IQWiG Reports – Commission No. A21-162

Lenvatinib (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 *Lenvatinib (Endometriumkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 April 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Lenvatinib (endometrial carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
14 December 2021

Internal Commission No.
A21-162

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Günter Emons, Department of Gynaecology and Obstetrics, University Medical Centre Göttingen, Germany

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.

IQWiG employees involved in the dossier assessment

- Sascha Abbas
- Lars Beckmann
- Tatjana Hermanns
- Stefan Kobza
- Prateek Mishra
- Volker Vervölgyi
- Katharina Wölke
- Pamela Wronski

Keywords: Lenvatinib, Pembrolizumab, Endometrial Neoplasms, Benefit Assessment, NCT03517449

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
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
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)
MMR	mismatch repair
pMMR	proficient mismatch repair
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 lenvatinib. 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 lenvatinib in combination with pembrolizumab (hereinafter referred to as "lenvatinib + pembrolizumab") in comparison with the appropriate comparator therapy (ACT) for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

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

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

Therapeutic indication	**ACT**[a]
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based chemotherapy 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 is deemed the treatment that ensures the best possible, individually optimized supportive care 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, the day the dossier was received, the G-BA adjusted the ACT as shown in Table 2. The adjustment added paclitaxel monotherapy as another treatment option (see Table 2). The present benefit assessment was conducted based on the adjusted ACT.

The company follows the ACT in that it designates therapy according to physician's choice as the ACT, but later restricts it to therapy according to physician's choice with special consideration given to doxorubicin. The company deems other drugs specified by the G-BA as

being of lesser importance and best supportive care (BSC) as being an insufficiently plausible treatment option. This discrepancy remains of no consequence because the company did not limit its information retrieval to the treatment option of doxorubicin.

Due to the adjustment, however, the company did not take into account paclitaxel monotherapy, one of the comparators cited as suitable in the G-BA's comments. The fact that the company did not include paclitaxel monotherapy in the information retrieval remains without consequence for the identification of relevant studies because other than the KEYNOTE 775/309 study presented by the company, no relevant study was identified in the check of completeness of the study pool which took into account all treatment options listed by the G-BA.

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

Study pool and study design

The benefit assessment used the randomized, active-control, open-label study KEYNOTE 775/309. This study compared lenvatinib + pembrolizumab with therapy according to physician's choice, consisting of either doxorubicin or paclitaxel. Therefore, the total population of the study is relevant for the benefit assessment. This approach departs from the company's, whose dossier assessed added benefit using the subpopulation of patients for whom the investigator made a pre-randomization choice of doxorubicin based on the originally specified ACT (not including the treatment option of paclitaxel monotherapy).

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

Lenvatinib and pembrolizumab 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 for 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 physician's choice consisting of either doxorubicin or paclitaxel, as used in the KEYNOTE 775/309 study, is deemed a sufficient implementation of the ACT. For the enrolled patients, the ACT's listed treatment options other than doxorubicin and paclitaxel (hormone therapies, platinum re-treatment, or BSC) tend to represent 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 lenvatinib + pembrolizumab 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.

Subpopulation submitted by the company:

Based on the originally specified ACT, Module 4 C of the company's dossier presents data on the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment, and the company used these data to assess added benefit. However, in this situation, the total population of the KEYNOTE 775/309 study is relevant for the benefit assessment because both treatment options administered in the study's comparator arm are included in the adjusted ACT. Compared to data on the subpopulation presented by the company, data on the total population therefore provide a more comprehensive picture of added benefit versus the 2 ACT options. In this situation, it is therefore appropriate to analyse the total population, on which the dossier's Module 4 C does not contain any data. The information provided in the study report likewise does not allow drawing comprehensive conclusions on benefit and harm for the total population because it contains data on overall survival, but not data such as time-to-event analyses for the outcomes regarding side effects.

Results

In the present situation, the total population of the KEYNOTE 775/309 study is relevant for the assessment because, compared to the subpopulation presented by the company, it offers a more comprehensive picture on added benefit in comparison with 2 ACT options. However, the company's dossier does not present sufficient data on the assessment-relevant total population of adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. See the section below for the derivation of added benefit.

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

In the present situation, it is appropriate to analyse the total population of the KEYNOTE 775/309 study. However, the company's dossier fails to provide sufficient data for the total population relevant for the assessment.

The G-BA simultaneously commissioned IQWiG with the benefit assessments of lenvatinib (commission A21-162) and pembrolizumab (commission A21-164), each in combination with the other drug, for the present therapeutic indication. In both dossiers, the respective companies presented results from the same study, KEYNOTE 775/309, using the same data cut-off. However, for the A21-164 Pembrolizumab benefit assessment (unlike for the A21-162 benefit assessment), Appendix 4G of the company's dossier also contained results for the assessment-relevant total population of the KEYNOTE 775/309 study, which allows drawing more comprehensive conclusions on the added benefit of pembrolizumab + lenvatinib in comparison with 2 ACT options. In this special situation, reference is therefore made to the contents of benefit assessment A21-164 Pembrolizumab (endometrial carcinoma) regarding the overall conclusion on added benefit of lenvatinib + pembrolizumab.

With reference to benefit assessment A21-164 Pembrolizumab (endometrial carcinoma), in summary, there is an indication of considerable added benefit of lenvatinib + pembrolizumab versus the ACT in the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation and for whom doxorubicin or paclitaxel is the suitable therapy according to physician's choice.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

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

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

Table 3: Lenvatinib + pembrolizumab – extent and probability 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 chemotherapy 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 therapy that 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 following prior treatment with platinum-containing therapy. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients with disease progression on prior treatment with platinum-containing 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 is 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 lenvatinib in combination with pembrolizumab (hereinafter referred to as "lenvatinib + pembrolizumab") in comparison with the ACT for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

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

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

Therapeutic indication	**ACT**[a]
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based chemotherapy 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 that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

On 7 December 2021, the day the dossier was received, the G-BA adjusted the ACT as shown in Table 4 [3]. The adjustment added paclitaxel monotherapy as another treatment option (see Table 4). The present benefit assessment was conducted in accordance with the adjusted ACT.

The company follows the ACT in that it designates therapy according to physician's choice as the ACT, but later restricts it to therapy according to physician's choice with special consideration given to doxorubicin. The company deems other drugs specified by the G-BA as being of lesser importance and BSC as being an insufficiently plausible treatment option. This discrepancy remains of no consequence because the company did not limit its information retrieval to the treatment option of doxorubicin.

Due to the adjustment of the ACT on 7 December 2021, however, the company has not taken into account the treatment option of paclitaxel monotherapy, i.e. one of the comparators cited as suitable in the G-BA's comments. The exclusion of paclitaxel monotherapy from the company's information retrieval remains without consequence for the identification of relevant studies because no relevant study other than the KEYNOTE 775/309 study presented by the company was found in the check of completeness of the study pool (see Section 2.3.1), which took into account all treatment options listed by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were 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 lenvatinib + pembrolizumab (status: 8 October 2021)
- bibliographical literature search on lenvatinib + pembrolizumab (last search on 8 October 2021)
- search in trial registries / trial results databases for studies on lenvatinib (last search on 8 October 2021)
- search on the G-BA website for lenvatinib + pembrolizumab (last search on 18 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 check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: lenvatinib + pembrolizumab 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 [4]	Yes [5,6]	Yes [7-9]

a. Study sponsored by the company.
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 lenvatinib + pembrolizumab 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). This approach departs from the company's, whose dossier assessed added benefit on the basis of the originally specified ACT (excluding the treatment option of paclitaxel monotherapy) and therefore used the subpopulation of patients for whom the investigator made the pre-randomization selection of doxorubicin treatment.

2.3.2 Study characteristics

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

Table 6: Characterization of the included study – RCT, direct comparison: lenvatinib + pembrolizumab 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 carcinoma and ▪ disease progression following prior treatment with systemic, platinum-containing chemotherapy[b] ▪ Maximum of 1 prior systemic chemotherapy (except adjuvant or neoadjuvant)[c] ▪ ECOG-PS 0 or 1	Lenvatinib + pembrolizumab (N = 411) Therapy according to physician's choice, selecting from doxorubicin or paclitaxel (N = 416) Subpopulation analysed by the company[d]: Lenvatinib + pembrolizumab (N = 298) Doxorubicin (N = 307)	Screening: 28 days Treatment: until confirmed disease progression[e], unacceptable toxicity, withdrawal of consent, or until completion of at most 24-month treatment with pembrolizumab[f] or cumulative life-long dose of 500 mg/m² doxorubicin. Follow-up observation: outcome-specific, at the longest until death, withdrawal of consent, lost 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 6/2018 – ongoing Data cut-off: 26/10/2020[g]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Patients were to have received a maximum of 2 prior platinum-containing chemotherapies, provided that 1 was administered as a neoadjuvant or adjuvant.
c. There were no limitations on hormone therapy prior to study inclusion.
d. Patients for whom the investigator made the pre-randomization choice of doxorubicin treatment.
e. 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 that the patient did not exhibit intolerance.
f. 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 pembrolizumab cycles 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 phase).
g. Prespecified interim analysis.

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

Study	Intervention	Comparison
KEYNOTE 775/309	Lenvatinib 20 mg orally, once daily + Pembrolizumab 200 mg i.v., every 3 weeks	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 ▪ Lenvatinib: incremental dose reductions possible to 14, 10 or 8 mg daily; treatment interruptions[b]/discontinuations due to toxicity allowed ▪ Pembrolizumab: no dose modification allowed; treatment interruption[b]/discontinuation due to toxicity allowed ▪ In case of discontinuation of lenvatinib or pembrolizumab, continued administration of the other drug (pembrolizumab or lenvatinib) was allowed. **Permitted pretreatment** ▪ Maximum of 1 prior systemic chemotherapy (except as an adjuvant or neoadjuvant) ▪ Maximum of 2 prior platinum-containing chemotherapies, so long as 1 of them was administered as a neoadjuvant or adjuvant ▪ No restrictions on prior hormone therapies **Nonpermitted 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] **Nonpermitted concomitant treatment** ▪ Other antineoplastic therapies such as chemotherapies, hormone therapies, radiotherapies (see above for exceptions), surgical interventions, and immunotherapies	

a. Applied 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 lenvatinib + pembrolizumab versus therapy according to physician's choice, selecting from doxorubicin and paclitaxel.

The study included adult patients with advanced or recurrent endometrial carcinoma and disease progression following systemic, platinum-containing chemotherapy. The approved therapeutic indication, however, also includes patients whose disease progression occurred while they were on prior platinum-containing therapy.

b. Patients were to have received a maximum of 2 prior platinum-containing chemotherapies, provided 1 of them was administered as a neoadjuvant or adjuvant. Furthermore, patients were 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 ≤ 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 included 827 patients. Prior to randomization, the investigator defined, based on criteria not specified in detail, which of the 2 options (doxorubicin or paclitaxel) was to be used for the therapy according to physician's choice in the event that the patient was allocated to the comparator arm. Patients were then randomized at a 1:1 ratio to either lenvatinib + pembrolizumab treatment (N = 411) or therapy according to physician'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).

Lenvatinib and pembrolizumab treatment in the intervention arm was largely in compliance with the specifications of the SPCs [10,11]. Deviating from the SPC, treatment with pembrolizumab was limited to a maximum duration of 35 cycles (approx. 24 months). According to the SPC, pembrolizumab treatment should be continued until cancer progression or unacceptable toxicity [10]. In the KEYNOTE 775/309 study, however, only 3 patients (0.7%) from the total population of the intervention arm reached the 35 treatment cycles; therefore, the deviations between the SPC and study protocol in their specifications of treatment duration are negligible.

Doxorubicin treatment in the comparator arm was in compliance with the SPC [12].

Paclitaxel is not approved in the therapeutic indication [13]. 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 the dosage of paclitaxel for the

present therapeutic indication [14]. The European guideline issued by ESGO, ESTRO, and ESP discusses weekly administration of paclitaxel as second-line therapy, but without any information on dosage, for patients with recurrent disease [15]. 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 patients in the comparator arm (7.7%) had already switched to lenvatinib + pembrolizumab treatment.

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 C, 26 October 2020, had been prespecified as the 1st interim analysis for overall survival after about 368 deaths in the study population 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.

Implementation of the ACT

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

- Endocrine therapy (medroxyprogesterone acetate, megestrol acetate)
- Systemic chemotherapy, potentially including platinum-containing 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 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 physician's choice consisting of either 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. This is explained below.

A review was conducted to determine the extent to which treatment options listed in the ACT other than doxorubicin and paclitaxel represent suitable treatments of physician's choice for the included patients.

Because the KEYNOTE 775/309 study's participants are in good general health, as determined by its inclusion criteria (ECOG-PS of 0 or 1 and adequate organ function in all participants), BSC alone and hormone therapy are to be deemed options of lesser importance. For instance, the S3 Guideline on the Diagnosis, Treatment, and Follow-up of Patients with Endometrial Cancer [14] describes hormone therapy as a treatment frequently administered to patients with recurrent endometrial carcinoma and reduced general health or advanced age. However, uncertainty remains regarding the eligibility of KEYNOTE 775/309 participants for hormone therapy. While both hormone receptor status and tumour grading are likely to affect response to hormone therapy, hormone receptor status was not surveyed, and no information was available on tumour grading at baseline [14,15].

According to the inclusion criteria, all patients in the KEYNOTE 775/309 study have already received at least 1 platinum-containing therapy. As per guidelines, platinum-containing re-treatment may be an option particularly in patients with an extended platinum-free interval (> 12 months) [15,16]. The combination of carboplatin and paclitaxel is described as the standard in first-line therapy of advanced/recurrent endometrial carcinoma [14,15]. According to the European Public Assessment Report (EPAR) on lenvatinib and pembrolizumab, about 35% of patients received the study medication as first-line treatment of the advanced/metastatic stage [7,8]. However, few of these patients had a platinum-free interval ≥ 12 months [8]; the median platinum-free interval was 6.2 months in the intervention arm and 5.6 months in the comparator arm [7]. Overall, platinum-containing re-treatment, including the platinum-containing treatment options of the ACT, are therefore rated as treatment options of lesser importance for KEYNOTE 775/309 participants.

On the basis of the originally defined SPC excluding the treatment option of paclitaxel monotherapy, the company argues in its dossier that G-BA-specified drugs and drug combinations other than doxorubicin are to be deemed of lesser importance and that the inclusion of BSC as an ACT is not appropriate. With regard to the importance of platinum-containing re-treatment and hormone therapy in the KEYNOTE 775/309 population, the company cites some arguments similar to those stated above. On the basis of the originally specified ACT, the company concludes that a comparison with doxorubicin is suitable for reflecting a relevant part of healthcare practice in Germany. Regarding the frequency of use of doxorubicin, the company refers to healthcare data it submitted as part of the benefit assessment procedure of dostarlimab in Module 3 A [17]. Based on the originally specified ACT, the company used for its assessment of added benefit the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment.

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 described uncertainties with regard to potential alternative treatment options as well as the dosing regimen of paclitaxel. However, the study allows drawing conclusions on the added benefit of lenvatinib + pembrolizumab 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.

Subpopulation submitted by the company:

As described above, based on the originally specified ACT, Module 4 C of the company's dossier presents data for the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment, and the company uses these patients to assess added benefit. However, in this situation, the total population of the KEYNOTE 775/309 study is relevant for the benefit assessment because both treatment options administered in the study's comparator arm are included in the adjusted ACT. Compared to data on the subpopulation presented by the company, data on the total population therefore provide a more comprehensive picture of added benefit versus the 2 ACT options. In this situation, it is therefore appropriate to analyse the total population, on which the dossier's Module 4 C does not contain any data. Nor does the information provided in the study report permit a comprehensive conclusion regarding any benefit or harm for the total population; this is because the study does contain data on overall survival, but not data such as time-to-event analyses for the outcomes on side effects.

2.4 Results on added benefit

In the present situation, the total population of the KEYNOTE 775/309 study is relevant for the assessment because, compared to the subpopulation presented by the company, it offers a more

comprehensive picture on added benefit in comparison with 2 ACT options. However, the company's dossier does not present sufficient data on the assessment-relevant total population of adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

See the section below for the derivation of added benefit.

2.5 Probability and extent of added benefit

In the present situation, it is appropriate to analyse the total population of the KEYNOTE 775/309 study. However, the company's dossier fails to provide sufficient data for the total population relevant for the assessment.

The G-BA simultaneously commissioned IQWiG with the benefit assessments of lenvatinib (commission A21-162) and pembrolizumab (commission A21-164), each in combination with the other drug, for the present therapeutic indication. In both dossiers, the respective companies presented results from the same study, KEYNOTE 775/309, using the same data cut-off [18,19]. However, in benefit assessment A21-164 Pembrolizumab, Appendix 4 G of the company's dossier (unlike the company's dossier for benefit assessment A21-162 lenvatinib) also presented results for the assessment-relevant total population of the KEYNOTE 775/309 study, on the basis of which more comprehensive conclusions on the added benefit of pembrolizumab + lenvatinib in comparison with 2 ACT options can be drawn [19]. In this special situation, for the overall conclusion on the added benefit of lenvatinib + pembrolizumab, reference is therefore made to the information provided in benefit assessment A21-164 Pembrolizumab (endometrial carcinoma) [20].

Referencing benefit assessment A21-164 Pembrolizumab (endometrial carcinoma) [20], in summary, an indication of considerable added benefit was found for lenvatinib + pembrolizumab in comparison with the ACT for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation and for whom doxorubicin or paclitaxel is the appropriate therapy according to physician's choice.

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

Table 8 summarizes the result of the assessment of added benefit of lenvatinib + pembrolizumab in comparison with the ACT.

Table 8: Lenvatinib + pembrolizumab – extent and probability 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 chemotherapy 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 within the framework of therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include 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]), and BSC alone. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. The KEYNOTE 775/309 study included only patients with an ECOG-PS of 0 or 1 and disease progression following prior treatment with platinum-containing therapy. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients with disease progression on prior treatment with platinum-containing therapy.

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

This 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 on 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 added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Lenvatinib (Neues Anwendungsgebiet: Endometriumkarzinom, nach Platin-basierter Therapie, Kombination mit Pembrolizumab); zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/776/#zweckmaessige-vergleichstherapie].

4. Eisai. A Multicenter, Open label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer; study KEYNOTE-775/309; clinical study report [unpublished]. 2021.

5. Eisai. A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer [online]. [Accessed: 08.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-004387-35.

6. Eisai. Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775]) [online]. 2021 [Accessed: 08.02.2022]. URL: https://ClinicalTrials.gov/show/NCT03517449.

7. European Medicines Agency. Keytruda; Assessment report [online]. 2021 [Accessed: 04.03.2022]. URL: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0105-epar-assessment-report-variation_en.pdf.

8. European Medicines Agency. Lenvima; Assessment report [online]. 2021 [Accessed: 04.03.2022]. URL: https://www.ema.europa.eu/documents/variation-report/lenvima-h-c-003727-ii-0042-epar-assessment-report-variation_en.pdf.

9. Makker V, Colombo N, Casado Herraez A et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022; 386(5): 437-448. https://dx.doi.org/10.1056/NEJMoa2108330.

10. MSD. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2022 [Accessed: 04.03.2022]. URL: https://www.fachinfo.de.

11. Eisai. Lenvima 4 mg/10 mg Hartkapseln [online]. 2021 [Accessed: 04.03.2022]. URL: https://www.fachinfo.de.

12. HEXAL. Doxorubicin HEXAL 2 mg/ml [online]. 2020 [Accessed: 05.04.2022]. URL: https://portal.cgmlauer.cgm.com/LF/default.aspx?p=12000.

13. Fresenius Kabi. Paclitaxel Kabi 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2020 [Accessed: 04.03.2022]. URL: https://www.fachinfo.de.

14. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3 Leitlinie Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom [online]. 2018 [Accessed: 04.03.2022]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/LL_Endometriumkarzinom_Langversion_1.0.pdf.

15. Concin N, Matias-Guiu X, Vergote I et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021; 31(1): 12-39. https://dx.doi.org/10.1136/ijgc-2020-002230.

16. Colombo N, Creutzberg C, Amant F et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016; 27(1): 16-41. https://dx.doi.org/10.1093/annonc/mdv484.

17. GlaxoSmithKline. Dostarlimab (Jemperli); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 06.10.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/708/#dossier.

18. Eisai. Lenvatinib (Lenvima); Dossier zur Nutzenbewertung gemäß § 35a SGB V. [Soon available under https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/776/#dossier].

19. MSD Sharp & Dohme. Pembrolizumab (Keytruda); Dossier zur Nutzenbewertung gemäß § 35a SGB V. 2021: [Soon available under https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/777/#dossier].

20. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Endometriumkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022. URL: https://www.iqwig.de/projekte/a21-164.html.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-162.html.