N = 416**
KEYNOTE 775 / 309		
Treatment duration[a] [months]		
Pembrolizumab + lenvatinib / therapy according to physician's choice (doxorubicin or paclitaxel)		
Median [min; max]	6.3 [0; 25.8][b]	3.4 [0; 25.8][b]
Mean (SD)	7.6 (6.1)[b]	3.6 (3.0)[b]
Lenvatinib		
Median [min; max]	6.9 [0; 26.8][b]	--
Mean (SD)	8.3 (6.3)[b]	--
Pembrolizumab		
Median [min; max]	6.9 [0; 25.8][b]	--
Mean (SD)	8.3 (6.3)[b]	--
Doxorubicin[c]		
Median [min; max]	--	2.84 [ND]
Mean (SD)	--	ND
Paclitaxel[c]		
Median [min; max]	--	ND
Mean (SD)	--	ND
Follow-up duration [months]		
Overall survival[d]		
Median [min; max]	12.2 [0.3; 26.9]	10.7 [0.3; 26.3]
Mean (SD)	12.7 (6.3)	11.0 (5.9)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a. Information is based on the patients who received at least 1 dose of the study medication: 406 vs. 388 patients.
b. IQWiG conversion from days to months.
c. In the control arm, 289 patients were treated with doxorubicin and 99 patients with paclitaxel.
d. The follow-up duration is defined as the time from randomization until death or up to the current data cut-off if the patient is still alive.

IQWiG: Institute for Quality and Efficiency in Health Care; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration in the intervention arm was 6.3 months, almost twice as long as in the control arm (3.4 months). This between-arm difference in median treatment duration is

also reflected by the treatment duration with the individual drugs, although no information is available on the duration of paclitaxel treatment.

The median follow-up duration for overall survival is 12.2 months in the intervention arm and 10.7 months in the comparator arm. For the total population, no information is available regarding the outcomes on morbidity, health-related quality of life, and side effects. For these outcomes, the follow-up duration was coupled to the treatment end (see Table 8). Therefore, it is safe to assume that the follow-up duration is shortened with respect to overall survival. For these outcomes, conclusions can therefore be drawn only for the period under treatment (plus 4 cycle lengths or plus 30 days or 120 days). In the intervention arm, this equals about half of the median follow-up for overall survival; in the comparator arm, it equals about one-third (Table 10). Data for the entire follow-up period are missing for these outcomes.

Information on subsequent therapies

Table 11 presents the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Drug class[b]** **Drug**	**Patients with subsequent therapy n (%)**	
	Pembrolizumab + lenvatinib N = 411	**Therapy according to physician's choice (doxorubicin or paclitaxel) N = 416**
KEYNOTE 775 / 309		
Any systematic subsequent antineoplastic therapies	115 (28.0)	200 (48.1)
Chemotherapy	97 (23.6)	129 (31.0)
Bortezomib	1 (0.2)	0 (0.0)
Capecitabine	2 (0.5)	0 (0.0)
Carboplatin	30 (7.3)	52 (12.5)
Cisplatin	9 (2.2)	24 (5.8)
Cyclophosphamide	6 (1.5)	10 (2.4)
Docetaxel	3 (0.7)	10 (2.4)
Doxorubicin	58 (14.1)	18 (4.3)
Epirubicin	3 (0.7)	2 (0.5)
Etoposide	0 (0.0)	1 (0.2)
Fluorouracil	1 (0.2)	1 (0.2)
Gemcitabine	15 (3.6)	35 (8.4)
Ifosfamide	0 (0.0)	1 (0.2)
Irinotecan	0 (0.0)	1 (0.2)
Melphalan	0 (0.0)	1 (0.2)
Mitoxantrone	0 (0.0)	1 (0.2)
Oxaliplatin	3 (0.7)	2 (0.5)
Paclitaxel	35 (8.5)	57 (13.7)
Tegafur	0 (0.0)	1 (0.2)
Topotecan	3 (0.7)	3 (0.7)
Vinorelbine	0 (0.0)	1 (0.2)
Hormone therapy	25 (6.1)	55 (13.2)
Anastrozole	3 (0.7)	5 (1.2)
Exemestane	1 (0.2)	1 (0.2)
Fulvestrant	3 (0.7)	2 (0.5)
Goserelin	0 (0.0)	2 (0.5)
Letrozole	9 (2.2)	15 (3.6)
Leuprorelin	1 (0.2)	0 (0.0)
Medroxyprogesterone	2 (0.5)	6 (1.4)
Megestrol	6 (1.5)	22 (5.3)
Tamoxifen	3 (0.7)	11 (2.6)
Not specified	2 (0.5)	0 (0.0)

Table 11: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Drug class[b]** **Drug**	**Patients with subsequent therapy n (%)**	
	Pembrolizumab + lenvatinib N = 411	**Therapy according to physician's choice (doxorubicin or paclitaxel) N = 416**
PD-1 / PD-L1 checkpoint inhibitors	4 (1.0)	53 (12.7)
Atezolizumab	0 (0.0)	1 (0.2)
Durvalumab	0 (0.0)	2 (0.5)
Nivolumab	0 (0.0)	4 (1.0)
Pembrolizumab	4 (1.0)	46 (11.1)
VEGF/VEGFR inhibitors	10 (2.4)	46 (11.1)
Bevacizumab	7 (1.7)	17 (4.1)
Lenvatinib	3 (0.7)	32 (7.7)
Pembrolizumab and lenvatinib	3 (0.7)	32 (7.7)
Targeted therapy	8 (1.9)	12 (2.9)
Abemaciclib	1 (0.2)	0 (0.0)
Adavosertib	0 (0.0)	1 (0.2)
Afatinib	0 (0.0)	1 (0.2)
Everolimus	4 (1.0)	5 (1.2)
Mak 683	1 (0.2)	0 (0.0)
Olaparib	0 (0.0)	4 (1.0)
Palbociclib	1 (0.2)	0 (0.0)
Temsirolimus	2 (0.5)	1 (0.2)
Other	7 (1.7)	16 (3.8)
Dexamethasone	1 (0.2)	0 (0.0)
Dimesna	0 (0.0)	1 (0.2)
LY 3300054	0 (0.0)	1 (0.2)
Metformin	0 (0.0)	2 (0.5)
Naptumomab estafenatox	0 (0.0)	1 (0.2)
Pertuzumab	0 (0.0)	1 (0.2)
Sacituzumab	1 (0.2)	0 (0.0)
Trastuzumab	1 (0.2)	4 (1.0)
Not specified	1 (0.2)	3 (0.7)
Unspecified antibodies	3 (0.7)	4 (1.0)
Other I-O agents	0 (0.0)	2 (0.5)
Ly 3321367	0 (0.0)	1 (0.2)
Tremelimumab	0 (0.0)	1 (0.2)

Table 11: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Drug class[b] Drug	Patients with subsequent therapy n (%)	
	Pembrolizumab + lenvatinib N = 411	Therapy according to physician's choice (doxorubicin or paclitaxel) N = 416

a. No data were provided on treatment regimens.
b. For any patient treated with more than 1 drug from the same drug class, this class was counted only once.

I-O: immuno-oncology; ITT: intention to treat; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: Programmed Cell Death Protein; PD-L1: Programmed Cell Death-Ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

Subsequent therapy following disease progression was allowed without restrictions in both study arms. Overall, 28.0% of intervention arm patients and 48.1% of comparator arm patients received subsequent systemic antineoplastic therapy. The most common subsequent therapy received was chemotherapy (23.6% versus 31.0%); most common in the intervention arm was doxorubicin (14.1%) and in the comparator arm, paclitaxel (13.7%). Between-arm differences are also found with regard to the use of hormone therapy (6.1% versus 13.2%), programmed-death-1 (PD-1) / programmed-death-ligand-1 (PD-L1) checkpoint inhibitors (1.0% versus 12.7%) as well as vascular endothelial growth factor (VEGF) / vascular endothelial growth factor receptor (VEGFR) inhibitors (2.4% versus 11.1%).

A total of 7.7% of comparator arm patients received subsequent therapy with pembrolizumab + lenvatinib (see Section 2.4.2).

Overall, the subsequent therapies used in the KEYNOTE 775/309 study are in line with the treatment options presented in the guidelines [15,16].

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 775 / 309	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the KEYNOTE 775/309 study.

Limitations resulting from the open-label study design are described in Section 2.4 under the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company pointed out that the KEYNOTE 775/309 study results can be extrapolated to the German health care context due to the characteristics of the investigated patient population, the study design, and the approval-compliant use of pembrolizumab and lenvatinib.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms surveyed using the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC – Quality of Life Questionnaire – Endometrial Cancer Module 24 (EORTC QLQ-EN24)
  - health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-EN24

- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs and severe AEs
  - hypertension (preferred term [PT], severe AEs)
  - bleeding
  - cardiotoxicity (operationalized as System Organ Class [SOC] cardiac disorders, severe AEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Immune-related SAEs[c]	Immune-related severe AEs[a,c]	Hypertension (PT, severe AEs[a])	Bleeding	Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs[a])	Further specific AEs[a,d]
KEYNOTE 775/309	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Discontinuation of 1 or more drug component in the intervention arm.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") is used.
d. The following events were assessed (MedDRA coding): headache (PT, AEs), alopecia (PT, AEs), urinary tract infection (PT, SAEs), blood and lymphatic system disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), lipase increased (PT, severe AEs), weight decreased (PT, severe AEs), metabolic and nutritional disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), proteinuria (PT, severe AEs), respiratory, thoracic, and mediastinal disorders (SOC, severe AEs), palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs).
e. No suitable operationalization is available.

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on analyses of the outcome categories of morbidity and health-related quality of life

- In the dossier's Appendix 4G, the company presents analyses for the total population, which is relevant for the assessment, regarding patient-reported outcomes (PROs) on symptoms and health-related quality of life, surveyed with the EORTC QLQ-C30 and EORTC QLQ-EN24 as well as on health status, surveyed with EQ-5D VAS. The analyses are based on continuous data (mean differences from baseline), which are analysed using an MMRM. The effect estimators represent between-group differences in changes from baseline averaged across a follow-up period. The company did not provide any information on outcome-specific follow-up periods. The curves of change over time which are provided with the analyses represent data up to Week 45.
- PROs were surveyed on the 1st day of the cycle in each case. In the intervention arm as well as for doxorubicin-treated comparator arm patients, the survey was therefore done

every 3 weeks. For paclitaxel-treated patients in the comparator arm, in contrast, the survey was done every 4 weeks (see Table 14). For the statistical analyses, these surveys performed at different times were combined into a 3-week regimen using a prespecified algorithm. In this process, the data from paclitaxel-treated comparator arm patients, which were surveyed every 4 weeks, were allocated to the data from all other patients surveyed every 3 weeks in such a way that the scheduled survey time points were very close together, a maximum of 1 week apart. Every 12 weeks, the survey time points fall on the same day. However, also every 12 weeks, starting at Week 6 (i.e. Weeks 6, 18, 30, etc.), paclitaxel-treated patients in the comparator arm have no matching survey in the analysis. This is shown in Table 14 presented below.

Table 14: Survey time points and allocation in the statistical analysis

Administered drugs	**Survey time points (weeks)**												
Pembrolizumab + lenvatinib	3	-	6	-	9	12	15	-	18	-	21	24	…
Doxorubicin													
Paclitaxel	-	4	-	8	-	12	-	16	-	20	-	24	…
Allocation in statistical analysis	**3**		**6**	**9**		**12**	**15**		**18**	**21**		**24**	**…**

- The company's approach of performing the survey on the 1st day of each cycle, regardless of cycle length, is appropriate because by doing so, the company avoids performing surveys at different time points within a cycle and thereby reduces potential bias caused by this factor. The company's allocation of the surveys for the statistical analyses with a separation by a maximum of 1 week is plausible in the present situation. Furthermore, this affects only about 25% of patients in the comparator arm, specifically those with prior paclitaxel treatment. Overall, the MMRM analyses of the PROs are suitable for the benefit assessment and are included in the assessment.

2.4.2 Risk of bias

Table 15 presents the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Immune-related SAEs[c]	Immune-related severe AEs[a,c]	Hypertension (PT, severe AEs[a])	Bleeding	Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs[a])	Further specific AEs[a,d]
KEYNOTE 775 / 309	L	L	H[e, f]	H[e, f]	H[e, f]	H[g]	H[g]	H[h]	H[g]	H[g]	H[g]	-[i]	H[g]	H[g, j]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Discontinuation of 1 or more drug component in the intervention arm.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") is used.
d. The following events were assessed (MedDRA coding): headache (PT, AEs), alopecia (PT, AEs), urinary tract infection (PT, SAEs), blood and lymphatic system disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), lipase increased (PT, severe AEs), weight decreased (PT, severe AEs), metabolic and nutritional disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), proteinuria (PT, severe AEs), respiratory, thoracic, and mediastinal disorders (SOC, severe AEs), palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs).
e. Lack of blinding in subjective recording of outcomes.
f. Strongly decreasing and widely differing questionnaire return rates.
g. Large difference in median follow-up duration between intervention arm and control arm; potentially informative censoring.
h. Lack of blinding in the presence of subjective decision on treatment discontinuation.
i. No suitable operationalization is available.
j. Lack of blinding in specific AEs which are not serious or not severe.

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; MedDRA: Medical Dictionary for Regulatory Activities; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the result on the outcome of overall survival was rated as low.

According to the study protocol, comparator arm patients were allowed to switch to pembrolizumab + lenvatinib treatment only starting with amendment dated 15 June 2021, which was after the present data cut-off of 26 October 2020. Nevertheless, during the study up to the present data cut-off, 32 patients (7.7%) switched from the comparator arm to pembrolizumab + lenvatinib treatment. No information is available on the timing of the

treatment switches. The information on the subsequent therapies does not show any signs of more effective treatments being systematically withheld from these patients (see Table 11). Additionally, the observed effect for the outcome of overall survival is very large (hazard ratio: 0.62; 95% CI: [0.51; 0.75]), with high event rates (58.9%) in the comparator arm. Overall, the premature treatment switch presumably does not call into question the observed effect.

For each of the outcomes of symptoms (EORTC QLQ-C30 and EORTC QLQ-EN24), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-EN24), the risk of bias of results is rated as high due to lack of blinding with subjective recording of outcomes as well as markedly decreasing and differential questionnaire return rates.

For the side effects outcomes, the risk of bias of the results is rated high due to incomplete observations for potentially informative reasons. Regarding the outcome of discontinuation due to AEs, the fact that the decision on discontinuation due to AEs was made subjectively led to high risk of bias. For specific non-serious/non-severe AEs, the lack of blinding in subjective recording of outcomes additionally contributed to the high risk of bias. Regarding the outcome of bleeding, no suitable operationalization is available, and therefore, the risk of bias was not assessed.

2.4.3 Results

Table 16 and Table 17 summarize the results on the comparison of pembrolizumab + lenvatinib with therapy according to physician's choice, selecting from doxorubicin or paclitaxel, in adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

The available Kaplan-Meier curves on the employed time-to-event analyses are presented in Appendix B of the full dossier assessment, whereas the results on common AEs, SAEs, and severe AEs as well as discontinuation due to AEs are found in Appendix D of the full dossier assessment.

For assessing clinical relevance as well as extent, the standardized mean difference (SMD) is used, provided the mean difference (MD) is statistically significant. The corresponding calculations are presented in Appendix 4 G of the company's dossier. Since no description of calculation methods was provided, results were checked by IQWiG calculations. For this purpose, an SMD analogous to Hedges' g was determined using the MD estimated from the MMRM analysis, the corresponding 95% CI as well as the respective sample size.

The results depart from the company's calculation. Therefore, IQWiG calculations were used for the assessment.

Table 16: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab + lenvatinib		Therapy according to physician's choice (doxorubicin or paclitaxel)		Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
KEYNOTE 775 / 309					
Mortality					
Overall survival	411	18.3 [15.2; 20.5] months 188 (45.7)	416	11.4 [10.5; 12.9] months 245 (58.9)	0.62 [0.51; 0.75]; < 0.001[b]
Side effects					
AEs (supplementary information)[c]	406	0.6 [0.4; 0.7] 405 (99.8)	388	0.6 [0.4; 0.7] 386 (99.5)	-
SAEs[c]	406	40.9 [30.0; 53.6] 214 (52.7)	388	NR [55.7; NR] 118 (30.4)	1.67 [1.33; 2.09]; < 0.001
Severe AEs[c, d]	406	5.1 [3.9; 6.3] 361 (88.9)	388	3.6 [2.3; 5.1] 282 (72.7)	1.07 [0.91; 1.25]; 0.412
Discontinuation due to AEs[c,e]	406	NR [77.4; -] 134 (33.0)	388	NR [59.1; NR] 31 (8.0)	2.81 [1.89; 4.20]; < 0.001
Immune-related SAEs[f]	406	NR 41 (10.1)	388	NR 1 (0.3)	29.55 [4.05; 215.69]; < 0.001
Immune-related severe AEs[d,f]	406	NR 53 (13.1)	388	NR 1 (0.3)	29.93 [4.11; 217.76]; < 0.001
Hypertension (PT, severe AEs[d])	406	NR 154 (37.9)	388	NR 9 (2.3)	17.49 [8.92; 34.30]; < 0.001
Bleeding	No usable data[g]				
Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs[d])	406	NR 11 (2.7)	388	NR 12 (3.1)	0.42 [0.17; 1.00]; 0.050
Headache (PT, AEs)	406	NR 101 (24.9)	388	NR 34 (8.8)	2.59 [1.75; 3.84]; < 0.001
Alopecia (PT, AEs)	406	NR 22 (5.4)	388	NR 120 (30.9)	0.12 [0.07; 0.18]; < 0.001
Urinary tract infection (PT, SAEs)	406	NR 13 (3.2)	388	NR 2 (0.5)	5.04 [1.13; 22.58]; 0.034

Table 16: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + lenvatinib**		**Therapy according to physician's choice (doxorubicin or paclitaxel)**		**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)**
	N	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Blood and lymphatic system disorders (SOC, severe AEs[d])	406	NR 45 (11.1)	388	NR [25.9; NR] 159 (41.0)	0.18 [0.13; 0.26]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[d])	406	NR [85.4; NR] 106 (26.1)	388	NR 41 (10.6)	1.63 [1.12; 2.37]; 0.010
Hepatobiliary disorders (SOC, severe AEs[d])	406	NR 27 (6.7)	388	NR 1 (0.3)	13.95 [1.87; 103.91]; 0.010
Lipase increased (PT, severe AEs[d])	406	NR 26 (6.4)	388	NR 5 (1.3)	3.08 [1.15; 8.29]; 0.026
Weight decreased (PT, severe AEs[d])	406	NR 42 (10.3)	388	NR 1 (0.3)	16.29 [< 2.21; 119.86], 0.006
Metabolism and nutrition disorders (SOC, severe AEs[d])	406	NR 97 (23.9)	388	NR 27 (7.0)	2.44 [1.58; 3.77]; < 0.001
Musculoskeletal and connective tissue disorders (SOC, severe AEs[d])	406	NR 30 (7.4)	388	NR 5 (1.3)	3.65 [1.39; 9.57]; 0.008
Proteinuria (PT, severe AEs[d])	406	NR 22 (5.4)	388	NR 1 (0.3)	16.16 [2.16; 120.89]; 0.007
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs[d])	406	NR 20 (4.9)	388	NR 26 (6.7)	0.44 [0.23; 0.82]; 0.009
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs[d])	406	NR 11 (2.7)	388	NR 0 (0.0)	ND; 0.006

a. HR, 95% CI and p-value (Wald test) using Cox proportional hazards regression
b. HR, 95% CI and p-value (Wald test) by means of Cox proportional hazards regression, stratified by MMR status, ECOG-PS, region, and prior pelvic radiotherapy.
c. In accordance with information in the study report without recording progression of the underlying illness.
d. Operationalized as CTCAE grade ≥ 3.
e. Discontinuation of 1 or more drug components in the intervention arm.
f. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") was used.
g. No suitable operationalization is available.

Table 16: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + lenvatinib**		**Therapy according to physician's choice (doxorubicin or paclitaxel)**		**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)**
	N	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
AE: adverse event; AEOSI: adverse event of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; MMR: mismatch repair; n: number of patients with event; N: number of analysed patients; ND: no data; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class					

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab + lenvatinib			Therapy according to physician's choice (doxorubicin or paclitaxel)			Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
KEYNOTE 775 / 309							
Morbidity							
EORTC QLQ-C30 – symptom scales[c]							
Fatigue	370	31.11 (22.53)	9.01 (0.84)	350	34.10 (25.56)	12.03 (0.95)	-3.02 [-5.41; -0.63]; ND SMD: -0.18 [-0.33; -0.04][d]
Nausea and vomiting	370	8.69 (17.45)	5.49 (0.73)	350	9.29 (18.38)	8.07 (0.83)	-2.58 [-4.66; -0.50]; ND SMD: -0.18 [-0.33; -0.03][d]
Pain	370	29.05 (27.53)	6.20 (0.95)	350	29.33 (28.57)	4.35 (1.06)	1.85 [-0.84; 4.53]; ND
Dyspnoea	370	15.59 (22.90)	2.05 (0.83)	350	16.38 (23.90)	7.62 (0.92)	-5.58 [-7.91; -3.24]; ND SMD: -0.35 [-0.50; -0.202][d]
Insomnia	370	24.50 (27.44)	1.53 (0.99)	350	28.38 (28.11)	4.32 (1.11)	-2.79 [-5.60; 0.02]; ND
Appetite loss	370	20.45 (27.64)	12.95 (1.07)	350	21.24 (29.69)	8.51 (1.22)	4.44 [1.37; 7.51]; ND SMD: 0.21 [0.06; 0.36][d]
Constipation	370	21.35 (28.47)	-1.23 (0.95)	350	23.05 (30.94)	2.67 (1.07)	-3.90 [-6.60; -1.20]; ND SMD: -0.21 [-0.36; -0.06][d]
Diarrhoea	370	6.94 (17.09)	11.15 (0.80)	350	7.43 (17.54)	5.38 (0.94)	5.77 [3.44; 8.10]; ND SMD: 0.36 [0.21; 0.51][d]

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab + lenvatinib			Therapy according to physician's choice (doxorubicin or paclitaxel)			Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
EORTC QLQ-EN24 – symptom scales[c]							
Lymphoedema	308	17.42 (26.38)	2.61 (1.00)	297	16.67 (24.00)	9.21 (1.10)	-6.60 [-9.37; -3.82]; ND SMD: -0.38 [-0.54; -0.22][d]
Urological symptoms	308	14.94 (17.95)	-0.93 (0.69)	297	16.13 (19.40)	2.24 (0.75)	-3.17 [-5.07; -1.27]; ND SMD: -0.27 [-0.43; -0.11][d]
Digestive symptoms	308	12.64 (14.11)	3.24 (0.58)	297	14.55 (14.65)	2.81 (0.65)	0.43 [-1.19; 2.05]; ND
Sexual/vaginal problems	No usable data[e]						
Back/pelvis pain	308	29.22 (29.68)	-0.69 (1.02)	297	31.76 (31.20)	1.52 (1.15)	-2.21 [-5.09; 0.67]; ND
Tingling/numbness	308	30.84 (30.63)	-3.33 (1.12)	297	27.05 (29.47)	3.81 (1.23)	-7.15 [-10.27; -4.03]; ND SMD: -0.36 [-0.53; -0.204][d]
Muscle pain	308	23.16 (26.59)	8.69 (1.12)	297	21.89 (27.87)	2.32 (1.25)	6.37 [3.22; 9.52]; ND SMD: 0.32 [0.16; 0.48][d]
Alopecia	308	15.37 (32.09)	-4.44 (1.25)	297	17.28 (34.67)	53.60 (1.39)	-58.03 [-61.54; -54.53]; ND SMD: -2.64 [-2.85; -2.42][d]
Taste change	308	11.47 (22.95)	14.31 (1.27)	297	15.60 (26.56)	23.90 (1.41)	-9.59 [-13.14; -6.04]; ND SMD: -0.43 [-0.59; -0.27][d]
Health status (EQ-5D VAS)[f]	375	73.70 (18.24)	-4.99 (0.70)	356	73.53 (18.91)	-7.61 (0.76)	2.62 [0.67; 4.57]; ND SMD: 0.19 [0.05; 0.34][d]

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab + lenvatinib			Therapy according to physician's choice (doxorubicin or paclitaxel)			Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
Health-related quality of life							
EORTC QLQ-C30f							
Global health status	370	65.74 (21.87)	-6.58 (0.76)	350	65.64 (22.72)	-8.03 (0.85)	1.45 [-0.69; 3.60]; ND
Physical functioning	370	78.68 (20.08)	-9.51 (0.76)	350	75.94 (20.90)	-9.24 (0.84)	-0.27 [-2.41; 1.86]; ND
Role functioning	370	78.38 (25.46)	-11.67 (0.99)	350	75.62 (27.83)	-11.92 (1.09)	0.24 [-2.53; 3.02]; ND
Emotional functioning	370	75.83 (19.85)	1.34 (0.76)	350	73.48 (21.68)	-2.17 (0.83)	3.51 [1.38; 5.64]; ND SMD: 0.24 [0.09; 0.39][d]
Cognitive functioning	370	84.28 (19.59)	-3.56 (0.76)	350	83.76 (18.43)	-5.23 (0.82)	1.68 [-0.44; 3.79]; ND
Social functioning	370	79.59 (23.80)	-6.99 (1.00)	350	78.57 (25.10)	-10.26 (1.09)	3.27 [0.48; 6.05]; ND SMD: 0.17 [0.03; 0.32][d]
EORTC QLQ-EN24							
Sexual interest[f]	306	8.28 (17.61)	-3.45 (0.54)	290	8.28 (17.11)	-4.24 (0.60)	0.79 [-0.72; 2.29]; ND
Sexual activity[f]	302	7.40 (15.86)	-3.63 (0.45)	289	5.88 (14.16)	-3.73 (0.50)	0.11 [-1.16; 1.37]; ND
Sexual enjoyment	No usable data[e]						
Body image problems[c,g]	308	22.40 (28.24)	1.51 (1.28)	297	24.80 (29.39)	13.23 (1.36)	-11.73 [-15.23; -8.22]; ND SMD: -0.53 [-0.69; -0.37][d]

a. Number of patients taken into account in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
b. From MMRM; effect presents the between-group difference in changes averaged over the course of the study from baseline to the respective measurement point.
c. Higher values on the respective scale indicate worse symptoms; a positive between-group difference indicates an advantage for pembrolizumab + lenvatinib.
d. IQWiG calculation.
e. About 82% of patients were excluded from the analyses.
f. Higher values on the respective scale indicate a better health status or better health-related quality of life; a positive between-group difference indicates an advantage for pembrolizumab + lenvatinib.
g. In departure from the company's approach, this scale was assigned to the health-related quality of life category, rather than the symptoms category.

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab + lenvatinib			Therapy according to physician's choice (doxorubicin or paclitaxel)			Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale							

The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. Due to high risk of bias, at most hints, e.g. of an added benefit, can be determined for all other outcomes.

Despite the high risk of bias, for individual outcomes, it is safe to assume high certainty of results and hence indications, e.g. of lesser harm can be derived based on the available data, including the Kaplan-Meier curves and the observed effect size.

Mortality

Overall survival

For the outcome of overall survival, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. This results in an indication of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-EN24)

Symptoms outcomes were recorded using EORTC QLQ-C30 and the EORTC QLQ-EN24. The MMRM analyses were evaluated in each case.

Pain, insomnia (EORTC QLQ-C30), gastrointestinal symptoms, back/pelvis pain (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the EORTC QLQ-C30 scales of pain and insomnia or for the EORTC QLQ-EN24 back/pelvis pain scale.

In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, constipation (EORTC QLQ-C30), urological symptoms (EORTC QLQ-EN24)

For each of the EORTC QLQ-C30 scales of fatigue, nausea and vomiting, and constipation as well as for the EORTC QLQ-EN24 scale of urological symptoms, there is a statistically significant difference in favour of pembrolizumab + lenvatinib. The SMD in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Appetite loss (EORTC QLQ-C30), muscle pain (EORTC QLQ-EN24)

For the EORTC QLQ-C30 scale of appetite loss and the EORTC QLQ-EN24 scale of muscle pain, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Dyspnoea (EORTC QLQ-C30), lymphoedema, tingling/numbness, taste change (EORTC QLQ-EN24)

For the EORTC QLQ-C30 dyspnoea scale as well as the EORTC QLQ-EN24 scales of lymphoedema, tingling/numbness, and taste change, a statistically significant difference was found in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For each of them, this results in a hint of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Diarrhoea (EORTC QLQ-C30)

For the EORTC QLQ-C30 diarrhoea scale, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. This results in a hint of lesser benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Sexual/vaginal problems (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual/vaginal problems because only 18.4% of patients were included in the analysis. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Hair loss (EORTC QLQ-EN24)

For the EORTC QLQ-EN24 hair loss scale, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For the outcome of hair loss, the curves of mean change over time from baseline (see Figure 22 of the full dossier assessment) show an immediate increase in symptoms in the comparator group curve and almost no change in the intervention group. Coupled with the size of the observed effect and the associated 95% CI, there is an indication of added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Health status (EQ-5D VAS)

The MMRM analyses were evaluated for the outcome of health status recorded with the EQ-5D VAS. A statistically significant difference was found in favour of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

Health-related quality of life outcomes were recorded using the EORTC QLQ-C30 and EORTC QLQ-EN24. The MMRM analyses were evaluated in each case.

Global health status, physical functioning, role functioning, cognitive functioning (EORTC QLQ-C30), sexual interest, sexual activity (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was shown for any of the following scales: EORTC QLQ-C30 global health status, physical functioning, role functioning, and cognitive functioning or EORTC QLQ-EN24 sexual interest and sexual activity. In each case, this resulted in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Emotional functioning, social functioning (EORTC QLQ-C30)

For each of the EORTC QLQ-C30 scales of emotional functioning and social functioning, there is a statistically significant difference in favour of pembrolizumab + lenvatinib. However, the 95% CI of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Sexual enjoyment (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual enjoyment because only 18.2% of patients were included in the analysis. This results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with the therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven.

Body image problems (EORTC QLQ-EN24)

For the scale of body image problems, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. This results in a hint of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Side effects

SAEs, discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. For each of them, this results in a hint of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Severe AEs

There was no statistically significant difference between treatment groups for the outcome of severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs and severe AEs, hypertension (severe AEs)

For each of the outcomes of immune-related SAEs and severe AEs as well as hypertension (severe AEs), there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The consideration of the Kaplan-Meier curves for the

outcomes of immune-related SAEs and severe AEs as well as hypertension (severe AEs) (see Figure 6 to Figure 8 of the full dossier assessment) showed an immediate decrease in the intervention group curve and an almost event-free, unchanged course in the comparator group curve. In conjunction with the size of the observed effect and the associated 95% CI, this results in an indication of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel, for each of them.

Bleeding

No usable data were available for the outcome of bleeding. This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Cardiotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of cardiotoxicity (severe AEs). This results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Headache (AEs), urinary tract infection (SAEs), gastrointestinal disorders (severe AEs), hepatobiliary disorders (severe AEs), lipase increased (severe AEs), weight decreased (severe AEs), metabolic and nutritional disorders (severe AEs), musculoskeletal and connective tissue disorders (severe AEs), proteinuria (severe AEs), palmar-plantar erythrodysaesthesia syndrome (severe AEs)

For each of the outcomes of headaches (AEs), urinary tract infection (SAEs), gastrointestinal disorders (severe AEs), hepatobiliary disorders (severe AEs), lipase increased (severe AEs), weight decreased (severe AEs), metabolic and nutritional disorders (severe AEs), musculoskeletal and connective tissue disorders (severe AEs), proteinuria (severe AEs), and palmar-plantar erythrodysaesthesia syndrome (severe AEs), there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. For each of them, this results in a hint of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

Alopecia (AEs), blood and lymphatic system disorders (severe AEs)

For each of the outcomes of alopecia (AEs) and blood and lymphatic system disorders (severe AEs), there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The evaluation of the Kaplan-Meier curves for the outcomes of alopecia (AEs) and blood and lymphatic system disorders (severe AEs) (see Figure 10 and Figure 12 of the full dossier assessment) shows an immediate decrease in the comparator group curve and an almost event-free, constant course of the intervention group curve. In conjunction with the size of the

observed effect and the associated 95% CI, this results in an indication of lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel, for each of them.

Respiratory, thoracic, and mediastinal disorders (severe AEs)

For the outcome of respiratory, thoracic, and mediastinal disorders (severe AEs), there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. This results in a hint of lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- histology (endometrioid vs. non-endometrioid)

The above characteristics were defined a priori. The characteristic of sex is disregarded since the underlying illness does not affect men.

For the total population, which is the population relevant for the assessment, however, subgroup analyses for both chosen characteristics are available only regarding the outcome of overall survival. No subgroup analyses at all are available for the total population, which is relevant for the assessment, regarding the further patient-relevant outcomes from the morbidity, health-related quality of life, and side effects categories. According to the G-BA's dossier template, the investigation of effect modifiers was required for all relevant outcomes [18].

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Insufficient information is available for determining the severity category for the outcomes of dyspnoea, diarrhoea, lymphoedema, tingling/numbness, hair loss, and taste change, surveyed with the EORTC QLQ-C30 and the EORTC QLQ-EN24, respectively. Therefore, the outcomes were allocated to the outcome category of non-serious/non-severe symptoms / late complications. The company presented no severity grading for these outcomes.

The outcome of discontinuation due to AEs was allocated to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs which led to discontinuation of therapy. The company presented no severity grading for these outcomes.

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Total follow-up duration		
Mortality		
Overall survival	18.3 months vs. 11.4 months HR: 0.62 [0.51; 0.75]; p < 0.001 Probability: indication	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: major
Shortened follow-up period		
Morbidity		
Symptoms (EORTC QLQ-C30) − symptom scales		
Fatigue	Mean: 9.01 vs. 12.03 MD: -3.02 [-5.41; -0.63] p = ND SMD: -0.18 [-0.33; -0.04][c]	Lesser/added benefit not proven
Nausea and vomiting	Mean: 5.49 vs. 8.07 MD: -2.58 [-4.66; -0.50] p = ND SMD: -0.18 [-0.33; -0.03][c],	Lesser/added benefit not proven
Pain	Mean: 6.20 vs. 4.35 MD: 1.85 [-0.84; 4.53] p = ND	Lesser/added benefit not proven
Dyspnoea	Mean: 2.05 vs. 7.62 MD: -5.58 [-7.91; -3.24] p = ND SMD: -0.35 [-0.50; -0.202] SMD: 0.35 [0.202; 0.50][c,d], Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Insomnia	Mean: 1.53 vs. 4.32 MD: -2.79 [-5.60; 0.02] p = ND	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Appetite loss	Mean: 12.95 vs. 8.51 MD: 4.44 [1.37; 7.51] p = ND SMD: 0.21 [0.06; 0.36][c],	Lesser/added benefit not proven
Constipation	Mean: -1.23 vs. 2.67 MD: -3.90 [-6.60; -1.20] p = ND SMD: -0.21 [-0.36; -0.06][c],	Lesser/added benefit not proven
Diarrhoea	Mean: 11.15 vs. 5.38 MD: 5.77 [3.44; 8.10] p = ND SMD: 0.36 [0.21; 0.51][c], Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Lesser benefit, extent: minor
Symptoms (EORTC QLQ-EN24) − symptom scales		
Lymphoedema	Mean: 2.61 vs. 9.21 MD: -6.60 [-9.37; -3.82] p = ND SMD: -0.38 [-0.54; -0.22] SMD: 0.38 [0.22; 0.54][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Urological symptoms	Mean: -0.93 vs. 2.24 MD: -3.17 [-5.07; -1.27] p = ND SMD: -0.27 [-0.43; -0.11][c],	Lesser/added benefit not proven
Digestive symptoms	Mean: 3.24 vs. 2.81 MD: 0.43 [-1.19; 2.05] p = ND	Lesser/added benefit not proven
Sexual/vaginal problems	No usable data	Lesser/added benefit not proven
Back/pelvis pain	Mean: -0.69 vs. 1.52 MD: -2.21 [-5.09; 0.67]; p = ND	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Tingling/numbness	Mean: -3.33 vs. 3.81 MD: -7.15 [-10.27; -4.03] p = ND SMD: -0.36 [-0.53; -0.204] SMD: 0.36 [0.204; 0.53][c,d], Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Muscular pain	Mean: 8.69 vs. 2.32 MD: 6.37 [3.22; 9.52] p = ND SMD: 0.32 [0.16; 0.48][c],	Lesser/added benefit not proven
Alopecia	Mean: -4.44 vs. 53.60 MD: -58.03 [-61.54; -54.53] p = ND SMD: -2.64 [-2.85; -2.42] SMD: 2.64 [2.42; 2.85][c,d] Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $0.40 < CI_u$ Added benefit, extent: considerable
Taste change	Mean: 14.31 vs. 23.90 MD: 9.59 [-13.14; -6.04] p = ND SMD: -0.43 [-0.59; -0.27] SMD: 0.43 [0.27; 0.59][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Health status (EQ-5D VAS)	Mean: -4.99 vs. -7.61 MD: 2.62 [0.67; 4.57] p = ND SMD: 0.19 [0.05; 0.34][c],	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales		
Global health status	Mean: -6.58 vs. -8.03 MD: 1.45 [-0.69; 3.60] p = ND	Lesser/added benefit not proven
Physical functioning	Mean: -9.51 vs. -9.24 MD: -0.27 [-2.41; 1.86] p = ND	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Role functioning	Mean: -11.67 vs. -11.92 MD: 0.24 [-2.53; 3.02] p = ND	Lesser/added benefit not proven
Emotional functioning	Mean: 1.34 vs. -2.17 MD: 3.51 [1.38; 5.64] p = ND SMD: 0.24 [0.09; 0.39][c]	Lesser/added benefit not proven
Cognitive functioning	Mean: -3.56 vs. -5.23 MD: 1.68 [-0.44; 3.79] p = ND	Lesser/added benefit not proven
Social functioning	Mean: -6.99 vs. -10.26 MD: 3.27 [0.48; 6.05] p = ND SMD: 0.17 [0.03; 0.32][c]	Lesser/added benefit not proven
EORTC QLQ-EN24		
Sexual interest	Mean: -3.45 vs. -4.24 MD: 0.79 [-0.72; 2.29] p = ND	Lesser/added benefit not proven
Sexual activity	Mean: -3.63 vs. -3.73 MD: 0.11 [-1.16; 1.37] p = ND	Lesser/added benefit not proven
Sexual enjoyment	No usable data	Lesser/added benefit not proven
Body image problems	Mean: 1.51 vs. 13.23 MD: -11.73 [-15.23; -8.22] p = ND SMD: -0.53 [-0.69; -0.37] SMD: 0.53 [0.37; 0.69][c,d] Probability: hint	Outcome category: health-related quality of life $0.30 < CI_u \leq 0.50$ Added benefit, extent: considerable
Side effects		
SAEs	40.9 vs. NR HR: 1.67 [1.33; 2.09] HR: 0.60 [0.48; 0.752][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Severe AEs	5.1 vs. 3.6 HR: 1.07 [0.91; 1.25] p = 0.412	Greater/lesser harm not proven
Discontinuation due to AEs	NR vs. NR HR: 2.81 [1.89; 4.20] HR: 0.36 [0.24; 0.53][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Immune-related SAEs	NR vs. NR HR: 29.55 [4.05; 215.69] HR: 0.03 [0.01; 0.25][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm; extent: major
Immune-related severe AEs	NR vs. NR HR: 29.93 [4.11; 217.76] HR: 0.03 [0.01; 0.24][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm; extent: major
Hypertension (severe AEs)	NR vs. NR HR: 17.49 [8.92; 34.30] HR: 0.06 [0.03; 0.11][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm; extent: major
Bleeding	No usable data	Greater/lesser harm not proven
Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs)	NR vs. NR HR: 0.42 [0.17; 1.00] p = 0.050	Greater/lesser harm not proven
Headache (AEs)	NR vs. NR HR: 2.59 [1.75; 3.84] HR: 0.39 [0.26; 0.57][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Alopecia (AEs)	NR vs. NR HR: 0.12 [0.07; 0.18] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm; extent: considerable

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Urinary tract infection (SAEs)	NR vs. NR HR: 5.04 [1.13; 22.58] HR: 0.20 [0.04; 0.88][d] p = 0.034 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Blood and lymphatic system disorders (severe AEs)	NR vs. NR HR: 0.18 [0.13; 0.26] p < 0.001 Probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm; extent: major
Gastrointestinal disorders (severe AEs)	NR vs. NR HR: 1.63 [1.12; 2.37] HR: 0.61 [0.42; 0.89][d] p = 0.010 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Hepatobiliary disorders (severe AEs)	NR vs. NR HR: 13.95 [1.87; 103.91] HR: 0.07 [0.01; 0.53][d] p = 0.010 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Lipase increased (severe AEs)	NR vs. NR HR: 3.08 [1.15; 8.29] HR: 0.32 [0.12; 0.87][d] p = 0.026 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable
Weight decreased (severe AEs)	NR vs. NR HR: 16.29 [2.21; 119.86] HR: 0.06 [0.01; 0.45][d] p = 0.006 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Metabolism and nutrition disorders (severe AEs)	NR vs. NR HR: 2.44 [1.58; 3.77] HR: 0.41 [0.27; 0.63][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major

Table 18: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Musculoskeletal and connective tissue disorders (severe AEs)	NR vs. NR HR: 3.65 [1.39; 9.57] HR: 0.27 [0.10; 0.72][d] p = 0.008 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Proteinuria (severe AEs)	NR vs. NR HR: 16.16 [2.16; 120.89] HR: 0.06 [0.01; 0.46][d] p = 0.007 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Respiratory, thoracic, and mediastinal disorders (severe AEs)	NR vs. NR HR: 0.44 [0.23; 0.82] p = 0.009 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm; extent: considerable
Palmar-plantar erythrodysaesthesia syndrome (severe AEs)	NR vs. NR HR: ND p = 0.006 Probability: hint	Outcome category: serious/severe side effects Greater harm; extent: non-quantifiable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale level of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. If the CI for the SMD in the form of Hedges' g is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. IQWiG calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_l: lower limit of confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire–Core 30; QLQ-EN24: Quality of Life Questionnaire–Multiple Myeloma Module 24; SMD: standard mean difference; SAE: serious adverse event; SOC: System Organ Class

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice selecting from doxorubicin or paclitaxel

Positive effects	**Negative effects**
Total follow-up duration	
Mortality ▪ Overall survival Indication of added benefit – extent: major	–
Shortened follow-up period	
Non-serious/non-severe symptoms / late complications ▪ Dyspnoea, lymphoedema, tingling/ numbness, taste change For each, hint of an added benefit – extent: minor ▪ Alopecia Indication of added benefit – extent: considerable	Non-serious/non-severe symptoms / late complications ▪ Diarrhoea Hint of lesser benefit – extent: minor
Health-related quality of life ▪ Body image problems Hint of added benefit – extent: considerable	–
Severe/serious side effects ▪ Blood and lymphatic system disorders (severe AEs) Indication of lesser harm – extent: major ▪ Respiratory, thoracic, and mediastinal disorders (severe AEs) Hint of lesser harm – extent: considerable	Severe/serious side effects ▪ SAEs Hint of greater harm – extent: considerable ▪ Immune-related SAEs, immune-related severe AEs For each: indication of greater harm – extent: major ▪ Urinary tract infection (SAEs) Hint of greater harm – extent: considerable ▪ Hypertension (severe AEs) Indication of greater harm – extent: major ▪ Gastrointestinal disorders, lipase increased (each severe AEs) For each, hint of greater harm – extent: considerable ▪ Hepatobiliary disorders, weight decreased, metabolic and nutritional disorders, musculoskeletal and connective tissue disorders, proteinuria (each severe AEs) For each, hint of greater harm – extent: considerable ▪ Palmar-plantar erythrodysaesthesia syndrome (severe AEs) Hint of greater harm – extent: non-quantifiable
Non-severe/non-serious adverse events ▪ Alopecia (AEs) Indication of lesser harm – extent considerable	Non-severe/non-serious adverse events ▪ Discontinuation due to AEs ▪ Headache (AEs) For each, hint of greater harm – extent: considerable
AEs: adverse events; SAE: serious adverse event	

Overall, both favourable and unfavourable effects were found, with probabilities of hint or indication and of various extents.

The key aspect for the derivation of added benefit is the indication of major added benefit of pembrolizumab + lenvatinib compared to the ACT for overall survival.

Regarding symptoms and health-related quality of life, favourable effects of pembrolizumab + lenvatinib predominate. Additionally, an indication of lesser harm of major extent was found in the outcome category of serious/severe side effects, for the outcome of blood and lymphatic system disorders (severe AEs).

Unfavourable effects, on the other hand, were found particularly in the category of serious/severe side effects, including hints of greater harm of considerable extent for the outcome of SAEs and several specific AEs as well as indications of greater harm of major extent for the outcome of immune-related SAEs, immune-related severe AEs, and hypertension (severe AEs). The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened observation time until treatment end (plus 4 cycle lengths or 30 or 120 days).

In summary, there is an indication of considerable added benefit of pembrolizumab + lenvatinib versus the ACT for adult patients with advanced or recurrent endometrial cancer whose disease has progressed on or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them and for whom doxorubicin or paclitaxel is the suitable therapy according to physician’s choice.

No added benefit is proven for patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy according to physician’s choice.

The result of the assessment of added benefit of pembrolizumab + lenvatinib in comparison with the ACT is summarized in Table 20.

Table 20: Pembrolizumab + lenvatinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them	Therapy according to physician's choice[b]	Patients for whom doxorubicin or paclitaxel is the suitable therapy according to physician's choice: indication of considerable added benefit[c]
		Patients for whom a therapy option other than doxorubicin or paclitaxel is the suitable therapy according to physician's choice: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in connection with therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), and BSC alone. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. The KEYNOTE 775/309 study included only patients with an ECOG-PS of 0 or 1 and disease progression after prior platinum-based therapy. It remains unclear whether the observed effects can be extrapolated to patients with an ECOG-PS ≥ 2 or to patients with disease progression on prior platinum-based therapy.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The above assessment departs from that by the company, which derived an indication of major added benefit for all patients in the therapeutic indication without restrictions, based on the results from the subpopulation of KEYNOTE 775/309 participants for whom the investigator made a pre-randomization choice of doxorubicin treatment.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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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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