NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from MSD

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Peaches Womb Cancer Trust
   b. NCRI-ACP-RCP-RCR

4. **Evidence Review Group report** prepared by PenTAG

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from MSD**
   a. TE response – addendum

7. **Technical engagement responses and statements from experts:**
   a. Dr Clare Green, Medical Oncologist - clinical expert, nominated by MSD
   b. Helen White - patient expert, nominated by Peaches Womb Cancer Trust
   c. Gracey Remmington Teeling – patient expert, nominated by Peaches Womb Cancer Trust
   d. Dr Susan Lalondrelle, Consultant Clinical Oncologist – clinical expert, nominated by the Royal College of Physicians (*see item 3b*)

8. **Technical engagement responses from consultees and commentators:**
   a. Eisai (commentator)

9. **Evidence Review Group critique of company response to technical engagement** prepared by PenTAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID3811 KN775 NICE STA Document B	V3	Yes	15 June 2022

Contents

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated advanced, metastatic or recurrent endometrial cancer	Adults with advanced or recurrent endometrial cancer who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation	Aligned to anticipated marketing authorisation
Intervention	Pembrolizumab with lenvatinib	Pembrolizumab with lenvatinib (PEM+LEN)	Not applicable
Comparator(s)	• Chemotherapy (such as paclitaxel, carboplatin, doxorubicin and cyclophosphamide) • Hormone therapy (such as medroxyprogesterone acetate and megestrol) • Best supportive care	• Chemotherapy (such as paclitaxel, carboplatin, doxorubicin)	Active comparators aligned with BGCS evidence-based recommendations[1] and clinical expert consultation[2]: • Cyclophosphamide is not used to treat advanced or recurrent EC. • Hormone therapy is only used if all other treatment options are exhausted or patients cannot tolerate further lines of chemotherapy and even then hormone therapy has a palliative intent rather than an expectation of clinical response; this is not the target position for PEM+LEN • Best supportive care reserved for patients not fit for active treatment; this is not the target position for PEM+LEN
Outcomes	• Progression-free survival • Overall survival • Response rates • Adverse effects of treatment	• Progression-free survival • Overall survival • Response rates • Adverse effects of treatment	Not applicable.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life	• Health-related quality of life	
Key: BGCS, British Gynaecological Cancer Society; PEM+LEN, pembrolizumab with lenvatinib.			

B.1.2. Description of the technology being appraised

The summary of product characteristics and the European public assessment report for KEYTRUDA® are presented in Appendix C.

The technology, pembrolizumab with lenvatinib (PEM+LEN), is described in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Lenvatinib (Lenvima®) Pembrolizumab (KEYTRUDA®)
Mechanism of action	Lenvatinib is an RTK inhibitor that selectively inhibits the kinase activities of VEGF receptors VEGFR1 (*FLT1*), VEGFR2 (*KDR*), and VEGFR3 (*FLT4*), in addition to other proangiogenic and oncogenic pathway-related RTKs. Lenvatinib has shown antiangiogenic properties in vitro and in vivo, and direct inhibition of tumour growth was also observed in in vitro models. Pembrolizumab is a humanized monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.
Marketing authorisation status	Pembrolizumab does have a UK marketing authorisation for the indication under appraisal. EMA approval was granted on 15 November 2021, and MHRA approval was granted on 22 November 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication under appraisal is[3]: 'KEYTRUDA (pembrolizumab), in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.' Pembrolizumab, as monotherapy or in combination with other agents, is licensed for specific indications in: • Melanoma • Non-small cell lung cancer • Classical Hodgkin lymphoma

	• Urothelial carcinoma • Head and neck squamous cell carcinoma • Renal cell carcinoma • Colorectal cancer • Oesophageal cancer • Triple-negative breast cancer • Endometrial carcinoma
Method of administration and dosage	The recommended dose of lenvatinib for endometrial cancer is 20 mg once daily self-administered orally via a hard capsule. The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. In KEYNOTE-775, treatment with pembrolizumab and lenvatinib continued until disease progression, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months.
Additional tests or investigations	No additional tests or investigations above those used to diagnose endometrial cancer in the first instance are needed prior to initiation of PEM+LEN.
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial and the total cost per administration is £5,260.
Patient access scheme (if applicable)	A patient access scheme (PAS) has been agreed with NHS England, with [redacted], therefore 200mg administration of pembrolizumab will cost [redacted] Due to the highly confidential nature of this figure MSD requests that documentation from the Assessment Group does not include the PAS price and instead references back to this table. Please note not to publish ICERs with applied discounts.
Key: EMA, European Medicines Agency; ICER, incremental cost-effectiveness ratio; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RTK, receptor tyrosine kinase; SmPC, summary of product characteristics; VEGF, vascular endothelial growth factor.	

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Health condition

Endometrial cancer (EC) is a cancer of the lining of the womb (uterus), known as the endometrium. Accounting for 94% of all cases of uterine cancer (UC)[4], EC and UC terminology are often used interchangeably. There were 8,081 new cases of UC reported in England for 2019 (ICD10 code C54) with incidence trends observed to be increasing over time.[5] Incidence rates are highest in people aged 75–79, and approximately 85% of cases are diagnosed in people aged ≥ 55 years.[5]

The most common symptom of EC is abnormal bleeding from the vagina, especially in people who have stopped having periods (post-menopausal women).[6] This common and obvious symptom allows EC to be diagnosed early in most cases, with only 16% of people diagnosed with advanced EC where the cancer has spread outside the womb (Stage III) or beyond the womb, bowel or bladder (Stage IV).[7] When diagnosed at its earliest stage (Stage I), over 90% of people with UC will survive their disease for 5 years or more, compared with 15% of people when the disease is diagnosed at the latest stage (Stage IV).[4]

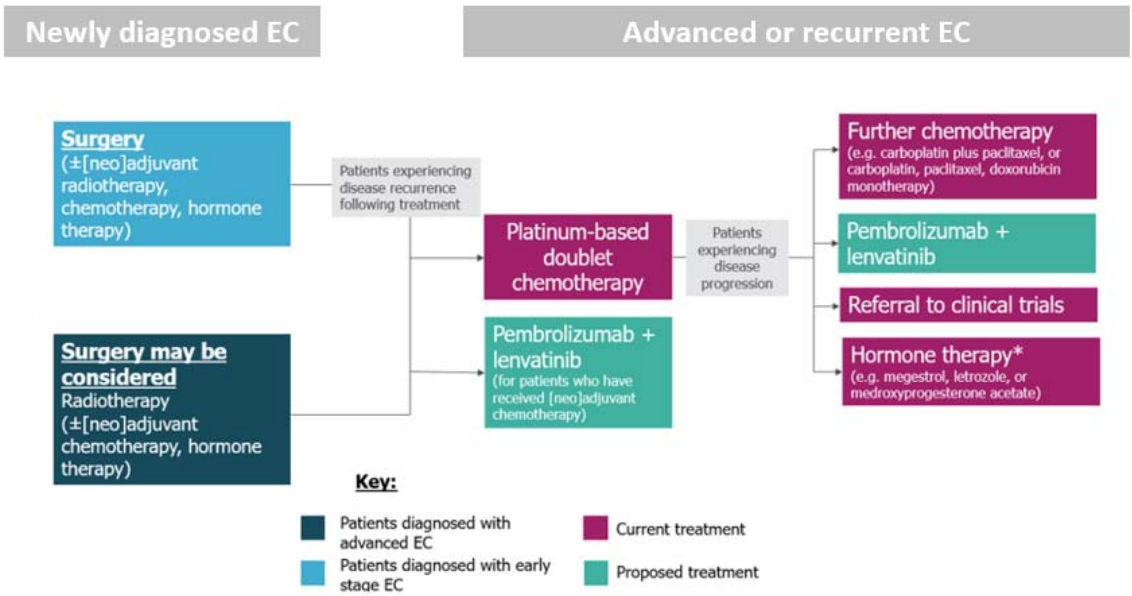
Approximately 13% of all cases of EC recur, with the risk of recurrence higher in people who are diagnosed with later-stage disease, who have Type II histology (endometrioid grade 3 and non-endometrioid carcinomas), who are older, and who have positive progesterone receptor expression.[8, 9] Like advanced disease, recurrent disease is associated with poor prognosis; the 5-year survival rate for people with recurrent disease is 20%, compared with 89% for people without recurrent disease (survival from diagnosis).[8] Patient health-related quality of life (HRQL) is also reported to decrease with disease recurrence, with an associated increase in anxiety and depression and more threatening illness perceptions reported after diagnosis of relapse.[10]

People with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy are unlikely to live beyond a year with current treatment options (see Section B.2.13.4).[2, 11]

B.1.3.2. Clinical pathway of care

The typical clinical pathway of care for people with EC in England, based on the British Gynaecological Cancer Society (BGCS) Guidelines[1] and validated by practicing clinicians is depicted in Figure 1. Detailed recommendations from BGCS Uterine Cancer Guideline Recommendations for Practice 2021 are provided in Appendix L.

Figure 1: Clinical pathway of care for people with endometrial cancer in England



Key: EC: endometrial cancer.
Notes: *hormone therapy is only used when all other treatment options have been exhausted or further chemotherapy cannot be tolerated.
Source: Adapted from BGCS treatment guidelines.[1]

Little progress has been made in EC management over the past decade, and there is no standard of care beyond platinum-based chemotherapy (carboplatin and paclitaxel) for advanced or recurrent EC, as acknowledged in the BGCS Guidelines.[1, 2, 12]

Platinum rechallenge is most likely used to treat people with advanced or recurrent EC who have only received platinum-based chemotherapy in the (neo)adjuvant setting.[1] There is no consensus on a standard treatment for people with advanced or recurrent EC who have received platinum-based chemotherapy in the systemic

setting, with limited efficacious treatments available for this patient population, and no treatment option demonstrating superiority over another in a robust clinical trial setting.[12]

Platinum rechallenge may be considered in people who relapse more than six months after first-line platinum-based chemotherapy.[1] Alternative treatment options are currently limited to non-platinum chemotherapy (paclitaxel or doxorubicin monotherapy) or hormone therapy, neither of which have proven efficacy and in practice are associated with low effect expectations and tolerability concerns.[2] Hormone therapy is specifically reserved for use only when all other treatment options have been exhausted or further lines of chemotherapy cannot be tolerated, and even then hormone therapy has a palliative intent rather than an expectation of clinical response.[2]

Pembrolizumab with lenvatinib (PEM+LEN) is intended as a new treatment option for adults with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting, and who are not candidates for curative surgery or radiation, aligning with its marketing authorization (Table 2). The most common position of use for PEM+LEN is expected to be after platinum-based chemotherapy in the systemic setting, aligning with the current evidence base for PEM+LEN (see Document A, Section A.6). Based on real-world evidence (see Section B.2.9), approximately [redacted] of people with advanced or recurrent EC previously treated with systemic therapy in the UK receive paclitaxel or doxorubicin monotherapy in current practice with the remaining [redacted] a mixture of platinum-based chemotherapy, such as carboplatin monotherapy or carboplatin and paclitaxel (data on file).

B.1.4. Equality considerations

No equality issues are foreseen.

B.2. Clinical effectiveness

Study identification

- A systematic literature review (SLR) identified two studies that provide efficacy and safety evidence for PEM+LEN in adult patients with advanced or recurrent endometrial cancer (EC) who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation:
  - Single-arm Phase Ib/II study, KEYNOTE-146 (NCT02501096)
  - Phase III randomised controlled trial (RCT), KEYNOTE-775 (NCT03517449)
- KEYNOTE-146 demonstrated that PEM+LEN provided a clinically meaningful objective response rate (ORR) (38.0%; 95% CI: 28.8, 47.8) in patients with previously treated EC
- KEYNOTE-775 is the subsequent confirmatory study for the results observed in KEYNOTE-146, and forms the main clinical evidence base for this submission

Efficacy

- The dual primary endpoints of progression free survival (PFS) and overall survival (OS) were met in KEYNOTE-775:[13]
  - PEM+LEN offers significant and clinically meaningful improvements in PFS (median PFS: 7.2 vs. 3.8 months), OS (median OS: 18.3 vs. 11.4 months), and overall response rate (ORR) (31.9% vs. 14.7%) compared with TPC in an all-comer population
  - Treatment with PEM+LEN also offers significant and clinically meaningful improvements in duration of response (DOR) (14.4 vs. 5.7 months) compared with TPC in an all-comer population
  - Across all patients with advanced EC, no substantial differences were observed in health-related quality of life (HRQoL)
- KEYNOTE-775 trial is the first randomised, controlled Phase III study evaluating a novel combination therapy in the previously treated advanced EC setting that has demonstrated positive results for both primary endpoints of OS and PFS across a broad range of participants, demonstrating the synergistic molecular effects of immune-oncology (IO) and tyrosine kinase inhibitor (TKI) therapy

Safety

- The KEYNOTE-775 trial demonstrates a safety profile consistent with the known safety profile of PEM+LEN, with similar overall incidence of treatment-emergent adverse events (TEAEs) and treatment-related AEs (TRAEs) across both arms[13]

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the systematic literature review (SLR) process and methods used to identify and select the clinical evidence relevant to the technology being appraised. Two studies were identified that provide efficacy and safety evidence for PEM+LEN in people with advanced or recurrent EC.

B.2.2. List of relevant clinical effectiveness evidence

Details of the PEM+LEN clinical effectiveness evidence are provided in Table 3.

The pivotal trial providing evidence of the clinical benefits of PEM+LEN is KEYNOTE-775: a Phase III trial comparing the efficacy and safety of PEM+LEN versus treatment of physician's choice (TPC: doxorubicin or paclitaxel monotherapy) in adults with advanced or recurrent EC. This pivotal trial informs the economic model presented in Section B.3.

Supportive evidence is provided by the earlier KEYNOTE-146 trial: a Phase Ib/II designed to (i) determine the maximum tolerated dose for lenvatinib in combination with 200 mg intravenous (IV) pembrolizumab every 3 weeks, and (ii) evaluate the efficacy and safety of PEM+LEN in people with solid tumours, including EC. This trial provides almost 3 years of median follow-up compared with the approximate 1 year median follow-up of KEYNOTE-775 and is therefore used to validate model extrapolations.

Table 3: Clinical effectiveness evidence

Study	KEYNOTE-775				KEYNOTE-146				
Study design	Multi-centre, open-label, randomised Phase III trial				Multi-centre, open-label, single-assignment Phase Ib/II basket trial				
Population	People with advanced (including metastatic) or recurrent EC who have disease progression following prior systematic therapy with platinum chemotherapy, and are not candidates for curative surgery or radiation.				Phase Ib: people with selected tumour types[a] who have progressed after treatment with approved therapies or for whom there are no standard effective therapies available. Phase II: people with metastatic selected solid tumour types who have received 0−2 prior lines of systemic therapy.				
Intervention(s)	PEM+LEN (n = 411)				PEM+LEN: Total EC (n = 124) Pre-treated EC (n = 108)				
Comparator(s)	TPC consisting of either doxorubicin or paclitaxel monotherapy (n = 416)				Not applicable				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes		**Indicate if trial used in the economic model**	Yes	
	No			No		No	✗		No	✗

Study	KEYNOTE-775	KEYNOTE-146
Rationale for use/non-use in the model	Pivotal trial providing comparative data for PEM+LEN vs standard care for people with advanced[a] or recurrent EC.	Early trial providing non-comparative data for PEM+LEN with longer-term follow-up; used to validate model extrapolations.
Reported outcomes specified in the decision problem	• **Progression-free survival** • **Overall survival** • Response rates • **Adverse effects of treatment** • **Health-related quality of life**	• Progression-free survival • Overall survival • Response rates • Adverse effects of treatment
All other reported outcomes	• Time to response • Duration of response • Disease control rate • Clinical benefit rate • Progression-free survival on next-line therapy	• Duration of response • Maximum tolerated dose (Ib) • Dose limiting toxicity (Ib)
Key: EC, endometrial cancer; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice. **Notes:** [a] Non-small-cell lung cancer, renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma. Bolded outcomes represent those incorporated into the model.		

Full details of the pivotal trial (KEYNOTE-775) are provided in Sections B.2.2 to B.2.6 of this submission. Relevant outcomes of the supportive trial (KEYNOTE-146) are provided in Section B.2.6; details of the methods and population are provided in Appendix O and safety data are provided in Appendix F.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

A summary of the trial methodology for KEYNOTE-775 is presented in Table 4.

KEYNOTE-775 is an ongoing Phase III, multi-centre, randomised, open-label study investigating the efficacy and safety of treatment with PEM+LEN compared with TPC.[14]. TPC consisted of either doxorubicin or paclitaxel monotherapy, which were chosen to reflect standard clinical practice.

The primary objective was to demonstrate that treatment with PEM+LEN is superior to TPC in improving PFS and OS.[3] The study is being conducted at 167 centres in 21 countries, with nine sites in the UK (Table 4). The first patient was enrolled on 11 June 2018, and the estimated study completion date is 25 January 2023.

Both proficient mismatch repair (pMMR) patients and deficient mismatch repair (dMMR) patients were eligible for the trial.[3] Approximately 15% of patients with dMMR were planned to be enrolled, to align with the expected prevalence of dMMR EC in this treatment setting.

B.2.3.1. Trial design

Eligible patients were randomly assigned in a 1:1 ratio to receive one of the following treatment arms:

- Arm A: pembrolizumab 200 mg administered via IV every 3 weeks (Q3W) up to 35 cycles, plus lenvatinib 20 mg every day (QD)
- Arm B: TPC consisting of either doxorubicin 60 mg/m2 Q3W up to a maximum cumulative dose of 500 mg/m2 or paclitaxel 80 mg/m2 every week (QW) on a 28 day cycle, 3 weeks on and 1 week off[3]

The KEYNOTE-775 trial design is presented in Figure 2. The trial consisted of three phases: screening, treatment and efficacy follow up.[3, 14] The screening period occurred for a duration of 28 days, during which informed consent was obtained and protocol eligibility was established according to the pre-determined inclusion and exclusion criteria. Eligible patients went on to complete the treatment period, which lasted from the time of randomisation until the completion of the end of treatment (EOT) visit. Patients received study treatment as continuous 21-day cycles (for patients treated with PEM+LEN and doxorubicin as the TPC choice), or continuous 28-day cycles (for patients receiving weekly paclitaxel as the TPC choice). The efficacy follow-up period is measured from the day after the EOT visit, and will continue for the duration of each patient's lifetime, or until the data cut-off date for the primary OS analysis if the participant is still alive.

Figure 2: KEYNOTE-775 trial design

Key: TPC, treatment by physician's choice.

Table 4: Summary of KEYNOTE-775 trial methodology

Trial name	KEYNOTE-775 (NCT03517449)
Location	International, multi-centre trial with 167 sites across 21 countries, including nine sites in the United Kingdom (other sites were located in Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Ireland, Israel, Italy, Japan, Korea, Mexico, New Zealand, Poland, Russia, Spain, Taiwan, Turkey and US)
Trial design	Multi-centre, randomised, open-label, Phase III study
Method of randomisation	Patients were randomised in a 1:1 ratio to receive PEM+LEN or TPC. Randomisation followed a predefined randomisation scheme based on the following stratification factors: • MMR status (pMMR or dMMR) • ECOG performance status (0 or 1) • Geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world) • Prior history of pelvic radiation (yes or no) First, patients were stratified according to MMR status. Patients within the pMMR stratum were further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata were used for the study.
Eligibility criteria for patients	**Key inclusion criteria:** • Female patients who were ≥18 years of age • Histologically confirmed EC • Documented evidence of advanced, recurrent, or metastatic EC • Radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC (participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting) [a]

	• Provided a fresh or archival tumour sample for determination of MMR status • Had at least 1 measurable target lesion according to RECIST 1.1, including a non-nodal target lesion ≥1 cm in the longest diameter and lymph node lesion that measured ≥1.5 cm in the short axis • ECOG Performance Status of 0 or 1 within 7 days of starting treatment • Adequately controlled blood pressure with or without antihypertensive medications (defined as ≤150/90 mm Hg at screening) **Key exclusion criteria:** • Had carcinosarcoma (malignant mixed Müllerian tumour), endometrial leiomyosarcoma and endometrial stromal sarcomas • Had central nervous system metastases, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study • Had gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib • Had a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula • Had significant cardiovascular impairment within 12 months of the first dose of study drug Full eligibility criteria are provided in Appendix N.1.
Trial drugs and method of administration	**Intervention (n=411)** Pembrolizumab (200 mg administered intravenously, every 3 weeks on Day 1 of a 21-day cycle; 35 doses maximum) plus lenvatinib (20 mg taken orally once daily) **Comparator (n=416)** Doxorubicin (60 mg/m2 administered intravenously, every 3 weeks on Day 1 of a 21-day cycle) or paclitaxel (80 mg/m2 administered intravenously, every week on Days 1, 8 and 15 of a 28-day cycle)[a] Participants continued to receive study treatment until disease progression was confirmed by BICR, development of unacceptable toxicity, withdrawal of consent, receipt of 35 administrations of pembrolizumab (approximately 2 years), or a lifetime cumulative dose of 500 mg/m² of doxorubicin Pembrolizumab and doxorubicin/paclitaxel were administered in the clinic by qualified site personnel, whilst lenvatinib was dispensed to patients for oral self-administration
Permitted and disallowed concomitant medication	**Permitted concomitant medications:** • Hormone replacement therapy • Thyroid hormone suppressive therapy

	• Adjuvant hormonal therapy for history of definitively treated breast cancer • Anticoagulants including low molecular weight heparin, warfarin, anti-Xa agents • Anti-inflammatory agents • Bisphosphonates or denosumab • Antihypertensive therapy (including additional antihypertensive treatment as appropriate if blood pressure increases once the participant is enrolled) • Palliative radiotherapy to non-target bone metastases or brain lesions may be permitted after consultation **Disallowed concomitant medications:** • Concurrent anticancer therapies such as chemotherapy, targeted therapies, hormonal therapy directed at EC, radiotherapy, antitumour interventions, or cancer immunotherapy • Other concurrent investigational drugs • Live vaccines • Systemic glucocorticoids for any purpose other than to modulate symptoms from an AR that is suspected to have immunologic aetiology
Primary endpoints	• PFS, defined as the time from date of randomisation to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause, whichever occurs first • OS, defined as the time from date of randomisation to date of death from any cause
Key secondary endpoints	• ORR, defined as the proportion of patients who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1 • HRQL, assessed using the global score of the EORTC QLQ-C30 – The EORTC QLQ-C30 physical functioning score, EORTC QLQ EN24 urological symptoms score and the EQ-5D-5L VAS score were included as exploratory endpoints • Incidence of treatment emergent AEs, SAEs, and immune-related AEs • Proportion of patients discontinuing study treatment due to treatment emergent AEs • Time to treatment failure due to toxicity, defined as the time from the date of randomisation to the date that a participant discontinues the study treatment due to treatment-emergent AEs[b] • Plasma concentration vs. time, clearance and AUC for lenvatinib[b]
Subgroup analysis	Pre-specified subgroup analyses were performed in the all-comer population for PFS, OS and ORR. The subgroup analyses were conducted using the same methods described for the primary

	efficacy endpoints (see Table 7) and were based on the following baseline demographic and disease characteristics: • Age (<65, ≥65 years) • Race (White, Asian, other) • Region (Region 1, Region 2) • MMR status (pMMR, dMMR) • ECOG status (0, 1) • Prior history of pelvic radiation (yes, no) • Histology (endometrioid, non-endometrioid) • Prior lines of therapy (1, 2, ≥3)
Key: AE: adverse event; AUC, area under the curve; BICR: Blinded Independent Central Review; CBR: clinical benefit rate; CR: complete response; CSR: clinical study report; DCR : disease control rate; dMMR: deficient mismatch repair; DOR: duration of response; ECOG : Eastern Cooperative Oncology Group; EORTC, European Organisation for the Research and Treatment of Cancer; HRQL: health-related quality of life; LVEF: Left ventricular ejection fraction; MMR: mismatch repair; ORR: overall response rate; OS: overall survival; PD: progressive disease; PEM+LEN, pembrolizumab with lenvatinib; PFS: progression free survival; PFS2: progression free survival on next line therapy; pMMR: proficient mismatch repair; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; SD: standard deviation; TTR: time to response; VAS, visual analogue scale. **Notes:** [a], There was no restriction regarding prior hormonal therapy; [b], These endpoints have not been presented as part of this submission but are available in the CSR. **Source:** KEYNOTE-775 Clinical Study Report.[3]	

B.2.3.2. Baseline characteristics

The baseline characteristics for patients evaluated in the KEYNOTE-775 trial are presented in Table 5.

The baseline demographic and disease characteristics are representative of a patient population with advanced EC. The two treatment groups were generally well balanced for all baseline characteristics. In the intention-to-treat (ITT) population, most patients were white, non-Hispanic, had a median age of 65 years, and had an ECOG performance status of 0.[3] The most frequently reported metastatic site at baseline per investigator assessment were lymph node, intra-abdominal, lung and liver. Multiple histopathological subtypes were presented in both treatment groups, with the majority of carcinomas classified as endometrioid, though carcinoma non-endometrioid subtypes were also well represented.

Table 5: Baseline characteristics for KEYNOTE-775

Characteristic	PEM+LEN (n=411)	TPC (n=416)
Sex, n (%)		
Female	411 (100)	416 (100)
Age in years, n (%)		

<65	206 (50.1)	204 (49.0)
≥65	205 (49.9)	212 (51.0)
Mean (SD)	63.2 (9.1)	63.8 (9.2)
Median (min, max)	64.0 (30, 82)	65.0 (35, 86)
Race, n (%)		
Asian	85 (20.7)	92 (22.1)
Black or African American	17 (4.1)	14 (3.4)
White	261 (63.5)	246 (59.1)
Other	12 (2.7)	20 (4.8)
Age in years at initial diagnosis, n (%)		
<65	253 (61.6)	255 (61.3)
≥65	158 (38.4)	161 (38.7)
Mean (SD)	61.3 (9.1)	61.5 (9.3)
Median (min, max)	62.4 (30, 81)	62.1 (27, 84)
Region,[a] n (%)		
Region 1	234 (56.9)	240 (57.7)
Region 2	177 (43.1)	176 (42.3)
MMR Status, n (%)		
pMMR	346 (84.2)	351 (84.4)
dMMR	65 (15.8)	65 (15.6)
ECOG, n (%)		
0	246 (59.9)	241 (57.9)
1	164 (39.9)	175 (42.1)
3	1 (0.2)	0 (0.0)
Prior history of pelvic radiation, n (%)		
Yes	168 (40.9)	173 (41.6)
No	243 (59.1)	243 (58.4)
Elapsed time in years from initial diagnosis		
Mean (SD)	2.4 (2.4)	2.9 (2.8)
Median (min, max)	1.7 (0, 21)	2.1 (0, 26)
Histology of initial diagnosis, n (%)		
Clear cell carcinoma	30 (7.3)	17 (4.1)
Endometrioid carcinoma	83 (20.2)	103 (24.8)
Endometrioid carcinoma with squamous differentiation	7 (1.7)	7 (1.7)
High grade endometrioid carcinoma	94 (22.9)	90 (21.6)
High grade mucinous carcinoma	0 (0.0)	1 (0.2)
High grade serous carcinoma	65 (15.8)	65 (15.6)
Low grade endometrioid carcinoma	59 (14.4)	54 (13.0)
Low grade mucinous carcinoma	1 (0.2)	0 (0.0)
Mixed	22 (5.4)	16 (3.8)

Neuroendocrine	2 (0.5)	0 (0.0)
Serous carcinoma	38 (9.2)	50 (12.0)
Unclassified	0 (0.0)	3 (0.7)
Undifferentiated histology	4 (1.0)	3 (0.7)
Other	6 (1.5)	7 (1.7)
FIGO stage at initial diagnosis, n (%)		
I	10 (2.4)	11 (2.6)
IA	54 (13.1)	64 (15.4)
IB	47 (11.4)	64 (15.4)
II	32 (7.8)	26 (6.3)
III	5 (1.2)	8 (1.9)
IIIA	28 (6.8)	33 (7.9)
IIIB	11 (2.7)	11 (2.6)
IIIC	30 (7.3)	24 (5.8)
IIIC1	17 (4.1)	25 (6.0)
IIIC2	27 (6.6)	27 (6.5)
IV	27 (6.6)	26 (6.3)
IVA	7 (1.7)	8 (1.9)
IVB	116 (28.2)	89 (21.4)
Brain metastasis,[c] n (%)		
Yes	2 (0.5)	2 (0.5)
No	409 (99.5)	414 (99.5)
Bone metastasis,[c] n (%)		
Yes	39 (9.5)	33 (7.9)
No	372 (90.5)	383 (92.1)
Liver metastasis,[c] n (%)		
Yes	101 (24.6)	98 (23.6)
No	310 (75.4)	318 (76.4)
Lung metastasis,[c] n (%)		
Yes	164 (39.9)	152 (36.5)
No	247 (60.1)	264 (63.5)
Intra-abdominal metastasis,[b,c] n (%)		
Yes	164 (39.9)	166 (39.9)
No	247 (60.1)	250 (60.1)
Lymph node metastasis,[c] n (%)		
Yes	224 (54.5)	225 (54.1)
No	187 (45.5)	191 (45.9)

Key: PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Notes: [a], Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World; [b], Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs; [c], Lesion location as determined by investigator review.
Source: KEYNOTE-775 Clinical Study Report (Table 10.5).[3]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Trial populations

Definitions of the key study populations analysed and the patient numbers included in each analysis set in the KEYNOTE-775 clinical trial are presented in Table 6.

Efficacy analyses were based on the ITT population, which included all patients in the treatment arm to which they were randomly assigned, regardless of whether they received treatment.[13] Patients were analysed in the treatment group to which they were randomised. No patients were excluded from the analyses.

Safety analyses were based on the all participants as treated (APaT) population, which included all randomly assigned patients who received at least 1 dose of study treatment.[13] Two populations were included in the ITT and APaT analyses: all-comer patients and pMMR patients. Given the anticipated license and positioning for PEM+LEN, only data on the all-comers population are presented within this submission.

For patient reported outcomes, HRQL analyses were based on the HRQL Full Analysis Set (FAS) population, defined as all randomised patients who had at least one HRQL assessment available for the specific endpoint and had received at least one dose of study intervention.[13] Patients were analysed in the treatment group to which they were randomised.

Table 6: KEYNOTE-775 trial populations

Population	Definition	Number of patients
		All-comers population
Screening population	Patients assessed for eligibility	1178
ITT population	All patients in the treatment arm to which they were randomly assigned, regardless of whether they received treatment	827
Safety population	All randomly assigned patients who received at least 1 dose of study treatment	794
FAS population	All randomly assigned patients who had at least one HRQL assessment available for the	EQ-5D: 731 EORTC QLQ-C30: 721

	specific endpoint and had received at least one dose of study intervention	

Key: EORTC, European Organisation for the Research and Treatment of Cancer; FAS, full analysis set; HRQL, health-related quality of life; ITT: Intention-to-treat.
Source: KEYNOTE-775 Clinical Study Report (Tables 10.3; 10.4).[13]

B.2.4.2. Statistical analyses

The trial hypotheses and statistical analysis methods are summarised in Table 7. Two sets of hypotheses were tested; primary statistical analyses were completed for 'pMMR participants' first, then for the entire study population ('all-comer participants').[14]

This approach was taken into account for the improved efficacy of pembrolizumab in people with dMMR tumours.[14] dMMR tumours are known to harbour hundreds to thousands of somatic mutations; tumours that have a large number of somatic mutations have been shown to be more susceptible to PD-1/PD-L1 inhibition. Through sample size powering and hypothesis testing of participants with pMMR tumours, potential positive bias from the improved efficacy of pembrolizumab in people with dMMR tumours is avoided.

Aligning with the marketing authorisation and population of relevance to the decision problem addressed in this submission, efficacy and safety data are provided for the all-comer population in Sections B.2.6, B.2.7 and B.2.9.3. Data for the pMMR population are provided in Appendix M. dMMR subgroup analyses are also provided in Appendix M.

Two interim analyses were planned along with the final analysis, as detailed in Table 7. The data presented in Section B.2.6 are from interim analysis 1 (IA1), providing final efficacy analysis for PFS and the first interim efficacy analysis for OS. The database cut-off date for IA1 was 26 October 2020.[14] Due to primary objectives being met in IA1, the requirement of interim analysis 2 (IA2) was removed through a protocol amendment.

Table 7: Summary of statistical analyses for KEYNOTE-775

Hypothesis objective	Hypothesis (H1): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in pMMR participants. Hypothesis (H2): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in pMMR participants. Hypothesis (H3): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in pMMR participants. Hypothesis (H4): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in all-comer participants. Hypothesis (H5): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in all-comer participants. Hypothesis (H6): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in all-comer participants.
Statistical analysis	Two interim analyses were initially planned, to be performed by an independent unblinded statistician and programmer. Results of these analyses were to be reviewed by the DMC. • Interim Analysis 1 (IA1) will be performed after both ~368 OS events have been observed in the pMMR participants and at least 6 months after last participant randomisation • Interim Analysis 2 (IA2) will be performed after both ~463 OS events have been observed in the pMMR participants and at least 12 months after last participant randomisation • Final Analysis (FA) will be performed after both ~526 OS events have been observed in the pMMR participants and at least 18 months after last participant randomisation After IA1, the requirement of IA2 was removed through a protocol amendment due to primary objectives being met in IA1. The next analyses performed will therefore be the FA. The primary hypotheses will be evaluated by comparing in PFS and OS using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan–Meier method. The total family-wise error rate (Type I error) among the two primary PFS and OS analyses, ORR analysis, and for pMMR and all-comer participants is strongly controlled at one-sided 0.025 level. A 0.0005 Type I error rate is initially allocated to test PFS and a 0.0245 Type I error rate is initially allocated to test OS between two treatment arms in pMMR participants. The study will be considered positive if either testing of PFS or testing of OS is significant in pMMR participants.
Analysis sets	Efficacy: intention to treat, defined as all randomised participants, analysed in the treatment group to which they were randomised.

	Safety: all participants as treated, defined as all randomised participants who received at least one dose of study treatment, analysed in the treatment group corresponding to the study treatment received.
Sample size, power calculation	The planned sample size is approximately 780 participants (660 pMMR participants and 120 dMMR participants) with 330 pMMR participants and 60 dMMR participants in each arm. For the pMMR participants: With approximately 564 PFS events at the planned PFS analysis, the study will have at least 99% of power to detect a hazard ratio of 0.55 at the one-sided 0.0005 significance level. With approximately 368, 463, and 526 OS events in the pMMR participants at the planned IA1, IA2, and final OS analysis, respectively, the study will have 90% power to detect a hazard ratio of 0.75 at the one-sided 0.0245 significance level.
Data management, patient withdrawals	PFS: participants who experience an event immediately after two or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. Any participant who initiates new anti-cancer therapy prior to documented progression will be censored at the last disease assessment prior to the initiation of new anti-cancer therapy. Participants who do not start new anti-cancer therapy and who do not experience an event will be censored at the last disease assessment. OS: participants without documented death at the time of analysis will be censored at the date of last known contact.
Key: DMC, data monitoring committee; dMMR, mismatch repair deficient; FA, final analysis; HR, hazard ratio; IA, interim analysis; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; TPC, treatment of physician's choice. **Source:** KEYNOTE-775 Clinical Study Protocol.[14]	

B.2.4.3. Patient disposition

Patient disposition by treatment group for the all-comer population is presented in in Appendix D. A total of 827 patients were randomised (39 randomised in the UK) in a 1:1 ratio to receive either PEM+LEN (n=411) or TPC (n=416).[11] 794 patients received at least one dose of study intervention. As of the latest data cut-off, 93 patients (24%) completed therapy due to reaching the maximum cumulative doses of doxorubicin or paclitaxel in the TPC group. The proportion of patients still receiving study medication was substantially higher in the PEM+LEN arm compared with the TPC arm. The proportion of all patients who discontinued treatment was similar between the two treatment arms.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The Cochrane Collaboration's Risk of bias tool (version 2)[15] was used to assess risk of bias in KEYNOTE-775, as presented in Appendix D.3.

Overall, this study is judged to be at risk of bias in one domain due to its open-label design, with all other domains judged to be at a low risk of bias.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. KEYNOTE-775

The median duration of follow-up at the time of IA1 (defined as the time from randomisation to date of death or database cut-off date) was 12.2 months (range: 0.3–26.9) in the PEM+LEN arm and 10.7 months (range: 0.3–26.3) in the TPC arm, and for all patients was 11.4 months (range: 0.3–26.9).[11, 13]

As described previously, data are presented for the all-comer population throughout this section. Key results observed in the dMMR and pMMR populations are presented in Appendix M.

B.2.6.1.1. Progression-free survival (primary endpoint)

Treatment with PEM+LEN is associated with significant improvement in progression free survival

The median PFS was significantly improved with PEM+LEN compared with TPC; 7.2 and 3.8 months respectively, with a HR of 0.56 (95% CI: 0.47, 0.66; p< 0.0001), crossing the pre-specified boundary for statistical significance at IA1 of ≤0.0005.[11]

PFS rates were also higher in the PEM+LEN group compared with the TPC group at 6 (53.5% vs. 34.3%), 12 (31.2% vs. 13.2%), 18 (25.0% vs. 7.6%) and 24 months (20.9% vs. 3.8%), as shown in Table 8.[13]

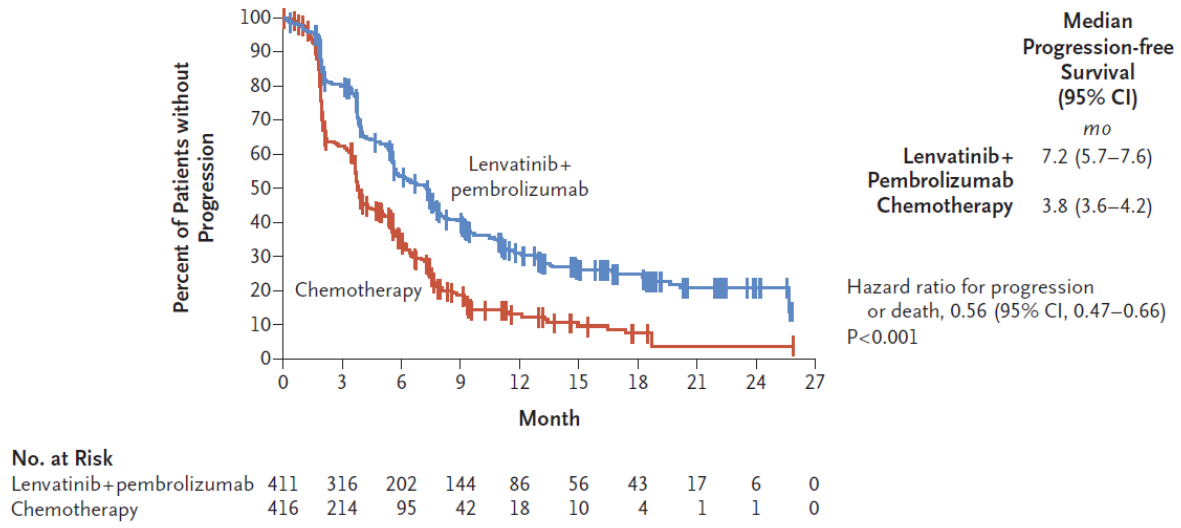
Table 8: Analysis of PFS in the KEYNOTE-775 trial (ITT all-comer population)

	PEM+LEN (n=411)	TPC (n=416)
Number of events, n (%)	281 (68.4)	286 (68.8)
Median PFS, months (95% CI, months)‡	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
PFS HR (95% CI)*	0.56 (0.47, 0.66)	
p-value†	< 0.0001	
6-month PFS, % (95% CI)‡	53.5 (48.4, 58.3)	34.3 (29.2, 39.4)
12-month PFS, % (95% CI)‡	31.2 (26.4, 36.0)	13.2 (9.3, 17.8)
18-month PFS, % (95% CI)‡	25.0 (20.4, 29.9)	7.6 (4.1, 12.6)
24-month PFS, % (95% CI)‡	20.9 (16.0, 26.2)	3.8 (0.6, 12.7)

Key: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT, intention-to-treat; MMR: mismatch repair; PEM+LEN, pembrolizumab with lenvatinib; PFS: progression free survival; TPC: treatment of physician's choice.
Notes: ‡, From product-limit (Kaplan–Meier) method for censored data; *, based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation; †, one-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
Source: KEYNOTE-775 Clinical Study Report (Tables 11.5, 11.6)[13]; Makker et al. 2022.[11]

The Kaplan–Meier curves for PFS clearly separated, starting at around the time of the first protocol scheduled imaging assessment (i.e., 8 weeks), and remained consistently separated throughout the duration of the evaluation period (Figure 3).[11]

Figure 3: Kaplan–Meier estimates of PFS in KEYNOTE-775 trial (ITT all-comer population)



Key: ITT, intention-to-treat; PFS, progression-free survival; TPC: treatment of physician's choice.
Source: Makker at al. 2022.[11]

B.2.6.1.2. Overall survival (primary endpoint)

PEM+LEN is superior to TPC with respect to overall survival in patients with advanced EC who have failed prior therapy

Median OS was significantly longer in the PEM+LEN group compared with the TPC group; 18.3 and 11.4 months respectively, with a HR of 0.62 (95% CI: 0.51, 0.75; p< 0.0001) at IA1, crossing the pre-specified boundary for statistical significance at IA1 of ≤0.0064.[11]

The OS rates were higher in the PEM+LEN group compared with the TPC group at 6 (82.4% vs. 75.4%), 12 (62.5% vs. 47.9%), 18 (50.9% vs. 28.6%), and 24 months (42.0% vs. 21.4%), as shown in Table 9.[13]

Table 9: Analysis of OS in the KEYNOTE-775 trial (ITT all-comer population)

	PEM+LEN (n=411)	**TPC (n=416)**
Number of events, n (%)	188 (45.7)	245 (58.9)
Median OS, months (95% CI, months) ‡	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
PFS HR (95% CI)*	0.62 (0.51, 0.75)	
p-value †	<0.0001	
6-month OS, % (95% CI) ‡	82.4 (78.4, 85.8)	75.4 (70.9, 79.3)
12-month OS, % (95% CI) ‡	62.5 (57.5, 67.1)	47.9 (42.7, 53.0)
18-month OS, % (95% CI) ‡	50.9 (45.2, 56.3)	28.6 (23.2, 34.3)
24-month OS, % (95% CI) ‡	42.0 (35.1, 48.8)	21.4 (14.2, 29.6)

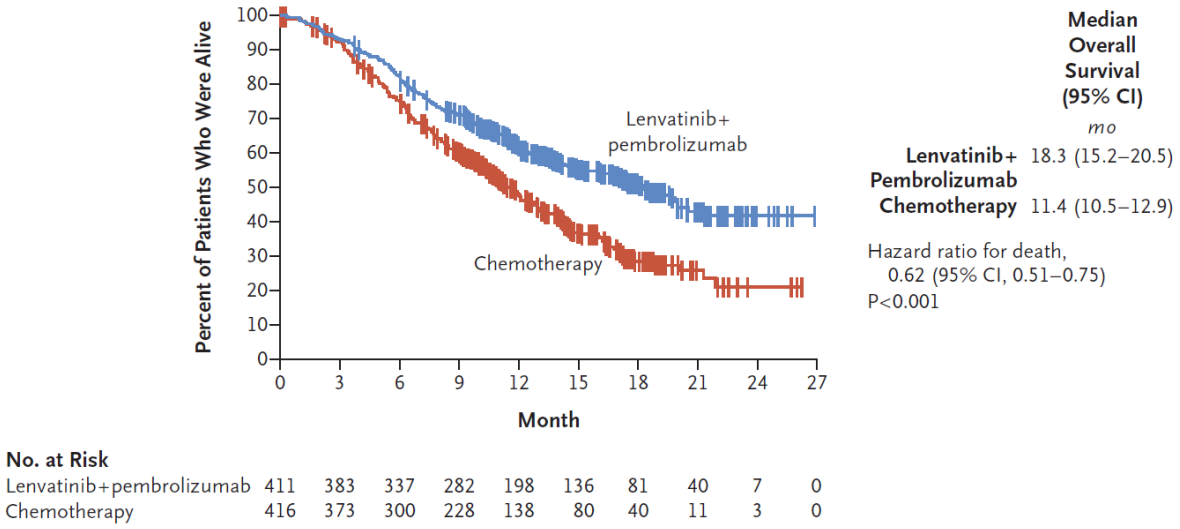
Key: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; KM: Kaplan–Meier; MMR; mismatch repair; OS: overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Notes: ‡, From product-limit (Kaplan–Meier) method for censored data; *, based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation; †, one-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
Source: KEYNOTE-775 Clinical Study Report (Tables 11.9, 11.10)[13]; Makker at al. 2022.[11]

The KM curves for OS clearly separated, starting at around 3 months and remained consistently separated throughout the duration of the evaluation period (Figure 4).[11] Overall, treatment with PEM+LEN led to OS improvements that were statistically significant and clinically meaningful, with the OS HR crossing the pre-specified boundary for statistical significance at IA1.

When interpreting survival data, it is important to acknowledge that nearly half of the patients (48%) in the TPC arm received subsequent anticancer therapy, compared with 28% of patients in the PEM+LEN arm (Table 46).[11] Of the patients in the TPC arm, [redacted]% received subsequent treatment with PD1/PDL1 regimens that are not currently available in the UK which likely dilutes the real-world survival benefit PEM+LEN offers to patients.[13] This is further discussed in Sections B.2.13 and B.3.5.4.

It should also be acknowledged that OS data from the IA1 dataset are subject to heavy censoring, but the study continues to mature with the final analysis database lock estimated in [redacted] (events dependent).

Figure 4: Kaplan–Meier estimates of OS in the KEYNOTE-775 trial (ITT all-comer population)



Key: ITT, intention-to-treat; OS, overall survival; TPC: treatment of physician's choice.
Source: Makker et al. 2022.[11]

B.2.6.1.3. Objective response rate (secondary endpoint)

Treatment with PEM+LEN led to statistically significant and clinically meaningful improvements in* objective response rate *(ORR)

ORR (per RECIST 1.1 by BICR) was 31.9% for the PEM+LEN group compared with 14.7% for the TPC group, with an estimated difference of 17.2% (95% CI: 11.5, 22.9%; p<0.0001).[11] The proportion of patients who achieved a CR was higher in the PEM+LEN group compared with the TPC group, as shown in Table 10.

Table 10: Analysis of best overall response in the KEYNOTE-775 trial (ITT all-comer population)

	PEM+LEN (n=411)	TPC (n=416)
Number of objective responses, n (%)	131 (31.9)	61 (14.7)
ORR, % (95% CI)‡	31.9 (27.4, 36.6)	14.7 (11.4, 18.4)
Estimated difference in % vs. TPC, % (95% CI)*	17.2 (11.5, 22.9)	
p-value†	<0.0001	
Best overall response, n (%)		
Complete response	27 (6.6)	11 (2.6)
Partial response	104 (25.3)	50 (12.0)
Objective response (CR+PR)	131 (31.9)	61 (14.7)
Stable disease	193 (47.0)	167 (40.1)
Disease control (CR+PR+[SD≥7 weeks])	296 (72.0)	194 (46.6)
Clinical benefit (CR+PR+[SD ≥23 weeks])	201 (48.9)	99 (23.8)
Progressive disease	61 (14.8)	123 (29.6)
Not evaluable	5 (1.2)	8 (1.9)
No assessment	21 (5.1)	57 (13.7)

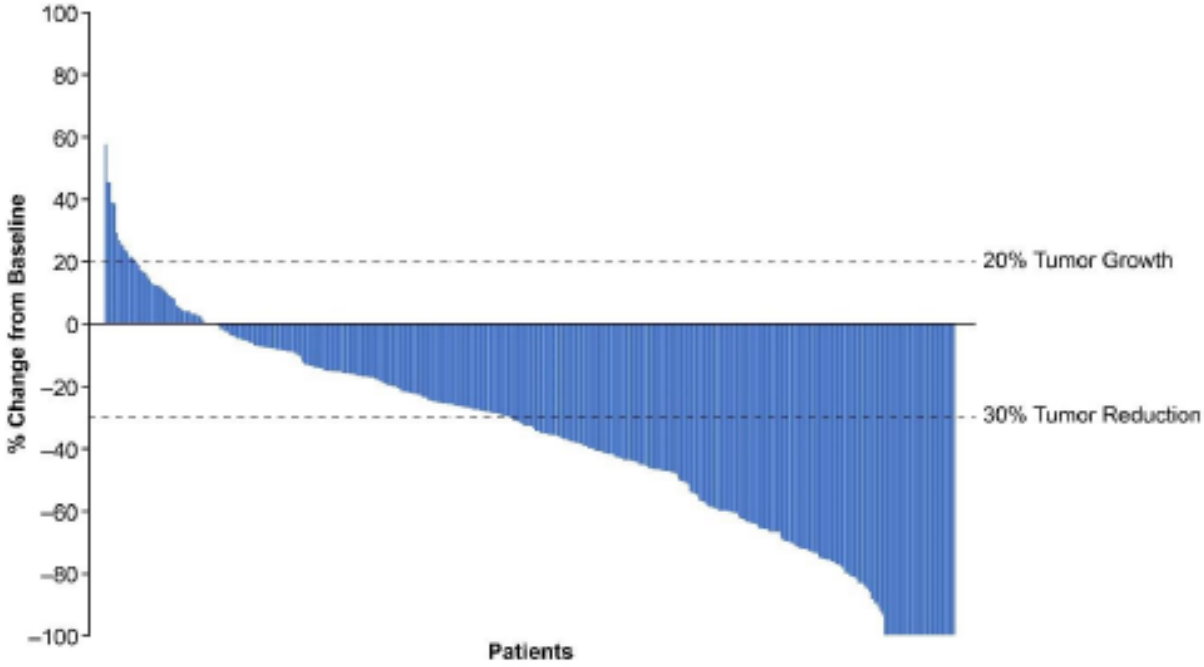
Key: BOR: best overall response; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: intention-to-treat; MMR: mismatch repair; ORR: overall response rate; PEM+LEN: pembrolizumab with lenvatinib; PR: partial response; SD: stable disease; TPC: treatment of physician's choice.
Notes: ‡, Based on binomial exact CI method; *, based on Miettinen & Nurminen method stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation; †, one-sided p-value for testing H0: difference in % = 0 vs. H1: difference in % > 0.
Source: KEYNOTE-775 Clinical Study Report (Tables 11.15, 11.16)[13]; Makker et al. 2022.[11]

B.2.6.1.3.1. Duration of response and tumour reduction (exploratory endpoints)

Among patients achieving a response, the median DOR was 14.4 months (range: 1.6, 23.7) in the PEM+LEN group compared to 5.7 months (range: 0.0, 24.2) for the TPC group (Appendix N).[11] A greater proportion of patients receiving PEM+LEN

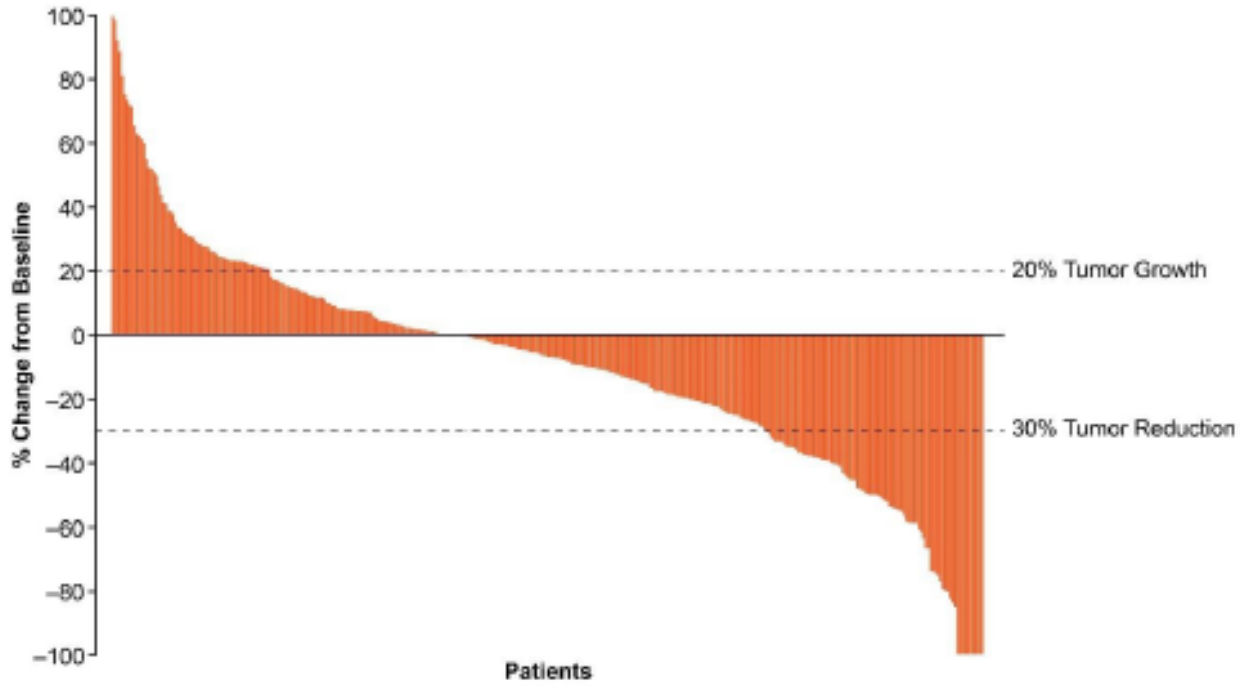
experienced a reduction in tumour size than those receiving TPC (Figure 5, Figure 6).

Figure 5: Waterfall plot of best percentage change from baseline for target lesions in the PEM+LEN arm of the KEYNOTE-775 trial (ITT all-comer population)



Source: Makker et al. 2022.[11]

Figure 6: Waterfall plot of best percentage change from baseline for target lesions in the TPC arm of the KEYNOTE-775 trial (ITT all-comer population)



Source: Makker et al. 2022.[11]

B.2.6.1.4. Exploratory efficacy outcomes

A summary of outcomes from the exploratory endpoints in the KEYNOTE-775 trial including DOR, TTR, DCR, CBR and PFS2 is provided in Appendix N.

B.2.6.1.5. Health-related quality of life

HRQL was generally similar between both treatment groups

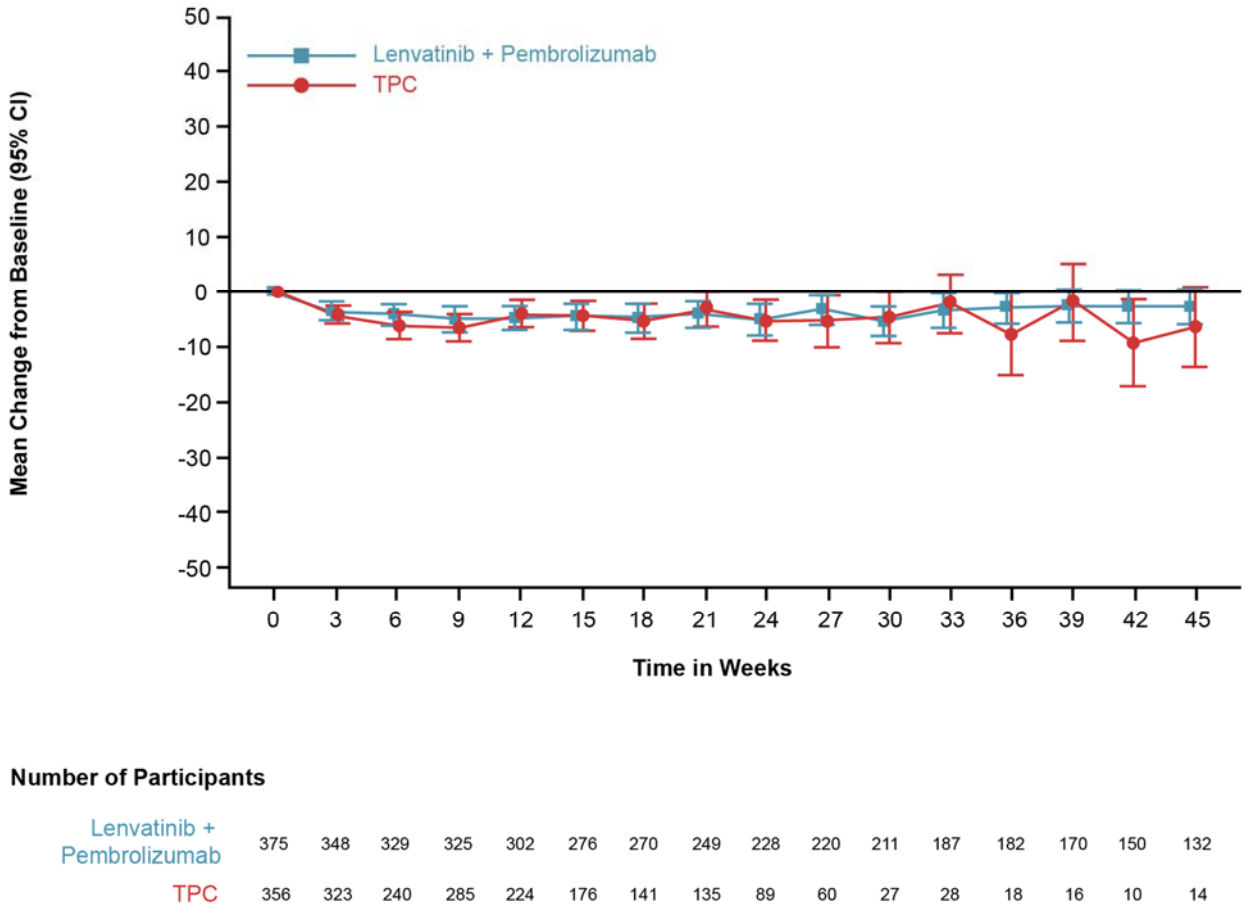
Patient reported outcome (PRO) scores were generally similar between the PEM+LEN group and the TPC group throughout the study[16], demonstrating that treatment with PEM+LEN has no adverse impact on patients HRQL compared with current treatments available for patients with advanced EC. Patients are therefore able to benefit from the improved responses and chances of survival without compromising their quality of life.

A summary of results for the global health status/quality of life (GHS/QoL) score of EORTC QLQ-30, the EORTC QLQ-C30 physical functioning score and EORTC QLQ EN24 urological symptoms are presented in Appendix N. EQ-5D-5L visual analogue

scale (VAS) is presented below and is used in the cost effectiveness model for this submission.

Over 12 weeks of follow-up, the EQ-5D-5L VAS scores decreased in both the PEM+LEN group (-4.44; 95% CI: -6.43, -2.46) and the TPC group (-6.79; 95% CI: -8.98, -4.60).[13] There was no significant difference between groups; difference in least squares (LS) mean change from baseline at Week 12 was 2.35 (95% CI: −0.44, 5.14; [redacted]). [13, 16] Empirical mean change from baseline and 95% CI for EQ-5D-5L VAS over 45 weeks for PEM+LEN and TPC groups are displayed graphically in Figure 7. A slight decrease in mean change was seen in both treatment groups over time.

Figure 7: Empirical mean change from baseline and 95% CI for the EQ-5D VAS score over time in KEYNOTE-775 (FAS all-comer population)



Key: CI, confidence interval; FAS, full analysis set; TPC, treatment of physician's choice; VAS, visual analogue scale.
Source: Lorusso et al. 2021.[16]

B.2.6.2. KEYNOTE-146

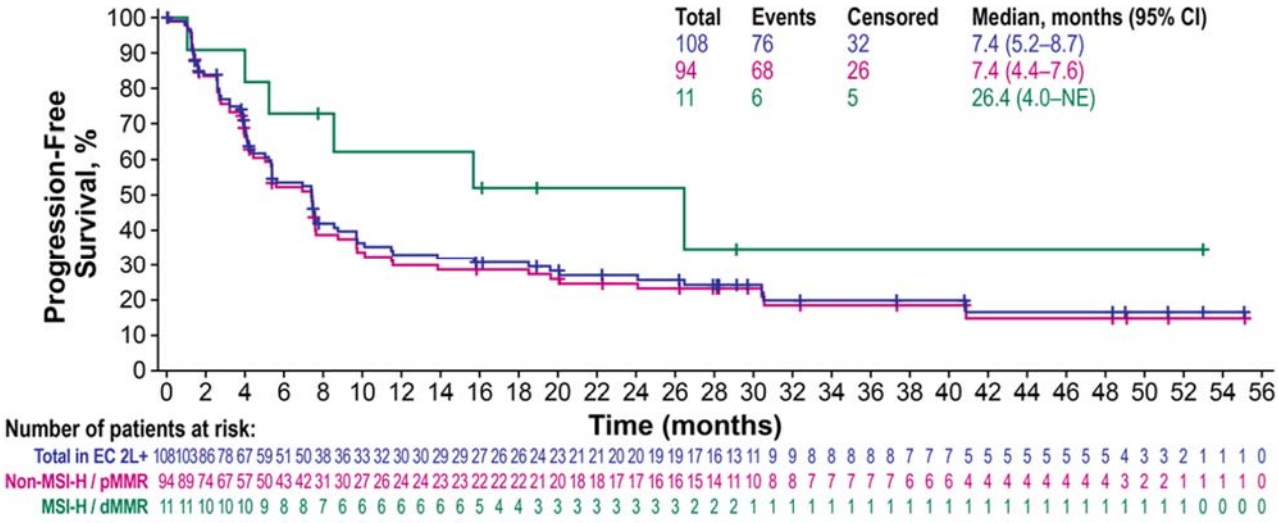
Data are presented for the pre-treated EC participants of relevance to the decision problem being addressed in this submission. PFS and OS data are presented here with ORR and DoR data presented in Appendix O.

The median duration of follow-up at the time of the most recent analysis (database cut-off 18 August 2020) presented below was 34.7 months (95% CI: 30.9, 41.2).[17]

B.2.6.2.1. Progression-free survival

The median PFS was 7.4 months (95% CI: 5.2, 8.7) for pre-treated EC participants (Figure 8).[17] These data are consistent with PFS observed for the PEM+LEN group in the most recent analysis of the KEYNOTE-775 trial (see Section **Error! Reference source not found.**).

Figure 8: Kaplan–Meier estimates of PFS in KEYNOTE-146 trial (pre-treated EC population)



Key: CI: confidence interval; dMMR: mismatch-repair deficient; EC: endometrial carcinoma; EC 2L+: endometrial cancer second-line (or greater) treatment; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NE: non estimable; PFS, progression-free survival; pMMR: mismatch-repair proficient; RECIST, response evaluation criteria in solid tumours.
Notes: PFS assessed by the investigator per immune-related RECIST
Source: Makker et al. 2021.[17]

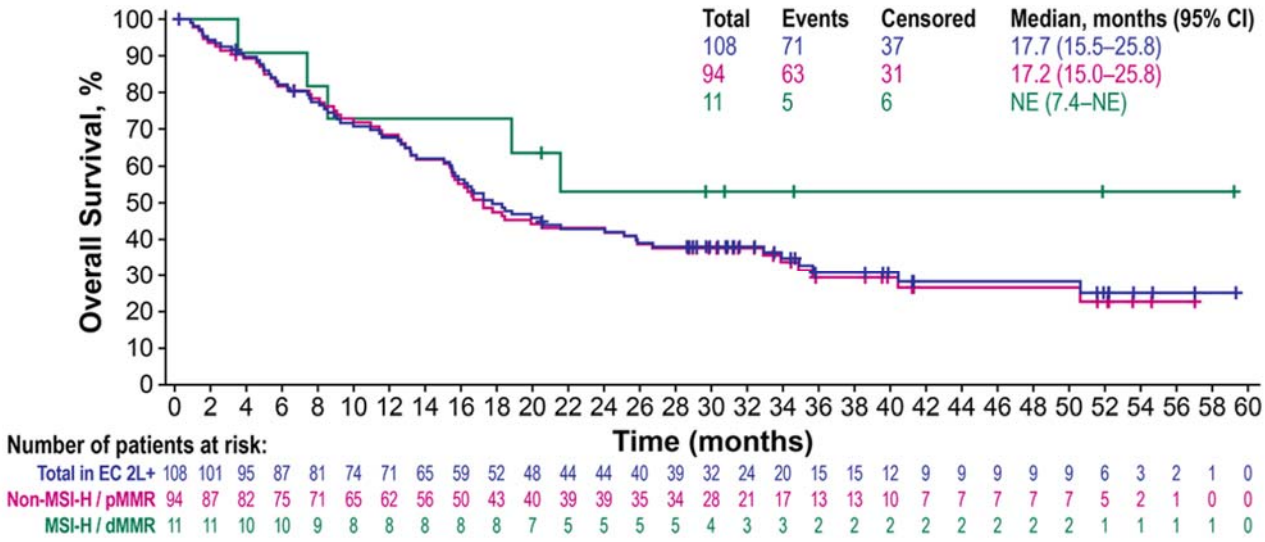
B.2.6.2.2. Overall survival

The median OS was 17.7 months (95% CI: 15.5, 25.8) for pre-treated EC participants (Figure 9).[17] These data are consistent with OS observed for the

PEM+LEN group in the most recent analysis of the KEYNOTE-775 trial (see Section **Error! Reference source not found.**).

The longer-term follow-up in KEYNOTE-146 demonstrates that the 5-year survival rate for patients treated with PEM+LEN is approximately 30% (Figure 9).[17]

Figure 9: Kaplan–Meier plot of OS in the KEYNOTE-146 trial (pre-treated EC population)



Key: CI: confidence interval; dMMR: mismatch-repair deficient; EC: endometrial carcinoma; EC 2L+: endometrial cancer second-line (or greater) treatment; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NE: non estimable; pMMR: mismatch-repair proficient.
Source: Makker et al. 2021.[17]

B.2.7. Subgroup analysis

The treatment benefit observed in PFS and OS for PEM+LEN compared with TPC in all-comer patients was consistent across all major subgroups, including by MMR status, histology and prior lines of therapy (Appendix E).[11]

B.2.8. Meta-analysis

KEYNOTE-146 and KEYNOTE-775 are heterogenous in terms of study design and population and formal meta-analyses have therefore not been conducted. A qualitative overview of key outcomes from both trials is provided in Table 11.

Table 11: Overview of key outcomes from KEYNOTE-775 and KEYNOTE-146

	KEYNOTE-146	KEYNOTE-775	
	PEM+LEN (n = 108)	PEM+LEN (n = 346)	TPC (n = 351)
ORR, %	39.8	31.9	14.7
CR, %	8.3	6.6	2.6
mDOR, months	22.9	14.4	5.7
mPFS, months	7.4	7.2	3.8
mOS, months	17.7	18.3	11.4

Key: CR, complete response; DOR, duration of response, ORR, objective response rate; OS, overall survival; m, median; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.
Source: Makker et al. 2021[17]; Makker et al. 2022.[11]

B.2.9. Indirect and mixed treatment comparisons

Two SLRs, one identifying interventional and one identifying observational evidence, were conducted to identify relevant published clinical evidence of pharmacological treatments for advanced or recurrent EC, in line with the population investigated in the KEYNOTE-775 trial.

Full details of the SLR search strategy, study selection process and results are presented in Appendix D for interventional and observational evidence.

B.2.9.1. Interventional evidence

A total of 34 trials were included in the interventional evidence base (including KEYNOTE-775 and KEYNOTE-146) SLR. However, the majority of treatments evaluated were not of direct relevance to UK clinical practice. For the comparators of relevance, interventional evidence was limited to three RCTs with a control arm of paclitaxel or doxorubicin and six single-arm trials of paclitaxel or doxorubicin (see Table 7 of Appendix D). As the KEYNOTE-775 trial provides head-to-head data for PEM+LEN versus paclitaxel or doxorubicin, any ITC would not provide additional informative data. Nonetheless, feasibility of an indirect treatment comparison (ITC) was considered, details of which are provided in Appendix D. The conclusion of this assessment was that ITC was not feasible and that the KEYNOTE-775 trial provides the only robust data for the comparison of PEM+LEN versus chemotherapy for the treatment of patients with advanced or recurrent EC who have disease progression after one prior systemic platinum-based chemotherapy regimen.

B.2.9.2. Observational evidence

A total of six studies were included in the observational evidence base SLR, all of which were retrospective cohort / claims database studies. Four studies provided data on platinum rechallenge, however there were several concerns with the quality and comparability of these data; the remaining two provided data on doxorubicin and therefore were not considered further.

A summary of the platinum rechallenge studies is presented in Table 12.

Two studies reported on platinum rechallenge in recurrent EC patients in Japan who had already received systemic platinum-based chemotherapy (aligning to the treatment positioning investigated in KEYNOTE-775). Both studies reported a significant relationship between treatment-free interval and effectiveness of platinum rechallenge[18, 19], as reflected in the BGCS Guidelines (see Section B.1.3.2). Patients who received platinum rechallenge within six months of their first-line platinum chemotherapy failed to respond and had a median OS of <12 months (Table 12). Patients who received platinum rechallenge later than six months from their first-line platinum chemotherapy had a better response and a median OS ranging from 14.8 months to 43.0 months depending on the treatment-free interval (Table 12).

Of the other two studies, one reported on platinum rechallenge in recurrent or metastatic EC patients in the US who had received platinum-based chemotherapy in the adjuvant setting, and the other reported on platinum chemotherapy use in advanced or recurrent EC, a small proportion of whom had received prior chemotherapy.[20, 21] Both studies had small patient numbers and reported highly varied and uncertain outcomes. Patients who received platinum rechallenge after adjuvant platinum-based chemotherapy had a low response rate of 10% but a median OS of 27.0 months (95% CI: 6, 117) (Table 12).

Formal ITC using these observational data would be inappropriate for multiple reasons and subject to a high degree of uncertainty. Marked differences in study design and associated data quality, study timing and patient populations are observed compared with the KEYNOTE-775 trial. Naïve comparison of outcomes for platinum rechallenge in those patients relapsing within 12 months of receiving first-line platinum chemotherapy show reasonable alignment to the TPC arm of

KEYNOTE-775. This represents the patient group which made up the majority of participants in the KEYNOTE-775 trial and would be expected in clinical practice. A highly uncertain ITC using these data would therefore not add value to the high-quality comparative data available from the KEYNOTE-775 Phase III RCT.

Table 12: Summary of observational data available for platinum rechallenge

Study ID	Study design Location	Population	N	Median OS (95% CI)	Median PFS (95% CI)	ORR
Nagao 2013[18]	Retrospective claims data analyses Japan	Patients with recurrent EC, who had a history of receiving first-line platinum-based chemotherapy and who received second-line platinum-based chemotherapy at the time of recurrence between January 2005 and December 2009	<6 months TFI: 64	<6 months TFI: 11.3 (7.9, 17.5)	<6 months TFI: 3.2 (2.3, 4.3)	<6 months TFI: 25%
			<12 months TFI: 129	<12 months TFI: 13.8 (10.6, 18.1)	<12 months TFI: 4.4 (3.7, 5.8)[a]	<12 months TFI: 32%
			≥24 months TFI: 133	≥24 months TFI: 40.9 (25.3, 54.2)	≥24 months TFI: 10.3 (8.2, 12.6)[a]	≥24 months TFI: 65%
Rubinstein 2019[20]	Retrospective claims data analyses US	Patients with EC who received paclitaxel and carboplatin in the adjuvant setting and were retreated with paclitaxel and carboplatin in the recurrent or metastatic setting between January 2000 and December 2014	20	27.0 (6, 117)	10.0 (2, 47)	10%
Sovak 2007[21]		Patients with advanced or recurrent	All patients: 85	13.2 (11.7, 18.2)	5.3 (4.6, 7.4)	n = 63 43%

	Retrospective claims data analyses US	EC who received paclitaxel and carboplatin between June 1996 and May 2004; some of whom had previously been treated with chemotherapy (n = 13)	Rechallenge: 13	25.4	5.4	n = 10 20%
Ueda 2011[19]	Retrospective cohort study Japan	Patients diagnosed with EC between 2000 and 2008, who were previously treated with a combined chemotherapy or taxane and platinum ± anthracycline and who received second-line chemotherapy, including carboplatin and paclitaxel ± epirubicin *(data reported for this group)*	24	13.0 (3. 44)	5.5 (2, 20)	38%
Key: EC, endometrial cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TFI, treatment-free interval.						

B.2.9.3. ECHO: Real-world evidence

Endometrial Cancer Health Outcomes – Europe (ECHO EU5) is a retrospective, multicentre chart review study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC patients previously treated with systemic therapy that has been commissioned by MSD (data on file). Data from the UK cohort of the ECHO study were available, as described below. The study was subsequently used for validating the survival outcomes in the comparator arm for in this appraisal (see Section B.3.3.3) [22]

EC-treating oncologists (medical oncologist or gynaecologic-oncologist) were screened and recruited from the publicly available data. In the UK, [redacted] physicians that consented to participate in the study provided data for [redacted] eligible patients. Physicians provided data obtained from medical records of adults diagnosed with advanced or recurrent EC between 1 July 2016 – 31 December 2018, and who had disease progression after a prior systemic therapy during 1 July 2016 – 30 June 2019. Other inclusion criteria were ≥18 years of age at the time of advanced or recurrent EC diagnosis; must not be a suitable candidate for curative-intent surgery; must not have participated in any EC-related clinical trial during treatment; and must have known medical history from the date of advanced or recurrent EC diagnosis. Patients were excluded if they had any prior malignancy active within the previous 3 years, except for locally curable cancers that have been cured.

All data was collected from diagnosis of advanced or recurrent EC until last available follow up. Key outcomes included patient demographics, clinical and treatment characteristics, and clinical outcomes. Descriptive analysis was conducted to report mean, standard deviation, median and range for all continuous variables, and count and frequency for categorical variable. Kaplan-Meier analyses were performed to estimate time to event outcomes such as real-world PFS and OS. Patients were censored at the last follow up and estimated probabilities of the events were provided at pre-determined time intervals. Real-world response to second-line therapy was abstracted as reported by the physician from patients' medical records. All statistical analyses were conducted using SAS version 9.4.

Treatment pattern and outcome data from ECHO UK are summarised below:

- [redacted] were used to treat the majority of patients ([redacted]), with the remaining [redacted] of patients receiving a mixture of [redacted] (data re-weighted to exclude investigative treatments).

- Median OS from the start of second line of systemic therapy was [redacted].

This survival outcome is closely aligned to that observed with the TPC arm of the KEYNOTE-775 trial, supporting the applicability of this trial to outcomes expected with current care in clinical practice. These data have been used to inform and validate economic scenario analyses (see Section B.3.8.3).

B.2.10. Adverse reactions

B.2.10.1. KEYNOTE-775

As described previously, data are presented for the all-comer population throughout this section.

B.2.10.1.1. Treatment exposure

The median duration of exposure to at least 1 drug was more than double for the PEM+LEN group compared with the TPC group. More patients in the PEM+LEN group had a duration of exposure of ≥6 months, ≥12 months and ≥18 months compared with the TPC group (Table 13).[11]

Table 13: Summary of drug exposure in the KEYNOTE-775 trial (safety all-comer population)

	PEM+LEN (n=406)	TPC (n=388)
Duration on therapy (days) [a]		
Mean	271.9	108.9
Median	231.0	104.5
SD	194.6	90.4
Range	1.0 – 817.0	1.0 – 785.0
Duration of exposure, (n)		
> 0 months	406	388
≥ 1 months	376	323
≥ 3 months	325	213
≥ 6 months	243	42
≥ 12 months	110	10
≥ 18 months	48	1
≥ 24 months	5	1
Duration on both pembrolizumab and lenvatinib (days) [b]		
Mean	231.5	N/A
Median	191.0	N/A
SD	185.4	N/A
Range	1.0 – 784.0	N/A

Duration on lenvatinib (days) [c]		
Mean	251.8	N/A
Median	211.5	N/A
SD	191.3	N/A
Range	1.0 – 817.0	N/A
Duration on pembrolizumab (days) [d]		
Mean	251.6	N/A
Median	211.0	N/A
SD	190.9	N/A
Range	1.0 – 784.0	N/A

Key: N/A: not applicable; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice; SD: standard deviation.
Notes: a, Duration on therapy is calculated as the days between first dose date and last dose date in each treatment arm; b, For PEM+LEN, defined as from the first date when both drugs were taken until the date when one of the two drugs was first discontinued; c, For PEM+LEN, defined as from the first date when lenvatinib was taken until the date when lenvatinib was discontinued; d, For PEM+LEN, defined as from the first date when pembrolizumab was taken until the date when pembrolizumab was discontinued.
Source: Makker et al. 2022.[11]

B.2.10.1.2. Summary of adverse events

The safety data from the KEYNOTE-775 trial showed that the incidences of Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs and drug-related SAEs, were higher for treatment with PEM+LEN group compared with TPC.[11] The incidence of drug-related deaths was similar in the two groups. A summary of the adverse events in the KEYNOTE-775 trial is provided in Table 14.

Table 14: Adverse event summary for the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
One or more AE	405 (99.8)	386 (99.5)
No AE	1 (0.2)	2 (0.5)
Treatment-related AEs	395 (97.3)	364 (93.8)
Toxicity grade 3-5 AEs	361 (88.9)	282 (72.7)
Toxicity grade 3-5 drug-related AE	316 (77.8)	229 (59.0)
SAEs	214 (52.7)	118 (30.4)
Treatment-related SAEs	135 (33.3)	55 (14.2)
Dose modification due to an AE	380 (93.6)	161 (41.5)
Dose interruption due to an AE	281 (69.2)	105 (27.1)
Interruption of pembrolizumab	203 (50.0)	0 (0.0)
Interruption of lenvatinib	238 (58.6)	0 (0.0)

Interruption of both pembrolizumab and lenvatinib	125 (30.8)	0 (0.0)
Dose reduction due to AE	270 (66.5)	50 (12.9)
Deaths	23 (5.7)	19 (4.9)
Deaths due to AEs	6 (1.5)	8 (2.1)
Discontinuations due to AEs	134 (33.0)	31 (8.0)
Discontinuation of pembrolizumab	76 (18.7)	0 (0.0)
Discontinuation of lenvatinib	125 (30.8)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	57 (14.0)	0 (0.0)
Discontinuation due to treatment-related AEs	108 (26.6)	22 (5.7)
Discontinuation of pembrolizumab	40 (9.9)	0 (0.0)
Discontinuation of lenvatinib	92 (22.7)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	20 (4.9)	0 (0.0)
Discontinuation due to SAE	88 (21.7)	14 (3.6)
Discontinuation of pembrolizumab	60 (14.8)	0 (0.0)
Discontinuation of lenvatinib	81 (20.0)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	50 (12.3)	0 (0.0)
Discontinuation due to a treatment-related SAE	61 (15.0)	8 (2.1)
Discontinuation of pembrolizumab	28 (6.9)	0 (0.0)
Discontinuation of lenvatinib	50 (12.3)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	17 (4.2)	0 (0.0)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE: serious adverse event TPC: treatment of physician's choice. **Source**: Makker et al. 2022.[11]		

The median duration of exposure was over twice as long for PEM+LEN compared with TPC.[11] When adjusted for exposure, the incidences of Grade 3 to 5 AEs and death were lower for the PEM+LEN arm compared with the TPC arm, and that of SAEs was similar between the two groups (Table 15).

Table 15: Exposure-adjusted adverse event summary (including multiple occurrences of events) in the KEYNOTE-775 trial (safety all-comer population)

AE, event count rate (events/100 person-months)	PEM+LEN (n=406)	TPC (n=388)
Total exposure in person-months	3919.48	1765.17
One or more AE	9091 (231.94)	4526 (256.41)
No AE	1 (0.03)	2 (0.11)
Drug-related AEs	5221 (133.21)	2703 (153.13)
Toxicity grade 3-5 AEs	1216 (31.02)	861 (48.78)
Toxicity grade 3-5 drug-related AE	726 (18.52)	609 (34.50)
SAEs	398 (10.15)	178 (10.08)
Treatment-related SAEs	202 (5.15)	72 (4.08)
Dose modification due to and AE	1486 (37.91)	328 (18.58)
Dose interruption due to an AE	830 (21.18)	203 (11.50)
Interruption of pembrolizumab	442 (11.28)	0 (0.0)
Interruption of lenvatinib	616 (15.72)	0 (0.0)
Interruption of both pembrolizumab and lenvatinib	228 (5.82)	0 (0.0)
Dose reduction due to AE	594 (15.16)	84 (4.76)
Deaths	23 (0.59)	19 (1.08)
Deaths due to AEs	6 (0.15)	8 (0.45)
Discontinuations due to AEs	196 (5.00)	41 (2.32)
Discontinuation of pembrolizumab	101 (2.58)	0 (0.0)
Discontinuation of lenvatinib	164 (4.18)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	69 (1.76)	0 (0.0)
Discontinuation due to treatment-related AEs	156 (3.98)	31 (1.76)
Discontinuation of pembrolizumab	56 (1.43)	0 (0.0)
Discontinuation of lenvatinib	124 (3.16)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	24 (0.61)	0 (0.0)
Discontinuation due to SAE	95 (2.42)	15 (0.85)

Discontinuation of pembrolizumab	61 (1.56)	0 (0.0)
Discontinuation of lenvatinib	85 (2.17)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	51 (1.30)	0 (0.0)
Discontinuation due to a treatment-related SAE	64 (1.63)	8 (0.45)
Discontinuation of pembrolizumab	29 (0.74)	0 (0.0)
Discontinuation of lenvatinib	53 (1.35)	0 (0.0)
Discontinuation of both pembrolizumab and lenvatinib	18 (0.46)	0 (0.0)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE: serious adverse event TPC: treatment of physician's choice. **Source:** KEYNOTE-775 Clinical Study Report (Table 12-2).[13]		

B.2.10.1.3. Adverse events

The types, incidence, and severity of AEs in the PEM+LEN group were generally consistent with the known safety profiles of pembrolizumab monotherapy or lenvatinib monotherapy.[11] These safety profiles are generally well managed with supportive medications and dose modifications.

The types, incidence, and severity of AEs in the TPC group were consistent with the known safety profile of doxorubicin or paclitaxel.[11] The most frequently reported AEs (incidence ≥30%) were hypertension, hypothyroidism, diarrhoea, nausea, decreased appetite, vomiting, weight decreased, fatigue, and arthralgia for the PEM+LEN arm. For the TPC arm, the most frequently reported AEs were anaemia, nausea, neutropenia, and alopecia.

All the most frequently reported AEs are common or very common AEs associated with pembrolizumab and Lenvatinib as monotherapies.[3]

A summary of the most frequently reported adverse events in the KEYNOTE-775 trial is presented in Table 16.

Table 16: Patients with AEs by decreasing incidence (incidence ≥10% in one or more treatment groups) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
Patients with one or more AE	405 (99.8)	386 (99.5)
Patients with no AE	1 (0.2)	2 (0.5)

Hypertension	260 (64.0)	20 (5.2)
Hypothyroidism	233 (57.4)	3 (0.8)
Diarrhoea	220 (54.2)	78 (20.1)
Nausea	201 (49.5)	179 (46.1)
Decreased appetite	182 (44.8)	82 (21.1)
Vomiting	149 (36.7)	81 (20.9)
Weight decreased	138 (34.0)	22 (5.7)
Fatigue	134 (33.0)	107 (27.6)
Arthralgia	124 (30.5)	31 (8.0)
Proteinuria	117 (28.8)	11 (2.8)
Anaemia	106 (26.1)	189 (48.7)
Constipation	105 (25.9)	96 (24.7)
Urinary tract infection	104 (25.6)	39 (10.1)
Headache	101 (24.9)	34 (8.8)
Asthenia	96 (23.6)	95 (24.5)
Dysphonia	93 (22.9)	2 (0.5)
Alanine aminotransferase increased	86 (21.2)	20 (5.2)
Palmar-plantar erythrodysaesthesia syndrome	86 (21.2)	3 (0.8)
Abdominal pain	83 (20.4)	53 (13.7)
Aspartate aminotransferase increased	80 (19.7)	17 (4.4)
Stomatitis	78 (19.2)	47 (12.1)
Hypomagnesaemia	72 (17.7)	26 (6.7)
Myalgia	72 (17.7)	19 (4.9)
Rash	61 (15.0)	13 (3.4)
Pyrexia	58 (14.3)	29 (7.5)
Abdominal pain upper	53 (13.1)	27 (7.0)
Cough	53 (13.1)	51 (13.1)
Hypokalaemia	53 (13.1)	26 (6.7)
Blood thyroid stimulating hormone increased	52 (12.8)	1 (0.3)
Hypertriglyceridaemia	51 (12.6)	11 (2.8)
Blood alkaline phosphatase increased	50 (12.3)	15 (3.9)
Platelet count decreased	50 (12.3)	22 (5.7)
Back pain	49 (12.1)	29 (7.5)
Mucosal inflammation	49 (12.1)	38 (9.8)
Oedema peripheral	49 (12.1)	36 (9.3)
Hyperthyroidism	47 (11.6)	4 (1.0)
Dyspnoea	46 (11.3)	42 (10.8)
Lipase increased	45 (11.1)	8 (2.1)
Pain in extremity	45 (11.1)	21 (5.4)

Blood creatinine increased	44 (10.8)	10 (2.6)
Thrombocytopenia	44 (10.8)	26 (6.7)
Dizziness	42 (10.3)	22 (5.7)
Pruritus	42 (10.3)	12 (3.1)
Neutropenia	30 (7.4)	131 (33.8)
Neutropenia	28 (6.9)	51 (13.1)
Alopecia	22 (5.4)	120 (30.9)
Neutrophil count decreased	22 (5.4)	94 (24.2)
White blood cell count decreased	94 (24.2)	60 (15.5)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE: serious adverse event TPC: treatment of physician's choice. **Source:** KEYNOTE-775 Clinical Study Report (Table 12-3)[13]; Makker et al. 2022.[11]		

Exposure-adjusted rates of most AEs were either lower for PEM+LEN compared with TPC or similar between the two groups (Appendix N).

A summary AEs of special interest in the KEYNOTE-775 trial is presented in Table 17; participants with AEs of special interest by category are summarised in Table 18.

Table 17: Summary of AEs of special interest in the KEYNOTE-775 trial (safety all-comer population)

	PEM+LEN (n=406)	**TPC (n=388)**
All AEs, n (%)		
One or more AE	273 (67.2)	17 (4.4)
No AE	133 (32.8)	371 (95.6)
Grade 3-5 AE	53 (13.1)	1 (0.3)
SAEs	41 (10.1)	1 (0.3)
AE led to death	1 (0.2)	0 (0.0)
Discontinued drug due to an AE	23 (5.7)	1 (0.3)
Discontinued drug due to a SAE	20 (4.9)	0 (0.0)
Treatment-related AEs, n (%)		
One or more AE	259 (63.8)	8 (2.1)
Grade 3-5 AE	46 (11.3)	0 (0.0)
SAEs	38 (9.4)	0 (0.0)
AE led to death	1 (0.2)	0 (0.0)
Discontinued drug due to an AE	22 (5.4)	0 (0.0)
Discontinued drug due to a SAE	19 (4.7)	0 (0.0)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE: serious adverse event; TPC: treatment of physician's choice. **Source:** KEYNOTE-775 Clinical Study Report (Table 14.3-67); Makker et al. 2022.[11]		

Table 18: Participants with AEs of special interest by category in the KEYOTE-775 trial (safety all-comer population)

	PEM+LEN (n=406)	TPC (n=388)
Adrenal Insufficiency	5 (1.2)	0 (0.0)
Colitis	19 (4.7)	1 (0.3)
Encephalitis	2 (0.5)	0 (0.0)
Hepatitis	6 (1.5)	0 (0.0)
Hyperthyroidism	47 (11.6)	4 (1.0)
Hypophysitis	2 (0.5)	0 (0.0)
Hypothyroidism	234 (57.6)	3 (0.8)
Infusion Reactions	12 (3.0)	6 (1.5)
Myasthenic Syndrome	1 (0.2)	0 (0.0)
Myocarditis	1 (0.2)	0 (0.0)
Myositis	2 (0.5)	0 (0.0)
Nephritis	2 (0.5)	0 (0.0)
Pancreatitis	5 (1.2)	0 (0.0)
Pneumonitis	5 (1.2)	1 (0.3)
Severe Skin Reactions	13 (3.2)	1 (0.3)
Thyroiditis	8 (2.0)	0 (0.0)
Type 1 Diabetes Mellitus	4 (1.0)	0 (0.0)
Uveitis	3 (0.7)	0 (0.0)
Vasculitis	1 (0.2)	2 (0.5)

Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE: serious adverse event; TPC: treatment of physician's choice.
Source: Makker et al. 2022.[11]

B.2.10.1.4. Treatment-related adverse events

The incidence of treatment-related AEs in the PEM+LEN group was similar compared with the TPC group (Table 19).[11] The most frequently reported treatment-related AEs (incidence ≥30%) were hypertension, hypothyroidism, diarrhoea, nausea, and decreased appetite for the PEM+LEN group. For the TPC group, the most frequently reported treatment-related AEs were nausea, anaemia, neutropenia and alopecia.

Table 19: Summary of treatment-related AEs (Incidence ≥5% in one or more arms) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
One or more treatment-related AE	395 (97.3)	364 (93.8)
Hypertension	248 (61.1)	4 (1.0)
Hypothyroidism	221 (54.4)	0 (0.0)

Diarrhoea	171 (42.1)	42 (10.8)
Nausea	158 (38.9)	157 (40.5)
Decreased appetite	149 (36.7)	64 (16.5)
Fatigue	113 (27.8)	92 (23.7)
Proteinuria	102 (25.1)	4 (1.0)
Vomiting	99 (24.4)	59 (15.2)
Weight decreased	90 (22.2)	7 (1.8)
Arthralgia	84 (20.7)	17 (4.4)
Palmar-plantar erythrodysaesthesia syndrome	84 (20.7)	3 (0.8)
Dysphonia	76 (18.7)	2 (0.5)
Asthenia	75 (18.5)	76 (19.6)
Stomatitis	70 (17.2)	46 (11.9)
Alanine aminotransferase increased	63 (15.5)	14 (3.6)
Anaemia	58 (14.3)	150 (38.7)
Aspartate aminotransferase increased	58 (14.3)	12 (3.1)
Myalgia	54 (13.3)	13 (3.4)
Headache	53 (13.1)	14 (3.6)
Rash	47 (11.6)	6 (1.5)
Mucosal inflammation	45 (11.1)	35 (9.0)
Platelet count decreased	43 (10.6)	20 (5.2)
Blood thyroid stimulating hormone increased	40 (9.9)	1 (0.3)
Hyperthyroidism	39 (9.6)	1 (0.3)
Hypomagnesaemia	38 (9.4)	12 (3.1)
Constipation	36 (8.9)	51 (13.1)
Dry mouth	33 (8.1)	9 (2.3)
Dysgeusia	32 (7.9)	26 (6.7)
Lipase increased	32 (7.9)	2 (0.5)
Thrombocytopenia	31 (7.6)	22 (5.7)
Abdominal pain	30 (7.4)	13 (3.4)
Abdominal pain upper	28 (6.9)	28 (6.9)
Pruritus	27 (6.7)	7 (1.8)
Blood alkaline phosphatase increased	26 (6.4)	5 (1.3)
Pyrexia	26 (6.4)	26 (6.4)
Epistaxis	25 (6.2)	7 (1.8)
Hypertriglyceridaemia	24 (5.9)	1 (0.3)
Neutropenia	22 (5.4)	127 (32.7)
Blood creatinine increased	21 (5.2)	2 (0.5)
Leukopenia	20 (4.9)	47 (12.1)
Alopecia	17 (4.2)	117 (30.2)
Neutrophil count decreased	17 (4.2)	93 (24.0)
Lymphopenia	15 (3.7)	26 (6.7)
White blood cell count decreased	15 (3.7)	58 (14.9)

Lymphocyte count decreased	10 (2.5)	22 (5.7)
Neuropathy peripheral	8 (2.0)	21 (5.4)
Febrile neutropenia	1 (0.2)	21 (5.4)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice. **Source**: KEYNOTE-775 Clinical Study Report (Table 12-5)[13]; Makker et al. 2022.[11]		

B.2.10.1.5. Grade 3 to 5 adverse events

The incidence of Grade 3 to 5 AEs in the PEM+LEN group was higher compared with the TPC group (88.9% vs 72.7%).[11] The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) were hypertension, weight decreased, decreased appetite, diarrhoea, lipase increased, anaemia, asthenia, proteinuria, fatigue, and hypokalaemia for the PEM+LEN group. For the TPC group, the most frequently reported Grade 3 to 5 AEs were neutropenia, neutrophil count decreased, anaemia, white blood cell count decreased, and febrile neutropenia (Table 20).

Table 20: Summary of Grade 3 to 5 AEs (Incidence ≥5% in one or more arms) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
Hypertension	154 (37.9)	9 (2.3)
Weight decreased	42 (10.3)	1 (0.3)
Decreased appetite	32 (7.9)	2 (0.5)
Diarrhoea	31 (7.6)	8 (2.1)
Lipase increased	26 (6.4)	5 (1.3)
Anaemia	25 (6.2)	57 (14.7)
Asthenia	24 (5.9)	15 (3.9)
Proteinurea	22 (5.4)	1 (0.3)
Fatigue	21 (5.2)	12 (3.1)
Hypokalaemia	21 (5.2)	6 (1.5)
Neutrophil count decreased	10 (2.5)	83 (21.4)
Neutropenia	7 (1.7)	100 (25.8)
White blood cell count decreased	6 (1.5)	41 (10.6)
Febrile neutropenia	2 (0.5)	22 (5.7)
Leukopenia	0 (0.0)	31 (8.0)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice. **Source:** KEYNOTE-775 Clinical Study Report (Table 12-6)[13]; Makker et al. 2022.[11]		

B.2.10.1.6. Grade 3 to 5 treatment-related adverse events

The incidence of treatment-related Grade 3 to 5 AEs in the PEM+LEN group was higher compared with the TPC group (77.8% vs 59.0%).[11] The most frequently reported

treatment-related Grade 3 to 5 AEs (incidence ≥5%) were hypertension, weight decreased, decreased appetite, and diarrhoea in the PEM+LEN group. For the TPC group, the most frequently reported treatment-related Grade 3 to 5 AEs were neutropenia, neutrophil count decreased, anaemia, white blood cell count decreased, leukopenia, and febrile neutropenia (Table 21).

Table 21: Summary of treatment-related Grade 3 to 5 AEs (Incidence > 5% in one or more arms) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
One or more treatment-related AE	316 (77.8)	229 (59.0)
Hypertension	146 (35.9)	1 (0.3)
Diarrhoea	25 (6.2)	3 (0.8)
Decreased appetite	24 (5.9)	0
Weight decreased	24 (5.9)	0
Neutropenia	4 (1.0)	95 (24.5)
Neutrophil count decreased	7 (1.7)	82 (21.2)
White blood cell count decreased	4 (1.0)	40 (10.3)
Leukopenia	0	27 (7.0)
Febrile neutropenia	1 (0.2)	21 (5.4)

Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Source: Makker et al. 2022.[11]

B.2.10.1.7. Serious adverse events

The incidence of SAEs in the PEM+LEN group was higher compared with the TPC group (52.7% vs 30.4%).[13] The most frequently reported SAEs (incidence ≥1%) were hypertension, urinary tract infection (UTI), diarrhoea, decreased appetite, vomiting, acute kidney injury, pyrexia, cholecystitis, colitis, pneumonia, death, dehydration, intestinal obstruction, sepsis, abdominal pain, ileus, and pulmonary embolism for the PEM+LEN group (Table 22). For the TPC group, the most frequently reported SAEs were febrile neutropenia, anaemia, neutropenia, pulmonary embolism, and sepsis.

Table 22: Summary of SAEs by (Incidence ≥ 1% in one or more arms) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
Hypertension	17 (4.2)	0 (0.0)
Urinary tract infection	13 (3.2)	2 (0.5)
Diarrhoea	10 (2.5)	3 (0.8)
Decreased appetite	9. (2.2)	0 (0.0)

Vomiting	9. (2.2)	3 (0.8)
Acute kidney injury	8 (2.0)	3 (0.8)
Pyrexia	8 (2.0)	3 (0.8)
Cholecystitis	7 (1.7)	0 (0.0)
Colitis	7 (1.7)	1 (0.3)
Pneumonia	6 (1.5)	3 (0.8)
Death	5 (1.2)	3 (0.8)
Dehydration	5 (1.2)	1 (0.3)
Intestinal obstruction	5 (1.2)	3 (0.8)
Sepsis	5 (1.2)	5 (1.3)
Abdominal pain	4 (1.0)	1 (0.3)
Ileus	4 (1.0)	0 (0.0)
Pulmonary embolism	4 (1.0)	5 (1.3)
Febrile neutropenia	2 (0.5)	16 (4.1)
Anaemia	1 (0.2)	9 (2.3)
Neutropenia	1 (0.2)	7 (1.8)
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice **Source:** Makker et al. 2022.[11]		

B.2.10.1.8. Treatment-related serious adverse events

The incidence of treatment-related SAEs was higher in the PEM+LEN group (33.3%) compared with the TPC group (14.2%).[11] The most frequently reported treatment-related SAEs (incidence ≥1%) were hypertension, colitis, decreased appetite, vomiting, diarrhoea, pyrexia, and acute kidney injury for the PEM+LEN group.[13] For the TPC group, the most frequently reported treatment-related SAEs were febrile neutropenia, neutropenia, and anaemia.[13]

B.2.10.1.9. Deaths

The incidence of AEs resulting in death in the PEM+LEN group was similar compared with the TPC group. When adjusted by exposure, the incidence of AEs resulting in death was lower in the PEM+LEN group than in the TPC group.[11]

Of 23 (5.7%) patients in the PEM+LEN group who experienced AEs resulting in death, 6 deaths (1.5%) were considered related to study intervention by the investigator.[11] One death due to multiorgan dysfunction syndrome was considered related to both lenvatinib and pembrolizumab. One death each due to cerebrovascular accident, right ventricular dysfunction, myelodysplastic syndrome, and death were considered related to lenvatinib, and 1 death due to colitis was considered related to pembrolizumab.[13] The preferred term

"death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term.

Of 19 (4.9%) patients in the TPC group who experienced AEs resulting in death, eight deaths (2.1%) were considered related to study intervention by the investigator. [11] These events were all considered related to doxorubicin: two events of pneumonia, and one event each of aspiration, pulmonary embolism, cardiogenic shock, toxic cardiomyopathy, cardiac failure, and sepsis.[13]

B.2.10.1.10. Discontinuation and interruption of treatment

The incidence of patients with AEs that led to discontinuation of any study intervention was higher in the PEM+LEN group compared with the TPC group; 14% of patients discontinued combined treatment of PEM+LEN, with discontinuation of lenvatinib (30.8%) higher than for pembrolizumab (18.7%).[11]

In the PEM+LEN group, the AEs that led to discontinuation of both drugs were generally consistent with the known safety profile of pembrolizumab and lenvatinib, both in combination and as monotherapies.[11] In the TPC group, the AEs that led to discontinuation were consistent with the known safety profile of doxorubicin or paclitaxel.

The incidence of patients with treatment-related AEs that led to discontinuation of any study intervention was higher in the PEM+LEN group compared with the TPC group; 4.9% [redacted] of patients in the PEM+LEN group discontinued treatment due to treatment-related AEs, with discontinuation of lenvatinib (22.7%) higher than for pembrolizumab (9.9%).[11]

The incidence of patients with AEs that led to interruption of any study intervention was higher in the PEM+LEN group compared with the TPC group.[11] 30.8% of patients in the PEM+LEN group experienced interruption, with interruption of lenvatinib (58.6%) higher than for pembrolizumab (50.0%).

The most common AEs resulting in treatment interruption of both drugs (>1%) were diarrhoea, [redacted] hypertension, [redacted] and vomiting for the PEM+LEN group.[11, 13] For the TPC group, the most common AEs resulting in treatment interruption of treatment were [redacted].[13]

B.2.10.1.11. Dose reduction due to adverse events

The pembrolizumab dose was fixed at 200 mg Q3W and dose reduction was not allowed.[13] The starting dose for lenvatinib was 20 mg QD, however dose modifications were allowed according to the approved label and standard practice. The incidence of patients with AEs that led to dose reduction of lenvatinib was higher compared to dose reduction in the TPC group (66.5% vs 12.9%).[11]

The AEs that most frequently led to lenvatinib dose reduction (incidence >5%) were hypertension, diarrhoea, PPES, proteinuria, decreased appetite, fatigue, and weight decreased, all of which are known to be associated with lenvatinib.[11] The AEs that most frequently (incidence >1%) led to dose reduction of doxorubicin or paclitaxel were [redacted], all of which are known to be associated with chemotherapy.[13]

B.2.10.1.12. Safety overview

The safety profile of PEM+LEN is as expected and consistent with previously reported studies

At the first interim analysis, the safety results of the KEYNOTE-775 trial demonstrate that PEM+LEN offers a manageable and predictable AE profile specific to the individual products, and that this safety profile was consistent across patients enrolled to the trial.[11] These data were consistent with those observed during the phase I/IIb KEYNOTE-146 trial (Appendix F)[23]; both studies demonstrate a similar safety profile.

The safety profiles observed were generally consistent with those expected for pembrolizumab and for lenvatinib as monotherapy agents.[11] Known AEs are generally managed with supportive medications and dose modifications, with approaches to manage any AEs for each monotherapy are well established through their usage and practice in prior indications. Based on these analyses, the safety profile of pembrolizumab in combination with lenvatinib can be considered well characterised.

B.2.10.2. KEYNOTE-146

A summary of safety data from KEYNOTE-146 are provided in Appendix F. These data were broadly consistent with those observed during the KEYNOTE-775 trial.

B.2.11. Ongoing studies

The KEYNOTE-775 trial is ongoing, with the final analysis database lock estimated in [redacted] (events dependent - see Table 7). There is also an active trial investigating the clinical benefits of PEM+LEN versus carboplatin and paclitaxel in adults with advanced or recurrent EC who have not received prior platinum-based chemotherapy outside of the adjuvant and/or neoadjuvant setting: LEAP-001.[24] Data from this trial are not expected [redacted]

B.2.12. Innovation

Lenvatinib is a potent multiple RTK inhibitor that acts as an anti-angiogenic agent. Pembrolizumab is a potent and highly selective PD-1 inhibitor that acts as an immunotherapeutic agent (Table 2). The combination of an immunotherapeutic agent (pembrolizumab) with an anti-angiogenic agent (lenvatinib) is thought to remodel the tumour microenvironment, enhancing cancer cell recognition by the immune system and thus priming response to pembrolizumab.[25-27] These synergistic molecular effects allow a rapid, stronger and more durable tumour response, with the combination of PEM+LEN building on their individual agent effect.

The KEYNOTE-775 trial is the first randomised, controlled Phase III study evaluating a novel combination therapy in the previously treated advanced EC setting that has demonstrated positive results for both primary endpoints of OS and PFS across a broad range of participants.[13] Efficacy results demonstrate that treatment with PEM+LEN is superior to TPC, irrespective of a person's stage, histology, or biomarker status. While the main health-related benefits of PEM+LEN will be captured in the quality-adjusted life year (QALY) calculation, the provision of an effective novel treatment option will provide additional benefits to patients, carers and healthcare professionals alike that are not captured in a QALY-only approach. This is especially important when considering the backdrop of historic unmet need for this population (see Section B.2.13.1).

The introduction of PEM+LEN to the current pathway of care would represent a step-change in EC management, providing a novel treatment option with proven efficacy to a group of people with poor prognosis, for whom there is a significant unmet medical need and no current standard of care (see Section B.2.13.1).

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Summary of unmet medical need

Little progress has been made in EC management over the past decade, and there is no standard of care beyond platinum-based chemotherapy (carboplatin and paclitaxel) for advanced or recurrent EC, as acknowledged in the BGCS Guidelines.[1, 2, 12]

There is currently no consensus on a standard treatment for people with advanced or recurrent EC who have received prior systemic therapy, with limited efficacious treatments available for this patient population, and no treatment option demonstrating superiority over another in a robust clinical trial setting.[12] People with advanced or recurrent EC who have disease progression on or following prior treatment with platinum-based chemotherapy are unlikely to live beyond a year with current treatment options (see Section B.2.13.4). This estimate is based on empirical data from KEYNOTE-775 and retrospective UK chart review (data on file), and supported by clinical expectations based on observations in real-world practice.[2, 11]

There is a clear unmet need for additional, novel treatment options with proven efficacy and manageable safety profiles for adults with advanced or recurrent EC, beyond platinum-based chemotherapy. PEM+LEN addresses this unmet need.

B.2.13.2. Principal findings from the evidence base

The KEYNOTE-775 trial provides the pivotal evidence supporting the use of PEM+LEN in people with advanced, or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.

Efficacy results from the KEYNOTE-775 trial demonstrate that treatment with PEM+LEN is superior to TPC and provides a statistically significant and clinically meaningful improvement in OS, PFS and ORR.[11] Kaplan–Meier curves for PFS and OS can be seen to separate early and definitively, remaining consistently separated through the duration of study follow-up. The PFS rate at 2 years was more than five times higher in the PEM+LEN arm compared with the TPC arm (20.9% versus 3.8%), and the OS rate at 2 years was twice as high (42.0% vs 21.4%).[13] This is despite extensive use of subsequent systemic anticancer therapy in the TPC arm that is not available to patients in the UK. The ORR rate

was also twice as high in the PEM+LEN arm compared with the TPC arm (31.9% vs 14.7%) with an estimated difference of 17.2%.[11]

The KEYNOTE-146 trial provides supportive evidence of the longer-term benefit of PEM+LEN in people with pre-treated metastatic EC, demonstrating an unprecedented 5-year survival rate for patients treated with PEM+LEN of approximately 30%.[23] This is discussed further in Section B.3.3 and Section B.3.8.

Safety results across the KEYNOTE-775 and KEYNOTE-146 trials showed PEM+LEN to offer a manageable safety profile, with most adverse events (AEs) resolved with supportive medication, dose interruption or reduction of lenvatinib and less commonly, with dose interruption of pembrolizumab.[11, 17] Safety profiles observed were generally consistent with those expected for pembrolizumab and lenvatinib as monotherapy agents, for which approaches to manage AEs are well established.

Importantly, HRQL data collected in KEYNOTE-775 show no clinically meaningful drop in patient quality of life during treatment with PEM+LEN, and there were no differences in HRQL for participants treated with PEM+LEN versus chemotherapy.[16]

B.2.13.3. Strengths and limitations of the evidence base

B.2.13.3.1. Study design

The KEYNOTE-775 trial is a phase III RCT of high-quality design and conduct with several steps taken to minimise the risk of bias. This included the restriction of dMMR participants and a staged statistical analyses approach to ensure ITT data were not positively biased in favour of the PEM+LEN arm.

Due to the differences in dosage and administration between pembrolizumab, lenvatinib, doxorubicin and paclitaxel, KEYNOTE-775 is an open-label study.[11] This study design (where investigators and patients were not blinded to treatment assignment) may introduce bias to which subjective measures, such as PROs, could be particularly susceptible to. To counteract this, treatment randomisation occurred centrally using an interactive response technology (IRT) system. Patients were stratified according to MMR status, and within the pMMR stratum, patients were further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. Furthermore, efficacy endpoints as per RECIST 1.1 were determined by a blinded independent central investigator through BICR assessment.

B.2.13.3.2. Study applicability to clinical practice

The KEYNOTE-775 trial provides data of direct relevance to the decision problem with regard to population, comparator and outcomes.

B.2.13.3.2.1. Population

Patients included in the KEYNOTE-775 trial had advanced, recurrent or metastatic EC and had disease progression on or following prior systemic, platinum-based chemotherapy treatment.[11] This is consistent with the most common position of use for PEM+LEN in clinical practice.

A broad range of participants were enrolled in terms of histology, MMR status and treatment history with PEM+LEN providing clinically meaningful and durable responses across all patients.[11] As such, biomarker testing is not a barrier to treatment, potentially resulting in a faster initiation. As the prognosis for patients with unresectable advanced or recurrent EC is particularly poor, earlier treatment initiation may lead to a significant impact on patients' survival and overall quality of life.

The median patient age in the KEYNOTE-775 trial was 64 years[11], which is generally aligned with the median age of UC patients in England, where the majority of patients diagnosed in 2019 were aged ≥ 55 years.[5] Clinical expert consultation suggested trial participants are slightly younger than UK patients and that the proportion of patients with dMMR is slightly higher in the UK, but they noted that baseline characteristics are generally representative of UK clinical practice.[2]

It should be acknowledged that there is a current evidence gap for PEM+LEN in adults with advanced or recurrent EC who have not received prior platinum-based chemotherapy outside of the adjuvant and/or neoadjuvant setting. This evidence gap will be filled by the ongoing LEAP-001 trial (see Section B.2.11).

B.2.13.3.2.2. Comparator

In the absence of a standard of care beyond platinum-based chemotherapy for advanced or recurrent EC, the TPC arm of KEYNOTE-775 was chosen to represent clinical practice and is considered generalisable to the decision problem being addressed, with TPC treatments representing the majority share of real-world treatment use in the UK (data on file).

This trial was not powered to analyse results by treatment option, as both doxorubicin and paclitaxel represent 'standard' clinical practice. Investigators must have selected and recorded the TPC option prior to randomisation, in the event that the participant was assigned to the TPC arm, limiting any selection bias.

B.2.13.3.2.3. Outcomes

The outcomes measured in KEYNOTE-775 can be considered relevant to patients, carers and healthcare professionals alike. Dual primary efficacy endpoints of PFS and OS reflect well established trial endpoints and monitoring endpoints adopted in clinical practice, but also outcomes that have the most impact on patients and carers. HRQL endpoints further assess the impact of disease on patients and also allow formal utility analyses to support economic modelling.

Current survival data from KEYNOTE-775 are limited to IA1 but show OS improvements with PEM+LEN that are statistically significant and clinically meaningful.[11] The OS HR of 0.62 (95% CI: 0.51, 0.75; p<0.0001) crossed the pre-specified boundary for statistical significance at IA1 of ≤0.0064. The KM curves for OS clearly separated, starting at around 3 months and remained consistently separated throughout the duration of the evaluation period. This was despite high use of subsequent anticancer therapy in the TPC group, including subsequent treatment with PD1/PDL1 regimens that are not currently available in the UK (see Section B.3.5.4) that likely dilutes the real-world survival benefit PEM+LEN offers.

Interim survival data from KEYNOTE-775 are supported with longer-term data from the earlier phase KEYNOTE-146 trial, that clearly demonstrate the longer-term benefit of PEM+LEN treatment for advanced or recurrent EC with an unprecedented 5-year survival rate of approximately 30%.[23] To put this into context, the 2-year survival rate with current care is around 20% (Table 23).

B.2.13.4. End-of-life criteria

PEM+LEN should be considered an end-of-life treatment, meeting the NICE criteria for such designation, as summarised in Table 23.

Table 23: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	Survival estimates for current standard of care from KEYNOTE-775: Median survival = 11.4 months	Section B.2.6.1 Page 30
	Survival estimates for current standard of care from economic modelling: Mean undiscounted survival = [redacted] months	Section B.3.3.3.2 and B.3.7.1 Page 85 and 124
	Survival estimates for current standard of care from retrospective chart review in the UK (ECHO): Median survival = [redacted] months	Section B.2.9.3 Page 52
	Clinical expert expectations of survival for current care: Median survival ≤ 12 months	Section B.2.13.1 Page 58
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	Survival estimates for PEM+LEN from KEYNOTE-775: Median survival = 18.3 months	Section B.2.6.2.2 Page 38
	Survival estimates for PEM+LEN from KEYNOTE-146: Median survival = 17.7 months	Section B.2.6 Page 37
	Survival estimates for PEM+LEN from economic modelling: Mean undiscounted survival = [redacted]months Mean undiscounted LY gain versus current care = 3.53	Section B.3.3.3.2 and B.3.7.1 Page 85 and 124
Key: PEM+LEN, pembrolizumab with lenvatinib; LY, life years.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

No relevant studies were identified in a systematic search for cost-effectiveness analyses of PEM+LEN for patients with advanced, metastatic, or recurrent EC who have received prior systemic therapy (reported in Appendix G). Based on an additional hand-search of economic models in the published domain, one abstract was identified that demonstrated the cost-effectiveness of PEM+LEN versus chemotherapy in the Swedish setting. The same model structure as per this submission with the Sweden specific inputs. Therefore, it is not informative for decision making in the UK.[28]

At the time of writing this submission, there were no published NICE appraisals for treatments for advanced, metastatic or recurrent EC. NICE have very recently recommended dostarlimab for a group of patients with previously treated advanced or recurrent EC with MSI-H or dMMR (ID3802, 08 February 2022). This appraisal was based on a single arm study (GARNET [an ongoing phase 1, open-label, single-arm, multicentre study of the efficacy and safety of dostarlimab]) and supplementary UK RWE conducted by the manufacturer. Given the proximity of the publication to this submission, there was not sufficient time to review the available evidence from ID3802 in full. A top-level assessment of data available from ID3802 showed that all efficacy and HRQL data have been redacted from the public domain, and it is therefore not informative for this appraisal of PEM+LEN.

Published NICE appraisals in similar gynaecological cancers were considered, where relevant, to inform the approach taken for the economic evaluation for PEM+LEN. An expanded targeted literature review of NICE technology appraisals considering uterine, cervical and ovarian cancers was conducted, and economic evaluation methods of published NICE appraisals are presented in Table 24.

B.3.2. Economic analysis

As no published cost-effectiveness studies relevant for the UK were identified by the SLR and no published NICE appraisals in EC, an economic model was developed to assess the cost-effectiveness of PEM+LEN. Previous NICE appraisals in gynaecological cancers were considered to inform the approach taken for the economic evaluation (Table 24).

B.3.2.1. Patient population

PEM+LEN is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation, as described in Section B.1.2. The economic analysis addresses this patient population directly in line with the decision problem, which is consistent with the KEYNOTE-775 trial population and the final scope issued by NICE.[29]

B.3.2.2. Model structure

The economic model developed to assess the cost-effectiveness of PEM+LEN in this indication follows a partitioned survival modelling approach. Previous NICE technology appraisals (TAs) in gynaecological cancers have included variations of the standard three-state partitioned survival structure (Table 24), where state membership is defined by disease status (progression-free [PF] versus progressed disease [PD]) and mortality status (Section B.3.1). Importantly, the partitioned survival modelling approach facilitates direct use of clinical trial evidence available from KEYNOTE-775, including the primary outcomes of progression-free survival (PFS) and overall survival (OS) endpoints. The cohort model structure accurately captures survival and HRQL implications for patients and cost and resource use implications for the National Health Service (NHS) (as reported in Sections B.3.4 and B.3.5, respectively), in line with the NICE reference case.[30]

Figure 10 illustrates the health states and possible transitions in each model treatment arm. The health states capture disease progression status (PF or PD) and treatment status (on or off treatment). Treatment-dependent costs and health outcomes associated with each arm are captured within each mutually exclusive heath state.

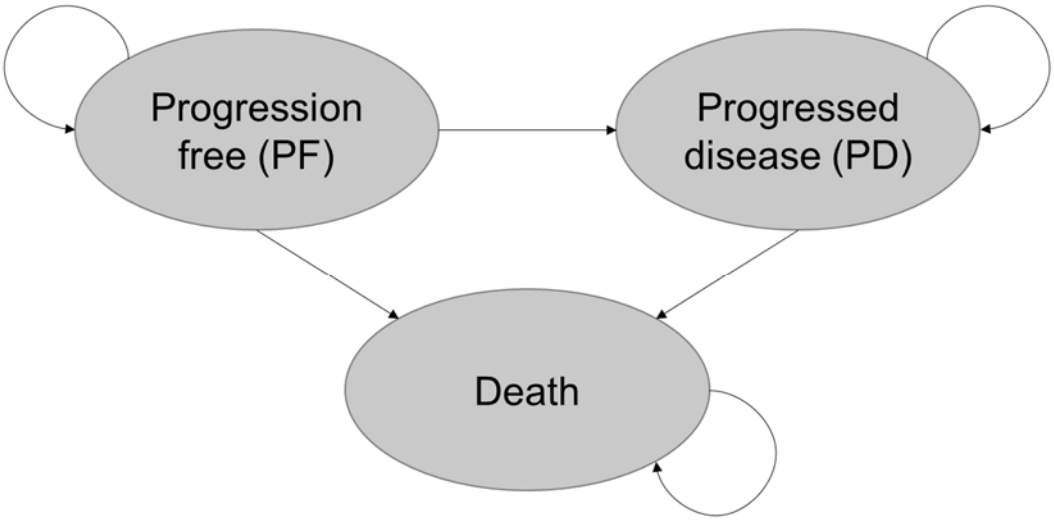
Patients with advanced or recurrent EC who have received prior systemic therapy enter the model in the PF state and are assumed to be on treatment. In each model cycle those in the PF stage can either remain in the PF state or move into the PD or death state. Those in the PD state can remain in the PD state or move into the death state. Death is included as an absorbing health state.

Additionally, the following adjustments are applied to maintain logical consistency in the patient flow of the model:

- The mortality risk at each model cycle is bound by age-matched general population predictions, sourced from the latest available Office for National Statistics Life Tables[31]

- A limit is built into the model to ensure that PFS cannot exceed OS. The limit is applied to the per cycle hazard of progression/death and hazard of death; if the hazard of death exceeds that of progression/death, the maximum hazard is assumed. This only occurs towards the end of the time horizon, after there are approximately 10% of PEM+LEN patients and 0% of TPC patients remaining alive. In addition, the hazard of death on both arms is capped by the hazard of death experienced by the general population.
- By the same logic, time on treatment (TOT) also cannot exceed OS; if TOT is estimated to be greater than OS at any time on any model arm, TOT is assumed to be equal to OS

Figure 10: Economic model structure



A 1-week cycle length is considered sufficiently short to reflect dosing regimens and accurately capture key clinical outcomes for patients. Given the short cycle length, a half-cycle correction is not applied to any cost or health outcomes. Table 24 summarises key features of the economic analysis, alongside corresponding features of completed appraisals in other gynaecological appraisals.

Table 24: Features of the economic analysis

	Previous appraisals						Current appraisal	
Factor	**TA528[32]**	**TA598[33]**	**TA611[34]**	**TA620[35]**	**TA673[36]**	**TA693[37]**	**Chosen values**	**Justification**
Indication (abbreviated)	Maintenance, relapsed ovarian cancer (platinum-sensitive)	Maintenance, BRCAm advanced ovarian cancer (after first-line platinum-based chemo)	Maintenance, relapsed ovarian cancer (platinum-sensitive)	Maintenance, relapsed ovarian cancer (platinum-sensitive)	Maintenance, advanced ovarian cancer (after first-line platinum-based chemo)	Maintenance, advanced ovarian cancer	Previously treated advanced, metastatic or recurrent endometrial cancer	N/A
Intervention	Niraparib	Olaparib	Rucaparib	Olaparib	Niraparib	Olaparib	PEM+LEN	N/A
Model structure	Three state decision analytic model	Three state partitioned survival model	Three-state cohort-based partitioned survival model	Three-state cohort-based partitioned survival model	Three-state cohort-based partitioned survival model	Four-state cohort-based partitioned survival model	Three-state partitioned survival model	Standard approach consistent with previous NICE TAs in oncology. Uses key endpoints from KN-775 (OS, PFS)
Time horizon	Lifetime horizon (40 years) .	Lifetime horizon (50 years)	Lifetime horizon (30 years)	Lifetime horizon (30 years)	Lifetime horizon (40 years)	Lifetime horizon (50 years)	Lifetime horizon (40 years)	To capture health and cost outcomes over patient lifetime, consistent with NICE reference case
Treatment waning effect?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Not applicable as with previous appraisals; validated by long-term KN-146 data
Source of utilities	NOVA trial	SOLO1 trial	ARIEL3 trial	TA528 (NOVA) and SOLO2 trial.	PRIMA trial	PAOLA-1	KN-775 EQ-5D-5L mapped onto 3L	As recommended in the NICE reference case.

Source of costs	BNF and NHS reference costs	BNF, CMU, eMIT, NHS reference costs	BNF, eMIT, NHS reference costs, Unit Costs of Health and Social Care	BNF, eMIT, NHS reference costs, Unit Costs of Health and Social Care	BNF, NHS reference costs, Unit Costs of Health and Social Care, UK published literature	BNF, eMIT, NHS reference costs, Unit Costs of Health and Social Care	BNF, eMIT, NHS reference costs, Unit Costs of Health and Social Care	Consistency with NICE reference case
Source of resource use	Assumptions from TA381 and clinical expert opinion	BCGS guidelines, TA528, TA381, ID1296, TA285 and clinical expert opinion	Clinical expert opinion	Assumptions from TA285 and clinical expert opinion	Assumptions from TA598 (originally BCGS guidelines) and clinical expert opinion	BCGS guidelines, TA598, TA528, TA381, ID1296, TA285 and clinical expert opinion	Assumptions from TA620	Best available source, validated for use by clinical expert opinion, and previous appraisals in gynaecological cancers
RDI applied?	Yes	Yes	Yes	Yes	Yes	Yes	No, full dose applied	Conservative assumption; only weekly observed dose of LEN component applied from KN-775
Key: BCGS, British Gynaecological Cancer Society; BNF, British National Formulary; BRCAm, mutated BReast CAncer gene; chemo, chemotherapy; eMIT, electronic Market Information Tool; KN-146, KEYNOTE-146; KN-775, KEYNOTE-775; LEN, lenvatinib; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; TA, technology appraisal. **Notes:** Previous technology appraisals abbreviated as “ovarian cancer” include ovarian, fallopian tube or primary peritoneal cancer.								

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

PEM+LEN combination treatment is implemented in the analysis according to the EMA and MRHA marketing authorisation described in Section B.1.2, and the KEYNOTE-775 trial (please see Section B.2.3.1 and Section B.2.4 for further information about PEM+LEN and the clinical trial protocol).

In KEYNOTE-775, the maximum treatment duration of pembrolizumab was 2 years from first dose (Section B.2.3.1). The cost-effectiveness analysis incorporates this treatment rule as described in Sections B.3.3 to B.3.5. The dose and administration schedule for PEM+LEN follows details obtained from the SmPC for PEM+LEN and the KEYNOTE-775 trial protocol, as summarised below[3, 14]:

- Pembrolizumab is administered at a dose of 200 mg once every 3 weeks until progression or for up to a maximum of 35 cycles (2 years)
- Lenvatinib is administered at a dose of 20 mg daily until progression

Scenario analysis investigates pembrolizumab administered at a dose of 400 mg once every 6 weeks until progression or for up to a maximum of 35 cycles (2 years). Scenario results are presented in Section B.3.9.2.

B.3.2.3.2. Comparators

As described in Section B.3.5.1, the most relevant comparators included in the cost-effectiveness model are paclitaxel and doxorubicin. This is incorporated in the TPC arm in the economic model, where treatment is implemented using time-to-event data from the TPC arm of the KEYNOTE-775 trial (containing 25.5% paclitaxel and 74.5% doxorubicin). Both paclitaxel and doxorubicin treatments are used in UK clinical practice as described in Section B.1.3.2.

The dose and administration schedule for TPC implemented in the model per KEYNOTE-775 are summarised below[14]:

- Paclitaxel is administered at a dose of 80 mg/m^2 once every 3 weeks until progression
- Doxorubicin is administered at a dose of 60 mg/m^2 3 weeks in every 4 until progression or a lifetime cumulative dose of 500 mg/m^2

Paclitaxel was administered once every 3 weeks in line with the KEYNOTE-775 trial regimen and expected regimen in clinical practice. The use of weekly paclitaxel is only supported by anecdotal evidence; based on the clinical efficacy in ovarian cancer and its good tolerability.[1] Therefore, no scenarios investigating alternative paclitaxel dosing patterns were investigated, although the impact of these scenarios is likely to be negligible.

The TPC arm in the model base case is the most relevant comparator for this appraisal, as it covers treatments used by the majority of patients in the UK. For completeness, we have explored the impact of additional scenarios:

- The NICE scope lists doxorubicin as a comparator. The base case in the economic model is considered conservative because it applies the lower cost of the generic formulary for doxorubicin based on the eMIT database. Clinical experts consulted for this appraisal confirmed that the more expensive branded liposomal/pegylated doxorubicin (Caelyx®) is primarily used in UK clinical practice. Caelyx is considered to have equivalent effectiveness but is preferred to non-pegylated doxorubicin due to being associated with a better toxicity profile.[2] The base case cost-effectiveness analysis uses generic non-pegylated doxorubicin, and, when using the more expensive costs of Caelyx® in scenario analysis to better reflect the type of doxorubicin used in the UK, the incremental cost-effectiveness ratios (ICERs) slightly improve in favour of PEM+LEN (Section B.3.5.1)
- An exploratory scenario is included which incorporates carboplatin in combination with paclitaxel (as re-challenge) and carboplatin monotherapy – in addition to paclitaxel and doxorubicin – in a mixed chemotherapy comparator arm.[1, 2] This scenario is included in recognition of a small number of UK patients who may be eligible to receive further platinum-based chemotherapy following initial response to treatment. As there are no robust data for these treatments in previously treated advanced EC, it was necessary and appropriate to assume equivalent efficacy between the mixed chemotherapy options and TPC arm of KEYNOTE-775. Treatment costs are weighted according to their expected use in clinical practice as informed by the ECHO study (as detailed in Section B.2.9.3) ([redacted]% paclitaxel, [redacted]% doxorubicin, [redacted]% carboplatin, and [redacted]% carboplatin plus paclitaxel).[22] The proportions used exclude investigational treatments and those that are not currently reimbursed in the UK. Results of these scenarios are presented in Section B.3.8.2

- Further scenario analyses investigate paclitaxel (as part of the TPC and mixed chemotherapy analysis) administered at a dose of 80 mg/m^2 every week until progression and the inclusion of a paclitaxel stopping rule after 6 cycles, based on feedback from UK clinical experts.[2]

Finally, hormone therapy and best supportive care in this setting are palliative in nature, primarily used to relieve symptoms for patients without translating into any survival benefits. Patients who can only receive symptom-relief are unlikely to be fit enough for any active anti-cancer treatment, and therefore the treatments described are not considered as appropriate comparators for this appraisal.

The approval of PEM+LEN in this indication would represent a step change improvement in the clinical care pathway for patients with advanced EC. PEM+LEN offers an alternative mechanism of action to currently available chemotherapies and has demonstrated long-term effectiveness in KEYNOTE-775 and KEYNOTE-146.

B.3.3. Clinical parameters and variables

B.3.3.1. Overview of clinical data sources and outcomes in the economic model

The following clinical outcomes are included in the economic model:

- OS
- PFS
- TOT
- HRQoL
- AEs

The clinical outcomes used to inform the economic analysis are based on patient-level data from the Phase III KEYNOTE-775 trial investigating PEM+LEN versus TPC in the base case. This trial provides the most robust and best available evidence for conducting the comparative cost-effectiveness analysis.

B.3.3.2. Approach to time-to-event analysis – KEYNOTE-775

Key efficacy outcomes (OS, PFS and TOT) for PEM+LEN and TPC were modelled using patient-level data from KEYNOTE-775 (data cut-off date of 26 October 2020). The median duration of follow-up was approximately 12 months in the PEM+LEN arm and

approximately 11 months in the TPC arm.[13] In line with the NICE reference case, to assess the cost-effectiveness of PEM+LEN over a lifetime horizon it was necessary to extrapolate the patient-level data beyond the trial period.[30, 38, 39]

The methods used to extrapolate OS, PFS and TOT followed guidance outlined in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[38, 39] As patient-level data are available for both PEM+LEN and TPC in KEYNOTE-775, and there are a large number of observations for each arm, it is appropriate to extrapolate survival outcomes using individually fitted curves for each trial arm. The parametric models used in the base-case analysis were assessed systematically for each endpoint, based on the following approach:

- Following NICE DSU TSD 14, six parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz and generalized gamma) were fitted to the observed data from KEYNOTE-775 and assessed for suitability considering[38]:
  - Visual fit to the observed Kaplan–Meier (KM) data within the trial period for KEYNOTE-775
  - Assessment of the underlying hazard functions
  - Statistical goodness of fit indicated by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values
- Additional flexible two-piece KM plus parametric models were explored where necessary, in accordance with NICE DSU TSD 21, and assessed for suitability based on the same process[39]
- Clinical validation of extrapolated models was sought from UK clinical experts, and extrapolations were compared against relevant evidence from the KEYNOTE-146 trial (see Section B.2.6.2 for further details)

The most appropriate and clinically plausible models for OS, PFS and TOT were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses. Models in the base case and scenarios are summarised in Table 25 for OS and PFS and Table 26 for TOT. Full details are provided in Section B.3.3.3 for OS, Section B.3.3.4 for PFS, and Section B.3.3.5 for TOT.

Table 25: Summary of OS and PFS models selected for economic analysis (PEM+LEN and TPC)

Analysis	OS model (Section B.3.3.3)	Justification	PFS model (Section B.3.3.4)	Justification
Base case	**PEM+LEN:** KM (first 26 weeks) + log-logistic **TPC:** KM (first 26 weeks) + exponential	Two-piece approach provides best fit to the observed data for PEM+LEN and TPC Strong evidence for 26-week inflection point in PEM+LEN and TPC arm based on visual assessment of observed KM and hazard of death, supported by Chow test Log-logistic distribution provided the best fit for PEM+LEN and exponential distribution for TPC based on visual assessment of survival and hazard, statistical fit, validation with clinical experts and external published data (KEYNOTE-146)	**PEM+LEN:** KM (first 10 weeks) + log-logistic **TPC:** KM (first 10 weeks) + log-logistic	10-week cut-off consistent with first radiological assessment of progression in KEYNOTE-775, similar time-point expected in UK clinical practice Log-logistic distribution provided a plausible fit for PEM+LEN and TPC based on visual assessment of survival, and the best statistical fit, and was validated with clinical experts
Cut-off scenarios	KM (first 52 weeks) + extrapolation	Evidence for 52-week inflection point in PEM+LEN and TPC arm based on visual assessment of hazard of death, supported by Chow test	Independent one-piece parametric model; KM (first 37 weeks) + extrapolation	Strong evidence for 37-week inflection point in PEM+LEN and TPC arm based on visual assessment of observed hazard of progression or death, supported by Chow test
OS/PFS distribution scenarios	**PEM+LEN:** Per base case **TPC:** KM (first 26 weeks) + Weibull	Maintain clinical plausibility in expected outcomes for PEM+LEN and TPC and fit to longer term KEYNOTE-146 data for PEM+LEN.	**PEM+LEN:** KM (first 10 weeks) + log-normal **TPC:** KM (first 10 weeks) + log-normal	Next best statistical fit
Key: KM, Kaplan–Meier; PFS, progression-free survival; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice. **Notes**: Alternative plausible assumptions tested in scenario analyses; given there were no other plausible OS curves, minimal scenarios for OS were included (see Appendix R for further detail)				

Table 26: Summary of TOT models selected for economic analysis (PEM+LEN and TPC)

Analysis	TOT model (Section B.3.3.5)	Justification	TOT constraints and justification (Section B.3.3.5.1)
Base case	**Pembrolizumab:** Generalized gamma **Lenvatinib:** Generalized gamma **TPC:** Generalized gamma	Plausible fit to pembrolizumab, lenvatinib and TPC KEYNOTE-775 TOT and provides a clinically plausible long-term extrapolation for lenvatinib	PEM: maximum duration of 2 years per anticipated license and KN-775 TPC: maximum cumulative doxorubicin dose of 500 mg/m^2 (5.75 months)
TOT distribution scenarios	**Pembrolizumab:** Weibull **Lenvatinib:** Weibull **TPC:** Weibull	Plausible fit to pembrolizumab, lenvatinib and TPC KEYNOTE-775 TOT and provides a clinically plausible long-term extrapolation for lenvatinib	
Other TOT scenarios	Consistent with treat-to-progression rule, apply constraint that does not allow TOT to exceed PFS KM data directly for pembrolizumab and TPC TPC: maximum of 6 doxorubicin cycles (4.14 months)	Expected use in clinical practice is treat to progression KM data are complete for pembrolizumab and 99% complete for TPC Expected paclitaxel use in clinical practice	

Key: KM, Kaplan–Meier; PEM, pembrolizumab; PFS, progression-free survival; TOT, time on treatment; TPC, treatment of physician's choice.

B.3.3.3. Overall survival

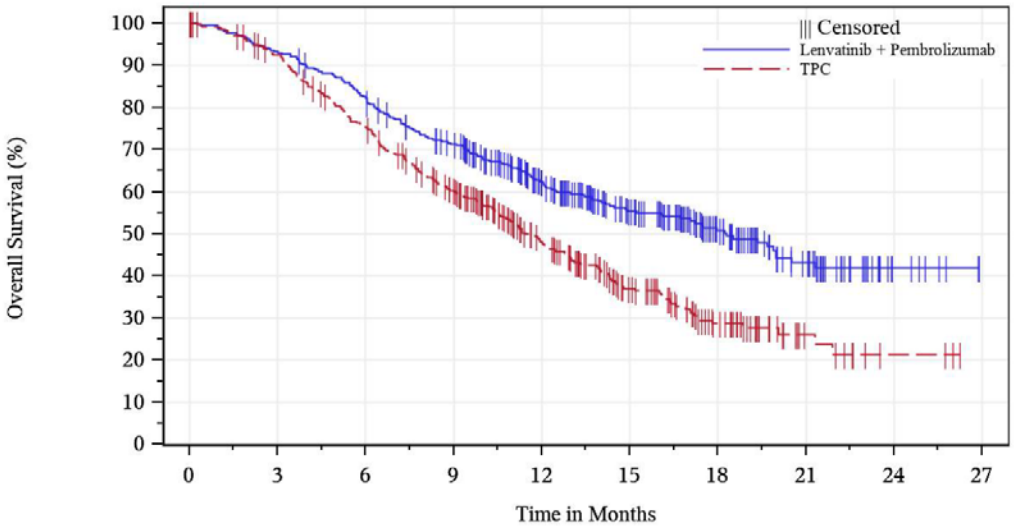
Figure 11 shows the OS KM data for all patients in KEYNOTE-775 and the corresponding underlying number at risk over time in the PEM+LEN and TPC arms of the trial. There is a clear separation in the KM plots from 3 months onwards, with increasing improvements in survival benefit for PEM+LEN that is sustained over the entire remaining observed period. Based on visual inspection, OS in the PEM+LEN arm appears to plateau at approximately [redacted]% survival from 21 months onwards while there remained a substantial number of patients at risk. This is considerably higher than in the TPC arm, where approximately [redacted]% of patients remained alive from the same time point. Figure 11 also includes the 5-year follow-up data observed in KEYNOTE-146, which demonstrates the prolonged long-term benefit of PEM+LEN in this indication. This is anticipated to continue to benefit patients throughout their lifetime.

Table 27. Number of events and level of maturity of OS in KN-775

Endpoint	Outcome	PEM+LEN N = 411	TPC N = 416
OS	Number of events	188	245
	Maturity (%)	45.7%	58.9%

Key: OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

Figure 11: PEM+LEN and TPC – OS, KM plot



n at risk

Lenvatinib + Pembrolizumab	411	383	337	282	198	136	81	40	7	0
TPC	416	373	300	228	138	80	40	11	3	0

Key: n, number; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

As NICE TSD 14 states, generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach. Nonetheless, the proportional hazards assumption was tested for completeness.[38] Details of the Schoenfeld residuals and log-cumulative hazard plots are provided in Appendix P which confirm that it is appropriate to extrapolate OS outcomes based on individually fitted curves for each trial arm.

An overlay of the independent one-piece parametric models and observed KM data from KEYNOTE-775 and KEYNOTE-146 are shown in Figure 12 for PEM+LEN (see Appendix P for further details). Based on assessment of the single-fitted curves against the observed data from KEYNOTE-775 and longer-term study KEYNOTE-146 (approximately 5-year follow-up), it is clear that the independent one-piece parametric survival curves are inappropriate for decision-making and should be disregarded on the basis of clinical implausibility:

- Observed long-term data from KEYNOTE-146 demonstrate that for patients treated with PEM+LEN, the 4 to 5-year survival rate is likely to be around 30% while the highest survival rates predicated by any independent one-piece parametric model was just 17%; this substantially underestimates the observed benefit of PEM+LEN (Figure 12)[17, 40]
- The hazard of death associated with each parametric survival model further confirms the importance of exploring more accurate methods of modelling lifetime survival across both arms, as the independent one-piece models are unable to capture the complex hazard profile, particularly beyond 26 weeks (Figure 13 and Figure 14, see further details provided in Appendix P)
  - The observed hazard of death increases until these timepoints before decreasing for the remaining observed period for PEM+LEN and plateauing for TPC; it is clear that the implied hazard profiles from some (most) of the parametric curves fit poorly to this shape for both PEM+LEN and TPC
  - The difference between the hazards based on the observed data and independent one-piece parametric fits is greater at later points in time in both arms, which emphasises the importance of exploring more accurate methods of modelling lifetime survival across both arms

Figure 12: OS independent one-piece parametric survival curves for PEM+LEN

Key: KM, Kaplan–Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib.

Figure 13: PEM+LEN OS hazard function

Key: OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib.
Note: The shaded region refers to 95% confidence intervals for the smooth spline estimates.

Figure 14: TPC OS hazard function

Key: OS, overall survival; TPC, treatment of physician's choice.
Note: The shaded region refers to 95% confidence intervals for the smooth spline estimates.

B.3.3.3.1. Two-piece extrapolation

Alternative survival models were explored to improve the validity of OS extrapolations for PEM+LEN and TPC. Consistent with guidance published in NICE DSU TSD 14 and 21, independent two-piece survival models (i.e. KM plus parametric extrapolation) were analyzed.[38, 41]

The independent two-piece models provided a substantially better fit to the observed data and are therefore preferable for the base-case analysis. An overlay of the independent two-piece parametric models and observed KM data from KEYNOTE-775 are shown in Figure 15 for PEM+LEN and Figure 16 for TPC. KEYNOTE-146 OS data have also been included in Figure 15 to inform the validity of long-term survival estimates. The AIC and BIC statistics corresponding to the independent two-piece parametric models fitted to KEYNOTE-775 are provided in Table 28.

Selection of the KM cut-off

Following visual inspection of the hazard of death for the PEM+LEN and TPC arm, a clear inflection point appears by 30 weeks indicating an appropriate timepoint for switching from KM to extrapolated data for the independent two-piece models. This observation is validated by supplementary Chow tests which suggest that the likely inflection point in OS is around 26 weeks, as shown in Appendix P It is also generally preferable to select earlier cut-off time points to retain as much statistical power as

possible for the two-piece survival analyses, as the number of patients at risk naturally decreases over time.

Therefore, 26 weeks was selected as an appropriate cut-off, where 337/411 and 300/416 patients were at risk on the PEM+LEN and TPC arms, respectively. Scenarios with different cut-offs were explored to understand the impact of this decision on the results, as shown in Section B.3.8.3.

Figure 15: OS independent two-piece parametric survival curves for PEM+LEN

[redacted]**Key**: KM, Kaplan–Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib.

Figure 16: OS independent two-piece parametric survival curves for TPC

[redacted]

Key: ECHO, endometrial cancer health outcomes study; KM, Kaplan–Meier; OS, overall survival; TPC, treatment of physician's choice; UK, United Kingdom.

Table 28: Fit statistics of overall independent two-piece survival extrapolation

Treatment	PEM+LEN		TPC	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.
Note: Cells in bold and italics represent the models with the best statistical fit.

Selection of the distribution for extrapolation beyond 26 weeks

Following determination of the 26-week cut-off for OS as an appropriate timepoint for the independent two-piece models, the distribution used for the extrapolated portion was partly informed by a comparison of the hazard of death associated with each

parametric survival model and the observed hazards (Figure 17 and Figure 18, respectively). Full details are provided in Appendix P.

The log-logistic model exhibits the closest properties to the observed hazard of death for PEM+LEN (decreasing hazards) and provides a plausible fit to the observed longer-term data from KEYNOTE-146. The exponential, Weibull and generalized gamma models do not adequately capture the complex hazard trend of PEM+LEN over the observed trial period and should be discounted for PEM+LEN extrapolation, as explained below and summarised in Appendix R:

- The hazard for TPC remains constant up to a time point of ~75 weeks (Figure 18). Although the observed hazard decreases after 75 weeks, this is largely attributed to low remaining numbers at risk in the data leading to variability in the results (Table 29). Simpler models, such as the exponential and Weibull, exhibit similar properties to the observed hazard of death for TPC over the period between 26 to 75 weeks, where there are a sufficiently large number of patients remaining at risk to inform the analysis. This assessment indicates that the log-logistic function is appropriate for PEM+LEN and the exponential function is appropriate for TPC
- When comparing the observed hazard of independent one-piece models (Figure 13 and Figure 14) with independent two-piece models (Figure 17 and Figure 18), the hazard of death associated with independent two-piece models over time appear to fit better to the remaining observed data than their independent one-piece counterparts. Independent one-piece models overfit to the initial steep increasing section of the smoothed spline hazard estimate, leading to an overestimation of long-term hazards. When cutting the data at 26 weeks, we simplify the survival section used to inform long term extrapolations, better fitting to medium- and long-term hazards

The survival models in the TPC arm were also validated using real-world survival data based on the UK cohort of the ECHO study (Section B.2.9.3), as shown in Figure 16. This demonstrated high consistency with outcomes from the TPC arm of the KEYNOTE-775 trial. As discussed in Section B.2.9.3, median OS from the start of second line of systemic therapy was [redacted] months in ECHO compared with a median OS of 11.4 months in KEYNOTE-775. Of note, ECHO included some patients who received investigational treatments not routinely available in UK clinical

practice as a subsequent treatment (such as PD-1/PD-L1 and VEGF/VEGFR inhibitors). Based on this, it is likely that the ECHO OS data may overestimate the 'true' comparative real-world outcomes for patients treated with second-line systemic therapy (TPC), and it is also expected that there are some differences compared to the TPC arm in KEYNOTE-775 which did allow subsequent line treatment PD-1/PD-L1 and VEGF/VEGFR inhibitors.

Figure 17: PEM+LEN OS hazard function, with breaking point at Week 26

Key: OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib.
Note: The shaded region refers to 95% confidence intervals for the smooth spline estimates.

Figure 18: TPC OS hazard function, with breaking point at Week 26

Key: OS, overall survival; TPC, treatment of physician's choice.
Note: The shaded region refers to 95% confidence intervals for the smooth spline estimates.

Table 29: Number of patients at risk, KN-775

Weeks	0	12	24	36	48	60	72	84	96	108	120
PEM+LEN	411	385	348	291	233	155	114	57	25	6	0
TPC	416	375	305	245	161	107	60	23	8	3	0

Key: KN-775, KEYNOTE-775; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

Following guidance in NICE DSU TSD 14, there is strong justification for the use of different survival distributions for each arm in the model.[38] The different mechanism of action for PEM+LEN and TPC are expected to translate into different survival trajectories and hazard profiles for patients:

- PEM+LEN is the first and only immuno-oncology (IO) drug to demonstrate superior efficacy based on Phase III clinical trial evidence in advanced, metastatic, and recurrent EC. Currently, there are no standard treatment options with highly limited treatment benefit associated with chemotherapies. There is clinical rationale supporting different hazard profiles for IO therapies compared with standard chemotherapy options (Section 0)

  - Immunotherapy differs from conventional anticancer treatments such as chemotherapy because it treats the immune system, and this is expected to translate into differential outcomes
  - The anti-angiogenic effect of lenvatinib (multi-TKI) in combination with the immune-stimulatory effect of pembrolizumab (anti-PD-1) results in a tumour microenvironment that may help overcome primary and acquired resistance to immunotherapy, improving tumour responses compared to either treatment alone. In preclinical murine models, PD-1 plus TKI inhibitors have demonstrated enhanced anti-tumour activity compared to either agent alone [26, 42]
  - In line with outcomes observed with pembrolizumab across multiple advanced malignancies, and with other IOs with similar mechanism of action, PEM+LEN is expected to offer a sustained treatment effect that is distinct from conventional chemotherapy options in EC.[43, 44] KEYNOTE-146 provides evidence of long-term effect after 5 years of follow-up, although the duration of sustained treatment effect beyond that time period is less clear and the impact on the results could be tested
  - Standard chemotherapy regimens are not expected to improve long-term outcomes, offering limited survival benefit for patients in the short-term only as is highlighted by the currently poor survival outcomes in this indication
- Clinical experts consulted for this appraisal support the above expectations of long-term benefit associated with PEM+LEN in this patient population
- Based on Phase III randomised clinical trial evidence, PEM+LEN has already demonstrated the potential to improve long-term survival in KEYNOTE-775. The extent of benefit observed with longer follow-up in KEYNOTE-146 has not been previously seen in this indication
- The observed underlying hazard profiles of PEM+LEN and TPC from KEYNOTE-775 follow distinct and different trajectories (Figure 12, Figure 13, Figure 17 and Figure 18). One major difference is that the hazards in the PEM+LEN arm have a strong decreasing trend after 26 weeks, which does not occur in the TPC arm

Finally, the clinical plausibility of long-term extrapolations was validated by oncologists experienced in endometrial cancer treatment in the UK.[2] As part of the

clinical validation process, the goodness of fit statistics, survival curves and estimates of long-term survival were presented for each extrapolation. All participants were more comfortable predicting plausible extrapolations for the TPC arm, given their experience in treating patients with chemotherapy regimens in this treatment area.[2] In particular:

- **TPC arm:** Due to some participants in the TPC arm of KEYNOTE-775 receiving subsequent PD-1/PD-L1 and VEGF/VEGFR inhibitor therapies that are not routinely available in the UK, the OS estimates may be overestimated in the trial. This could underestimate the incremental benefit of PEM+LEN versus TPC although it is not possible to test and adjust for the potential impact without introducing substantial uncertainty in the analysis. The bottom group of curves in Figure 16 provide a more plausible estimate of survival reflecting current UK clinical practice, with the exponential or Weibull extrapolations fitting well to the observed KEYNOTE-775 data. Furthermore, the hazard of death is not expected to reduce or change dramatically over time
- **PEM+LEN arm:** The log-logistic extrapolation fits well to the observed KEYNOTE-775 and longer-term KEYNOTE-146 data and provides a plausible estimate of long-term survival. Furthermore, a reduction in hazard for patients treated with PD-1/VEGFR inhibitor combination treatments such as PEM+LEN would be expected

B.3.3.3.2. Summary of modelled extrapolations

The most appropriate and clinically plausible models for OS are used in the base-case analysis, shown in Figure 19.

For PEM+LEN, KEYNOTE-775 KM data were used directly until a 26-week cut-off, after which the log-logistic function was fitted to OS time-to-event data reported in KEYNOTE-775. The KM + log-logistic model provides the most appropriate fit to PEM+LEN KEYNOTE-775 and KEYNOTE-146 survival, observed PEM+LEN hazard, and provides a clinically plausible long-term extrapolation.

For TPC, KEYNOTE-775 KM data were used directly until a cut-off at 26 weeks, after which the exponential function was fitted to OS time-to-event data reported in

KEYNOTE-775. The KM + exponential model provides an appropriate fit to TPC KEYNOTE-775 survival and hazard and provides a clinically plausible long-term extrapolation.

Alternative plausible assumptions tested in scenario analyses. Given there were no other plausible OS curves, minimal scenarios for OS were included (see Table 25 and Section B.3.8.2 and Appendix R for a summary of the plausibility of the assessed curves).

Figure 19: Selected OS curve fits for PEM+LEN and TPC

Key: ECHO, endometrial cancer health outcomes study; KM, Kaplan–Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice; UK, United Kingdom.

B.3.3.3.3. Mixed chemotherapy scenario

As mentioned in Section B.3.2.3.2, a scenario analysis is considered where carboplatin plus paclitaxel and carboplatin monotherapy are included alongside paclitaxel and doxorubicin in a mixed chemotherapy comparator arm. In the absence of efficacy data for these treatments in previously treated advanced EC, the mixed chemotherapy arm is assumed to have equal efficacy to the TPC arm as detailed in B.3.3.3.1 above. This approach was validated with UK clinicians.[2]

B.3.3.4. Progression-free survival

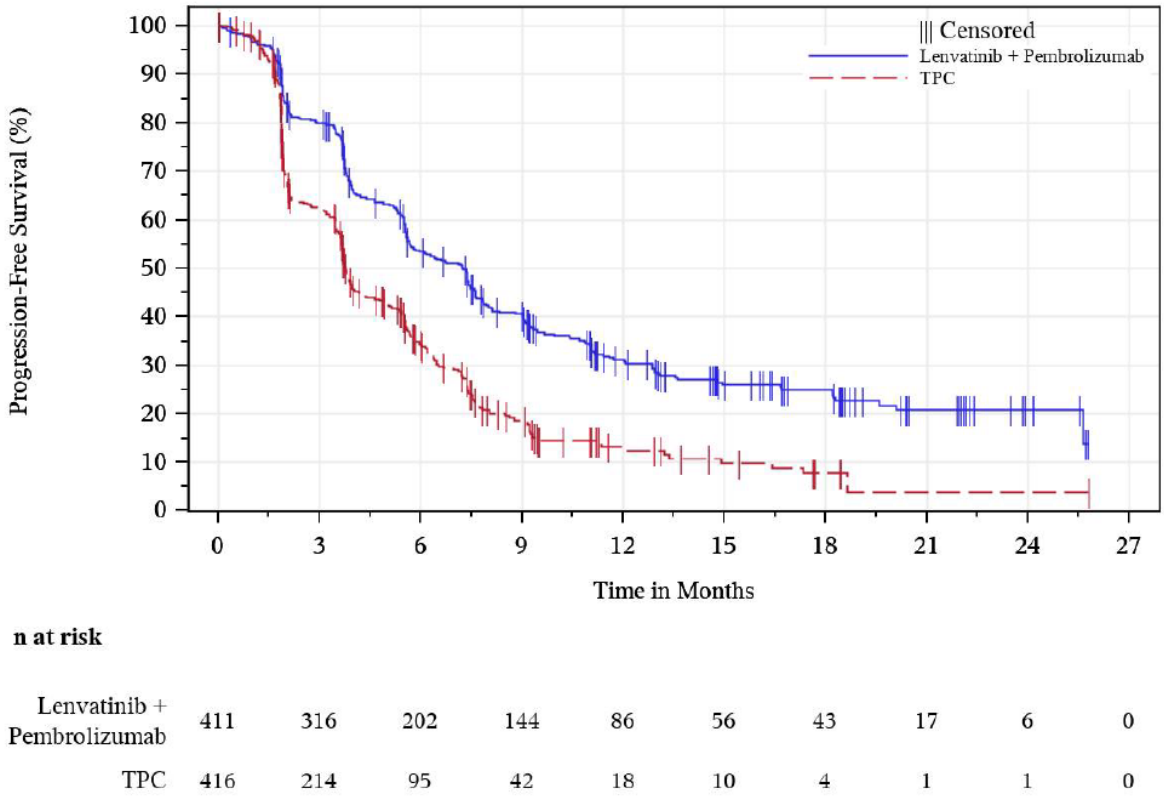
Figure 20 shows the PFS KM data for all patients in KEYNOTE-775 and the corresponding underlying number at risk over time in the PEM+LEN and TPC arm of the trial. There is clear separation in the KM plots from two months onwards, with sustained improvements in PFS benefit for PEM+LEN that is sustained over the entire remaining observed period. PFS in the PEM+LEN arm appears to plateau at approximately 21% from 18 months onwards. This plateau is considerably higher than in the TPC arm, where approximately 4% of patients remained progression free from the same time point with much fewer patients at risk.

Table 30. Number of events and level of maturity of PFS in KN-775

Endpoint	Outcome	PEM+LEN N = 411	TPC N = 416

PFS	Number of events	281	286
	Maturity (%)	68.4%	68.8%
Key: PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.			

Figure 20: PEM+LEN and TPC – PFS, KM plot



Key: n, number; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.

As with OS, the proportional hazards test for PFS also suggests that the proportional hazards assumption can be rejected given that the log-cumulative hazard of PEM+LEN and physician's choice chemotherapy PFS cross. Details of Schoenfeld residuals and log-cumulative hazard plots for the PFS proportional hazards test are presented in Appendix P.

Following a similar analytical approach to the OS analysis of independent one-piece parametric curves in B.3.3.3, independent two-piece extrapolations were also preferred for PFS. This section provides details of the independent two-piece models

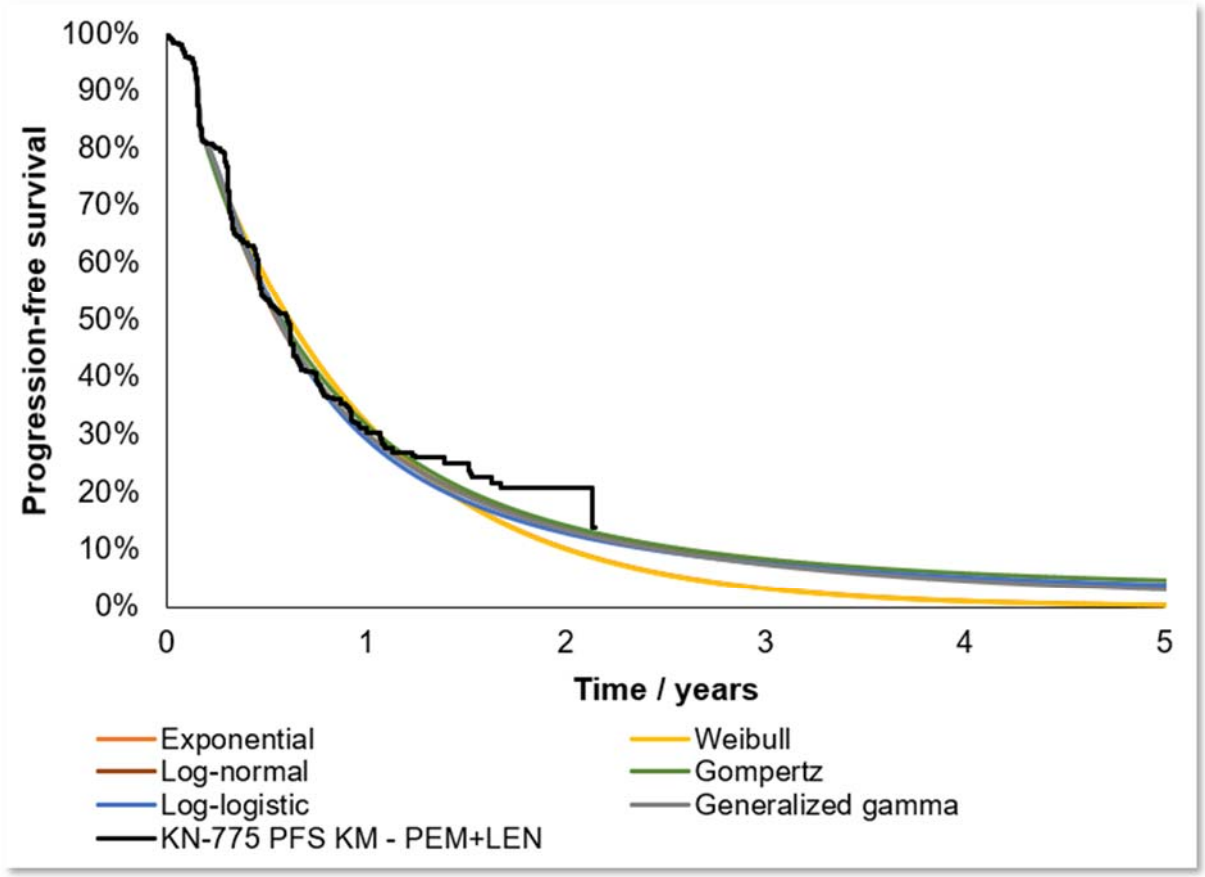
relevant to the model base case; details of the independent one-piece models are available in Appendix P.

B.3.3.4.1. Two-piece extrapolation

A 10-week cut-off point was used, at which point there had been a large number of progression/death events, resulting in a steep initial drop off in the PFS KM which corresponded to the first scheduled radiological assessment of progression defined in the KEYNOTE-775 protocol (week 8 ± 7 days). Scenarios with different cut-offs were explored to understand the impact of this decision on the results, as shown in Section B.3.8.2.

An overlay of the independent two-piece parametric models and observed KM data from KEYNOTE-775 are shown in Figure 21 for PEM+LEN and Figure 22 for TPC. The AIC and BIC statistics corresponding to the independent two-piece parametric models fitted to KEYNOTE-775 are provided in Table 31. Hazard plots for PFS are presented in Appendix P.

Figure 21: PFS independent two-piece parametric survival curves for PEM+LEN



Key: KM, Kaplan–Meier; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival.

Figure 22: PFS independent two-piece parametric survival curves for TPC

[redacted]

Key: KM, Kaplan–Meier; PFS, progression-free survival; TPC, treatment of physician's choice.

Table 31: Fit statistics of PFS independent two-piece survival extrapolation

Treatment	PEM+LEN		TPC	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.
Note: Cells in bold and italics represent the models with the best statistical fit.

When considering the observed PFS data for the TPC arm, there is minimal variability between PFS extrapolations given the maturity of the KEYNOTE-775 data. All independent two-piece models provide plausible fits.

When considering the observed data for the PEM+LEN arm, all independent two-piece models underestimate PFS after 1 year, and are therefore considered conservative. The Gompertz, generalized gamma, log-normal and log-logistic models may be considered a conservative, but plausible estimates of long-term PFS, given the appearance of a plateau at around 20% in KEYNOTE-775 PFS KM data after 1 year.

Clinical plausibility of the PFS extrapolations were validated. The goodness of fit statistics, survival curves and estimates of long-term PFS were presented to clinical experts to validate the plausibility of each extrapolation[2]:

- **TPC arm:** The experts agreed that all independent two-piece extrapolations seem to fit well to the observed KEYNOTE-775 data and provide plausible estimates of long-term PFS
- **PEM+LEN arm:** There was some variability in responses from clinical experts, suggesting that the exponential, log-normal, Gompertz or generalized gamma could provide plausible estimates

B.3.3.4.2. Summary of modelled extrapolations

The most appropriate and clinically plausible models for PFS are used in the base case analysis, shown in Figure 23.

For PEM+LEN, KEYNOTE-775 KM data were used directly until a 10-week cut-off, after which the log-logistic function was fitted to PFS time-to-event data reported in

KEYNOTE-775. This provides the most plausible fit to the observed data and provides a clinically plausible conservative long-term extrapolation.

For TPC, KEYNOTE-775 KM data were used directly until a 10-week cut-off, after which the log-logistic function was fitted to PFS time-to-event data reported in KEYNOTE-775. The KM + log-logistic model provides a plausible fit to the observed data and provides a clinically plausible long-term extrapolation.

Alternative models tested in scenario analyses are summarised in Table 25 and Section B.3.8.2.

Figure 23: Selected PFS curve fits for PEM+LEN and TPC

Key: KM, Kaplan–Meier; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.

B.3.3.4.3. Mixed chemotherapy scenario

As mentioned in Section B.3.2.3.2 and Section B.3.3.3.1, in the absence of efficacy data for these treatments in previously treated advanced EC, the mixed chemotherapy arm is assumed to have equal efficacy to the TPC arm from KEYNOTE-775.

B.3.3.5. Time on treatment

TOT is modelled based on KEYNOTE-775 to determine the cohort of patients remaining on treatment at each model cycle to accurately accrue treatment-related costs. TOT for PEM+LEN is implemented individually in the PEM+LEN arm. Given the relatively short treatment duration and low treatment costs associated with paclitaxel and doxorubicin, implementing TOT data for these components individually would have minimal impact on the results, so they are not split in the TPC arm in favour of simplicity. Median TOT for pembrolizumab, lenvatinib and TPC are presented in Table 32.

Table 32: KN-775 median TOT

Treatment	Weeks	Months
Pembrolizumab (PEM+LEN)	[redacted]	[redacted]
Lenvatinib (PEM+LEN)	[redacted]	[redacted]
TPC	[redacted]	[redacted]
Key: KN-775, KEYNOTE-775; PEM+LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice.		

B.3.3.5.1. One-piece extrapolations

An overlay of the independent one-piece parametric models and observed KM data from KEYNOTE-775 are shown in Figure 24 for pembrolizumab, Figure 25 for lenvatinib and Figure 26 for TPC. AIC and BIC statistics corresponding to the parametric models fitted to KEYNOTE-775 are provided in Table 33.

Figure 24: TOT parametric curves for pembrolizumab (PEM+LEN arm)

Key: KM, Kaplan–Meier; PEM+LEN, pembrolizumab with lenvatinib; TOT, time on treatment.

Figure 25: TOT parametric curves for lenvatinib (PEM+LEN arm)

Key: KM, Kaplan–Meier; PEM+LEN, pembrolizumab with lenvatinib; TOT, time on treatment.

Figure 26: TOT parametric curves for TPC

Key: KM, Kaplan–Meier; TOT, time on treatment; TPC, treatment of physician's choice.

Table 33: Fit statistics of TOT extrapolation

Treatment	PEM		LEN		TPC	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; LEN, lenvatinib; PEM, Pembrolizumab; TOT, time on treatment; TPC, treatment of physician's choice **Note:** Cells in bold and italics represent the models with the best statistical fit.						

The generalized gamma model provides a plausible fit to observed data from KEYNOTE-775 for pembrolizumab and lenvatinib in the PEM+LEN arm. When considering the observed data for the pembrolizumab component in the first 2 years, the exponential, Weibull, and Gompertz also seemed plausible. These distributions also fit well to the observed data for the lenvatinib component, where all curves except the Gompertz provided plausible long-term extrapolations.

The generalized gamma model provides a plausible fit to the TOT data in the TPC arm of KEYNOTE-775, as well as the exponential, Weibull, and Gompertz distributions.

The goodness of fit statistics, survival curves and estimates of long-term TOT were presented to clinical experts to validate the clinical plausibility of each extrapolation[2]:

- **PEM+LEN arm:** Clinical experts suggested that if patients exhibit good response to PEM+LEN treatment they would stop treatment at 2 years, in line with the license for pembrolizumab and use in KEYNOTE-775 trial. Experts also suggested that the majority of patients would not be receiving treatment with lenvatinib after 10 months, but they would expect a small number to receive treatment beyond discontinuation of pembrolizumab
- **TPC arm:** Clinical experts noted that chemotherapy is typically administered for a maximum of six cycles (18–24 weeks) in UK clinical practice. As median TOT from KEYNOTE-775 KM data is 14.86 weeks, TOT estimates are in line with expectations in clinical practice. However, scenarios are investigated using this 6-cycle stopping rule for paclitaxel (and carboplatin plus paclitaxel and carboplatin monotherapy), further described in Section B.3.3.5.3 and results presented in Section B.3.8.3

B.3.3.5.2. Summary of modelled extrapolations

The most appropriate and clinically plausible models for TOT are used in the base-case analysis, shown in Figure 27.

For PEM+LEN, pembrolizumab and lenvatinib components were extrapolated separately to accurately capture the costs associated with each intervention. The

generalized gamma function was fitted to pembrolizumab TOT time-to-event data reported in KEYNOTE-775, up to a maximum of 24 months. The generalized gamma function was also fitted to lenvatinib TOT time-to-event data reported in KEYNOTE-775. The generalized gamma model provides a good fit for both components.

For TPC, the generalized gamma function was fitted to TOT time-to-event data reported in KEYNOTE-775. The generalized gamma model provides a plausible fit to TPC KEYNOTE-775 TOT and provides a clinically plausible long-term extrapolation.

Alternative models and extrapolation methods tested in scenario analyses are summarised in Table 25 and Section B.3.8.2.

Figure 27: Selected TOT curve fits

[redacted]**Key**: KM, Kaplan–Meier; PEM+LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice.

B.3.3.5.3. Treatment stopping rules

Treatment stopping rules are also included in the model base case in line with the administration of treatments in KEYNOTE-775.[13] Pembrolizumab treatment is limited to a maximum duration of 24 months (35 cycles); therefore, all patients in the PEM+LEN arm of the model were assumed to discontinue pembrolizumab treatment from 24 months onwards. Doxorubicin treatment is limited to a lifetime cumulative dose of 500 mg/m²; based on a dose of 60 mg/m^2 per administration, the maximum cumulative dose is reached at 5.75 months, after which the proportion of patients receiving doxorubicin in the TPC (or mixed chemotherapy in scenario analysis) arm is set to 0%.[14, 45]

A scenario was implemented to investigate the impact of implementing a maximum duration of six cycles of paclitaxel administration (affecting only costs in the model), in line with expected clinical practice. Given the short time on treatment and low cost of paclitaxel, this scenario has a negligible impact on cost-effectiveness results (Section B.3.8.2).

A further scenario was implemented to reflect the close relationship between progression status and treatment status and the expected use of PEM+LEN in clinical practice until treatment progression (applied in addition to the maximum duration of treatment outlined above). This scenario incorporates a treat-to-progression rule by ensuring that patients are not treated beyond progression at any model cycle (i.e. TOT cannot exceed PFS to maintain logic in the patient flow). The change slightly improved the ICER per quality-adjusted life year (QALY) for PEM+LEN versus TPC (Section B.3.8.2).

B.3.4. Measurement and valuation of health effects

It is well-documented that daily quality of life is severely impacted for women with advanced, metastatic, or recurrent EC. Common physical symptoms associated with aggressive disease and disease progression include pain and difficulty with urinating, unusual vaginal discharge, or bleeding (particularly after menopause), and pain during sexual intercourse (Section B.1.3.1). There is a substantial unmet need for tolerable and effective treatment options for patients in this indication, leading to a negative impact on emotional and mental well-being.

PEM+LEN is the first and only IO to demonstrate superior efficacy based on Phase III clinical trial evidence in advanced, metastatic, and recurrent EC. Currently, there are no standard treatment options, with highly limited evidence supporting treatment benefit with chemotherapies. PEM+LEN represents a step-change improvement in the treatment pathway for patients with advanced, metastatic or recurrent EC who have received prior systemic therapy (Section 0).

In line with the NICE reference case, and to incorporate the important impact on HRQoL described above, EQ-5D data collected from the KEYNOTE-775 trial were analysed and used in the economic model.[30] The model includes two approaches, as summarised below, and detailed in the following sections:

- **Base case:** A time-to-death utility approach captures patients' HRQoL over time, which is clinically appropriate as time states closer to death are likely to be associated with worse HRQoL and a lower utility value. Utilising a time-to-death approach can remove the dependence on subjective clinical assessment of progression status

- **Scenario analysis:** A health-state utility approach based on progression assigns a value to each health state using data collected before and after progression events in the trial. It is logical that patients who are progression-free will generally experience a higher level of HRQoL than those who have progressive disease

Additionally, decrements to HRQoL due to AEs and natural decline of age-related HRQoL were considered in line with the NICE reference case[30]

B.3.4.1. Health-related quality-of-life data from clinical trials

The KEYNOTE-775 protocol specified patient completion of the EQ-5D-5L questionnaire[13]:

- For patients receiving PEM+LEN: On Day 1 of each 21-day study cycle, for the equivalent of 4 cycle lengths, and at the end of treatment (EOT) visit
- For patients receiving paclitaxel: On Day 1 of each 28-day study cycle, for the equivalent of 4 cycle lengths, and at the EOT visit
- For patients receiving doxorubicin: On Day 1 of each 21-day study cycle, for the equivalent of 4 cycle lengths, and at the EOT visit

Of note, completion of the HRQoL questionnaires following the EOT visit (i.e. post-treatment discontinuation) was not mandatory, although continued recording of questionnaire responses was encouraged via a Web Diary.

B.3.4.2. Mapping

Consistent with the current NICE position statement on the use of EQ-5D measurements in technology appraisals, EQ-5D-5L data from KEYNOTE-775 was analysed and mapped to EQ-5D-3L using the van Hout crosswalk, as described in Section B.3.4.1.[46]

Mixed effects regression models account for within- and between-patient variation and are therefore more representative of the range of HRQoL experienced by patient populations over time compared with a simple means-based approach. The regression analysis includes a random effect to account for the correlation between multiple observations from the same patient. Linear mixed effects regression models were formally fitted to the available data from KEYNOTE-775 to estimate utility

values. Based on clinical drivers of HRQoL, the presence of AEs (Grade 3 and above), progression status (PF or PD) and patients' time to death were included as explanatory variables (see Appendix P for further details).

B.3.4.2.1. Base case analysis: Utilities by time-to-death

Table 35 presents the results of the HRQoL analysis based on the presence of Grade 3 and above AEs and patients' time to death (split into five categories), which reflects the known decline in HRQoL during the terminal phase of the disease. A time-to-death approach captures the decrease in utility as patients move closer to death, driven by the underlying impact of the disease over time, removing the dependence on clinical assessment of progression status. The utility values in the economic model are driven by the underlying impact of the disease over time based on patients' time to death applied to both the PEM+LEN and TPC arms, independent of treatment choice. This approach has been previously accepted in other oncology appraisals by NICE, including but not limited to TA531 in metastatic squamous non-small cell lung cancer and TA357 in advanced melanoma.[43, 44]

Table 34: Model 2: Coefficients for HRQoL analyses

Parameter	Coefficients	SE	P-value
(Intercept)	[redacted]	[redacted]	[redacted]
No Grade 3+ AE	[redacted]	[redacted]	[redacted]
Time to death, 360 days or more	[redacted]	[redacted]	[redacted]
Time to death, 270 to 360 days	[redacted]	[redacted]	[redacted]
Time to death, 90 to 180 days	[redacted]	[redacted]	[redacted]
Time to death, 30 to 90	[redacted]	[redacted]	[redacted]
Time to death, under 30 days	[redacted]	[redacted]	[redacted]
Key: AE, adverse event. **Note:** Intercept reflects 180-270 days to death.			

Table 35: Mean utility values based on time to death included in the economic model

Time to death	Mean time to death utility value	Lower bound	Upper bound
< 30 days	[redacted]	[redacted]	[redacted]
30–89 days	[redacted]	[redacted]	[redacted]
90–179 days	[redacted]	[redacted]	[redacted]
180–269 days	[redacted]	[redacted]	[redacted]
270–359 days	[redacted]	[redacted]	[redacted]
≥ 360 days	[redacted]	[redacted]	[redacted]

B.3.4.2.2. Scenario analysis: Utilities by progression status

Table 36 presents the coefficients of the HRQoL analysis, which shows that utility values decrease with the presence of Grade 3 and above AEs and disease progression, in line with expectations. The mean values are assumed to be driven by disease status irrespective of treatment choice and are applied to both PEM+LEN and TPC arms in the model (Table 37).

Table 36: Model 1: Coefficients for HRQoL analyses

Parameter	Coefficient estimate	SE	P-value
(Intercept)	[redacted]	[redacted]	[redacted]
No Grade 3+ AE	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; SE, standard error.			

Table 37: Model 1: Mean health state utility values applied in the economic model (scenario analysis)

Health state	Mean health state utility value	Lower bound	Upper bound
PF	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Key: PD, progressed disease; PEM+LEN, pembrolizumab with lenvatinib; PF, progression free; Tx, treatment.			

B.3.4.3. Health-related quality-of-life studies

A systematic search for published studies reporting relevant HRQoL data for patients with recurrent early-stage, advanced/metastatic or surgically unresectable endometrial cancer was conducted, and full details are presented in Appendix H.

No HRQoL studies relevant to the UK setting were identified for use in the economic model, and, as previously described, at the time of writing this submission there were no published NICE appraisals for treatments for advanced, metastatic or recurrent EC. Previous NICE appraisals in similar gynaecological cancers (uterine, cervical and ovarian) were hand-searched (Table 38), with the results demonstrating a high degree of consistency with the analysis in this appraisal, suggesting these values are robust and valid for decision-making.

The EQ-5D analysis from the KEYNOTE-775 trial remains the most relevant and robust source of data for this appraisal and follows methods outlined in the NICE reference case (see Section B.3.4.2).[13, 30]

Table 38: HRQoL data from previous NICE appraisals for the treatment of gynaecological cancers

NICE TA	Indication	Intervention	PFS utility	PD utility	Notes
TA528[32]	Relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer	Niraparib	0.812	0.728	Company submitted utility values dependent on treatment arm. Utilities retrieved from NOVA study EQ-5D-5L
TA598[33]	BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy	Olaparib	0.812	0.728	Patient-reported EQ-5D-5L data collected from the NOVA trial (as used in TA528). EQ-5D-5L mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.
TA611[34]	Relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer	Rucaparib	0.830	Redacted	Patient-reported EQ-5D-3L data collected from the ARIEL3 trial.
TA620[35]	Relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer	Olaparib	0.812	0.728	Patient-reported EQ-5D-5L data collected from the NOVA trial (as used in TA528). EQ-5D-5L mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.
TA673[36]	Advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy	Niraparib	Redacted	Redacted	Patient-reported EQ-5D-5L data collected from the PRIMA trial. EQ-5D-5L mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.
TA693[37]	Advanced ovarian, fallopian tube or primary peritoneal cancer	Olaparib + bevacizumab	On Tx: Redacted	PD1: Redacted PD2: 0.680	Patient-reported EQ-5D-5L data collected from the PAOLA-1 trial. EQ-5D-5L mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al.

Key: NICE, National Institute for Health and Care Excellence: PFS, progression-free survival; PD, progressive disease; TA, technology appraisal; Tx, treatment.

B.3.4.4. Adverse reactions

The impact of AEs on HRQoL is incorporated into the economic model. The occurrence of AEs and number of episodes of AEs per patient from KEYNOTE-775 were used to estimate the incidence probabilities. Treatment-specific Grade 3+ AEs with incidence of greater than 5% of patients on either arm of KEYNOTE-775 were included.[13] The number and proportion of patients who experienced AEs are shown in Table 39.[13] The mean number of AE episodes per patient is combined with the number of participants with one or more Grade 3+ AEs to capture recurrence and reflect the true number of each AEs experienced in KEYNOTE-775. The recurrence of AEs was assumed to be the same regardless of treatment received.

The duration of AEs and AE utility decrements were used to calculate a QALY decrement due to AEs applied at each model cycle. AE data are based on analysis of data from KEYNOTE-775, as shown in Table 39, with AE utility decrements described in Section B.3.4.1.

Scenario analysis demonstrated that the inclusion or exclusion of the AE utility decrements had minimal impact on the results (Section B.3.8.2).

Table 39: Grade 3+ adverse events occurring in 5% or more patients in either arm in KN-775, and number of episodes per patient included in the economic model

Adverse event	Incidence of Grade 3+ AEs per arm		Total number of episodes per patient[13]	
	PEM+LEN n (%)	TPC n (%)	Number of episodes	SD
Hypertension	154 (38%)	9 (2%)	[redacted]	[redacted]
Weight decreased	42 (10%)	1 (0%)	[redacted]	[redacted]
Decreased appetite	32 (8%)	2 (1%)	[redacted]	[redacted]
Diarrhoea	31 (8%)	8 (2%)	[redacted]	[redacted]
Lipase increased	26 (6%)	5 (1%)	[redacted]	[redacted]
Anaemia	25 (6%)	57 (15%)	[redacted]	[redacted]
Asthenia	24 (6%)	15 (4%)	[redacted]	[redacted]
Proteinuria	22 (5%)	1 (0%)	[redacted]	[redacted]
Hypokalaemia	21 (5%)	6 (2%)	[redacted]	[redacted]
Fatigue	21 (5%)	12 (3%)	[redacted]	[redacted]
Neutrophil count decreased	10 (2%)	83 (21%)	[redacted]	[redacted]
Neutropenia	7 (2%)	100 (26%)	[redacted]	[redacted]
White blood cell count decreased	6 (1%)	41 (11%)	[redacted]	[redacted]
Febrile neutropenia	2 (0%)	22 (6%)	[redacted]	[redacted]
Leukopenia	0 (0%)	31 (8%)	[redacted]	[redacted]

Key: n, number of patients with one or more event; PEM+LEN, pembrolizumab with lenvatinib; SD, standard deviation.

Table 40: Adverse event durations

Adverse event	Duration (days) [13]	
	Mean	SD
Hypertension	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]

Adverse event	Duration (days) [13]	
	Mean	SD
Fatigue	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Key: SD, standard deviation.		

AE utility decrements were informed using data from KEYNOTE-775 (Section 6.4.1.1). AE utility decrements were calculated by taking the "No Grade3+ AE" coefficient in the regression models as a decrement (Table 34 and Table 36). So, the AE utility decrement was [redacted] for the time to death approach in the base case and [redacted] for the health state approach in scenario analysis.

Applying the utility decrement of -0.040 for PEM+LEN and TPC to the cycle probability of each event produced AE cycle decrements of [redacted] and [redacted] for patients receiving PEM+LEN and TPC, respectively.

B.3.4.5. Health-related quality of life data used in the cost-effectiveness analysis

In line with the NICE reference case, trial-based utility values from KEYNOTE-775 are included in the economic model.[30] EQ-5D-5L data were collected in KEYNOTE-775 and mapped to EQ-5D-3L values using public preference tariffs per the UK time trade-off (TTO) valuation set. The impact of AEs on HRQoL were also included. Additionally, at each model cycle, utility values are adjusted account for the natural decline in quality of life associated with age based on a standard published regression algorithm commonly used in NICE technical appraisals.[47]

Table 41 summarises the utility values used in the base case cost-effectiveness analysis.

Table 41: Summary of utility values used for cost-effectiveness analysis

Time to death	Utility value	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
≥ 360 days	[redacted]	Section B.3.6.1	Section B.3.4.2	Estimated directly from KEYNOTE-775 EQ-5D data, in line with the NICE reference case.[48] Time-to-death approach can remove the dependence on subjective clinical assessment of progression status
270–359 days	[redacted]			
180–269 days	[redacted]			
90–179 days	[redacted]			
30–89 days	[redacted]			
< 30 days	[redacted]			
AE disutility while experiencing Grade 3+ AEs	[redacted]			
Scenario analysis				
PF	[redacted]	Section B.3.6.1	Section B.3.4.2	Estimated directly from KEYNOTE-775 EQ-5D data, in line with the NICE reference case.[48] Progression-based approach utilises progression status typically assessed in clinical practice
PD	[redacted]			
AE disutility while experiencing Grade 3+ AEs	[redacted]			

Key: AE, adverse event; PD, progressed disease; PFS, progression-free.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

A systematic search for published studies that reported cost and healthcare resource use data for patients with recurrent early-stage, advanced/metastatic or surgically unresectable endometrial cancer was conducted, and full details are presented in Appendix I. In total, 19 unique studies from 22 publications were identified. Of these, only three were applicable to the UK including two which were specific to England, however data were highly limited.[49-51] The studies were not deemed useful for the

analysis as the type of resource use information were not published in sufficient detail for inclusion in the economic model, and the study populations were highly restricted compared with the patient population for which PEM+LEN is indicated:

- One study estimated the mean total cost of palliative care of advanced uterine cancer patients in the UK[49]
- A prospective cohort study conducted in England for patients with endometrial cancer estimated the average cost of treatment of Stage IV disease 5-years after diagnosis[50]
- A cost–consequence analysis based on a randomised controlled trial conducted in England estimated the mean healthcare cost associated with recurrent Stage 1 endometrial cancer patients[51]

The following cost categories are incorporated in the economic model, as described in this section:

- Drug acquisition costs
- Drug administration costs
- Health state resource use costs (e.g. ongoing monitoring and follow-up)
- AE costs
- Cost of testing
- Subsequent treatment costs
- End-of-life care costs

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Drug acquisition costs

Treatment costs are calculated based on the recommended dosing regimen for each drug for the modelled treatment duration detailed in Section B.3.3.5. The recommended dose per administration, administration schedule and list prices for relevant treatments are presented in Table 42 (see Appendix Q for further PAS details). The total calculated drug acquisition costs per administration are also provided.

As previously described, PEM+LEN is implemented in the economic model according to the EMA and MHRA marketing authorisation and the KEYNOTE-775 trial protocol.[14] TPC is also implemented as per KEYNOTE-775 (see Section B.3.2.3). Treatments included in the mixed chemotherapy scenario analysis were implemented as per KEYNOTE-775 for paclitaxel and doxorubicin and the literature for carboplatin and carboplatin plus paclitaxel. Drug acquisition costs were based on the full recommended dose, which is a conservative approach that is likely to lead to higher incremental costs for PEM+LEN in favour of TPC as it does not account for dose interruptions and reductions over the treatment period that would be expected in clinical practice.

Table 42: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators

Drug	Cost per vial/pack	Vial size/ tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per administration	Source (cost, regimen)
Pembrolizumab	£2,630	100 mg x 1	200 mg Q3W	2	£5,260	MIMS: Accessed 8 November 2021[52], KN-775 protocol[14]
			400 mg Q6W	4	£10,520	
Lenvatinib	£1,437	4 mg x 30	20 mg daily	0.17	£239.50	MIMS: Accessed 8 November 2021[52], KN-775 protocol[14]
	£1,437	10 mg x 30		0.07	£95.80	
Paclitaxel	£4.15	30 mg x 1	80 mg/m^2 Q3W	0.94	£3.88	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], KN-775 protocol[14]
	£8.06	100 mg x 1		0.34	£2.73	
	£10.15	150 mg x 1		0.59	£5.96	
	£15.97	300 mg x 1		0.00	£0.00	
Doxorubicin	£2.83	10 mg x 1	60 mg/m^2 3 weeks out of 4	1.48	£4.21	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], KN-775 protocol[14]
	£7.09	50 mg x 1		1.93	£13.67	

	£20.20	200 mg x 1		0.00	£0.00	
Paclitaxel (in combination with carboplatin)	£4.15	30 mg x 1	175 mg/m^2 Q3W	2.00	£8.30	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Miller D et al., 2020[54]
	£8.06	100 mg x 1		1.00	£8.06	
	£10.15	300 mg x 1		0.28	£4.44	
	£15.97	30 mg x 1		2.00	£8.30	
Carboplatin (in combination with paclitaxel)	£3.18	50 mg x 1	6 AUC (900 mg) Q3W	18.00	£57.16	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Miller D et al., 2020[54]
	£6.08	150 mg x 1		6.00	£36.46	
	£13.51	450 mg x 1		2.00	£27.03	
	£20.28	600 mg x 1		2.00	£40.55	
Carboplatin	£3.18	50 mg x 1	5 AUC (750 mg) Q3W	15.00	£47.63	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Hoskins PJ et al., 2001[55]
	£6.08	150 mg x 1		5.00	£30.38	
	£13.51	450 mg x 1		2.00	£27.03	
	£20.28	600 mg x 1		2.00	£40.55	
Doxorubicin (liposomal doxorubicin hydrochloride, caelyx)	£360.23	20 mg x 1	60 mg/mg^2 by IV Q3W	0.96	£344.68	MIMS: Accessed 8 November 2021[52], KN-775 protocol[14]
	£712.49	50 mg x 1		1.93	£1,373.14	

Key: AUC, area under the curve; eMIT, electronic market information tool; MIMS, monthly index of medical specialities; KN-775, KEYNOTE-775; Q3W, once every 3 weeks; Q6W, once every 6 weeks; RDI, relative dose intensity.
Notes: Costs presented using list prices for all treatments.

B.3.5.1.2. Observed dosing data for lenvatinib (KEYNOTE-775)

In order to accurately estimate the total costs associated with the PEM+LEN arm, it is necessary to implement actual observed dosing data for the lenvatinib component from KEYNOTE-775. This is directly aligned to the currently approved label for lenvatinib (on which standard dosing for lenvatinib is based) and consistent with the administration of lenvatinib per the KEYNOTE-775 clinical trial protocol on dose reductions and modifications for optimal AE management. Clinical experts confirmed that this approach is valid (aligned with use of lenvatinib in practice).[2]

In the economic model, patients in the PEM+LEN arm started at a dose of 20 mg for lenvatinib. Patient-level dosing data from KEYNOTE-775 were used to calculate the total cost of lenvatinib per week as observed in KEYNOTE-775 (Appendix P), aligned with the realistic dose expected in the real-world setting.

B.3.5.1.3. Drug administration costs

In the economic model, drug administration costs are accrued for the duration of treatment in the PEM+LEN and TPC arms (Section B.3.3.5). The unit costs of the intravenous (IV) administration of pembrolizumab, paclitaxel and doxorubicin (and carboplatin and carboplatin plus paclitaxel in scenario analysis) were sourced from NHS reference costs (Table 43).[56] Lenvatinib is administered orally and is assumed to incur no cost.

For simplicity, pre-medication costs are not included in the analysis, leading to conservative estimates of cost-effectiveness for PEM+LEN compared with TPC. As mandated by the SmPC for paclitaxel, patients must be given corticosteroids, antihistamines and H2-receptor antagonists prior to paclitaxel administration, in order to prevent severe hypersensitivity reactions, and excluding these medications results in underestimating the costs associated with TPC in the model.[57]

Table 43: Administration costs

Administration	Unit cost	Source
Intravenous administration	£281.28	2019/20 National Cost Collection data version 2: SB12Z: Chemotherapy[56]

Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	£403.84	2019/20 National Cost Collection data version 2: SB14Z: Chemotherapy[56]
Deliver Subsequent Elements of a Chemotherapy Cycle – Outpatient	£253.77	2019/20 National Cost Collection data Version 2: SB15Z: Chemotherapy[56]
Oral therapy	£0.00	Assumption
Key: NHS, National Health Service.		

B.3.5.2. Health-state unit costs and resource use

Costs associated with ongoing disease management, monitoring and patient follow-up are included in the economic model. Healthcare resources were included that were specific to each health state (i.e. PF or PD). Costs were applied to each resource and accrued according to the time spent in each health state. In line with the NICE reference case, the relevant unit costs were sourced from either the Personal Social Services Research Unit (PSSRU) or the NHS reference cost documentation and reflect 2019–2020 prices.[56, 58]

As there were no UK-specific resource use or cost studies identified in the systematic search or in published NICE technology appraisals in EC at the time of writing this submission (Section B.3.5 and Appendix I), resource use items and frequency of use were obtained by conducting hand searches of other health technology appraisals in related disease areas including uterine, cervical and ovarian cancers. HCRU used in this model has been accepted by NICE previously and UK clinical experts advised us of their generalisability for this indication.[2] As these searches showed a high degree of consistency in resource use values, the same values have been assumed in this appraisal for PEM+LEN versus TPC.[2]

Table 44 details the resource use and unit cost estimates for disease management used in the base case analysis, alongside supporting sources.

Table 44: Resource use and costs associated with model health states

Health state	Resource	Frequency per week	Source	Cost	Source
PF	Outpatient visit	0.23 (once a month)	TA620[35]	£131.03	2019/20 National Cost Collection data Version 2, outpatient attendance 503; gynaecological oncology non-admitted face-to-face outpatient attendance, weighted average consultant led and non-consultant led[56]
	CT scan	0.11 (once every 2 months)	TA620[35]	£107.34	2019/20 National Cost Collection data Version 2: Weighted average of outpatient computerised tomography scans of one and two areas with and without contrast (RD20A, RD21A, RD22Z)[56]
	Blood test	0.23 (once a month)	TA620[35]	£2.56	2019/20 National Cost Collection data Version 2: Haematology (DAPS05)[56]
	Pain medication	0.00	NICE ID1547 (Table B.3.47)[59]; NICE TA581 (Table 36)[60]; NICE TA417[61] (TA333, Table 44)*	£3.72	eMIT national database 01/07/2020 - 30/06/21 Accessed 15 October 2021.[53] Morphine sulphate 50mg/50ml solution for infusion vials
Total weekly cost associated with PF health states				**£43.06**	
PD	Outpatient visit	0.07 (once every 3 months)	TA620[35]	£131.03	2019/20 National Cost Collection data Version 2, outpatient attendance 503; gynaecological oncology non-admitted face-to-face outpatient attendance, weighted average consultant led and non-consultant led[56]
	CT scan	0.00	TA620[35]	£107.34	2019/20 National Cost Collection data Version 2: Weighted average of outpatient computerised

Health state	Resource	Frequency per week	Source	Cost	Source
					tomography scans of one and two areas with and without contrast (RD20A, RD21A, RD22Z)[56]
	Blood test	0.00	TA620[35]	£2.56	2019/20 National Cost Collection data Version 2: Haematology (DAPS05)[56]
	Pain medication	7.00	NICE ID1547 (Table B.3.47)[59]; NICE TA581 (Table 36)[60]; NICE TA417[61] (TA333, Table 44)*	£3.72	eMIT national database 01/07/2020 - 30/06/21 Accessed 15 October 2021.[53] Morphine sulphate 50mg/50ml solution for infusion vials
Total weekly cost associated with PD health states				**£35.08**	

Key: CT, computerised tomography; NHS, National Health Service; PD, progressed disease; PF, progression-free; TA, technology appraisal.
Source: NICE TA620, Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer; NICE ID1547, Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma; NICE TA581, Nivolumab with ipilimumab for untreated advanced renal cell carcinoma; NICE TA417, Nivolumab for previously treated advanced renal cell carcinoma.
*Resource use for the pain management was taken from other NICE technology appraisals

B.3.5.3. Adverse reaction unit costs and resource use

Table 45 shows the per-episode unit costs associated with resolving AEs included in the economic model, primarily sourced from NHS National Cost Collection Data Version 2 (2019/20).[56]

Total average AE management costs are calculated based on the incidence, recurrence and duration of Grade 3+ AEs that were observed in more than 5% of patients in KEYNOTE-775 as detailed in Sections B.2.9.3 and B.3.4.4. Costs are accrued based on the per-cycle probability of each AE in the PEM+LEN and TPC arm of the economic model, resulting in a calculated cost of £10.74 and £42.19 per cycle, respectively. For the mixed chemotherapy scenario analysis, AE rates are assumed equal to TPC as a simplifying assumption, so weekly costs for mixed chemotherapy was calculated to be £42.19 per cycle.

Table 45: AE costs

Adverse event	Cost per episode (£)	Source
Hypertension	£370.38	2019/20 National Cost Collection data Version 2. EB04Z (NES): Hypertension[56]
Weight decreased	£0.00	Assumed no cost
Decreased appetite	£0.00	Assumed no cost
Diarrhoea	£145.33	2019/20 National Cost Collection data Version 2. 301: Gastroenterology outpatient attendance (total)[56]
Lipase increased	£0.00	Assumed no cost
Anaemia	£535.10	2019/20 National Cost Collection data Version 2. SA04K (NES): Iron Deficiency Anaemia with CC Score 2-5[56]
Asthenia	£178.08	2019/20 National Cost Collection data Version 2. 300: General medicine outpatient attendance (total)[56]
Proteinuria	£0.00	Assumed no cost
Hypokalaemia	£0.00	Assumed no cost
Fatigue	£178.08	2019/20 National Cost Collection data Version 2. 300: General medicine outpatient attendance (total)[56]
Neutrophil count decreased	£0.00	Assumed no cost
Neutropenia	£555.92	2019/20 National Cost Collection data Version 2. SA35D (NES): Agranulocytosis with CC Score 2-4[56]
White blood cell count decreased	£0.00	Assumed no cost
Febrile neutropenia	£3,218.60	NICE DSU report on the cost of febrile neutropenia 2007, inflated to 2020 cost year using ONS CPI Index for Health. Based on hospitalisation and intravenous antibiotics for the majority of patients, while a small proportion receive oral antibiotics combined with a short period of hospitalisation.[62]
Leukopenia	£555.92	2019/20 National Cost Collection data Version 2. SA35D (NES): Agranulocytosis with CC Score 2-4[56]
Key: AE, adverse event; CC, complexity and comorbidity; NES, non-elected short stay.		

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Subsequent therapy

After progressing on PEM+LEN or TPC, some patients will receive subsequent anti-cancer treatment in NHS centres (see Section B.1.3.2). These costs are considered in the economic model as a calculated one-off cost, applied at the point of treatment discontinuation if alive at each model cycle. The total average cost per model cycle is based on the proportion of patients receiving subsequent therapies, the distribution of each subsequent treatment, drug acquisition and administration costs (**Table 47**), and the observed duration of subsequent treatments associated with the PEM+LEN and TPC arms in KEYNOTE-775 (Table 48).

In KEYNOTE-775, 28% and 48% of patients received subsequent treatment in the PEM+LEN and TPC arms, respectively (Section **Error! Reference source not found.** and B.2.13.2).[11] The proportion of patients receiving each type of subsequent treatment in the base case analysis is presented in Table 46, informed by the observed use of treatments in KEYNOTE-775 excluding treatments that are not reimbursed in the UK setting. As discussed in Section **Error! Reference source not found.**, of the patients who received subsequent treatment in the TPC arm, [redacted]% received subsequent treatment with PD1/PDL1 regimens that are not currently available in the UK. As these treatments are anticipated to lead to improvements in long-term response and survival in the TPC arm, results in the base case analysis are conservative (patients in the TPC arm of the model receive the full benefits associated with subsequent PD1/PDL1 regimens, without applying any costs as these are not reimbursed in the UK setting). This simplifying assumption was applied in the base case analysis as a conservative, pragmatic approach to account for differences between within-trial and real-world treatment patterns without sacrificing power in the analysis.

For the mixed chemotherapy scenario analysis, subsequent treatment proportions are assumed equal to TPC as a simplifying assumption. Clinical experts confirmed that these values are appropriate for use in the base case analysis, noting that between 20% to 50% of patients could be offered subsequent therapy.[2]

A scenario was included to test the impact of using an alternative distribution of each subsequent treatment as informed by the ECHO study (detailed in Section B.2.9.3), presented in Table 46.[22] In this scenario the proportion of patients that received subsequent treatment were consistent to those in KEYNOTE-775 as supported by clinical expert opinion during validation.[2] This scenario accounts for systemic therapy agents used in third line treatment, with the exclusion of investigational treatments that are not currently available in the UK. This has minimal impact on the results, demonstrating that the base case results are robust to alternative assumptions related to subsequent treatment costs and that these inputs are not a key driver of the results.

Table 46: Subsequent therapies received by patients in KN-775 in the base case analysis

Treatment	Subsequent treatment distributions (base case - KN-775 adjusted to UK setting)[13]		Subsequent treatment distributions (scenario – ECHO study)[22]
	Initial treatment		Systemic therapy agents used for third line treatment (UK)[×]
	PEM+LEN	TPC and mixed chemotherapy	
Paclitaxel	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Pembrolizumab*	[redacted]	[redacted]	[redacted]
Bevacizumab*	[redacted]	[redacted]	[redacted]
Lenvatinib*	[redacted]	[redacted]	[redacted]
Hormonal therapy[+]	[redacted]	[redacted]	[redacted]

Key: KN-775, KEYNOTE-775; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.
Notes:
*Proportion of patients receiving pembrolizumab, bevacizumab and lenvatinib reweighted uniformly across other treatment options.

[+]Patients receiving hormonal therapy can receive one of five individual treatments (anastrozole, letrozole, medroxyprogesterone, megestrol and tamoxifen). The proportion of patients receiving each therapy was calculated based by taking a weighted average of the observed use of treatments in KN-775.[14]

[×]Proportion patients receiving systemic therapy agents, excluding investigational treatments and those that are not reimbursed in the UK.[22]

Table 47: Subsequent therapy – drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, intervention and active comparators

Drug	Cost per vial/pack	Vial size/tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per week	Source (cost, regimen)
Paclitaxel	£4.15	30 mg x 1	80 mg/m^2 by IV 3 weeks in every 4	0.94	£121.60	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], KN-775 protocol[14]
	£8.06	100 mg x 1		0.34		
	£10.15	150 mg x 1		0.59		
	£15.97	300 mg x 1		0.00		
Doxorubicin	£2.83	10 mg x 1	60 mg/m^2 by IV Q3W	0.94	£99.72	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], KN-775 protocol[14]
	£7.09	50 mg x 1		0.94		
	£20.20	200 mg x 1		0.94		
Doxorubicin (caelyx)	£360.23	20 mg x 1	60 mg/m^2 by IV Q3W	0.96	£666.37	MIMS: Accessed 8 November 2021[52], KN-775 protocol[14]
	£712.49	50 mg x 1		1.93		
Carboplatin	£3.18	50 mg x 1	400 mg/m^2 by IV Q3W	15.00	£142.29	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Hoskins PJ et al., 2001[55]
	£6.08	150 mg x 1		5.00		
	£13.51	450 mg x 1		2.00		
	£20.28	600 mg x 1		2.00		
Gemcitabine	£2.56	200 mg x 1	800 mg/m^2 by IV 2 weeks in every 3	2.51	£197.14	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Grisham RN et al., 2012[63]
	£7.89	1000 mg x 1		1.01		
Cisplatin	£6.03	50 mg x 1	50 mg/m^2 by IV Q3W	0.13	£117.67	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], Thigpen JT et al., 1989[64]
	£8.97	100 mg x 1		0.00		
	£205.55	100 mg x 1		1.49	£842.92	

Drug	Cost per vial/pack	Vial size/tablets per pack	Dosing regimen	Vials/ tablets per admin	Total cost per week	Source (cost, regimen)
Bevacizumab	£810.10	400 mg x 1	15 mg/kg by IV Q3W	2.40		MIMS: Accessed 8 November 2021[52], Avastin SmPC[65]
Anastrozole	£0.98	1 mg x 28	1 mg oral daily	0.04	£0.25	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], BNF[66]
Letrozole	£1.63	2.5 mg x 28	2.5 mg oral daily	0.04	£0.41	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], BNF[67]
Medroxyprogesterone	£1.84	400 mg x 30	400 mg oral daily	0.03	£0.43	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], BNF[68]
Megestrol	£19.52	160 mg x 30	160 mg oral daily	0.03	£4.55	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], BNF[69]
Tamoxifen	£4.20	20 mg x 30	20 mg oral daily	0.07	£1.96	eMIT national database 01/07/2020 – 30/06/21 Accessed 15/10/21[53], BNF[70]

Key: BNF, British National Formulary; eMIT, electronic market information tool; IV, intravenous; MIMS, monthly index of medical specialities; PAS, patient access scheme; Q4W, once every 4 weeks; QD, once daily; RDI, relative dose intensity.

Notes: Bevacizumab is associated with a confidential PAS but is included at list price in the base case analysis.

Anastrozole, letrozole, medroxyprogesterone, megestrol and tamoxifen are the hormone therapies included in the model.

Table 48: Duration of subsequent therapies

Subsequent therapy	Average length of subsequent treatment (weeks)	Source
Paclitaxel	[redacted]	KN-775 descriptive results IA1: Section 4.2.3: Table 4.2–6
Doxorubicin	[redacted]	
Carboplatin	[redacted]	
Bevacizumab	[redacted]	
Anastrozole	[redacted]	
Letrozole	[redacted]	
Medroxyprogesterone	[redacted]	
Megestrol	[redacted]	
Tamoxifen	[redacted]	

B.3.5.4.2. Testing

In line with the final NICE scope and decision problem for this appraisal, the modelled population considers all patients with previously treated advanced, metastatic or recurrent EC. The treatment benefit of PEM+LEN compared with TPC was consistent across all the major subgroups tested in patients with advanced EC, including by histology (Section B.2.7).

Recent guidelines for Lynch syndrome (caused by a germline pathogenic variant in one of four DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2) have recommended that all patient's tumours are tested for MSI/MMR status.[71] As PEM+LEN would be eligible for the indicated population without any additional testing requirements, there are no applicable testing costs to be included in the economic model, and, if included, the costs for testing would offset.

B.3.5.4.3. End-of-life costs

End-of-life care is applied as a one-off cost upon transition to death in the economic model. The cost per patient was sourced from Georghiou et al. (2014)[72] (a Nuffield Trust report that explored care costs towards the end of life) which reported a value of £6,015. This cost was inflated to the current cost year using PSSRU inflation indices to give a cost of £6,520.55.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A tabular summary of the variables applied in the economic model, their base case values and the uncertainty distribution and magnitude assumed for each variable, is provided in Appendix P.

B.3.6.2. Assumptions

Key assumptions of the economic analysis are summarised in Table 49. The approach to modelling has been designed to make the best use of the available data to inform the decision problem. In the absence of data, assumptions are designed to minimise potential bias in the analysis. These two statements are illustrated by the likely direction of bias and justification for analysis assumptions, summarised in Table 49.

Table 49: Summary of assumptions of the economic analysis

#	Assumption	Likely direction of bias	Justification
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS England costs.	No bias expected	Section B.3.2.2
2	Based on the different mechanism of action for PEM+LEN and TPC and long-term data from KN-775 and KN-146, PEM+LEN and TPC are expected to have different survival trajectories and hazard profiles; this is best reflected by independent two-piece models for OS and PFS selected in the base case (and tested in scenarios).	No bias expected	Section B.3.3.2 to B.3.3.4

#	Assumption	Likely direction of bias	Justification
3	The duration of treatment based on the KN-775 TOT KM data for pembrolizumab, lenvatinib and TPC adequately reflect the expected time on treatment for patients in England	No bias expected	Section B.3.3.5
4	Patients receiving PEM+LEN are assumed to stop treatment with pembrolizumab at 24 months, which is applied to pembrolizumab acquisition and administration costs.	No bias expected	Sections B.3.2.3.1 and B.3.3.5
5	Patients receiving TPC are assumed to stop treatment with doxorubicin at a lifetime cumulative dose of 500mg/m^2, which is applied to doxorubicin acquisition and administration costs.	No bias expected	Sections B.3.2.3.2 and B.3.5
6	HRQL is captured by the mixed model analysis of EQ-5D-5L data from KN-775 patients mapped to EQ-5D-3L using the Van Hout algorithm. The time-to-death approach captures the decrease in utility as patients move closer to death, driven by the underlying impact of the disease over time, removing the dependence on clinical assessment of progression status and independent of treatment arm.	No bias expected	Section B.3.4
7	The base case analysis assumes the generic formulation of doxorubicin, although the more expensive liposomal/pegylated doxorubicin (Caelyx) is primarily used in English clinical practice. It is assumed that generic doxorubicin and Caelyx will have equivalent effectiveness and this leads to conservative cost-effectiveness results in favour of TPC.	Small - in favour of TPC	Sections B.3.2.3.2 and B.3.5.1.1
8	Disease management costs are assumed to be dependent upon disease status (progressed versus progression-free) and comprise outpatient and nurse visits, CT scans, blood tests and pain medication.	No bias expected	Section B.3.5.2
9	After discontinuation from PEM+LEN or TPC, approximately 28% and 48% of patients who will go on to receive some subsequent systemic treatment, respectively.	No bias expected	Section B.3.5.4.1

Key: CT, computerised tomography; EQ-5D-3L, EuroQol 5 Dimensions 3 levels; HRQL, health-related quality of life; KM, Kaplan–Meier; KN-146, KEYNOTE-146; KN-775, KEYNOTE-775; m, meter; mg, milligram; NHS, National Health Service; OS, overall survival; PEM+LEN, pembrolizumab plus lenvatinib; PFS, progression-free survival; PPS, post-progression survival; TOT, time on treatment; TPC, treatment of physician's choice.

B.3.7. Base-case results

Summary of key points:
• Based on list prices for all treatments, the estimated ICER for PEM+LEN versus paclitaxel and doxorubicin is £65,111 per QALY gained. Appendix Q presents the ICERs incorporating the patient access scheme [PAS] currently agreed for pembrolizumab, which show that PEM+LEN is highly likely be cost-effective when the confidential discounts are included • These ICERs should be considered in the context of PEM+LEN being an innovative, end-of-life technology that presents a step-change improvement for patients with advanced or recurrent EC who have received prior platinum-containing therapy in an area of high unmet need • All relevant health outcomes and costs were included in line with the NICE reference case: – OS and PFS were the main efficacy inputs used in the economic model were directly based on KEYNOTE-775 data to model health outcomes over patients' lifetime – Cost categories included treatment acquisition and administration costs, health state resource use costs (e.g. ongoing monitoring and follow-up), AE costs, subsequent treatment costs and costs associated with end-of-life care

B.3.7.1. Base-case incremental cost-effectiveness analysis results – LIST PRICE for P+L

All results presented in this section assume the list price for treatments. Please see Appendix Q for additional results that incorporate the patient access scheme [PAS] currently agreed for pembrolizumab and list price for lenvatinib.

The cost-effectiveness results for PEM+LEN versus TPC are presented in Table 50 and disaggregated results are available in Appendix J. The results show that PEM+LEN is estimated to offer a substantial incremental health benefit compared with TPC, offering an additional 3.53 LYs and 1.75 QALYs per patient lifetime (a total of [redacted] LYs and [redacted] QALYs for PEM+LEN compared with [redacted] LYs and [redacted] QALYs for TPC). This level of benefit supports the importance of PEM+LEN as a

treatment for patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy who would otherwise face a poor prognosis under highly limited treatment options. At list prices, treatment with PEM+LEN is associated with an additional cost of £[redacted], primarily driven by a longer duration of treatment for PEM+LEN coupled with the cost difference between treatments given that TPC is available in generic formulation. The resulting ICER in the base case analysis is £65,111 per QALY gained for PEM+LEN vs TPC.

Appendix Q presents the ICERs incorporating the PAS currently agreed for pembrolizumab, which show that the combination would be very likely be cost effective when these discounts are included. These ICERs should be considered in the context of PEM+LEN being an innovative, end-of-life technology that presents a step-wise improvement for patients with advanced or recurrent EC who have received prior platinum-containing therapy.

Table 50: Base-case results – List prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	3.53	1.75	£65,111

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously over a number of iterations by sampling their values from uncertainty distributions. Whenever available, the standard error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, variability was

assumed as 10% of the mean value. The appropriate probability distributions were used, as described in Appendix P.

The results of the PSA based on 1,000 simulations are presented in Table 51, along with the results illustrated in a scatterplot in Figure 28. The mean outcomes from the PSA are highly consistent with the base case results presented in Section B.3.7 (£65,511 compared with £65,111 per QALY gained, respectively). Therefore, the outcomes from the cost-effectiveness model are considered robust to uncertainty from parameter distributions. Figure 29 shows the cost-effectiveness acceptability curve associated with PEM+LEN versus TPC.

Figure 28: PSA scatterplot, PEM+LEN versus TPC – List prices

[redacted]**Key:** ICER, incremental cost-effectiveness ratio; PEM+LEN, pembrolizumab + lenvatinib; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

Figure 29: Cost-effectiveness acceptability curve – List prices

[redacted]**Key:** ICER, incremental cost-effectiveness ratio; PEM+LEN, pembrolizumab + lenvatinib; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

Table 51: Mean probabilistic base case results, pairwise analysis – List prices

	Total costs	Total life years	Total QALYs	Incremental, PEM+LEN versus TPC			ICER
				Costs	Life years	QALYs	
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	3.56	1.78	£65,511

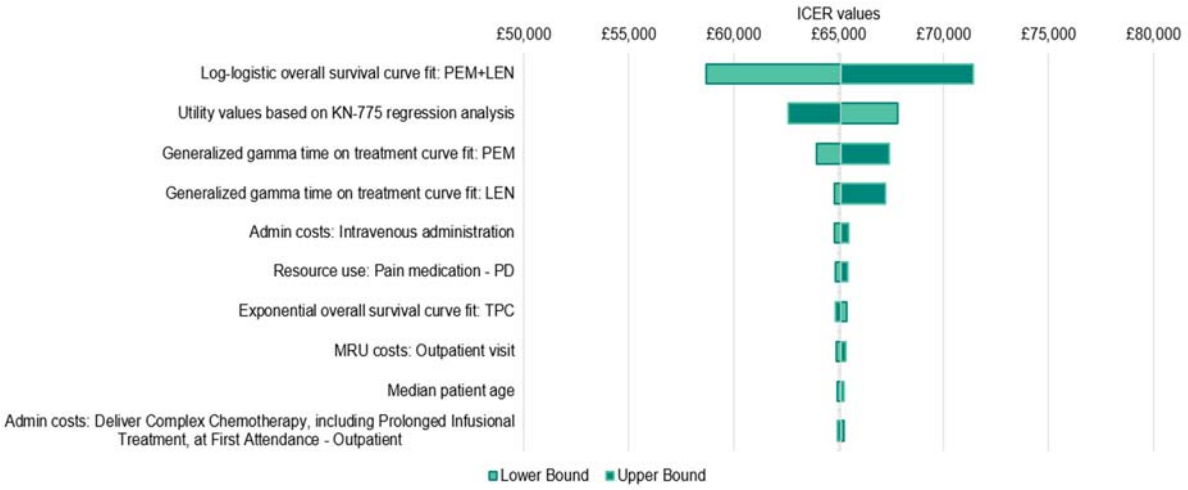
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

B.3.8.2. Deterministic sensitivity analysis

In the one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the confidence intervals reported in Appendix P. Multivariate parameters are treated as having univariate uncertainty distributions as is standard for this analysis.[73, 74]

Figure 30 shows tornado diagrams depicting the 10 parameters that have the greatest influence on the ICER for PEM+LEN versus TPC. As expected, the key drivers of the deterministic sensitivity analysis results include overall survival and time on treatment extrapolations, and utility values estimated from KEYNOTE-775.

Figure 30: Tornado diagram showing OWSA results, PEM+LEN versus TPC – List price



[redacted]**Key:** ICER, incremental cost-effectiveness ratio; KN-775, KEYNOTE-775; LEN, lenvatinib; MRU, medical resource use; OS, overall survival; OWSA, one-way sensitivity analysis; PD, progressed disease; PEM, pembrolizumab; PEM+LEN, pembrolizumab + lenvatinib; TPC, treatment of physician's choice.

B.3.8.3. Scenario analysis

To provide a complete understanding of the impact of changing one or more model inputs (i.e. related to methodological, parameter-specific or structural assumptions), an extensive list of scenarios was tested. Table 52 describes the various scenarios tested, including a brief rationale for including each scenario, and the results.

As demonstrated in Table 52, the scenario results are generally robust to changes, indicating a relatively small impact of uncertainty on the base-case results. The most impactful scenarios are those associated with discount rate, time on treatment extrapolation and utility values.

Table 52: Scenario analysis – PEM+LEN versus TPC – List prices

	Parameter	Justification	ICER	Percentage change
	Base case		£65,111	**NA**
1	Time horizon, 30 years	Test impact of assuming a shorter alternative time horizon (Section B.3.2.2)	£65,655	1%
2	Discount rate (costs and utilities) – 1.5%	Test impact of alternative time discounting assumptions (Section B.3.2.2)	£55,727	-14%
	Mixed chemotherapy setting			
3	Comparators: mixed chemotherapies	Test the impact of including the cost of different chemotherapies in the comparator arm (Section B.3.2.3.2)	£64,641	<1%
	Treatment dosing and duration			
4	Paclitaxel: maximum duration of 6 months	Align use of chemotherapies with expected use in clinical practice (Section B.3.2.3.2)	£65,317	<1%
5	Doxorubicin: no maximum dosing rule		£65,008	<1%
6	Pembrolizumab dosing: 400mg Q6W	Alternative pembrolizumab dosing regimen (Section B.3.2.3.1)	£65,755	1%
7	Lenvatinib weekly dosing: full 20mg dose	Conservative assumption assuming no dose reductions associated with lenvatinib (not likely to hold in clinical practice) (Section B.3.5.1.2)	£69,002	6%
8	ToT: Weibull (both arms)	Alternative structural assumptions surrounding TOT extrapolation (Section B.3.3.5, B.3.2.3.1 and B.3.2.3.2)	[redacted]	[redacted]
9	ToT cannot exceed PFS (both arms)		[redacted]	[redacted]
10	ToT: Directly based on full KM (pembrolizumab and TPC)		[redacted]	[redacted]
	Efficacy assumptions*			
11	PFS PEM+LEN 10-week KM + log-normal PFS TPC 10-week KM + log-normal	Testing the impact of next-best fit for PFS in the economic model	£65,028	<1%
12	OS KM used for first 52 weeks		£66,097	2%

13	PFS KM used for first 37 weeks	Test impact of using alternative cut-off points for the independent two-piece models (Section B.3.3.3 and B.3.3.4)	£65,071	<1%
14	PFS PEM+LEN: independent one-piece log-logistic PFS TPC: independent one-piece log-logistic	Test impact of using a single parametric curve for PFS (Section B.3.3.4)	£64,989	<1%
	Utility inputs			
15	Use health state utility values	Understand the impact of using alternative assumptions for utility value inputs (Section B.3.4)	£71,637	10%
16	Use TTD utility model but exclude AE decrement		£64,279	-1%
17	Utility: Age-adjusted utilities, No		£61,410	-6%
	Cost inputs			
18	Use Caelyx® cost for doxorubicin	Test the impact of including the cost of a different chemotherapy in the comparator arm (TPC) (Section B.3.5.1.1)	£61,535	-5%
19	Exclude AE costs	Understand the impact of AE costs on the model results (Section B.3.5.3)	£65,168	<1%
20	Assume there is vial sharing (no wastage)	Assume that there is no drug wastage (unlikely to hold in clinical practice for drugs stored in vials) (Section B.3.5.1.1)	£65,168	<1%
21	Exclude subsequent treatment costs	Understand the impact of using different assumptions related to the cost of subsequent therapy (Section B.3.5.4.1)	£65,368	<1%
22	Alternative distribution of subsequent treatments (ECHO)		£65,223	<1%

Key: ECHO, endometrial cancer health outcomes study; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PEM+LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice.
Notes:
Alternative plausible assumptions tested in scenario analyses; given there were no other plausible OS curves, minimal scenarios for OS were included (see Appendix R for further detail).
<1% change denote changes less than 1%.

B.3.8.4. Summary of sensitivity analyses results

Sensitivity and scenario analysis results showed results to be robust to uncertainty around most input parameters. However, changing OS and TOT extrapolation methods impact cost-effectiveness results. While there is uncertainty around the cost effectiveness of PEM+LEN, care has been taken to inform uncertain assumptions with the best data available, and to be transparent in illustrating the uncertainty around results.

B.3.9. Subgroup analysis

Not relevant; no subgroup analyses were explored.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

The cost-effectiveness model was developed in line with the NICE reference case and guidance from the NICE DSU TSDs where appropriate. The cost-effectiveness model itself is quality-assured by the internal processes of the external economists who constructed the economic model. In these processes, an economist not involved in developing the cost-effectiveness model reviewed the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies. The validation process was documented via a checklist of modelling errors and corrections applied.

This is the first economic evaluation assessing the cost-effectiveness of PEM+LEN for patients with advanced or recurrent EC in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation in the UK. No study assessing the UK cost-effectiveness of PEM+LEN for the target population specified above was identified from the SLR; therefore, it was not possible to compare the results of the economic model developed in this appraisal with a previous study.

B.3.10.2. Clinical validation

All key model assumptions were validated by UK clinical experts and supplementary evidence, where possible.

The cost-effectiveness model uses parametric survival models to extrapolate clinical data observed in KEYNOTE-775. The survival models in the base case analysis considered the visual and statistical fit to the observed data from KEYNOTE-775, and clinical plausibility of long-term estimates based on supplementary evidence and clinical expert opinion (as described in Section B.3.3). There is a clear paucity of data in the literature for EC, as highlighted by the absence of relevant publications identified by the SLR. Notably, KEYNOTE-146 provides the best source of data for validating the modelled outcomes with PEM+LEN, as data are available for a longer period of follow-up (Section B.2.6.2). Supplementary ECHO RWE study data provided information based on a UK setting, and confirmed the validity of the TPC arm extrapolations based on KEYNOTE-775.

Table 53 presents median OS and PFS estimated in the cost-effectiveness model alongside median OS and PFS extracted from KEYNOTE-775 and KEYNOTE-146.

There are some differences between modelled and reported values. The analysis slightly underestimates PEM+LEN PFS and TPC OS, and overestimates PEM+LEN OS and TPC PFS when compared with the reported medians. Median OS and PFS reported in KEYNOTE-146 further implies that the selected models may be conservative in their estimation of short-term PFS but may overestimate short-term OS.

Table 53: Comparison between reported and modelled median survival

	PEM+LEN		TPC	
Health State	**PFS (months)**	**OS (months)**	**PFS (months)**	**OS (months)**
Modelled (KN-775 informed)	6.67	18.63	3.91	11.27
Reported (KN-775)	7.23	18.30	3.78	11.43
Reported (KN-146)	7.50	16.70	NA	NA

Key: KN-146, KEYNOTE-146; KN-775, KEYNOTE-775; OS, overall survival; PEM+LEN, pembrolizumab in combination with lenvatinib; PFS, progression-free survival; TPC, treatment of physician's choice.

In addition to the validation process outlined above, UK clinical experts consulted by MSD provided clinical validation to confirm the treatment pathway, and provide further validation for the following model inputs: curve selection for OS and PFS,

utility values, resource use estimates and subsequent treatments.[2] This ensured consistency of the modelled population with the UK decision problem.

B.3.11. Interpretation and conclusions of economic evidence

The key evidence presented in this submission are based directly on data from the KEYNOTE-775 trial, a Phase III randomised clinical trial which assessed the efficacy and safety of PEM+LEN for patients with advanced or recurrent EC who have received prior systemic therapy versus current treatment. Pembrolizumab demonstrated superior efficacy to TPC and is the first and only IO to do so in a Phase III randomised clinical trial setting.

In line with the NICE reference case and final NICE scope, a cost-effectiveness model was developed to compare PEM+LEN versus TPC, using patient-level data from KEYNOTE-775. This is aligned to UK practice, where clinicians typically administer either paclitaxel or doxorubicin treatment following an assessment of the likely benefit to each patient. In the TPC arm of KEYNOTE-775, treatment was administered per physician's choice; 25.5% of patients received paclitaxel, with the remaining 74.5% receiving doxorubicin. A range of parametric analyses based on time-to-event data for OS, PFS and TOT were conducted according to best practice guidance to model health outcomes for PEM+LEN and TPC over a lifetime horizon. The approaches were assessed for robustness and appropriateness for use in the economic model based on NICE DSU TSD guidance. The base case analysis used the best-fitting and most clinically valid survival models, with alternative plausible models tested in an extensive range of scenarios as summarised in Section B.3.3.2.

With all treatments at list prices, the estimated ICER for PEM+LEN versus TPC is £65,111 per QALY gained. The results show that PEM+LEN is estimated to offer a substantial incremental health benefit compared with TPC, offering an additional 3.53 LYs and 1.75 QALYs per patient lifetime that is associated with an incremental cost of £[redacted]. This level of benefit supports the importance of PEM+LEN as a treatment for patients in this treatment setting who would otherwise face a poor prognosis under highly limited treatment options. The incremental costs are primarily driven by a longer duration of treatment for PEM+LEN coupled with the cost difference between treatments given that TPC is available in generic formulation.

Appendix Q presents the ICERs incorporating the PAS currently agreed for pembrolizumab, which show that PEM+LEN is highly likely be cost-effective when the confidential discounts are included. These ICERs should also be considered in the context of PEM+LEN being an innovative end-of-life technology that presents a step-wise improvement for patients with advanced or recurrent EC who have received prior platinum-containing therapy.

The base case results are wholly supported by the sensitivity and scenario analysis, which demonstrate a high degree of consistency. Based on the mean PSA results, PEM+LEN is expected to offer an additional 3.56 LYs and 1.75 QALYs versus TPC at an additional cost of £[redacted]. The probabilistic ICER was £65,511, almost the same as that of £65,111 recorded in the base case analysis. When varying the willingness-to-pay threshold to £35,000 and above, PEM+LEN is the most probable cost-effective treatment option in the analysis compared with TPC.

B.4. References

1. Morrison J, Balega J, Buckley L, et al. BGCS uterine cancer guidelines: Recommendations for practice. 2021.
2. Merck Sharp and Dohme (MSD) UK Ltd. Clinical Expert Consultation. 2021-2022 2021. Data on file.
3. Merck Sharp & Dohme B.V. Summary of Product Characteristics Pembrolizumab in combination with lenvatinib. 2021. Accessed: 7 December 2021.
4. Cancer Research UK. Uterine cancer statistics. 2018.
5. National Cancer Registration and Analysis Service (NCRAS). Cancer Incidence C54: Malignant neoplasm of corpus uteri. 2019.
6. Cancer Research UK. About cancer: Womb cancer. 2018.
7. National Disease Registration Service. Case-mix adjusted percentage cancers diagnosed at Stages 1 and 2 by CCG in England, 2019 data tables. 2021.
8. Huijgens AN and Mertens HJ. Factors predicting recurrent endometrial cancer. *Facts Views Vis Obgyn*. 2013; 5(3):179-86.
9. Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. *Gynecologic oncology*. 2006; 101(3):520-9.
10. de Rooij BH, Ikiz H, Boll D, et al. Recurrent Cancer Is Associated With Dissatisfaction With Care-A Longitudinal Analysis Among Ovarian and Endometrial Cancer Patients. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. 2018; 28(3):614-22.
11. Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *New England Journal of Medicine*. 2022.
12. Bradford LS, Rauh-Hain JA, Schorge J, et al. Advances in the management of recurrent endometrial cancer. *American journal of clinical oncology*. 2015; 38(2):206-12.
13. Merck Sharp and Dohme (MSD) Corp. 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. (Clinical Study Report: P775V01MK3475) 22 February 2021.
14. Merck Sharp and Dohme (MSD) Corp. 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. (Clinical Study Protocol: 775-07/E7080-G000-309) 12 June 2020.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2019; 366:l4898.
16. Lorusso D CN, Casado Herraez A, et al. Health-Related Quality of Life in Advanced Endometrial Cancer Patients Treated With Lenvatinib + Pembrolizumab or Treatment of Physician's Choice. American Society of Clinical Oncology Annual Meeting. 4-8 June 2021. Poster
17. Makker V, Aghajanian C, Cohn AL, et al. Lenvatinib and pembrolizumab in advanced endometrial carcinoma (EC): long-term efficacy and safety update from a phase 1b/2 study. The Society For Immunotherapy of Cancer's 36th Annual Meeting and Pre-Conference Programs 2021. 10-14 November 2021. 354.

18. Nagao S, Nishio S, Michimae H, et al. Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study. *Gynecologic oncology*. 2013; 131(3):567-73.
19. Ueda Y, Miyake T, Egawa-Takata T, et al. Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. *Cancer chemotherapy and pharmacology*. 2011; 67(4):829-35.
20. Rubinstein M, Halpenny D, Makker V, et al. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. *Gynecologic oncology reports*. 2019; 28:120-3.
21. Sovak MA, Dupont J, Hensley ML, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. 2007; 17(1):197-203.
22. (ECHO) ECHO. Europe (ECHO EU5): A retrospective, multicenter chart review study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC (aEC) patients previously treated with systemic therapy in United Kingdom. . 2021.
23. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020; 38(26):2981-92.
24. ClinicalTrials.gov. Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9 / MK-7902-001) (LEAP-001). 2019.
25. Grünwald V, Powles T, Choueiri TK, et al. Lenvatinib plus everolimus or pembrolizumab versus sunitinib in advanced renal cell carcinoma: study design and rationale. *Future oncology (London, England)*. 2019; 15(9):929-41.
26. Kudo M. Systemic Therapy for Hepatocellular Carcinoma: 2017 Update. *Oncology*. 2017; 93 Suppl 1:135-46.
27. Lacal PM and Graziani G. Therapeutic implication of vascular endothelial growth factor receptor-1 (VEGFR-1) targeting in cancer cells and tumor microenvironment by competitive and non-competitive inhibitors. *Pharmacological research*. 2018; 136:97-107.
28. Upadhyay N,

Ralph, L., Ljungcrantz C, Merchant A, et al. Long-term clinical and economic value of pembrolizumab + lenvatinib compared with chemotherapy in previously treated advanced endometrial cancer patients in Sweden: A cost-effectiveness analysis. *European Society of Medical Oncology (ESMO)*. 2021.
29. ClinicalTrials.gov. 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]). 2020.
30. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. 2013.
31. Office for National Statistics (ONS). National life tables. 2021.
32. National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA528]. 2018.

33. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [TA598]. 2019.
34. National Institute for Health and Care Excellence (NICE). Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [TA611]. 2019.
35. National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [TA620]. 2020.
36. National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [TA673]. 2021.
37. National Institute for Health and Care Excellence (NICE). Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer [TA693]. 2021.
38. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient level data

2013.
39. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 21: Flexible Methods for Survival Analysis. 2020.
40. Taylor MH, Lee CH, Makker V, et al. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020; 38(11):1154-63.
41. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. 2014.
42. Chen DS and Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017; 541(7637):321-30.
43. National Institute for Health and Care Excellence (NICE). Final appraisal document: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. 2018.
44. National Institute for Health and Care Excellence (NICE). Final appraisal document: Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab [TA357]. 2015.
45. Baird RD, Tan DS and Kaye SB. Weekly paclitaxel in the treatment of recurrent ovarian cancer. *Nature reviews Clinical oncology*. 2010; 7(10):575-82.
46. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L value set for England (updated October 2019). 2019.
47. Ara R and Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010; 13(5):509-18.
48. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013.
49. Guest JF, Ruiz FJ, Greener MJ and Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. . *Eur J Cancer*. 2006; 15(1):65-73.

50. Pennington M, Gentry-Maharaj A, Karpinskyj C, et al. Long-term secondary care costs of endometrial cancer: A prospective cohort study nested within the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). . *PLoS ONE*. 2016; 11(11).
51. Dixon P, Beaver K, Williamson S, et al. Cost-Consequence Analysis Alongside a Randomised Controlled Trial of Hospital Versus Telephone Follow-Up after Treatment for Endometrial Cancer. *Appl Health Econ Health Policy* 2018; 16(3):415-27.
52. Monthly Index of Medical Specialities (MIMS). 2021.
53. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). Pharmex data for the period 01/01/2021 - 30/06/2021, for Pharmex products shown as Generic in the period 01/07/20 - 30/06/21. 2021.
54. Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020; 38(33):3841-50.
55. Hoskins PJ, D. SK, A. PJ, et al. Paclitaxel and Carboplatin, Alone or With Irradiation, in Advanced or Recurrent Endometrial Cancer: A Phase II Study. *Journal of Clinical Oncology*. 2001; 19(20):4048-53.
56. UK Department of Health National Health Services (NHS). 2019/20 National Cost Collection data Version 2. 2021.
57. Compendium. EM. Summary of Product Characteristics: Paclitaxel. 2020.
58. Personal Social Services Research Unit (PSSRU). Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2019/20. 2020.
59. National Institute for Health and Care Excellence (NICE). Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [TA645]. 2020.
60. National Institute for Health and Care Excellence (NICE). Nivolumab with ipilimumab for untreated advanced renal cell carcinoma [TA581]. 2019.
61. National Institute for Health and Care Excellence (NICE). Nivolumab for previously treated advanced renal cell carcinoma [TA417]. 2016.
62. National Institute for Health and Care Excellence (NICE) Decision Support Unit. The risk and costs of febrile neutropenia in patients with non small cell lung cancer treated with docetaxel. 2007.
63. Grisham RN, Adaniel C, Hyman DM, et al. Gemcitabine for advanced endometrial cancer: a retrospective study of the Memorial sloan-Kettering Cancer Center experience. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. 2012; 22(5):807-11.
64. Thigpen JT, Blessing JA, Homesley H, et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecologic oncology*. 1989; 33(1):68-70.
65. European Medicines Agency (EMA). Summary of Product Characteristics: Bevacizumab. 2021.
66. British National Formulary (BNF). Anastrozole indications and dose. 2021.
67. British National Formulary (BNF). Letrozole indications and dose. 2021.
68. British National Formulary (BNF). Medroxyprogesterone Acetate indications and dose. 2021.
69. British National Formulary (BNF). Megestrol Acetate indications and dose. 2021.
70. British National Formulary (BNF). Tamoxifen indications and dose. 2021.

71. England NHS. Implementing Lynch syndrome testing and surveillance pathways: A handbook to support local systems. 2021.
72. Georghiou TB, M. Exploring the cost of care at the end of life. *Nuffield Trust*. 2014.
73. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Medical decision making : an international journal of the Society for Medical Decision Making*. 2012; 32(5):722-32.
74. Claxton K. Exploring Uncertainty in Cost-Effectiveness Analysis. *PharmacoEconomics*. 2008; 26(9):781-98.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Clarification questions

4 April, 2022

File name	Version	Contains confidential information	Date
[ID3811] V2 Pembrolizumab & lenvatinib for EC_ERG clarification queries	1.0	Yes	4 April 2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. The intervention searches reported in Appendix D apply the SIGN filter for clinical trials and, correspondingly, the Embase strategy (reported in D.1.1.1.1, Table 1) excludes abstracts from the search results. However, as a result, the Embase search may have missed relevant conference abstracts published in proceeding titles not included in hand-searches. Please provide the rationale for restricting the Embase search to exclude conference abstracts.

Response: Conference abstracts typically undergo less rigorous peer review and contain limited information on study design, patient characteristics, and outcomes. As full-text publications generally supersede conference abstracts, only conference abstracts in the past three years, based on the conference date, were of interest to this SLR. To accomplish this, conference abstracts were excluded back to database inception in Embase. Then major recent conferences were searched using the Northern Lights database and manual searching of conference proceedings that were not indexed in Northern Lights.

A2. Please provide further details of the searches conducted in ClinicalTrials.gov and the EU Clinical Trials Register for ongoing studies. Search terms used in these sources have not been provided, and the numbers of results for these searches have not been included in the PRISMA flow diagram (Appendix D, Figure 1).

Response: The search term “endometrial cancer” was used for both ClinicalTrials.gov and the EU Clinical Trials Register. For ClinicalTrials.gov, results were limited to "last update posted 1/26/21 to 11/17/21" leading to 81 hits. For the EU Clinical Trials Register, results were limited to “date 1/26/21 to 11/17/21”, which led to 121 hits. However, no trials that met the inclusion criteria and had posted results but were otherwise unpublished in the literature were identified from either source.

A3. Please confirm the total number of included citations in the SLR of interventional evidence. The results and PRISMA flow diagram describe 53 publications, but Table 7 in Appendix only lists 51 references.

Response: Two references were missed in error. Table 1 provide all 53 references included for this systematic literature review.

Table 1: Studies included in the clinical SLR

Trial ID	Trial Number	Study Design	Reference
Del Campo 2016	NCT01420081	RCT	Del Campo JM, Birrer M, Davis C, et al. A randomised phase II non-comparative study of PF- 04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecologic oncology. 2016;142(1):62-69.
KEYNOTE-775	NCT03517449	RCT	Makker V. A multicenter, open-label, randomised, phase III study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer. Paper presented at: SGO 20212021.
			Colombo N, Lorusso D, Herráez AC, Santin A, Colomba E, Miller D, et al. 726MO Outcomes by histology and prior therapy with lenvatinib plus pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer (Study 309/KEYNOTE-775). Annals of Oncology. 2021;32:S729-S30.
			Lorusso D, Colombo N, Casado Herraez A, Santin A, Colomba E, Miller DS, et al. Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC). Wolters Kluwer Health; 2021
Lheureux 2020	NCT03367741	RCT	Lheureux S, Matei D, Konstantinopoulos PA, et al. A randomised phase II study of cabozantinib and nivolumab versus nivolumab in recurrent endometrial cancer. Journal of Clinical Oncology. 2020;38(15_suppl):6010-6010
McMeekin 2015	NCT00883116	RCT	McMeekin S, Dizon D, Barter J, et al. Phase III randomised trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecologic oncology. 2015;138(1):18-23.
Miller 2018	NCT01767155	RCT	Miller DS, Scambia G, Bondarenko I, et al. ZoptEC: Phase III randomised controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (NCT01767155). Journal of Clinical Oncology. 2018;36(15_suppl):5503-5503.
Rimel 2021	NCT03660826	RCT	Rimel B. A Randomised, Phase II Study Comparing Single-Agent Olaparib, Single Agent Cediranib, and the Combination of Cediranib/Olaparib in Women with Recurrent, Persistent or Metastatic Endometrial Cancer. Paper presented at: SGO 20212021.
Rubinstein 2019	NCT03015129	RCT	Rubinstein MM, Caird I, Zhou Q, et al. A phase II trial of durvalumab with or without tremelimumab in patients with persistent or recurrent endometrial carcinoma and

			endometrial carcinosarcoma. Journal of Clinical Oncology. 2019;37(15_suppl):5582-5582.
Scambia 2020	NCT02725268	RCT	Scambia G, Han SN, Oza AM, et al. Randomised phase II study of sapanisertib (SAP) + paclitaxel (PAC) versus PAC alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer. Journal of Clinical Oncology. 2020;38(15_suppl):6087-6087.
Angioli 2007	--	Single-arm	Angioli R, Palaia I, Calcagno M, et al. Liposome-encapsulated doxorubicin citrate in previously treated recurrent/metastatic gynecological malignancies. International Journal of Gynecologic Cancer. 2007;17(1).
Dhani 2020	NCT01935934	Single-arm	Dhani NC, Hirte HW, Wang L, et al. Phase II Trial of Cabozantinib in Recurrent/Metastatic Endometrial Cancer: A Study of the Princess Margaret, Chicago, and California Consortia (NCI9322/PHL86). Clinical Cancer Research. 2020;26(11):2477-2486.
			Dhani NC, Hirte HW, Burnier JV, et al. Phase II study of cabozantinib (cabo) in patients (pts) with recurrent/metastatic endometrial cancer (EC): A study of the Princess Margaret, Chicago, and California phase II consortia. Journal of Clinical Oncology. 2017;35(15_suppl):5524-5524.
			Dhani NC, Hirte HW, Butler MO, et al. Phase II study of cabozantinib in recurrent/metastatic endometrial cancer (EC): A study of the Princess Margaret, Chicago and California Phase II Consortia. Journal of Clinical Oncology. 2016;34(15_suppl):5586-5586.
Di Legge 2011	--	Single-arm	Di Legge A, Trivellizzi IN, Moruzzi MC, Pesce A, Scambia G, Lorusso D. Phase 2 trial of nonpegylated doxorubicin (Myocet) as second-line treatment in advanced or recurrent endometrial cancer. International Journal of Gynecologic Cancer. 2011;21(8).
Fracasso 2006	NCT00071929	Single-arm	Fracasso PM, Blessing JA, Molpus KL, Adler LM, Sorosky JI, Rose PG. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecologic oncology. 2006;103(2):523-526.
Garcia 2008	NCT00085332	Single-arm	Garcia AA, Blessing JA, Nolte S, Mannel RS. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. Gynecologic oncology. 2008;111(1):22-26.
GARNET	NCT02715284	Single-arm	Oaknin A, Tinker AV, Gilbert L, et al. Clinical activity and safety of the anti–programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: a nonrandomised Phase 1 clinical trial. JAMA oncology. 2020;6(11):1766- 1772.

			Oaknin A, Duska LR, Sullivan RJ, Pothuri B, Ellard SL, Leath CA, et al. Preliminary safety, efficacy, and pharmacokinetic/pharmacodynamic characterization from GARNET, a phase I/II clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-h and MSS endometrial cancer. Gynecologic Oncology. 2019;154:17.
			Kristeleit R, Matthews C, Redondo A, et al. Patient-reported outcomes (PROs) in the GARNET trial in patients (pts) with advanced or recurrent mismatch repair deficient/microsatelite instability-high (dMMR/MSI-H) endometrial cancer (EC) treated with dostarlimab. Paper presented at: Annals of Oncology 2020.
			Kristeleit RS, Mathews CA, Redondo A, et al. Patient-reported outcomes (PRO) in patients (pts) with advanced or recurrent dMMR/MSI-H endometrial cancer (EC) treated with dostarlimab in the GARNET trial. Journal of Clinical Oncology. 2020;38(29_suppl):275-275.
			Kristeleit R, Mathews CA, Redondo A, Huang J, Eliason L, Im E, et al. Patient-reported outcomes (PRO) in patients (pts) with advanced or recurrent dMMR/MSI-H endometrial cancer (EC) treated with dostarlimab in the GARNET trial. American Society of Clinical Oncology; 2020.
			Oaknin A. Safety and antitumor activity of dostarlimab in patients (pts) with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer (EC): Results from GARNET. Paper presented at: ESMO; 18 Sep 2020, 2020.
			Oaknin A, Tinker AV, Gilbert L, et al. Safety and efficacy of the anti-PD-1 monoclonal antibody dostarlimab in patients with recurrent or advanced dMMR endometrial cancer. Paper presented at: SGO 2020, 2020.
			Pothuri B. Interim analysis of the immune-related endpoints of the mismatch repair deficient (dMMR) and proficient (MMRp) endometrial cancer cohorts from the GARNET study. Paper presented at: SGO 2021, 2021.
			Oaknin A, Gilbert L, Tinker A, Brown J, Mathews C, Press J, et al. 272 Dostarlimab in advanced/recurrent mismatch repair deficient/microsatellite instability high or proficient/stable endometrial cancer: the GARNET study. BMJ Specialist Journals; 2021.
			Oaknin A, Gilbert L, Tinker A, Brown J, Mathews C, Press J, et al. 76P Analysis of antitumor activity of dostarlimab by tumor mutational burden (TMB) in patients (pts) with endometrial cancer (EC) in the GARNET trial. Annals of Oncology. 2021;32:S388-S9.
			Berton D, Banerjee SN, Curigliano G, Cresta S, Arkenau H-T, Abdeddaim C, et al. Antitumor activity of dostarlimab in patients with mismatch repair-

			deficient/microsatellite instability–high tumors: A combined analysis of two cohorts in the GARNET study. Journal of Clinical Oncology. 2021;39(15_suppl):2564-. doi: 10.1200/JCO.2021.39.15_suppl.2564.
GOGO-EM2	--	Single-arm	Tanaka Y, Ueda Y, Nakagawa S, et al. A phase I/II study of GLIF combination chemotherapy for taxane/platinum-refractory/resistant endometrial cancer (GOGO-EM2). *Cancer chemotherapy and pharmacology.* 2018;82(4):585-592.
GOP 129-P	--	Single-arm	Dizon DS, Blessing JA, McMeekin DS, Sharma SK, DiSilvestro P, Alvarez RD. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: gynecologic oncology group trial 129-P. Journal of clinical oncology. 2009;27(19):3104.
Hasegawa 2017	Japic CTI-132287	Single-arm	Hasegawa K, Kagabu M, Mizuno M, et al. Phase II basket trial of perifosine monotherapy for recurrent gynecologic cancer with or without PIK3CA mutations. Investigational new drugs. 2017;35(6):800-812.
Homesley 2008	--	Single-arm	Homesley HD, Meltzer NP, Nieves L, Vaccarello L, Lowendowski GS, Elbendary AA. A phase II trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer. International journal of clinical oncology. 2008;13(1):62-65.
Janku 2021	NCT03601897	Single-arm	Janku F, Hamilton EP, Mathews CA, Chu C, Diamond JR, Hays JL, et al. Open-label, multicenter, phase 1b/2 study of rebastinib in combination with paclitaxel to assess safety and efficacy in patients with advanced or metastatic endometrial cancer. Wolters Kluwer Health; 2021.
Lincoln 2003	--	Single-arm	Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecologic oncology. 2003;88(3):277-281.
Liu 2021	NCT03668340	Single-arm	Liu JF, Xiong N, Campos SM, Wright AA, Krasner C, Schumer S, et al. Phase II Study of the WEE1 Inhibitor Adavosertib in Recurrent Uterine Serous Carcinoma. Journal of Clinical Oncology. 2021;39(14):1531-9.
Makker 2019	NCT02501096 (KEYNOTE-146 study)	Single-arm	Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. The Lancet Oncology. 2019;20(5):711-718.
			Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib (LEN) plus pembrolizumab (PEMBRO) for early-line treatment of advanced/recurrent endometrial cancer (EC). Journal of Clinical Oncology. 2020;38(15_suppl):6083-6083.
			Makker V, Vogelzang NJ, Cohn A, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: Final analysis of a multicentre, open-label, single-arm, phase 2 trial. Paper presented at: SGO 2020, 2020.

			Makker V, Taylor M, Aghajanian C, et al. Lenvatinib (LEN) and pembrolizumab (PEMBRO) in advanced endometrial cancer (EC). Annals of Oncology. 2019;30:v404-v405.
			Makker V, Rasco DW, Vogelzang NJ, et al. Lenvatinib + pembrolizumab in patients with advanced endometrial cancer: Updated results. Journal of Clinical Oncology. 2018;36(15_suppl):5596-5596.
Martin 2013	--	Single-arm	Martin LP, Krasner C, Rutledge T, et al. Phase II study of weekly PM00104 (ZALYPSIS®) in patients with pretreated advanced/metastatic endometrial or cervical cancer. Medical Oncology. 2013;30(3):627.
Matulonis 2015	NCT01013324	Single-arm	Matulonis U, Vergote I, Backes F, et al. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. Gynecologic oncology. 2015;136(2):246-253.
Nishio 2003	--	Single-arm	Nishio S, Ota S, Sugiyama T, et al. Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: a preliminary study. International journal of clinical oncology. 2003;8(1):0045- 0048.
Nishio 2018	UMIN00017097	Single-arm	Nishio S, Shimokawa M, Tasaki K, et al. A phase II trial of irinotecan in patients with advanced or recurrent endometrial cancer and correlation with biomarker analysis. Gynecologic oncology. 2018;150(3):432-437.
Ray- Coquard 2013	NCT00870337	Single-arm	Ray-Coquard I, Favier L, Weber B, et al. Everolimus as second-or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. *British journal of cancer.* 2013;108(9):1771-1777.
Schilder 2004	NCT00005031	Single-arm	Schilder RJ, Blessing JA, Pearl ML, Rose PG. Evaluation of irofulven (MGI-114) in the treatment of recurrent or persistent endometrial carcinoma: A phase II study of the Gynecologic Oncology Group. *Investigational new drugs.* 2004;22(3):343-349.
Tait 2011	NCT00820898	Single-arm	Tait DL, Blessing JA, Hoffman JS, et al. A phase II study of gemcitabine (gemzar, LY188011) in the treatment of recurrent or persistent endometrial carcinoma: a gynecologic oncology group study. *Gynecologic oncology.* 2011;121(1):118-121.
TOPIC/VHIO10001	NCT03276013	Single-arm	Fariñas-Madrid L, Rubio M, Redondo A, Javierre GV, Esteban AY, Romero I, et al. 798P A phase II study of pembrolizumab (P) in combination with doxorubicin (D) in advanced endometrial cancer (AEC): TOPIC trial/VHIO10001. Annals of Oncology. 2021;32:S761-S2.
Vergote 2020a	NCT02025985	Single-arm	Vergote I, Lund B, Peen U, et al. Phase 2 study of the Exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies. *Gynecologic oncology.* 2020;156(2):308-314
Vergote 2020b	NCT01111461	Single-arm	Vergote, I, Powell, MA, Teneriello, MG, et al. Second-line lenvatinib in patients with recurrent endometrial cancer. *Gynecologic oncology*. 2020;156(3), 575–582.

Wei 2021	NCT04157491	Single-arm	Wei W, Ban X, Yang F, Huang Y, Li J, Qiu Y, et al. Anlotinib plus sintilimab in patients with recurrent advanced endometrial cancer: A prospective open-label, single-arm, phase II clinical trial. Journal of Clinical Oncology. 2021;39(15_suppl):5583-. doi: 10.1200/JCO.2021.39.15_suppl.5583.
			Wei W, Ban X, Yang F, Huang Y, Li J, Cheng X, et al. 799P Anlotinib plus sintilimab in patients with recurrent advanced endometrial cancer: A prospective open-label, single-arm, phase II clinical trial. Annals of Oncology. 2021;32:S762.
Woo 1996	--	Single-arm	Woo H, Swenerton K, Hoskins P. Taxol is active in platinum-resistant endometrial adenocarcinoma. *American journal of clinical oncology.* 1996;19(3):290-291.
Key: RCT, randomised controlled trial. **Note:** Grey highlighting denotes studies that include a treatment arm of potential relevance to the UK.			

A4. Please provide details of how the following citations for KEYNOTE-146 and KEYNOTE-775 were identified:

- Makker V, Aghajanian C, Cohn AL, et al. Lenvatinib and pembrolizumab in advanced endometrial carcinoma (EC): long-term efficacy and safety update from a phase 1b/2 study. The Society For Immunotherapy of Cancer's 36th Annual Meeting and Pre-Conference Programs 2021. 10-14 November 2021. 354.

- Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. New England Journal of Medicine. 2022

These references are cited in Document B, but do not appear in Table 7 in Appendix D.

Response: To capture late-breaking publications on pembrolizumab + lenvatinib that were published after the SLR search date, a targeted literature search was conducted using search terms for these agents and advanced endometrial carcinoma. In all, two publications meeting the inclusion criteria were identified.

A5. The Embase search strategy for observational studies (Table 9, D.1.2.2, Appendix D) applies limit of 'Article' or 'Article in Press' to exclude conference abstracts from search results. This approach may have missed conference abstracts not published in the specific titles searched in line #26 or hand-searched. Please provide the rationale for excluding conference abstracts from this search.

Response: Conference abstracts typically undergo less rigorous peer review and contain limited information on study design, patient characteristics, and outcomes. As full-text publications generally supersede conference abstracts, only conference abstracts in the past two years, based on the conference date, were of interest to this SLR and supplemental to the main search. The main database search is focused on 'Article' or 'Article in Press' and any missing abstracts in the last two years would be picked up by the line #26 or hand searched.

A6. Please provide details of how the ECHO study (described in Document B, Section B.2.9.3) was identified. This does not appear to have been retrieved in the searches for the observational SLR (reported in Appendix D, D.1.2).

Response: The ECHO study is an internal MSD study that recently finished data collection and analysis. The UK data have not been published, and therefore do not appear in the searches for the observational SLR.

A7. The bibliographic database search strategies applied in the observational, cost-effectiveness, HRQoL and cost & resource use SLRs used search terms for uterine/uterus cancer in addition to endometrial/endometrium cancer. Please explain why these terms were not also used in the SLR of interventional evidence.

Response: Database subject headings (i.e., Emtree and MeSH terms) and keywords were selected to strike an ideal balance between the specificity and sensitivity of the search. The rationale for not using search terms related to “uterus” and “uterine” is that the population of interest was women with endometrial cancer specifically rather than women with any type of uterine cancer (including cervical cancer, which is classified as a subtype of uterine cancer in Emtree and MeSH term hierarchies). Therefore, using subject headings and keywords related to “uterus” and “uterine” would have reduced the specificity of the search without a large impact on its sensitivity and without adding any more relevant clinical evidence for consideration to the clinical SLR.

A8. The number of records identified through database searching (n=5345) in the PRISMA flow diagram for the SLR of observational and real-world evidence (Figure 2, Appendix D) does not match the total number of records retrieved from the MEDLINE, Embase and CDSR database searches (n=5238). Please can you confirm the total number of records from database searching.

Response: N=5345 is the count from final numbers based on the search from July 2020, which was the latest number. N=5238 is from the search strategies that were included in the protocol (added as an appendix in the original submission), which served as

preliminary search to define the scope. The date of the protocol search was in June 2020.

Systematic review methods

A9. The company state in Appendix D, Section D1.2. that the observational and RWE systematic review was conducted in July 2020. As this is more than six months old, please update the review from July 2020 to present, to include any recent relevant evidence.

Response: The observational and RWE systematic review was prepared by Eisai and was shared with the MSD. Unfortunately, more up to date later systematic review is not available. Please also note that the evidence of clinical effectiveness is primarily derived from the SLR of interventional studies which is up to date and relevant to inform the final scope of the decision problem.

A10. The company state in Appendix D.1.1.2.2 that Cochrane Risk of Bias version 2 (RoB2) has been used in the quality assessment of KEYNOTE-775, citing the relevant paper by Sterne et al. The described domains and summary assessments (low, unclear or high) does not, however, correspond with RoB 2. Results of the assessment (Appendix D.2, Table 15) also suggest the assessment was conducted at the trial level, and not at the outcome or endpoint level. Please provide quality assessments by outcome or endpoint if the RoB2 approach was followed or, alternatively, update the text to reflect that RoB1 was used.

Response: A table is presented below with risk of bias assessments for each domain of the Risk of Bias 2 tool. Responses to the signalling question are available in the appendix (Table 9).

Table 2: Risk of bias assessments for each domain of the Risk of Bias 2 tool

Bias domain	Makker et al (2022) PFS	Makker et al (2022) OS
1. Bias arising from the randomisation process	Lower risk of bias	Lower risk of bias
2. Bias due to deviations from intended interventions	Some concerns	Some concerns

3. Bias due to missing outcome data	Lower risk of bias	Lower risk of bias
4. Bias in measurement of the outcome	Lower risk of bias	Lower risk of bias
5. Bias in selection of the reported result	Lower risk of bias	Lower risk of bias
Overall bias	Some concerns	Some concerns

Clinical Data

A11. As per Table 5 (Document B, Section 2.3.2), please provide a table of patient characteristics for the ECHO study (Document B, Section B2.9.3) including, where possible: age, race, country or geographic region, time since diagnosis, age at diagnosis, elapsed time in years from initial diagnosis, location of any metastases, programmed death-ligand 1 (PD-L1) status, mismatch repair status (proficient [pMMR] or deficient [dMMR]), Eastern Cooperative Oncology Group (ECOG) performance status, International Federation of Gynecology and Obstetrics (FIGO) staging, histology (endometrioid vs. non-endometrioid), prior history of pelvic radiation, number of prior lines of therapy.

Response: ECHO RWE UK patient characteristics (n=101) are summarised in the table below (Table 3). Please note that not all categories sum up to n=101/100% due to missing/not reported data.

Table 3: ECHO UK patient characteristics summary

Variable	Statistic or Category	UK (N = 101)
Age in years at initial diagnosis	N	101
	Mean | SD	***** *****
	Range	*****
Age at initial diagnosis, below versus above 65 years, N | %	<65 years	***** *****
	>=65 years	***** *****
Age at diagnosis of advanced or recurrent EC (years)	N	*****
	Mean | SD	***** *****
	Range	*****
Age at diagnosis of advanced or recurrent EC, below versus above 65 years, N | %	<65	***** *****
	>=65	***** *****
Race, N | %	White or Caucasian	***** *****
	Black or African/ Caribbean-origin	***** *****

	Middle Eastern/ North-African	*****	*****
	Asian	*****	*****
MMR Status, N | %	dMMR	*****	*****
	pMMR	*****	*****
MSI status, N | %	MSI-H/dMMR	*****	*****
	Non-MSI-H/pMMR	*****	*****
	Mixed	*****	*****
ECOG at recurrent or advanced diagnosis, N | %	0	*****	*****
	1	*****	*****
	2	*****	*****
Radiation, N | %	Yes	*****	*****
Elapsed time in years from initial diagnosis	Mean | SD	*****	*****
	Range	*****	
Diagnosis carcinoma type, N | %	Clear Cell Carcinoma	*****	*****
	Carcinosarcoma	*****	*****
	Endometrioid carcinoma	*****	*****
	Undifferentiated Carcinoma/ Mixed cell tumours	*****	*****
	Serous Carcinoma	*****	*****
	Uterine carcinosarcoma	*****	*****
	Mucinous Carcinoma	*****	*****
Staging at initial diagnosis, N | %	IA	*****	*****
	IB	*****	*****
	II	*****	*****
	IIIA	*****	*****
	IIIB	*****	*****
	IIIC	*****	*****
	IV	*****	*****
Metastatic site(s) at diagnosis, N | %	Yes	*****	*****
Liver metastasis, N | %	No	*****	*****
	Yes	*****	*****
Distant lymph node(s), N | %	No	*****	*****
	Yes	*****	*****
Lung metastasis, N | %	No	*****	*****
	Yes	*****	*****
Bone metastasis, N | %	No	*****	*****
	Yes	*****	*****
Brain metastasis, N | %	No	*****	*****
Pancreas metastasis, N | %	No	*****	*****
Kidney metastasis, N | %	No	*****	*****
Other metastasis, N | %	No	*****	*****

	Yes	[redacted]	[redacted]

A12. The ERG were not able to locate the CSR for KEYNOTE-146 in the reference pack provided. Please provide the CSR for KEYNOTE-146.

Response: The sponsor and the owner of the KEYNOTE-146 CSR is Eisai. MSD is a collaborator for this study. As discussed at the Clarification Question Meeting (25th April) MSD is unable to provide this document. Phase III randomised KEYNOTE-775 is the pivotal study for this indication while the KEYNOTE-146 (open-label Phase 1b/2 basket study) was used to support with a longer-term data.

The key publications for this study that reported endometrial subgroup results are:

- Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. The Lancet Oncology. 2019;20(5):711-8. [1]
- Makker V, Taylor M, Aghajanian C, et al. Lenvatinib (LEN) and pembrolizumab (PEMBRO) in advanced endometrial cancer (EC). Annals of Oncology. 2019;30:v404-v405. [2]
- Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. Journal of Clinical Oncology. 2020;38(26):2981-92. [3]
- Makker V, Vogelzang NJ, Cohn A, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: Final analysis of a multicentre, open-label, single-arm, phase 2 trial. Paper presented at: SGO 2020, 2020.[4]
- Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib (LEN) plus pembrolizumab (PEMBRO) for early-line treatment of advanced/recurrent endometrial cancer (EC). Journal of Clinical Oncology. 2020;38(15_suppl):6083-6083.[5]
- Makker V, Aghajanian C, Cohn AL, et al. Lenvatinib and pembrolizumab in advanced endometrial carcinoma (EC): long-term efficacy and safety update

from a phase 1b/2 study. The Society For Immunotherapy of Cancer's 36th Annual Meeting and Pre-Conference Programs 2021. 10-14 November 2021. 354.[6]

A13. Please indicate whether information is available on (i) for KEYNOTE-146, location of any metastases, geographical region, age at diagnosis, prior radiation and elapsed time in years from initial diagnosis (ii) for KEYNOTE-775, PD-L1 status? If so, please supply as additional rows to Appendix O, Table 55 and Document B, Table 5.

i) Response: As discussed in A12, the sponsor of KEYNOTE-146 is Eisai. The patient characteristics provided in Appendix O of the company submission, are those reported in Makker et al 2019 and Makker et al 2020 [3, 7].

ii) MSD cannot provide the additional information requested and neither believes this would be of use when considering KEYNOTE-146 is a basket trial and of a single arm design which is only used for model validation.

iii) Response: PD-L1 status was not assessed for participants in KEYNOTE-775 as results of KEYNOTE- 028 and KEYNOTE-158 did not demonstrate any association between PD-L1 status and response to pembrolizumab monotherapy, and an exploratory analysis of KEYNOTE-146 demonstrated a comparable response rate regardless of PD-L1 status. For KEYNOTE-775 The regulatory licence for this indication does not have a restriction based on the PD-L1 status.

A14. Please provide entries for KEYNOTE-146 FIGO grade 4 or grade 0 in Appendix O, Table 55. Also provide counts of any missing values in the table.

Response: Makker et al (2019) [7] reported patient characteristics for patients in KEYNOTE-146. FIGO staging is only provided for those with the histology subtype of endometrioid adenocarcinoma. None were reported as having FIGO grade 0 or 4.

A15. The company states in Document B, Section 2.9.3 that, for the ECHO study, 'Physicians provided data [on] … advanced or recurrent EC between 1 July 2016

– 31 December 2018, and … disease progression after a prior systemic therapy during 1 July 2016 – 30 June 2019.' In Document B, Figure 16, Kaplan-Meier data are plotted for only 24 months, not the expected 30 or 36 months - please clarify this discrepancy. Also, have further data emerged from ECHO since 2018/2019?

Response: Please see the updated OS curve from the ECHO study with an appropriate follow up frame (Figure 1). There have been no further data that have emerged from the ECHO study since the submission took place.**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**

Figure 1: ECHO overall survival since start of second line of treatment

[redacted]

A16. PRIORITY QUESTION: Please clarify why [redacted] of the patients randomised to pembrolizumab and lenvatinib in KEYNOTE-775 had completed study medication (Appendix D.1.3, Table 14), given that trial enrolment commenced in June 2018 and the stated data cut is 26 October 2020, thereby providing sufficient time for [redacted] to have received 35 infusions of pembrolizumab every three weeks.

Response**:** There was no maximum dose defined for lenvatinib and participants continued to receive therapy and did not complete, thus none of the patients randomised to pembrolizumab and lenvatinib had completed study medication on both pembrolizumab and lenvatinib. Of note, three patients have completed 35 cycles of pembrolizumab without going into second course phase and thus considered completed study medication on pembrolizumab (CSR Table 14.1-5). Treatment was ongoing for lenvatinib for these patients.

A17. The ERG notes the regional distribution of participants in KEYNOTE-775 (Document B, Table 5) and that participants from nine UK sites were included, but further note very little information on UK-specific participants are provided

here or in the clinical study report (CSR). Please provide characteristics as noted in table 5 from the whole trial population for the 39 participants from the UK included per trial arm in KEYNOTE-775, if possible. The ERG also requests that, if possible, the outcome data for these UK participants are provided in summative form (no individual patient data required, as the heavy censoring of the dataset is noted).

Response: Baseline characteristics for the UK-specific participants are provided in Table 4 below. Descriptive statistics of OS and PFS for the UK-specific participants, for each treatment arm, including incidence (count and percentage), median time to event and its 95% confidence interval (if median is reached) are presented in Table 5 and Table 6 below. Key opinion leaders have reviewed UK patient characteristics and validated that KN775 patients are generalizable for the UK population.

Table 4: KEYNOTE-775 UK-specific participant characteristics All-comer Participants (Intention-to-Treat Population)

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	19		20		39	
Sex						
Female	19	(100.0)	20	(100.0)	39	(100.0)
Age (Years)						
< 65	[redacted]					
>= 65						
Mean						
SD						
Median						
Range						
Race						
Asian	[redacted]					
Black Or African American						
White						
Missing						
Ethnicity						
Hispanic Or Latino	[redacted]					
Not Hispanic Or Latino						
Not Reported						
Unknown						

Age (Years) Group						
< 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years) at Initial Diagnosis						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years) at Initial Diagnosis						
Participants with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region [a]						
Region 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR Status						
pMMR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
dMMR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior History of Pelvic Radiation						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology of Initial Diagnosis						
Clear Cell Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endometrioid Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endometrioid Carcinoma With Squamous Differentiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High Grade Endometrioid Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High Grade Serous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low Grade Endometrioid Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serous Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIGO Stage at Initial Diagnosis						
I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IIIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIC2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain Metastasis [c]						
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone Metastasis c						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver Metastasis c						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung Metastasis c						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intra-abdominal Metastasis b c						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node Metastasis c						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight at Baseline (kg)						
Participants with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height at Baseline (cm)						
Participants with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Body Surface Area at Baseline (m2)						
Participants with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Prior Lines of Systemic Therapy						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Therapy Received by Setting						
Neo-adjuvant/adjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease/relapse only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment in both neo-adjuvant/adjuvant and PD/relapse setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Applicable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World.
[b] Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs.
[c] Lesion location as determined by investigator review.
TPC = Treatment of Physician's Choice of doxorubicin or paclitaxel
Database Cut-off Date: 26OCT2020

Table 5: KEYNOTE-775 Analyses of Overall Survival All-comer Participants from UK (Intention-to-Treat Population)

Treatment	N	Number of Events (%)	Estimated Median time in Weeks	95% CI of Estimated Median time in Weeks	Estimated Mean time in Weeks	SE of Estimated Mean time in Weeks	95% CI of Estimated Mean time in Weeks
Lenvatinib + Pembrolizumab	19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of participants: intention-to-treat population
Estimated median and mean time is from product-limit (Kaplan-Meier) method
CI = Confidence Interval; SE = Standard Error; TPC = Treatment of Physician's Choice of doxorubicin or paclitaxel
Database Cut-off Date: 26OCT2020

Table 6: KEYNOTE-775 Analyses of Progression-Free Survival (BICR Primary censoring rule) All-comer Participants from UK (Intention-to-Treat Population)

Treatment	N	Number of Events (%)	Estimated Median time in Weeks	95% CI of Estimated Median time in Weeks	Estimated Mean time in Weeks	SE of Estimated Mean time in Weeks	95% CI of Estimated Mean time in Weeks
Lenvatinib + Pembrolizumab	19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of participants: intention-to-treat population
Estimated median and mean time is from product-limit (Kaplan-Meier) method
CI = Confidence Interval; SE = Standard Error; TPC = Treatment of Physician's Choice of doxorubicin or paclitaxel
Database Cut-off Date: 26OCT2020

A18. The company state in Document B, Section B.2.10.1.2 that '…the median duration of exposure was over twice as long for PEM+LEN compared with TPC', and that adjustments were made for exposure. Please provide a detailed description of

how these adjustments to account for exposure were made to derive adverse events incidences.

Response: In Table 15 of Section B.2.10.1.2, exposure-adjusted adverse event was defined as event rate per 100 person-months of exposure, which is calculated as event count times 100 divided by person-months of exposure. The drug exposure was calculated as time between the first dose date + 1 day and the minimum of the last dose date during the initial treatment phase + 30 days and the cut-off date. Second course phase was not considered. In this Table, multiple occurrences of events; including multiple occurrences of the same event within the same participant, were included in the analysis of exposure-adjusted adverse events

As reported in Document B Table 15 (Table 12-2 of the KEYNOTE-775 CSR [8], the median duration of exposure in person-months was 3919.48 and 1765.17 on the PEM+LEN and TPC treatment arms respectively.

Clinical Effectiveness

A19. PRIORITY QUESTION: The primary comparator in the company's economic analysis was physician's choice (assumed to be doxorubicin and paclitaxel). Please provide further evidence which supports the equivalence in clinical effectiveness of these treatments.

Response: For patients presenting with advanced endometrial cancer recurring after platinum-based doublet chemotherapy (as enrolled on KEYNOTE-775) treatment options are very limited. No standard of care has been identified for patients in this treatment setting. According to the current European Society for Medical Oncology [9] and European Society of Gynecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines [10] weekly paclitaxel and doxorubicin are considered to be active drugs in advanced endometrial cancer.

The study design of KEYNOTE-775 including the comparator arm of TPC (doxorubicin 60 mg/m2 Q3W or paclitaxel 80 mg/m2 given weekly, 3 weeks on/1 week off) was

supported by above mentioned professional guidelines, multiple international scientific experts, and evaluated with FDA and CHMP during protocol development. During the end of Phase 2 interaction, the FDA agreed with the overall study design and expressed no concerns regarding the two TPC treatment options. CHMP also acknowledged there was no standard treatment for 2L endometrial cancer and concluded that based upon the limited evidence available both doxorubicin and paclitaxel are considered valid second-line treatment options after platinum-based chemotherapy of endometrial cancer. This was also confirmed in October 2021 in the CHMP assessment of the Type II variation application for advanced EC.

Weekly low-dose administration of paclitaxel (60–100 mg/m2 delivered over 1 hour) has been shown to be reasonably well tolerated and an active management strategy, for several malignancies, including endometrial cancer [11]. In the treatment of second–line endometrial cancer, weekly low dose paclitaxel (80 mg/m2) produced response rates of 27% in a small Phase 2 study (15 evaluable patients) [11]. The shorter infusion time was more convenient for patients, adverse effects were minimal, and because toxicity was managed on a week to week basis, negligible Grade 3 and Grade 4 toxicities were reported.

Doxorubicin 60 mg/m2 Q3W which is approved in several countries in the EU and the UK for treatment of advanced or recurrent endometrial cancer [[12] was utilised as a TPC option in a Phase III randomised trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer with at least one failed prior platinum-based chemotherapeutic regimen [13]. Median OS was 10.9 months in the ixabepilone group and 12.3 months in the control chemotherapy group. The median PFS was 3.4 months in the ixabepilone group compared with 4.0 months in the control chemotherapy group. Objective responses were observed in 15.2% and 15.7% of patients in the ixabepilone and control group, respectively.

Doxorubicin 60 mg/m2 Q3W has been further used as the control arm (N=255) in the Phase III randomised ZoptEC study comparing zoptarelin with doxorubicin as second line therapy for patients with locally advanced, recurrent, or metastatic endometrial

cancer who had failed prior platinum and taxane therapy. The median OS for patients treated with zoptarelin was 10.9 months compared to 10.8 months for patients treated with doxorubicin. PFS was 4.7 months for both, and ORR was 12% vs 14% in the zoptarelin and control group (doxorubicin), respectively [14]. The efficacy of the TPC in both of these studies were consistent with that reported in KEYNOTE-775 in a similar population.

Please also note that a clinical SLR conducted to identify clinical trials evaluating any intervention in the population of interest. Therefore, the searches were not restricted by intervention and would have been sufficient to identify an RCT comparing doxorubicin and paclitaxel. No published RCT comparing these two drugs was identified by McMeekin et al. 2015.

In addition to KEYNOTE-775, McMeekin et al. 2015, was an RCT comparing investigator's choice of paclitaxel or doxorubicin to an investigational agent. However, results were only reported for the control arm in aggregate and no information on the relative efficacy of paclitaxel versus doxorubicin was available.

Across all studies identified by the SLR, six study arms evaluated paclitaxel and five evaluated doxorubicin. Because none of these arms were compared head-to-head, differences in study design and patient characteristics (including line of therapy) preclude a meaningful naive comparison of survival outcomes between these drugs in different studies.

Based on the above provided rationale and given that patients with advanced or recurrent EC with disease progression following prior systemic therapy in any setting are predominantly older women (median age of 65 years in KEYNOTE-775) with frequent comorbidities, doxorubicin 60 mg/m2 Q3W and paclitaxel 80 mg/m2 given weekly (3 weeks on/1 week off) are considered appropriate choices for the comparator arm of TPC in KEYNOTE-775 [15] with both agents offering consistent and limited survival benefit to this patient population.

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please explain the rationale for limiting PubMed searches in the cost-effectiveness, HRQoL and cost SLRs to the publisher-supplied citation subset (publisher[sb]) as reported in the embedded Word documents in Table 25, Appendix G; Table 32, Appendix H; and Table 37, Appendix I.

Response: The PubMed.com interface provides access to both MEDLINE® and MEDLINE® In-Process. However, in the current SLRs, the PubMed.com interface has only been used to search studies indexed as MEDLINE® In-Process, while MEDLINE® has been accessed via Embase.com. Consequently, to restrict the searches across PubMed.com interface to author submitted manuscripts or 'in process' articles only, the below mentioned search facet has been used:

(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)

The above facet includes two different segments, combined using the Boolean apparatus 'OR'. The significance in terms of retrieval of 'in process' hits by using either of the segments is explained below.

- *publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook*: This complete facet captures citations recently added to PubMed via electronic submission from a publisher, and will soon be included as an ahead of print citation in PubMed

- *pubstatusaheadofprint:* This facet captures articles that appear on the web prior to their publication in final or print format.

B2. The number of records identified through database searching in the update search for the cost and resource review (n=3244) in the PRISMA flow diagram does not match the total number of records retrieved from the Embase, MEDLINE, Econlit and NHS

EED/HTA searches. Please can you confirm the total number of records from database searching in the update searches completed in January and November 2021.

Response: The search tables included in the company submission for November 2021 update for the cost and resource use SLR was an incorrect attachment. The correct search tables for this update are attached below.

Search%20strategy_ CRU_08%20Novemb

Table 7 details the number of hits identified from each of the databases during the SLR updates conducted in January 2021 and November 2021, respectively. The total number of records included during these updates from database searches equates to n=3244, as indicated in the PRISMA flow diagram.

Table 7: Search hits from the January and November 2021 updates of cost and resource use SLRs

Databases	January 2021 update	November 2021 update
Embase® and MEDLINE (using Embase.com)	2,314	633
MEDLINE® In-Process (using PubMed.com)	127	165
EconLit™ (using Ebsco.com)	5	0
Centre for Reviews and Dissemination (CRD), York	0	0
Total	**2,446**	**798**
Grand total	**3,244**	

Model structure

B3. It would be helpful if you could clarify what happens to patients when they discontinue active treatment and/or progress into the PD health state. The ERG understand that a proportion of patients will receive subsequent treatments (as

per KEYNOTE-775). For the patients that do not receive subsequent treatment, do they receive BSC? If yes, please specify BSC treatment(s).

Response: As mentioned in Document B Sections B.2.6.1.2. and B.3.5.4.1., in KEYNOTE-775, 28% and 48% of patients received subsequent anti-cancer treatment in the PEM+LEN and TPC arms, respectively. The remaining proportion of patients on each arm (72% and 52% in the PEM+LEN and TPC arms respectively) did not receive subsequent anti-cancer treatment. These proportions were validated by clinical experts and deemed appropriate for use in the cost effectiveness analysis.[16]

The costs associated with subsequent treatment are applied to the proportion of patients described, at the point of each new incidence of treatment discontinuation (if alive) at each model cycle.

Patients that did not receive subsequent treatment continue to receive weekly resource use costs associated with patients in the progressed disease (PD) state including outpatient visits and pain medication as detailed in Document B Table 44, which would be considered best supportive care as standard and there is no further need to cost any additional items. As validated with UK clinical experts, this is an appropriate assumption for use in the cost effectiveness analysis.[16]

B4. Please explain why the model includes an ‘on treatment’ component and an ‘off treatment’ component i.e., according to treatment status. A conventional approach is that patients in the PFS health state will be on treatment and when they have progressed disease, they will be off treatment. Why is there a need to split into PFS (on/off treatment) and PD (on/off treatment)?

Response: An ‘on treatment’ and an ‘off treatment’ component of the PFS and PD states was included in the model patient flow sheets by incorporating the extrapolated time on treatment curve. By accounting for treatment status within each health state the model provides a more accurate way of accruing ongoing costs over the model time horizon. For both PFS and PD states, the following costs were accounted for in the ‘on treatment’ component: drug acquisition, drug administration, adverse event

management and disease management. Additionally, disease management costs were accounted for in the 'off treatment' component.

PFS and OS extrapolation

B5. Please explain the choice of the KM + log-log model as base case for PemLen when AIC would suggest KM + Weibull (based on AIC) or KM + exponential (BIC) is a better fit to the observed data.

Response: As detailed in Document B Section B.3.3.3.1. and Appendix R, both KM (first 26 weeks) + Weibull and KM (first 26 weeks) + exponential are implausible and inappropriate to inform decision making. We acknowledge the good statistical fit of these two-piece models to the observed data from KEYNOTE-775 (Document B, Table 28). However, both models described provide an insufficient fit to decreasing hazards observed in KEYNOTE-775 (Document B, Figure 17) and the observed longer-term KEYNOTE-146 KM data (Document B, Figure 15). As highlighted in NICE DSU TSD 14 it is important to ensure survival models selected are valid against external clinical sources (i.e. KEYNOTE-146) and it is clear that the Weibull and exponential models described generate implausible, underestimated long term survival extrapolations.[17]

As detailed in Document B Section B.3.3.3.1. and Appendix R, there is substantial evidence to support the selection of KM (first 26 weeks) + log-logistic as the base case PEM+LEN OS curve. The log-logistic model provides good visual and statistical fit to the observed data from KEYNOTE-775 (Document B, Figure 15 and Table 28). In addition, the log-logistic model exhibits the closest properties to the observed hazard of death for PEM+LEN (decreasing hazards) (Document B, Figure 17) and provides a plausible fit to the observed longer-term data from KEYNOTE-146 (Document B, Figure 15). Furthermore, the log-logistic model generates a plausible estimate of long-term survival. This evidence described supporting the selection of the log-logistic model was further validated by UK clinicians.[16]

B6. CS Appendix P states that 'Chow test' results are presented for 'two-piece extrapolation' for OS and PFS, but the ERG could not locate these. Please supply or identify these results.

Response: The Chow test statistics described have been provided below.

Figure 2: Plot of multiple Chow test statistics to detect break points in OS in group treated with PEM+LEN

Key: OS, overall survival; PEM+LEN, pembrolizumab plus lenvatinib.

Figure 3: Plot of multiple Chow test statistics to detect break points in OS in group treated with TPC

Key: OS, overall survival; TPC, treatment of physician's choice.

Figure 4: Chow test statistics to detect break points in IRC-assessed PFS in group treated with PEM+LEN

Key: IRC, independent review committee; PFS, progression-free survival; PEM+LEN, pembrolizumab plus lenvatinib.

Figure 5: Chow test statistics to detect break points in IRC-assessed PFS in group treated with TPC

Key: IRC, independent review committee; PFS, progression-free survival; TPC, treatment of physician's choice.

B7. Please provide revised Kaplan-Meier (KM) OS and PFS data for KEYNOTE-775 (currently in OS!BU27:BZ849 and PFS!BP27:BU849). The ERG would like this is in standard survival analysis form: times of events, with an indicator whether each event is censored or uncensored, which trial arm, and without the row repeats currently in these data. Please provide the same for KEYNOTE-146 (currently OS only, in OS!CH27:CI454).

Response:

i) For KN775, additional information regarding time (in weeks), censoring indicator, survival estimates, and n at risk has been provided in a separate file embedded below. Please note that the data itself and associated analyses should be treated as commercial in confidence.

ii) KN146 is not available as the study sponsor and data owner is Eisai.

B8. Please provide a KM plot from the ECHO study restricted to those patients receiving paclitaxel or doxorubicin only (about [redacted] of patients, Document B, Section 2.9) i.e. excluding [redacted].

Response: Figure 6 provides OS KM for the ECHO study patients that received paclitaxel or doxorubicin/ doxorubicin liposomal.

Figure 6: Overall survival of ECHO study patients restricted to those receiving paclitaxel or doxorubicin only

[redacted]

Note: OS since start of the second line of treatment.

B9. Please explain why a restricted cubic spline model was not considered as an appropriate means of modelling PFS and OS in your economic analysis.

Response: The modelling approach for OS and PFS is fully described in Document B Section B.3.3.3. and B.3.3.4. which demonstrates that the base case curves provide a good fit to the data. Based on this, other types of flexible parametric models (FPM) are not required and they are unlikely to be able to resolve any further uncertainty, as expanded on below.

The approach taken in this submission follows NICE DSU TSD 14 and 21 guidance, which emphasises that parametric models used to estimate survival benefit of a given intervention or comparator in cost-effective analysis should exhibit both internal and external validity.[17, 18] The selected model must be representative of the observed data, specifically including a good visual and statistical fit to trial outcomes and underlying hazards. The extrapolated portion of the model beyond the trial period must also be clinically plausible to appropriately estimate cost-effectiveness over a lifetime horizon. In addition, validation of selected models can be achieved through the use of external data sources and clinical expert opinion.

In the company approach, time-to-event analyses using independent one-piece models were initially fitted to the KEYNOTE-775 OS and PFS data. As mentioned in Document B.3.3.3., based on assessment of the one-piece models against the observed data from KEYNOTE-775 and longer-term study KEYNOTE-146 for PEM+LEN OS (Document B, Figure 12), it was clear that they did not exhibit internal or external validity. Thus, the use of these curves would be inappropriate for decision-making and they should be disregarded on the basis of clinical implausibility.

In direct accordance with recommendations from TSD 21, more flexible, two-piece KM plus parametric models were explored. In a comprehensive assessment of the fitted curves, the two-piece approach was able to reasonably estimate the long-term extrapolation. Clinical experts agreed with the extrapolation beyond the observed period from KEYNOTE-775 and longer-term follow-up from KEYNOTE-146 in the case of PEM+LEN OS (Document B, Figures 15, 16, 21 and 22). Specifically, the models selected were validated as a clinically plausible expectation of long-term survival (i.e. at 5 and 10 year timepoints). Overall, internal and external validity were sufficiently met by two-piece models, and, following TSD 21, further exploration of alternative methods (i.e. spline models) is not necessary. The company approach also aligns with previous appraisals of pembrolizumab treatment in advanced malignancies in which two-piece models have been deemed appropriate to model survival by the ERG.[19, 20]

It is further significant to note that flexible parametric models often require additional assumptions, as described in TSD 21.[18] For example, the assumption on the number and location of knots can substantially affect the extrapolation using spline-based. models. More importantly, although a more flexible model may fit the observed data extremely well, it is not guaranteed that the extrapolation will be reliable.

B10. PRIORITY QUESTION`: Please give further details of the form of the 'smooth spline' fit shown in Figs. 13,14,17,18, including details of numbers of knots and their spacing, degree of the splines, and software used.

Response**:** The legend does indicate the term 'Smooth spline estimate'. It should have been accurately labelled as a smoothed estimate of the hazard. The smooth spline

hazard estimate is based on B-splines from the perspective of generalised linear mixed models. We took the default number of knots (31) for B-splines; default degree of B-spline, 1. R-package of bshazard (version 1.1) based on Rebora P, Salim A, Reilly M (2014) [21].

B11. PRIORITY QUESTION: For 'one-piece' and 'two-piece' models separately, for both OS and PFS, and for each arm, please provide

(i) figures showing the hazard function under a restricted cubic spline fit

(ii) figures showing extrapolation of the survival curve with a restricted cubic spline fit

(iii) further AIC/BIC results for the restricted cubic spline fits in the relevant tables (Doc B Tables 28 and 31; Appendix Tables 58 and 59).

Response: Following NICE DSU TSD 14 and 21 guidance, the two-piece parametric curves provide good statistical fit to the data and good visual fit to the underlying hazards. Also, the long-term clinical plausibility of the base case curves was validated externally against Phase II trial data and clinical expert opinion. One-piece models were also considered and they did not show internal or external validity. As stated in the response to B9, flexible parametric models require assumptions on the number and location of knots without necessarily improving internal or external validity. The current approaches within this submission meet the internal and external validity criteria and as such further options were not considered.

B12. PRIORITY QUESTION: Please provide plots of the hazard function for OS and PFS in each arm of KEYNOTE-775 with minimal smoothing.

Response: The *bshazard* package in R was used to generate the smoothed hazard estimate. This package is based on the B-splines from the perspective of generalised linear mixed models. Figure 7 – Figure 10 provide hazard function for OS and PFS plots for each arm of KEYNOTE-775 with minimal smoothing.

Figure 7: The graph with minimal smoothing for pembrolizumab + lenvatinib OS hazard

*****

Figure 8: The graph with minimal smoothing for TPC OS hazard

*****

Figure 9: The graph with minimal smoothing for the pembrolizumab + lenvatinib PFS hazard

*****

Figure 10: The graph with the minimal smoothing of the TPC PFS hazard

*****

B13. PRIORITY QUESTION: It would be helpful if you could provide scenario analyses whereby the restricted cubic spline model is used to model OS and PFS for both treatment arms. Please provide the updated economic model which includes the spline functionality.

Response: Response to the B9 question outlines the rationale of why spline model was not implemented for this response. Internal and external validity were sufficiently met by the provided two-piece models, and, following TSD 21, further exploration of alternative methods (i.e. spline models) is not necessary. The extrapolated portion of the model beyond the trial period must be clinically plausible to appropriately estimate cost-effectiveness over a lifetime horizon and the 2-piece models meet this validity criterion. The company approach is consistent with previous appraisals of pembrolizumab treatment in advanced malignancies in which two-piece models have been deemed appropriate to model survival by the ERG.[19, 20]

B14. The ERG noted that a scenario analysis has been provided using an independent one-piece model for PFS in both treatment arms (Scenario 14, Table 52). Please

provide a scenario analysis which uses an independent one-piece model to extrapolate OS in both treatment arms. Provide justification for model choice.

Response: As detailed in the company response to question B9, Document B Section B.3.3.3. and Appendix R, there is substantial evidence to support the notion that independent one-piece models for OS in both PEM+LEN and TPC treatment arms are clinically implausible and inappropriate to inform decision making. Thus, we maintain the position that it is not appropriate to explore one-piece models (to extrapolate OS in both treatment arms) in scenario analysis.

One-piece models provide an insufficient fit to the complex hazard profile observed in KEYNOTE-775 data, particularly beyond 26 weeks (Document B, Figure 13 and 14) and an insufficient fit to longer-term KEYNOTE-146 KM data (Document B, Figure 12). In addition, one-piece models generate implausible underestimated long-term survival extrapolations.

The evidence described confirms the importance of utilising more accurate methods of modelling lifetime survival across both arms (i.e. independent two-piece models) in accordance with NICE DSU TSD 14 and 21.[17, 18]

Modelled treatment costs

B15. The OWSA provided did not explore the impact of varying the drug acquisition costs of pembrolizumab and lenvatinib. Please provide the results of this.

Response: A patient access scheme (PAS) has been agreed with NHS England . The list price drug acquisition costs of pembrolizumab remain constant. For the lenvatinib acquisition cost we used the list price, provided scenarios of potential PAS discounts and the range of ICERs. Therefore is no need for the drug acquisition costs to be included in the OWSA, instead RDI is explored in a scenario by excluding lenvatinib dose reductions while the RDI for the other comparators remains 100%.

B16. Switching from KEYNOTE-775 trial data to RDI (relative dose intensity) to account for 'lenvatinib dose reductions' (Controls!H136) increases the cost in the pembrolizumab

+ lenvatinib arm. Please explain the logic of this? It is the ERG's understanding that the RDI already takes into account the actual trial data.

Response: When the "RDI" setting is selected, lenvatinib is costed assuming 2 x 10 mg tablets are required daily while the patient is on treatment. This is a daily cost of £95.80. The RDI for lenvatinib is set at 100% in the range *dc_LEN_RDI*. With this assumed RDI, no dose titration is assumed in this setting.

When the "KN-775 trial data" setting is selected, lenvatinib is costed according to a more complex calculation that takes into account titration down from 20 mg per day during the course of the trial, and the fact that, with flat pricing of lenvatinib (a 4 mg tablet costs the same as a 10 mg tablet), costs are proportional to the number of pills received by a patient, not necessarily the dose. For example, a dose of 8 mg per day requires 2 x 4 mg tablets and is therefore twice as costly as a dose of 10 mg, which requires only 1 x 10 mg tablet. The daily cost is £47.90 if one pill is required or £95.80 if two pills are required.

In general, the "KN-775 trial data" setting produce lower costs for lenvatinib because this setting takes account of dose reductions, and the possibility that one pill may be used each day rather than two. The "RDI" setting, with its assumption of RDI=100%, does not take account of dose reductions. We have adopted the "KN-775 trial data" setting in the base case because this method accounts for dose titration experienced in KN-775 and the costs of the two available pill strengths.

As detailed in Document B Section 3.5.1.2, the "KN-775 trial data" setting is aligned to the currently approved label for lenvatinib (on which standard dosing for lenvatinib is based) and consistent with the administration of lenvatinib per the KEYNOTE-775 clinical trial protocol on dose reductions and modifications for optimal AE management. Clinical experts confirmed that this approach is valid in real-world practice, so it is deemed to be the most realistic setting for the base case analysis.[16] Observed dose intensity for the other trial comparators is set to 100%. Clinical experts confirmed that this approach is valid in real-world practice, so it is deemed to be the most realistic

setting for the base case analysis.[16] Observed dose intensity for the other trial comparators is set to 100%.

B17. Drug costs. We were unable to locate the prices for medroxyprogesterone and megestrol on the eMIT database cited, and the price stated for tamoxifen is for 10mg, not 20mg. Please confirm the sources and doses for these drugs. Finally, note doxorubicin 200mg (Drug costs!F37) is entered as £20.20, when the price should be £20.02.

Response: Thank you for seeking clarification on these prices.

i) Cost of medroxyprogesterone was obtained from MIMS.[22] For medroxyprogesterone the incorrect price from MIMS has been used. The correct price is £58.67. When this correction is applied in the model there is a <0.01% change in the base case ICER.

ii) Price of megestrol was obtained from MIMS and is correct in the model.[22] Only the source has been provided incorrectly here.

iii) We acknowledge the price stated for tamoxifen is for the 10mg formulation. This has been correctly accounted for in the 'packs per administration' calculation ('Drug costs'!M109).

iv) We acknowledge that the incorrect price was entered for doxorubicin 200 mg. We wish to clarify that using the correct price (£20.02) does not impact deterministic results.

Modelled clinical effectiveness and quality of life

B18. Please provide further explanation as to why treatment waning was not considered as part of your analysis.

Response: As noted throughout Document B, long-term OS data after 5 years of follow-up are available from KEYNOTE-146. The observed data proved durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN. This is corroborated by data from KEYNOTE-775 (Document B Figure 9), which details distinct

evidence of sustained OS for PEM+LEN in the form of a plateau with 30% of patients alive at 5 years. Thus, in the absence of evidence of a waning treatment effect, this was not explored further in the model.

In addition, longer term immunotherapeutic effects have been demonstrated after cessation of pembrolizumab treatment across multiple advanced malignancies (and with other IOs with similar mechanism of action).[23, 24] This aligns with the expectation that PEM+LEN is highly likely to offer a sustained treatment effect that is distinct from conventional chemotherapy options in EC, directly contradicting the fundamental assumptions of treatment-effect waning. Furthermore, clinical experts consulted for this appraisal confirmed the expectations of long-term benefit associated with PEM+LEN in this patient population.

B19. Given the claim to higher efficacy of pembrolizumab in dMMR (document B, section B2.4.2, paragraph 2), why was a subgroup analysis in these patients not considered in the economic analysis? (and by pMMR only too). Note the reference supporting this claim is to the KEYNOTE-775 protocol. Please cite the original source(s) for these.

Response: This paragraph refers to the statistical analyses of KEYNOTE-775 and such claim was not made by MSD in relation to the decision problem itself. The MHRA and EMA license for this indication is for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation [25, 26]. **The indication covers the overall patient population irrespective of MMR status.** As such the cost-effectiveness analyses focus on the overall patient population and such claim was not made by MSD as it would deviate from the final scope issues by NICE.

B20. PRIORITY QUESTION: Please provide full details of the analysis to calculate time to death (TTD) utilities, in particular completeness of data at each of the timepoints and assessment as to whether missingness was at random

or not. Please also add footnotes to Tables 60 and 61 (Appendix P, P159) defining variable names.

Response: In the analysis of EQ-5D utilities by time to death status, time to death status was coded as follows, with the months presented as number of days:

- Death less than 1 month away (<30 days)
- Death more or equal than 1 month away but less than 3 months (30 to <90 days)
- Death more or equal than 3 months away but less than 6 months (90 to <180 days)
- Death more or equal than 6 months away but less than 9 months (180 to <270 days)
- Death more or equal than 9 months away but less than 12 months (270 to < 360 days)
- Death more or equal than 12 months away (≥360 days) [including participants who were censored for overall survival with time to censor more than 12 months away]
- "Unknown" for participants who were censored for overall survival with time to censor less than 12 months away

The time from EQ-5D assessment date to death was defined as the number of days between the date of EQ-5D completion and the date of death. EQ-5D baseline assessment was not included. For analysis by time to death status for all participants, for censored participants whom time from EQ-5D assessment to censoring date was <360 days then their time to death status was set as "Unknown" category. For censored participants whom time from EQ-5D assessment to censoring date was ≥360 days then their time to death status was included in the "≥360" category.

The completion rates and compliance rates for EQ-5D at each of the timepoints can be found in CSR (Table 14.2-104).

Section C: Textual clarification and model

C1. In Doc B Fig 19, please confirm whether 'Modelled TPC (log-logistic)' should be 'Modelled TPC (exponential)'.

Response: Thank you for spotting this mistake in the original submission document - the correct Figure has been provided below.

Figure 11: Selected OS curve fits for PEM+LEN and TPC

Key: ECHO, endometrial cancer health outcomes study; KM, Kaplan–Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice; UK, United Kingdom.

C2. The exponential, Gompertz, gamma and Weibull fits are not clearly visible in Doc B Fig 18 – are they overlayed? Weibull, Gompertz and exponential fits are not visible in Doc B Fig 16 either – are they overlayed? Please provide extended/alternative figures if necessary.

Response:

In Doc B Figure 18, the Gompertz, Weibull, and exponential fits are overlayed. The figure below magnifies the y-axis showing the close approximation of these fits.

Figure 12: Zoomed in CS Figure 18 – TPC OS hazard function, with breaking point at Week 26

Below is alternative plot for Fig 16, for long-term extrapolation; Weibull, Gompertz and exponential are again very close with each other.

Figure 13: Zoomed in CS Figure 18 – TPC OS hazard function, with breaking point at Week 26

C3. In Appendix D1.3 p31, please complete this sentence "considered for liposomal doxorubicin, gemcitabine and docetaxel (the only comparators considered that

were of relevance to the UK) presented Kaplan–Meier curves which are required for the reconstruction of individual patient level data for unanchored ITC."

Response: We acknowledge that this sentence is incomplete. The corrected sentence has been provided below.

"No studies considered for liposomal doxorubicin, gemcitabine and docetaxel (the only comparators considered that were of relevance to the UK) presented Kaplan–Meier curves which are required for the reconstruction of individual patient level data for unanchored ITC."

C4. Please could the company provide the following full-text reference missing from the reference pack accompanying the submission: (ECHO) ECHO. Europe (ECHO EU5): A retrospective, multicenter chart review study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC (aEC) patients previously treated with systemic therapy in United Kingdom 2021.

Response: As discussed at the clarification meeting, this is data on file and a publication reference is not yet available.

C5. There are a number of minor typos in the model, e.g. the base case discount rate for life years is set to 0% not 3.5%, and labelling of axes on some graphs is incorrect (states overall survival when should just state 'survival' on Controls!Efficacy settings etc). Please also verify that the LY numbers reported in Docs A and B are the discounted ones.

Response:

i) We acknowledge that the y axes of the graphs described in the model 'controls' sheet can alternatively be labelled 'survival'. We are happy to clarify any minor typos if the ERG would like to query anything in particular. The revised model will be shared with this document.

ii) Please note that life years specifically are not discounted in the base case, in accordance with the applicable NICE reference case at the time of the

company submission.[27] So the discount rate of 0% for life years is correct (not a typo) and does not need updating.

C6. In Settings > Baseline characteristics, the deterministic results do not change when height, weight and %MSI-H/dMMR are changed.

Response: It is correct that changes in the baseline characteristics described do not change the deterministic results:

i) Changes to 'average patient height (cm)' and 'average patient weight (kg)' impact the results when vial sharing is included. Vial sharing is not selected in the base case, thus deterministic results will not change.

ii) Changes to 'percentage patients MSI-H/dMMR (%)' impact the results when the cost of MSI-H testing is included. MSI-H testing is not selected in the base case, thus deterministic results will not change.

C7. In Settings > Cost settings, please state the inflation index used rather than just the place published (PSSRU lists several indices)

Response: As detailed on the 'Lists' sheet in the model, the NHS cost inflation index (NHSCII) was used from PSSRU (Section 15.3).[28]

C8. In Settings > Cost settings, reset to base settings does not reset cells Controls!H153:I153 and Controls!H42:I46 do not sum to 100% (minor rounding error).

Response:

i) Thank you for this question. The 'reset to base case' button is implemented to reset input cells that may be changed by the user. Cells Controls!H153:I153 are calculations and are not intended to be user-amenable as detailed on the 'Introduction' sheet of the model. Thus, there is no need to reset these cells and they are not included in the model 'reset to base case' functionality.

ii) We acknowledge the minor rounding error in cells Controls!H42:I46. The proportions sum to 100% correct to 15 decimal places. We wish to clarify that

this does not impact scenario analysis results where mixed chemotherapy treatment shares are investigated.

C9. Drug costs!F16:I16 – please explain the logic of the coding here for vial sharing – why does vial sharing calculate the min whilst no vial sharing is the sum of the different formulations? The model does also not allow for vial sharing of pembrolizumab (and pack sharing of Lenvatinib). Please outline why vial sharing was not explored as a scenario analysis.

Response:

i) If vial sharing is selected in the 'controls' sheet, the relevant calculation to reflect the 'packs per administration' for each formulation of a given drug is initially made in column M of the 'drug costs' sheet. This is directly referenced in the 'total cost per treatment' calculations in column N where 'packs per administration' are multiplied by 'cost per vial/pack (£)'. Formulae in 'Drug costs'!F16:I16 would then select the drug formulation for vial sharing that produces the cheapest 'total cost per treatment' in column N.

ii) By comparison when vial sharing is not selected (as in the base case) 'packs per administration' in column M are based on calculations made in the 'method of moments' sheet. Formulae in 'Drug costs'!F16:I16 then take the sum of 'total cost per treatment' in column N.

iii) Pembrolizumab treatment is administered via flat dosing and lenvatinib pack sharing was not considered plausible in clinical practice, so vial/pack sharing for these drugs were not included in the model.

iv) We wish to clarify that vial sharing was explored in scenario analysis. This caused <0.1% change in the base case ICER. Please see Document B Table 52: scenario 20.

C10. Minor point: Appendix P, Table 57. We would advise three decimal places for discount rates – 3.5% has been rounded to 4% in the table.

Response: We agree it would have been more helpful to report discount rates to three decimal places in Document B Appendix P Table 57 and apologise for any inconvenience caused. We wish to clarify that this is simply a cosmetic error and has not impacted deterministic results.

C11. Please clarify Table 35 (Doc B, P103): the mean time to death utility values appear to be listed in an incorrect order.

Response: The mean time to death utility values have been listed in the incorrect order in Document B Table 35. The corrected table has been provided below.

Table 8: Mean utility values based on time to death included in the economic model

Time to death	Mean time to death utility value	Lower bound	Upper bound
< 30 days	[redacted]	[redacted]	[redacted]
30–89 days	[redacted]	[redacted]	[redacted]
90–179 days	[redacted]	[redacted]	[redacted]
180–269 days	[redacted]	[redacted]	[redacted]
270–359 days	[redacted]	[redacted]	[redacted]
≥ 360 days	[redacted]	[redacted]	[redacted]

C12. Please verify that the PSA is implemented correctly. For example, (i) TPC treatment share is modelled as Dirichlet (which presumably reduces to a beta given only two options), but Parameters!T32:T33 are blank. (ii) Subsequent treatment shares are modelled as independent betas when they should be Dirichlets to ensure probabilities sum to 1. Please also state the parameter values for the Dirichlet distributions in Table 57, Doc B Appendix P, P139 (and indeed for all distributions, rather than just 95%CIs)

Response:

We can confirm that the PSA is implemented correctly in the model.

i) We acknowledge that cells Parameters!T32:T33 are blank. For TPC treatment shares, Dirichlet formulae have instead been implemented in cells

Parameters!M32:M33. Thus, the active values in cells Parameters!X32:X33 change as expected when cells Parameters!U32:U33 are set equal to 4 as the PSA is run.

ii) We acknowledge that a Dirichlet distribution can alternatively be used for subsequent treatment shares. As mentioned above, where applicable, parameter values for Dirichlet distributions have been provided in column M of the 'parameters' sheet. Alpha and beta parameters have been provided in columns N and O, lower and upper bound parameters have been provided in columns R and S. We would be happy to help the ERG identify any parameters of particular interest.

Appendix

Table 9: RoB assessment for KEYNOTE-775

Trial ID	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	3.1	3.2	3.3	3.4	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3
KEYNOTE-775	Y	PY	N	Y	Y	PN	NA	NA	Y	NA	Y	NA	NA	NA	N	PN	PN	NA	NA	Y	PN	PN

References

1. Lee CH, Shah AY, Rasco D, Rao A, Taylor MH, Di Simone C, et al. Lenvatinib plus pembrolizumab in patients with either treatment-naive or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): a phase 1b/2 study. The Lancet Oncology. 2021;22(7):946-58.
2. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib (LEN) and pembrolizumab (PEMBRO) in advanced endometrial cancer (EC). Annals of Oncology. 2019;30:404-+.
3. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(26):2981-92.
4. Makker V, Rasco D, Vogelzang N, Brose M, Cohn A, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: Final analysis of a multicentre, open-label, single-arm, phase 2 trial. Gynecologic oncology. 2020;159:6-7.
5. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib (LEN) plus pembrolizumab (PEMBRO) for early-line treatment of advanced/recurrent endometrial cancer (EC). Journal of Clinical Oncology. 2020;38(15).
6. Makker V, Aghajanian C, Cohn A, Romeo M, Bratos R, Brose M, et al. Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Ec): Long-Term Efficacy and Safety Update from a Phase 1b/2 Study. Journal for Immunotherapy of Cancer. 2021;9:A381-A.
7. Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. The Lancet Oncology. 2019;20(5):711-8.
8. MSD. Clinical Study Report KEYNOTE-826 Report date 10 Aug 21. 2021.
9. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6(suppl_6):vi33-8.
10. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2021;31(1):12-39.
11. Homesley HD, Meltzer NP, Nieves L, Vaccarello L, Lowendowski GS, Elbendary AA. A phase II trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer. Int J Clin Oncol. 2008;13(1):62-5.
12. eMC. doxorubicin hydrochloride 2mg/ml solution for infusion 2020 [Available from: https://www.medicines.org.uk/emc/product/4613/smp.
13. McMeekin S, Dizon D, Barter J, Scambia G, Manzyuk L, Lisyanskaya A, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecologic oncology. 2015;138(1):18-23.

14. Miller D, Scambia G, Bondarenko I, Westermann A, Oaknin A, al. e. ZoptEC: Phase III randomized controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer. Journal of Clinical Oncology. 2018;36((May 20, 2018)):5503-.
15. Fleming GF. Systemic therapy for advanced or recurrent endometrial carcinoma. Curr Oncol Rep. 1999;1(1):47-53.
16. Merck Sharp and Dohme (MSD) UK Ltd. Clinical Expert Consultation. 2021.
17. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient level data

2013.
18. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 21: Flexible Methods for Survival Analysis. 2020.
19. National Institute for Health and Care Excellence (NICE). Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. 2018.
20. National Institute for Health and Care Excellence (NICE). Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer [TA737]. 2021.
21. Rebora P, Salim A, Reilly M. bshazard: A Flexible Tool for Nonparametric Smoothing of the Hazard Function. R J. 2014;6(2):114-22.
22. Monthly Index of Medical Specialities (MIMS). 2021 [Available from: http://www.mims.co.uk/drugs.
23. National Institute for Health and Care Excellence (NICE). Final appraisal document: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. 2018.
24. National Institute for Health and Care Excellence (NICE). Final appraisal document: Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab [TA357]. 2015.
25. MSD. Summary of Product Characteristics KEYTRUDA 31/03/2022 2022 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/37dc9110dfb9b3a81861dbe25ff8b6098b6a3d5c.
26. EMA. Keytruda 2022 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda.
27. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. 2013.
28. Personal Social Services Research Unit (PSSRU). Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2019/20. 2020.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Peaches Womb Cancer Trust
3. Job title or position	Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	Peaches Womb Cancer Trust is a charitable organisation with the mission to improve the lives of those affected by womb cancer by funding vital womb cancer research, increasing public awareness and providing support during and after diagnosis and treatment. The charity is funded through fundraising and donations.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No funding received.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We conducted several focus groups and asked women with lived experience of advanced or recurrent endometrial cancer to complete a questionnaire. This included women with stage 1 and 3, and a carer of a woman with stage 4 endometrial cancer, who had undergone primary treatment with surgery and/or chemotherapy and radiotherapy. The discussion and questionnaire focused on living with advanced or recurrent endometrial cancer and their experiences with current treatments.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of advanced endometrial cancer has a significant impact on every aspect of women's lives. Many found their physical symptoms debilitating. At the time of diagnosis these included bleeding, pain and discomfort, reduced appetite, nausea and fatigue. Following treatment, one woman has had issues with ascites and required recurrent drainage, leaving her with reduced mobility, in pain and unable to eat. All the women we spoke to are also experiencing long term physical effects following treatment that have impacted significantly on their quality of life. These include ongoing pain and discomfort, bowel issues, bladder issues and fatigue. "I get a lot of pain and discomfort around my bladder and bowel following my op and first chemo which has caused nerve damage and incontinence." Furthermore, there is the impact of repeated intimate examinations psychologically on sexual function and intimacy, leading to distance in relationships. Physical symptoms have impacted on quality of life in a number of ways. For some, it has affected their confidence going out to social events/ gatherings due to tiredness, access to the toilet and fear of 'accidents' such as urinary leakage.

	"I try to plan things like seeing friends [but] I have to cancel so often due to the pain, anxiety and constant tiredness." For others, limited mobility and pain means they are unable to leave the house. This takes a significant toll on their mental health. Furthermore, many have been left unable to work due to ongoing symptoms, or have to work less than full time, affecting them financially. This leads to additional concerns and anxiety around how they might afford the cost of living. Even if they have felt well enough to go back to work, women report anxiety around controlling their symptoms at work and access to a private toilet; one described how she now needed to wear incontinence underwear when travelling for work. A small number were unable to live fully independently due to physical symptoms and limited mobility, meaning they have had to access help from family members for a number of activities of daily living, including; cooking, cleaning, help with bathing and medications. This leaves them feeling frustrated and a burden on family members. "I had to get a cleaner in and have help from my 74-year-old mother as I can't cope with daily living tasks." As a carer this impacts financially due to time off work, psychologically due to constant worry and anxiety about your loved one and less time for yourself, and physically due to the additional activities on top of your own day to day living. Furthermore, it causes disruption to family life and reduces quality time spent together. "My sister and I have shared the week between us staying over, … including our young children, to care for Mum [and] to help her move and support with meals and medication." Many women told us that the impact on their mental health was much bigger than they thought it might have been: "Taken aback by how vulnerable it made me" "Like living on a knife edge with constant anxiety about my future and that of the people I care about" Several women described diagnosis induced feelings of terror and fear at having to face one's own mortality. Many felt in 'limbo' following treatment due to the uncertainty of recurrence. Some felt unable to

	cope with small things following treatment, affecting their previously positive outlook and crying more easily.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Women were unanimously dissatisfied and frustrated by current treatments for advanced and recurrent endometrial cancer, which include surgery, chemotherapy and radiotherapy. In particular, women found chemotherapy challenging and unacceptable due to a multitude of short- and long-term side effects, which have affected their quality of life. Short term effects included fatigue, nausea and vomiting, hair loss, change in bladder and bowel habit and neutropenia. Due to these, it was impossible for women to have any quality of life during treatment. Several women mentioned the effect of chemotherapy on the immune system and felt it left them vulnerable. Long term side effects included bowel and bladder issues and lymphoedema, which have left women anxious and affected their confidence leaving the house. Treatments including hysterectomy and radiotherapy significantly impacted on sexual intimacy due to discomfort, bleeding and the vulnerability that comes with repeated intimate examinations. Furthermore, current treatments impacted on women's lives financially, both through the time it takes to receive treatment and the long-term side effects. This included; cost of travel to and parking at hospital, long term sick leave with implications to pay, and cost of living at home (e.g. heating) and alternative therapies.
8. Is there an unmet need for patients with this condition?	Many women expressed frustration, disappointment, anger and feelings of being abandoned due to limited effective treatment options for advanced and recurrent endometrial cancer. They felt that women affected by endometrial cancer had less effective treatment options compared with other cancers. "In my Mum's case, the first line of chemotherapy was the only treatment that had an effect in pushing back the growth. Nothing else has worked." "[There is] no [treatment] option for late-stage presentation, stage 4 metastatic [cancer] … other than archaic chemo with side effects of hair loss, appetite reduction [and] limited life quality." "I was alarmed to realise that all I would be offered in both first and second line (if I progressed) would be just the bog-standard traditional chemotherapy. Not a level playing field!" "All the other cancers get 'ibs' and 'mabs' but we get nothing - we are the poor relation."

	Whilst they expressed the need for a treatment that extended survival, what was more important was one that gave them a better quality of life and time with family and friends. Women felt that there needed to be a treatment that had fewer side effects, was less invasive, was quicker to administer, allow them to recover quicker and maintain their independence. They also wanted to live life as fully as possible and do more of the things that give them enjoyment; for example, eating out, travelling and going for a swim or spa day. Concern was expressed regarding the availability of current treatments if one was unwell or had significant co-morbidities such as cardiac or renal impairment, and many felt they would not receive treatment if they were in this position. They felt that there should be effective treatment options available to all, even if you were particularly unwell.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have been unable to consult women who have had experience of the technology.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We have been unable to consult women who have had experience of the technology.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Endometrial cancer is associated with obesity and there are a number of women with morbid obesity in whom certain current treatments pose an unacceptable risk, for example surgery. Dosing of chemotherapy and radiotherapy is also more challenging in this cohort of patients. Advanced or recurrent endometrial cancer can have a significant toll systemically on other major organs, and may leave women too unwell or 'unfit' for chemotherapy. In addition, there are a number of women with pre-existing medical problems that affect their cardiac and kidney function, which may be exacerbated by chemotherapy. For some of these women, chemotherapy may pose an unacceptable risk, leaving them with no treatment options at all to alleviate symptoms or give them any hope of survival.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Ease and frequency of administration of the technology should be considered. Tertiary oncology centres are often difficult and expensive for patients to access on a regular basis, so it is important that therapies could be administered at local hospitals or at home to improve access and availability to all, regardless of income or disability.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Limited effective treatment options for advanced and recurrent endometrial cancer provoke feelings of frustration, disappointment, anger, abandonment and hopelessness
- Maintaining quality of life is most important to women with advanced and recurrent endometrial cancer
- Women want effective treatments that will improve survival and quality of life with fewer short- and long-term side effects, are less invasive and allow them to maintain their independence longer.
- Women want treatments that have less burden on them financially, due to absence from employment secondary to illness and travel to and from hospital, and time spent in hospital receiving treatments.
- Women want equal opportunity of access to newer targeted treatments which are available to people with other cancers.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	■
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	National Cancer Research Institute Gynaecological Croups- national co-ordination of clinical trials in gynaecological cancer- made up of multidisciplinary experts in the treatment of gynaecological cancer, patient and charity representative; scientists and academic clinicians.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of this treatment is in terms of reducing symptoms from metastatic endometrial cancer and improve quality of life and to slow the progression (worsening) of cancer thereby prolonging progression free survival (PFS) and overall survival (OS) -and also to assess how this differed based on the presence of mismatch repair deficiency (MMR status). Further aims included assessing safety and toxicity of the treatment.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Control of symptoms and survival are considered meaningful endpoints for this group of patients with advanced endometrial cancer, who have limited effective treatment options at recurrence. In this setting Lenvatinib plus pembrolizumab led to a significantly longer progression-free survival and overall survival than chemotherapy and this is an important advance for patients. This outcome has a significant and meaningful impact to patients and their families in terms of survival, but also improved quality of survival by management of symptoms.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Standard therapy for advanced endometrial cancer after failure of platinum-based chemotherapy remains unclear.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There are no standard treatment options for women with relapsed endometrial cancer. Patients with symptoms and who are fit are considered for hormones therapy or standard 2nd line chemotherapy that has a response rate (shrinkage rate) of about 10–15%. Regimens such as Weekly paclitaxel and anthracyclines (including pegylated liposomal doxorubicin when available) are considered to be active drugs. Retreatment with carboplatin may also be considered after a prolonged interval from the last platinum treatment, based on the results of a single-centre retrospective series in patients treated with a median platinum-free interval of 25 (8–79) months. (Rubinstein M , Halpenny D , Makker V , *et al* . Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: a retrospective study of the Memorial Sloan Kettering Cancer Center experience. Gynecol Oncol Rep 2019;**28**:1203.doi:10.1016/j.gore.2019.04.002 pmid:http://www.ncbi.nlm.nih.gov/pubmed/31011610)

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. (Concin N et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021 Jan;31(1):12-39. doi: 10.1136/ijgc-2020-002230. Epub 2020 Dec 18. PMID: 33397713)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway in most centres in the UK will follow the guidelines details above.
• What impact would the technology have on the current pathway of care?	The availability of pembrolizmab and Lenvatinib would add a much needed new effective (symptom control and extension of survival) option for patients with relapsed endometrial cancer, who up until now have had a poor overall outlook. It is important that women in the UK have access to the best treatment options to ensure that our outcomes remain in line with that of other similar countries.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in line with current care in the UK, but would be a new treatment option for patients.

• How does healthcare resource use differ between the technology and current care?	Currently patients with relapse receive intravenous chemotherapy for up to 6 cycles and attendance is dependent on the regimen but can be weekly for those receiving taxol alone, or week 3 weekly. Pembrolizumab/ Lenvatinib: these patients would attend 3 weekly for pembrolizumab and would continue to take oral Lenvatinib at home until disease worsening/ toxicity. There would not be any increase in resource use, and this regimen could also have a positive impact as patients will not have to attend weekly. Furthermore if disease control is more effective with this regimen there could also be a positive impact on symptom related review/admissions. There is significant toxicity associated with the combination and the NCRI group would advocate real world evaluation of toxicity.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment will be in tertiary care within specialist oncology clinics. Treatment will be initiated and supervised by clinicians who have specialist experience in the treatment of endometrial cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Immunotherapies and anti angiogenic agents, such as pembrolizumab and Lenvatinib respectively, are already routinely used in the treatment of a number of different cancers and all cancer centres/ units in the UK have experience/ SOPs in place so no additional facilities/training will be required. As this treatment will be instigated and monitored by specialists in the treatment of endometrial cancer they will be familiar with the expected side effects of the combination and will provide appropriate training / support to staff and patients, as with the introduction of all new technologies.
11. Do you expect the technology to provide clinically	Yes we expect pembrolizumab and Lenvatinib to provide clinically meaningful benefit in terms of and survival and symptom control for patients with advanced/ relapsed endometrial cancer.(ref: Makker V, et al Study 309–KEYNOTE-775 Investigators. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022 Feb 3;386(5):437-448. doi: 10.1056/NEJMoa2108330. Epub 2022 Jan 19. PMID: 35045221.)

meaningful benefits compared with current care?	KEYNOTE-775 N Engl J Med. 2022 Feb 3;386(5):437-448 In an phase 3 trial, patients with advanced endometrial cancer who had previously received at least one platinum-based chemotherapy regimen were randomly assigned, in a 1:1 ratio, to receive either lenvatinib (20 mg, administered orally once daily) plus pembrolizumab (200 mg, administered intravenously every 3 weeks) or chemotherapy of the treating physician's choice (doxorubicin at 60 mg per square meter of body-surface area, administered intravenously every 3 weeks, or paclitaxel at 80 mg per square meter, administered intravenously weekly [with a cycle of 3 weeks on and 1 week off]). The two primary end points were progression-free survival as assessed on blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and overall survival. The end points were evaluated in patients with mismatch repair–proficient (pMMR) disease and in all patients. Safety was also assessed. RESULTS A total of 827 patients (697 with pMMR disease and 130 with mismatch repair deficient disease) were randomly assigned to receive lenvatinib plus pembrolizumab (411 patients) or chemotherapy (416 patients). The trial demonstrated that among patients with a response, the median duration of response in the pMMR population was 9.2 months (range, 1.6 to 23.7) with lenvatinib plus pembrolizumab and 5.7 months (range, 0.0 to 24.2) with chemotherapy; among patients with a response, the median duration of response in the overall trial population was 14.4 months (range, 1.6 to 23.7) and 5.7 months (95% CI, 0.0 to 24.2), respectively. Overall, more patients in the lenvatinib–pembrolizumab group than in the chemotherapy group had tumor shrinkage. Although the trial was not designed or powered to compare lenvatinib plus pembrolizumab with chemotherapy in the dMMR (deficient) population, clinically meaningful improvement was observed across all groups.

	Median progression-free survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (**pMMR** population: 6.6 vs. 3.8 months; hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.50 to 0.72; P<0.001; **overall**: 7.2 vs. 3.8 months; hazard ratio, 0.56; 95% CI, 0.47 to 0.66; P<0.001). **Median overall survival** was longer with lenvatinib plus pembrolizumab than with chemotherapy (**pMMR** population: 17.4 vs. 12.0 months; hazard ratio for death, 0.68; 95% CI, 0.56 to 0.84; P<0.001; **overall**: 18.3 vs. 11.4 months; hazard ratio, 0.62; 95% CI, 0.51 to 0.75; P<0.001). **Side effects:** grade 3 or higher adverse events occurred in 88.9% of the patients who received lenvatinib plus pembrolizumab and in 72.7% of those who received chemotherapy. CONCLUSIONS Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer.
• Do you expect the technology to increase length of life more than current care?	Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer as described above. The median duration of treatment was 231 days (range, 1 to 817) with lenvatinib plus pembrolizumab and 104.5 days (range, 1 to 785) with chemotherapy (standard treatment/current care in the UK).
• Do you expect the technology to increase health-related quality of life more than current care?	The trial above demonstrated improved control of symptoms and this will have a positive impact on a patient's overall well being and quality of life in routine use. However side effects will need to be closely monitored by specialist teams.
12. Are there any groups of people for whom the technology would be more or	The combination was effective in all groups ie in the MMR proficient and deficient group and could be considered in all patients. However we would advocate this combination in the group of patients with MMR proficient disease as those with dMMR (deficient) disease could be considered for single agent immunotherapy (dostarlimab –

less effective (or appropriate) than the general population?	TA779)available via the Cancer Drugs Fund for women with relapsed MMR deficient endometrial cancer) and spared the additional toxicities of Lenvatinib. Approximately 20% of patients with endometrial cancer have the subtype with high microsatellite instability (MSI) or DNA mismatch repair (MMR) deficiency biomarkers and so this combination is an important advance for a significant majority of women with relapsed disease who have proficient disease.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There will be no additional visits associated with administration of intravenous pembolizimab. Immunotherapies such has pembrolizumab are already routinely used in the treatment of a number of different cancers and all cancer centres/ units in the UK have experience/ SOPs in place so no additional facilities/training will be required for this agent. No specific additional concerns are expected with the use of this agent in women with endometrial cancer/ patient acceptability. Lenvatinib – is an oral agent and so no additional visits. However sites/ patients will need guidance regarding management of side effects – a number of other small molecule VEGF inhibitors are routinely used in the treatment of other cancers e.d sunitinib/sorafenib/axitinib- renal cancer) and so most sites will have appropriate SOPs in place that can be adapted as required. There are no anticipated concerns over patient acceptability.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients MMR status should be known prior to consideration for this therapy (MMR deficient patients can be considered for single agent dostarlimab instead via the Cancer Drugs Fund). Treatment would be expected to be continued providing there is disease control (assessed clinically and via standard cross-sectional imaging, usually CT, as required) and toxicity is acceptable.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None known.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes as per previous responses.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes as per previous responses. – first to show a survival benefit in patients with relapsed endometrial cancer (all comers/ including the MMR proficient group).
• Does the use of the technology address any particular unmet need of the patient population?	Yes as per previous responses.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Almost all the patients in the two treatment groups had some expected side effects during treatment, with the most common being hypertension (in 64.0% of the patients) with lenvatinib plus pembrolizumab and anaemia (in 48.7%) with chemotherapy. Among patients receiving lenvatinib plus pembrolizumab, adverse events of any grade led to dose reduction of lenvatinib in 66.5%, to interruption (of lenvatinib, pembrolizumab, or both) in 69.2%, and to trial-drug discontinuation in 33.0% (discontinuation of lenvatinib in 30.8%, of pembrolizumab in 18.7%, and of both in 14.0%). The median time to the first dose reduction of lenvatinib was 1.9 months (range, 0.1 to 22.8); 45.6% of the patients in the lenvatinib–pembrolizumab group had two or more dose reductions of lenvatinib

	Adverse events of interest with regard to pembrolizumab occurred in 67.2% of the patients; hypothyroidism was the most common, with an incidence of 57.6% (grade 1 in 17.2% and grade 2 in 38.9%) among patients who received lenvatinib plus pembrolizumab QLQ-C30 was completed for more than 95% of the patients in the two treatment groups at baseline; scores at 12 weeks after randomization were available for 80% of the patients in the lenvatinib–pembrolizumab group and for 62% of those in the chemotherapy group. No substantial between-group differences were observed in the QLQ-C30 global health status quality-of-life scores over time
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the control arm used in the trial referenced below is the current standard of care in the UK. (N Engl J Med. 2022 Feb 3;386(5):437-448.)
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced and recurrent endometrial cancer, with effective palliation of symptoms. This represents a major advance in therapy in an area of significant need.
• If surrogate outcome measures were used, do	NA

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
20. How do data on real-world experience compare with the trial data?	Currently no real world data, but due to the toxicity associated with this combination the NCRI Gynaecological group have proposed a real world evaluation of toxicity/safety and to assess the diversity of the patients who are access this combination.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- New treatment option for relapsed endometrial cancer
- Provides symptomatic benefit.
- Extension of survival in a difficult to treat setting with limited standard options
- Area of need.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]:

A Single Technology Appraisal

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter.
EX1 2LU

Authors

Brian O'Toole[1]
Maxwell S Barnish[1]
Edward CF Wilson[1]
Justin Matthews[1]
Helen Coelho[1]
Naomi Shaw[1]
Melanie Powell[2]
Neil Ryan[3]
Emma Crosbie[4]
Alexandra Taylor[5]
Louise Crathorne[1]
G.J. Melendez-Torres[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter

[2] Consultant Clinical Oncologist, St Bartholomew's Hospital, London

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter.
EX1 2LU

[3] Specialty Registrar in Obstetrics and Gynaecology, Severn Deanery

[4] NIHR Advanced Fellow, Professor and Honorary Consultant in Gynaecological Oncology, Manchester

[5] Consultant in Clinical Oncology, The Royal Marsden NHS Foundation Trust

Correspondence to

Brian O'Toole
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; b.otoole@exeter.ac.uk

Date completed 01/06/2022

Source of funding This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/50/59.

Declared competing interests of the authors Authors have no interests to declare.

Acknowledgments The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).

Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows O'Toole B, Barnish MS, Wilson ECF, Coelho H, Shaw N, Powell M, Ryan N, Crosbie E, Taylor A, Crathorne L, Melendez-Torres GJ. Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2022.

Author Contributions:

Brian O'Toole	Project lead. Lead for the ERG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input

Author Contributions:	
Maxwell S. Barnish	Lead for the ERG's critical appraisal of the clinical evidence of the company submission, writing and editorial input
Edward CF Wilson	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out ERG base case analyses and further scenario analyses, drafted economic sections of the report and editorial input
Justin Matthews	Critical appraisal of the clinical evidence and drafted sections of the report
Helen Coelho	Critical appraisal of the clinical evidence and drafted sections of the report
Naomi Shaw	Critical appraisal of the literature search strategies, conducted additional literature searching, and editorial review
Melanie Powell	Clinical advice
Neil Ryan	Clinical advice and review of draft report
Emma Crosbie	Clinical advice and review of draft report
Alexandra Taylor	Clinical advice
Louise Crathorne	Editorial review
G.J. Melendez-Torres	Critical appraisal of the clinical and economic evidence, editorial review

Table of Contents

List of tables

List of Figures

Abbreviations

AE	Adverse event
BNF	British National Formulary
CS	Company submission
CSR	Clinical study report
dMMR	Deficient mismatch repair
EC	Endometrial Cancer
ERG	Evidence Review Group
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
KM	Kaplan-Meier
LY	Life year
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OS	Overall survival
OWSA	One way sensitivity analysis
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PEM+LEN	Pembrolizumab with lenvatinib
PFS	Progression free survival
pMMR	Proficient mismatch repair
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoI	Quality of life
SLR	Systematic literature review
SmPC	Summary of product characteristics
ToT	Time on treatment
TPC	Treatment of physicians choice
TTD	Time to death
UK	United Kingdom

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail, and Section 1.7 presents the preferred assumptions of the ERG. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

A brief overview of the key issues identified by the ERG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Table 1: Summary of key issues

ID[3811]	Summary of issues	Report sections
#1 and #2	Clinically distinct subgroups in the evidence base	Section 1.3, 1.5 and 4.2.3
#3	Uncertainty surrounding modelled OS	Section 1.5 and 4.2.6
#4	Uncertainty surrounding base case utility values (time to death approach)	Section 1.5 and 4.2.8
#5	Treatment waning	Section 1.5 and 4.2.6.3

Abbrevations: MMR, mismatch repair; OS, overall survival; ToT, time-on-treatment

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and ERG's preferred assumptions

	Company's preferred assumption	ERG preferred assumption	Report Sections
Capping survival to ensure PFS ≤ OS	Blended approach	Hazards-based approach	Section 4.2.6.2 and 6.2.1
Proportion of patients receiving doxorubicin or paclitaxel in TPC	As observed in KEYNOTE-775 (74.5% received doxorubicin, 25.5% paclitaxel)	50/50 split between doxorubicin and paclitaxel	Section 4.2.3 and 6.2.2
Time on treatment	As observed in KEYNOTE-775	Capped to disease progression	Section 6.2.7
Health state utilities	Based on time to death	Based on health state (progression-free and progressed disease)	Section 4.2.8 and 6.2.6
Patient weight	70 kg	85 kg (plus associated increase in BSA)	Section 4.2.3 and 6.2.8
Patient age	63.5 years (median)	75 years	Section 4.2.3 and 6.2.9
OS for TPC	KM+Exponential	KM+Log-logistic	Section 4.2.6

Abbreviations: BSA, body surface area; ERG, evidence review group; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice (control arm of KN775).

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Keeping a higher proportion of patients in the progression-free survival (PFS) and progressed disease (PD) health states, for longer. As PEM+LEN is modelled to delay progression and extend survival, patients accrue more QALYs and gain more life years (LYs) compared to those receiving doxorubicin or paclitaxel.
- Time spent in the PD health state and use of time-to-death to estimate utilities, as most of the PEM+LEN incremental QALY gain (73%) is accrued in the PD health state.

Overall, the technology is modelled to affect costs by:

- Drug acquisition costs, as PEM+LEN results in substantially higher costs compared to the comparator treatment arm (treatment of physician's choice, or TPC, of doxorubicin or paclitaxel). Drug costs are a key driver of incremental costs.
- Adverse event costs, end of life costs and subsequent treatment costs, as these are lower in the PEM+LEN arm (however the incremental cost difference between treatment arms is considered minor).

The modelling assumptions that have the greatest effect on the ICER are as follows:

- Based on scenario analysis conducted by the ERG, results are most sensitive to variation in OS extrapolation assumptions and treatment waning (see Section 6.2.10).
- Based on scenario analyses submitted by the company, the assumptions with the largest impact on the ICER were the discount rate for costs and benefits (1.5% for both), no dose reduction for lenvatinib (based on full dose of 20mg per week), health state utilities based on progression status (not time to death), basing the cost of doxorubicin on Caelyx® (branded liposomal/pegylated doxorubicin), and restricting time-on-treatment (ToT) to PFS. The company did not perform a sensitivity analysis on acquisition cost of pembrolizumab or lenvatinib. The results are moderately sensitive to these parameters.

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issues for the committee's consideration

Key Issue 1: Clinically distinct subgroups in the evidence base

Report sections	Sections 2.4 and 3.2.3.1
Description of issue and why the ERG has identified it as important	The ERG noted that there were two clinically distinct subgroups in the population of the pivotal KEYNOTE-775 trial. Point estimate results suggested patients in the dMMR subgroup may have performed better than patients in the pMMR subgroup on both OS and PFS outcomes, although it should be noted that the study was not specifically powered to explore the impact of MMR status on survival outcomes and the follow-up period of KEYNOTE-775 was limited.
What alternative approach has the ERG suggested?	Clinical effectiveness results for dMMR and pMMR subgroups were provided. However, the company did not provide cost effectiveness subgroup results nor did the company model offer

Report sections	Sections 2.4 and 3.2.3.1
	the functionality to allow the ERG to implement sub-groups as a scenario analysis. The ERG recognised that the subgroups were not pre-defined in the NICE scope, but rather emerged from the clinical effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The expected impact on cost effectiveness of each subgroup remains unclear. However, due to improved OS in the dMMR subgroup, compared to the pMMR subgroup, the ICER for PEM+LEN is likely to be lower in this subgroup, all else remaining equal.
What additional evidence or analyses might help to resolve this key issue?	The provision of subgroup-specific cost effectiveness scenario analyses and the model functionality to produce these analyses would help resolve the uncertainty.

Abbreviations: dMMR, deficient mismatch repair; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; pMMR, proficient mismatch repair

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

No clinical effectiveness key issues were identified.

1.5. The cost effectiveness evidence: summary of the ERG's key issues

Key Issue 2: Uncertainty surrounding the cost effectiveness of PEM+LEN within dMMR and pMMR subgroups

Report sections	Section 1.3 and 4.2.3
Description of issue and why the ERG has identified it as important	The company presented cost effectiveness results which were in alignment with the NICE final scope and the company's marketing authorisation i.e. for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. However, based on clinical expert opinion to the ERG, prognosis and treatment is likely to differ for patients based on MMR status. As part of KEYNOTE-775, the company conducted subgroup analyses for both the dMMR and pMMR patients, however cost effectiveness results were not presented. Given that overall OS for PEM+LEN varies depending on MMR status (as per the subgroup data outlined in Section 3.2.3.1), cost effectiveness results are expected to vary between subgroups. The company's base case analysis therefore does not explore the cost

Report sections	Section 1.3 and 4.2.3
	effectiveness of PEM+LEN in two clinically relevant subgroups, which represents an area of uncertainty for the ERG.
What alternative approach has the ERG suggested?	Cost effectiveness results presented for the dMMR and pMMR subgroups would have adequately addressed uncertainty. The ERG were unable to conduct subgroup analyses, due to time and data constraints.
What is the expected effect on the cost-effectiveness estimates?	The expected impact on cost effectiveness of each subgroup remains unclear. However, due to improved OS in the dMMR subgroup, compared to the pMMR subgroup, the ICER for PEM+LEN is likely to be lower in this subgroup, all else remaining equal.
What additional evidence or analyses might help to resolve this key issue?	Provision of cost effectiveness results for each subgroup would resolve this issue.

Abbreviations: dMMR, deficient mismatch repair; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MMR, mismatch repair; NICE, National Institute for Health and Care Excellence; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; pMMR, proficient mismatch repair

Key Issue 3: Uncertainty surrounding extrapolation of OS

Report sections	Sections 4.2.6, 6.2 and 6.2.5
Description of issue and why the ERG has identified it as important	Based on clinical opinion to the ERG there was some concern surrounding the long term overall survival estimates modelled by the company, namely that the extrapolated curves lacked clinical plausibility and were too far apart. Specifically, five year OS in the PEM+LEN arm was considered optimistic whilst this was considered pessimistic in the doxorubicin or paclitaxel arm. The ERG considered that the company's base case extrapolation approach potentially biases the analysis in favour of PEM+LEN by overestimating life years, and underestimating life years in the doxorubicin or paclitaxel arm. Additionally, the ERG noted concerns surrounding the following: • The company's dismissal of alternative modelling approaches, including the use of restricted cubic splines (see Section 4.2.6 for commentary). • The use of the ECHO study as a means of validating OS in the doxorubicin or paclitaxel arm (see Section 4.2.6.4). • The ERG did not have access to the KEYNOTE-146 CSR, which introduced further uncertainty. The company included

Report sections	Sections 4.2.6, 6.2 and 6.2.5
	this trial in its submission, but is not the sponsor or owner of the CSR.
What alternative approach has the ERG suggested?	The ERG conducted additional scenario analyses using alternative parametric curves for OS extrapolation. For PEM+LEN, the KM + Weibull was used and for the doxorubicin or paclitaxel arm, the KM + Log logistic curve was used. The ERG also conducted a combined scenario analysis which used both of these alternative curves (see Section 6.2.5).
What is the expected effect on the cost-effectiveness estimates?	The impact of these changes caused the OS gap between treatment arms to narrow, thereby reducing the incremental LY gain in the PEM+LEN arm. Results were highly sensitive to these scenario analyses (see Section 6.2.5 for results).
What additional evidence or analyses might help to resolve this key issue?	Whilst the ERG acknowledged ECHO provided supplementary supportive evidence with respect to OS, the ERG identified several limitations with this study (see Section 3.3). Furthermore, in order to explore uncertainty surrounding OS extrapolation, the company could have also provided results using alternative modelling approaches including the use of restricted cubic splines.

Abbreviations: CSR, clinical study report; ERG, Evidence Review Group; KM, Kaplan-Meier; LY, life year; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib

Key Issue 4: Uncertainty surrounding the company's time to death utility approach

Report sections	Sections 4.2.8, and 6.2.6
Description of issue and why the ERG has identified it as important	In the base case analysis, the company used a TTD approach to derive utility values for modelled health states. The ERG considered that a more reasonable approach was to base utility values on progression status i.e. PF and PD. This approach is consistent with the company's model structure which includes progression-free and progressed disease as health states. Furthermore, the ERG noted that in the company's base case TTD approach, varying the PFS curve (whilst keeping OS unchanged) did not have an impact on QALYs, but did impact costs. This result appeared somewhat counter-intuitive. Based on scenario analysis provided by the company, results were sensitive to the estimation of utility values based on progression status.
What alternative approach has the ERG suggested?	The ERG preferred to base health state utility values on progression status. This preference forms part of the ERG base case.

Report sections	Sections 4.2.8, and 6.2.6
What is the expected effect on the cost-effectiveness estimates?	This scenario had a relatively small upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Estimating health state utilities based on progression status mostly resolves this issue. However, longer-term QoL data would be helpful to validate modelled estimates.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life year; QoL, quality of life; TTD, time-to-death

Key issue 5: Treatment waning

Report sections	Sections 4.2.6.3 and 6.2.3
Description of issue and why the ERG has identified it as important	The company's base case analysis assumes no waning of treatment effect i.e. after patients discontinue PEM+LEN the treatment effect is assumed to be maintained over time. Although the company provided some justification for not including treatment waning (see Section 4.2.6.3 and response to B.18 of the company's clarification response), the ERG considered there to be some uncertainty surrounding the maintenance of the PEM+LEN treatment effect. Clinical opinion to the ERG noted data on treatment waning are limited, however it may be reasonable to assume gradual waning once patients stop treatment.
What alternative approach has the ERG suggested?	The ERG conducted a scenario analysis which included a treatment waning effect in the PEM+LEN arm between years 2 and 5 (see Section 6.2.3 for details). The ERG did not include this scenario as part of its preferred base case due to the lack of data supporting this assumption. However, this scenario does highlight the sensitivity of results to the use of alternative treatment effect assumptions.
What is the expected effect on the cost-effectiveness estimates?	Results were highly sensitive to this scenario (see Section 6.2.10 for results).
What additional evidence or analyses might help to resolve this key issue?	Robust long-term treatment effectiveness data would help to resolve this uncertainty.

Abbreviations: dMMR, deficient mismatch repair; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MMR, mismatch repair; NICE, National Institute for Health and Care Excellence; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; pMMR, proficient mismatch repair

1.6. Other issues: summary of the ERG's views

Issue 6: Time-on-treatment, percentage of patients receiving doxorubicin or paclitaxel, modelled baseline patient characteristics and approach to capping survival

Report sections	Sections 4.2.7, 4.2.4, 4.2.3.1, 6.2.7, 6.2.2, 6.2.8 and 6.2.9
Description of issue and why the ERG has identified it as important	ToT: In the base case analysis, the company modelled ToT independently for PEM+LEN i.e. a generalised gamma curve was used for both arms. The ERG considered that a more appropriate method is to cap ToT by PFS (for all treatments), as ToT should be coterminous with PFS. See section 4.2.7 for further discussion. Percentage of patients receiving doxorubicin or paclitaxel: In the base case analysis, the company assumed that 75% of patients would receive doxorubicin and 25% would receive paclitaxel. Based on clinical input to the ERG, a more even split (50/50) is likely to better represent clinical practice (see section 4.2.4 for further discussion). Modelled baseline patient characteristics: In the base case the company based patient weight and age on patient characteristics from KEYNOTE-775. Based on clinical input, patients in the UK are likely to be heavier and older than those in KEYNOTE-775 (see section 4.2.3 for further discussion). Capping of overall survival: The company used a 'hybrid' approach to capping overall survival to general population survival and PFS to OS. The ERG's preference is for the hazards-based approach as this generates more plausible estimates of survival (see Section 4.2.6.2 for further discussion).
What alternative approach has the ERG suggested?	ToT: The ERG conducted a scenario analysis which capped ToT by PFS (for all treatments). This has been included as part of the ERG's preferred base case. Percentage of patients receiving doxorubicin or paclitaxel: The ERG conducted scenario analyses which varied the proportion of patients receiving either doxorubicin or paclitaxel (see Section 6.2.2). The ERG preferred base case assumes that 50% of patients receive doxorubicin and 50% receive paclitaxel. Modelled patient baseline characteristics: The ERG has conducted a scenario analysis which increased mean patient weight to 85 kg (and BSA to 1.96 m^2) and patient age to 75 years. This has

Report sections	Sections 4.2.7, 4.2.4, 4.2.3.1, 6.2.7, 6.2.2, 6.2.8 and 6.2.9
	been included as part of the ERG's preferred base case. Capping of overall survival: In this scenario the ERG have used two alternative approaches to capping overall survival, the 'simple' approach and 'hazards' approach (see Section 6.2.1). The ERG preferred base case uses the hazards approach.
What is the expected effect on the cost-effectiveness estimates?	ToT capped by PFS: This caused the ICER for PEM+LEN to decrease (due to reduced drug costs). See Section 6.2.7. Percentage of patients receiving doxorubicin or paclitaxel (50/50): This scenario had minimal impact on the ICER. See Section 6.2.2. Modelled patient baseline characteristics: Altering patient age had a mild upward impact on the ICER, however increasing patient weight did not have a meaningful impact. See Section 6.2.8.
What additional evidence or analyses might help to resolve this key issue?	The additional analyses conducted by the ERG have addressed these issues.

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; ToT, time-on-treatment

1.7. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred base case results are presented below. Please note that the results include the PAS for pembrolizumab and list price for lenvatinib. [redacted] All of the ERG's analyses therefore include the latest PAS.

Table 3: ERG preferred assumptions (deterministic)

	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	5.1.1.1	[redacted]	1.75	[redacted]
ERG corrected company base case				
Drug costs corrected + additional PAS	6.1	[redacted]	1.75	[redacted]
ERG Preferred base case assumptions **(applied individually)**				

	ERG report section	Incremental cost	Incremental QALYs	ICER
Survival capped by hazards	6.2.1 and 6.2.10	[redacted]	1.77	[redacted]
50% of patients receive doxorubicin and 50% receive paclitaxel	6.2.2 and 6.2.10	[redacted]	1.75	[redacted]
ToT capped by PFS	6.2.7 and 6.2.10	[redacted]	1.76	[redacted]
Health state utilities based on progression status	6.2.6 and 6.2.10	[redacted]	1.59	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	6.2.8 and 6.2.10	[redacted]	1.75	[redacted]
Patient age increased to 75 years	6.2.9 and 6.2.10	[redacted]	1.55	[redacted]
OS for doxorubicin or paclitaxel (KM +Log logistic)	6.2.5 and 6.2.10	[redacted]	1.31	[redacted]
Cumulative impact of ERG's preferences	1.7 and 6.3	[redacted]	1.07	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

Table 4: ERG preferred assumptions (probabilistic)

	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	5.1.1.1	[redacted]	1.77	[redacted]
ERG corrected company base case				
Drug costs corrected + additional PAS	6.1	[redacted]	1.76	[redacted]
ERG Preferred base case assumptions (applied incrementally)				
Survival capped by hazards	6.2.1 and 6.2.10	[redacted]	1.77	[redacted]
50% of patients receive doxorubicin and 50% receive paclitaxel	6.2.2 and 6.2.10	[redacted]	1.75	[redacted]

	ERG report section	Incremental cost	Incremental QALYs	ICER
ToT capped by PFS	6.2.7 and 6.2.10	[redacted]	1.76	[redacted]
Health state utilities based on progression status	6.2.6 and 6.2.10	[redacted]	1.61	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	6.2.8 and 6.2.10	[redacted]	1.76	[redacted]
Patient age increased to 75 years	6.2.9 and 6.2.10	[redacted]	1.56	[redacted]
OS for doxorubicin or paclitaxel (KM +Log logistic)	6.2.5 and 6.2.10	[redacted]	1.32	[redacted]
Cumulative impact of ERG's preferences	1.7 and 6.3	[redacted]	1.05	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Merck, Sharp and Dohme (MSD) in support of pembrolizumab with lenvatinib (PEM+LEN) for previously treated advanced, metastatic or recurrent endometrial cancer (EC).

2.2. Critique of the company's description of the underlying health problem

The ERG is broadly in agreement with the company's description of the underlying health problem. The company describe Stage III EC as advanced cancer that has spread outside the womb and Stage IV EC as cancer that has spread beyond the pelvis (womb, bowel or bladder). For clarity, the ERG refer to the BGCS Uterine Cancer Guideline Recommendations for Practice 2021[1] where Stage III and Stage IVA (spread to other areas of the pelvis) EC are described as advanced and Stage IVB (distal spread) as metastatic. These guidelines use internationally recognized FIGO and TNM staging methods.

The company provide information about the age of the population (i.e. highest incidence in people aged 75-79 years) but not about weight. The ERG noted that a large proportion of the population are overweight or obese.[2]

The ERG highlights the importance of separately considering the mismatch repair, or MMR, subgroups within the target population. Section B.2.4.2 of the CS provides an acknowledgment that the efficacy of PEM+LEN is expected to be greater for those with deficient MMR, or dMMR, EC (vs proficient MMR, or pMMR, EC), and clinical effectiveness data are provided according to MMR subgroups in Appendix P of the CS. However, these important subgroups are not highlighted in the CS from the outset, and not separately considered in the economic analyses. Clinical expert advice to the ERG confirms that dMMR tumours are generally (but not always) considered to have a better treatment response and prognosis than pMMR tumours, and most importantly are more likely to respond to immunotherapy. Recently, a clear difference in the treatment pathway has emerged for people with dMMR EC compared to those with pMMR EC: those with advanced or recurrent previously treated EC displaying dMMR are now able to access dostarlimab as monotherapy (NICE Technology Appraisal Guidance TA779).[3]

2.3. Critique of the company's overview of current service provision

The company provide a description of the clinical pathway for people with advanced, metastatic or recurrent EC (refer to B.1.3.2 and Appendix L in the company submission) alongside a diagram of the clinical pathway (refer to Figure 1, Section B.1.3.2 in the company submission). The ERG agree that this is largely consistent with the BGCS guidelines,[1] and accurate for the population in England and Wales, with the following exceptions:

- The description of service provision given by the company is mostly applicable to people with pMMR tumours. People with previously treated advanced or recurrent EC with MSI/dMMR may be responsive to immunotherapy monotherapy and can now be offered dostarlimab monotherapy (TA779).[3]
- Clinical expert advice to the ERG suggests that radiotherapy may sometimes be used in the advanced/recurrent setting for tumours not previously treated with radiotherapy (i.e. in the (neo)adjuvant setting).

2.4. Critique of company's definition of decision problem

The decision problem provided by the company (refer to B.1.1 in the company submission) is largely consistent with the NICE scope:

The company appropriately clarify that the target population are those who "have disease progression on or following prior treatment with a platinum-containing therapy" and that the population would be those who are "not candidates for curative surgery or radiation". The company also state that this can be in any setting, thereby opening up two positions for PEM+LEN: firstly, as a treatment option following platinum-containing chemotherapy provided in the advanced/recurrent setting; and secondly, for those with recurrent, advanced or metastatic cancer who had received platinum-based chemotherapy in the (neo)adjuvant setting. The ERG agree that these are appropriate treatment positions, but noted that for the latter positioning, re-challenge with platinum-containing doublet chemotherapy may be the first-choice treatment (for those receiving adjuvant platinum-based chemotherapy at least 12 months before), and would, therefore, be a useful comparator for this positioning. Whilst both carboplatin and doxorubicin are included as comparators, the key trial in the company submission does not use this doublet as a comparator.

The company has also narrowed the comparator in comparison with the NICE scope, with hormone therapy and best supportive care no longer considered. The ERG agreed that, even though best supportive care is not always limited to those not suitable for active treatment (occasionally people suitable for active treatment may choose best supportive care), the aims of this treatment differ from those of PEM+LEN and the exclusion of this comparator is, therefore, acceptable. The ERG also agree that hormone therapy is given with palliative intent in the recurrent/advanced population and it is reasonable to exclude such treatments as comparators. The ERG noted that the company listed cyclophosphamide as being a comparator in the NICE scope, whereas it was not listed in the NICE final scope document.[4]

The ERG agree that paclitaxel and doxorubicin are reasonable comparators and that both of these treatments are used in the UK setting and are considered to be equally effective. Following advice from clinical experts, the ERG noted that paclitaxel and doxorubicin are used in similar numbers of people with recurrent, advanced or metastatic endometrial cancer (rather than the preference towards doxorubicin in the KEYNOTE 775 data (see Section 3.2.2).

The ERG highlight that the treatment and population in the company's decision problem are aligned with the NICE scope. However, it is important to highlight that due to recent changes in the treatment pathway (those with EC displaying MSI-H/dMMR can now access dostarlimab monotherapy through the CDF (TA779)),[3] the treatment may bemore appropriate for people with pMMR EC than for those with dMMR EC. Clinical advice to the ERG indicated that immunohistochemistry was more accurate for identifying MMR status where available compared to MSI. Ideal comparators for PEM+LEN in this subgroup would, therefore, be immune checkpoint inhibitors as monotherapy.

The ERG noted that in certain cancers, use and licensing of PD-1/PD-L1 checkpoint inhibitor is conditioned on extent of PD-L1 expression. The company indicated that 'the treatment benefit of PEM+LEN compared with TPC was consistent across all the major subgroups tested in patients with advanced EC, including by histology' and explained that 'the regulatory license for this indication does not have a restriction based on the PD-L1 status'. Therefore the ERG did not consider PD-L1 expression any further. Clinical advice to the ERG indicated that MMR status is of much greater use in EC than PD-L1 expression.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with advanced, metastatic or recurrent endometrial cancer, previously treated with platinum-based therapy who are not able to receive curative surgery or radiation	For the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation	Aligned to anticipated marketing authorisation	The ERG considered the decision problem addressed in the company submission was in alignment with the NICE scope. However, based on clinical expert opinion to the ERG, two clinically distinct subgroups exist within the overall population i.e. patients with dMMR and pMMR cancers. The company conducted subgroup analyses in these subgroups, however cost effectiveness results were not presented (See Section 4.2.3). The ERG noted that people with dMMR EC now have access to dostarlimab (TA779),[3] as monotherapy. Therefore, PEM+LEN may be most appropriately positioned for people with pMMR EC. Furthermore, whilst clinically appropriate, the positioning of PEM+LEN following platinum-based

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				treatment in any setting (including following platinum-based chemotherapy in the (neo)adjuvant setting) creates questions about useful comparators (see below).
Intervention	Pembrolizumab with Lenvatinib	Pembrolizumab with lenvatinib (PEM+LEN)	N/A	The ERG agreed that the intervention is consistent with the NICE final scope.
Comparator(s)	Chemotherapy (including carboplatin and paclitaxel, paclitaxel monotherapy, doxorubicin monotherapy and carboplatin monotherapy Hormone therapy (such as medroxyprogesterone acetate and megestrol) Best supportive care	Chemotherapy (such as paclitaxel, carboplatin, doxorubicin)	Active comparators aligned with BGCS evidence-based recommendations and Company's consultation with clinical experts: • Cyclophosphamide is not used to treat advanced or recurrent EC. • Hormone therapy is only used if all other treatment options are exhausted or patients cannot tolerate further lines of chemotherapy and even then hormone therapy	The primary comparators were based on the physician's choice. This was assumed by the company to be doxorubicin or paclitaxel. The ERG considered these comparators to be reasonable (see Section 3.2.2.4 for further comment). However, for the dMMR subpopulation, the ideal comparators are likely to be immune checkpoint inhibitors as monotherapy. Nevertheless, the ERG acknowledge that such trials, using a population in England and Wales, would not be expected to be available, due to the recency of the availability

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			has a palliative intent rather than an expectation of clinical response; this is not the target position for PEM+LEN • Best supportive care reserved for patients not fit for active treatment; this is not the target position for PEM+LEN	of dostarlimab through the CDF (TA779).[3] The ERG agreed with the exclusion of cyclophosphamide (but noted that this was not in the NICE final scope), best supportive care and hormone therapy as comparators. The ERG also noted that when PEM+LEN is positioned as first-line treatment in the advanced, metastatic or recurrent setting, a useful comparator is re-challenge with platinum-based chemotherapy (see p.62 and p.63).
Outcomes	Progression-free survival Overall survival Response rates Duration of response Adverse effects of treatment Health-related quality of life	As per the NICE final scope	N/A	The ERG agreed that the outcomes assessed and presented by the company were in line with the NICE final scope.
Economic analysis	The cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year	As per the NICE final scope	N/A	A cost utility analysis was provided by the company and results were presented as cost per QALY as appropriate. The time horizon used in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	The time horizon for estimating cost-effectiveness was set at a lifetime horizon to sufficiently reflect any differences in costs or outcomes between the technologies being compared • Costs are considered from a NHS and Personal Social Services perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account			the company's base case (40 years) was considered reasonable.
Subgroups	Not stated in final scope	No economic subgroup analyses were submitted by the company, which is consistent with the NICE final scope	N/A	PEM+LEN may be expected to perform better in people with dMMR EC but be most appropriately positioned for people with pMMR EC (those with dMMR EC now have access to dostarlimab as monotherapy).
Special considerations including issues related to equity or equality	None	None	N/A	The ERG did not identify any issues related to equity or equality.

Abbreviations: BGCS, British Gynaecological Cancer Society; dMMR, deficient mismatch repair; EC, endometrial cancer; ERG, Evidence Review Group; N/A, not applicable; NICE, National Institute for Health and Care Excellence; PEM+LEN, pembrolizumab with lenvatinib; pMMR, proficient mismatch repair; QALY, quality-adjusted life years

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of pembrolizumab in combination with lenvatinib (PEM+LEN) for people with advanced, metastatic or recurrent endometrial cancer, previously treated with platinum-based therapy who are not able to receive curative surgery or radiation.

The ERG reviewed the details provided on:

- Methods implemented to identify, screen, extract data and assess the risk of bias in relevant evidence
- Clinical efficacy of PEM+LEN
- Safety profile of PEM+LEN
- Assessment of comparative clinical effectiveness of PEM+LEN against relevant comparators

A detailed description of an aspect of the CS is only provided where the ERG disagreed with the company's assessment or proposal, or where the ERG identified a particular area of concern that the ERG considered necessary to highlight for the Committee.

The ERG did not identify any clinical effectiveness key issues.

3.1. Critique of the methods of review(s)

The Company undertook two systematic literature reviews (SLRs) related to clinical effectiveness: an SLR of interventional evidence and one of real-world evidence (RWE).

3.1.1. Critique of the methods of the interventional evidence SLR

The SLR of interventional evidence was aimed at identifying randomised controlled trials (RCTs) or single-arm studies assessing the clinical effectiveness and safety of PEM+LEN, and comparator interventions, for recurrent or advanced cancer in people with disease progression on or following prior treatment with a platinum containing chemotherapy who were not candidates for curative surgery or radiation. The Company make clear in their inclusion criteria that their definition of advanced cancer is inclusive of stage IV metastatic disease (Appendix D.1.1.2, Table 5, in the Company submission), which is in line with the NICE scope.

The SLR of interventional evidence identified two relevant studies. One was a Phase III RCT (KEYNOTE-775),[5] relevant to the decision problem, and providing direct evidence on the clinical effectiveness and safety of PEM+LEN versus treatment of physician's choice (doxorubicin or paclitaxel monotherapy). A critique of the choice of comparator is in section 2.4. The other study was a single-arm Phase Ib/II study (KEYNOTE-146)[6] that was a precursor of KEYNOTE-775.

Overall, the ERG found this SLR to be of reasonable quality and likely to have identified all studies relevant to the Company's decision problem. A summary of the ERG's critique of the methods implemented in this SLR is presented in Table 6.

Table 6: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D.1.1.1, Tables 1-4	The searches of bibliographic databases are considered broadly appropriate, however, the ERG noted the following limitation: the Ovid Embase search strategy applied a filter excluding conference abstracts from search results. Database searches and manual searches of four conference proceedings may have mitigated this issue. The ERG conducted an additional search on Embase (reported in Appendix A) to check if any conference abstracts were missed by Company searches and is satisfied all relevant evidence has been identified.
Inclusion criteria	Appendix D.1.1.2, Table 5	The inclusion criteria were in line with the Company's decision problem.
Screening	Appendix D.1.1.2	Standard accepted methods
Data extraction	Appendix D.1.1.2.1, Table 6	Standard accepted methods
Tool for quality assessment of included study or studies	Appendix D.1.1.2.2	The Company state that RoB2 was used to assess KEYNOTE-775 (Appendix D.1.1.2.2 in the Company submission.). However, the described domains and summary assessments (low, unclear or high) do not correspond with RoB2. Following clarification, a

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		RoB2 assessment was provided to the ERG (see section 3.2.2.6). The company state that KEYNOTE-146 was assessed using the Newcastle-Ottawa Scale. This is an appropriate tool, but the ERG could not check this assessment because these results were not presented.
Evidence synthesis	Appendix D.1.4	The ERG agrees that NMA/unanchored ITC were not feasible

Abbreviations: CS, Company submission; ERG, Evidence Review Group; ITC, Indirect Treatment Comparison; NMA, network meta-analysis; RoB2, Cochrane Risk of Bias version 2

3.1.2. Critique of the methods of the real-world evidence SLR

The SLR of real-world evidence (RWE) had the objective of identifying observational and cross-sectional studies on clinical efficacy, safety, epidemiological burden and treatment for people with recurrent or advanced endometrial cancer. Overall, the ERG found this review to be of reasonable quality and the methods were likely to have identified the relevant observational and cross-sectional evidence available at the time the searches were conducted. However, the searches for this SLR were conducted in 2020 and are, therefore, out of date. The company were unable to provide updated results, pointing to the fact that the RWE does not form the primary basis of the clinical effectiveness evidence. Whilst the ERG agree that this is the case, the RWE is nevertheless important, and the lack of an up-to-date review risks bias in the choice of studies used to validate the data from KEYNOTE-775.

This SLR identified six retrospective cohort studies,[7-12] four providing data on re-challenge with platinum-based chemotherapy[9-12] and two relating to doxorubicin[7,8] and not considered further. It was not clearly stated why the doxorubicin studies were not used to validate data from the comparator arm of KEYNOTE-775, although presumably this was because of the composite nature of the comparator arm in KEYNOTE-775. Instead, an extra study was reported (the ECHO study,[13] Document B, Section B.2.9.3) and used to confirm/validate the survival data for the comparator arm in KEYNOTE-775. The ERG highlight that the ECHO study[13] was not identified through the SLR of RWE and the company have clarified that ECHO is a recently completed internal study and that the UK data have not yet been published. The inclusion of a

study identified through non-systematic methods introduces a risk of bias, particularly because the SLR of RWE is not up to date and could potentially have identified alternative relevant validation studies.

A summary of the ERG's critique of the methods implemented in this SLR is presented in Table 7.

Table 7: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem (SLR of real world evidence)

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D.1.2.1 and D.1.3.2, Tables 8-11	Searches were conducted in July 2020 and, therefore, it is not known if other relevant evidence has since become available. Searches did not include web searches for grey literature sources not included in bibliographic databases (e.g., UK cancer registries or reports derived from electronic health records).
Inclusion criteria	Appendix D.1.3.3, Table 12	The inclusion criteria were in line with the Company's decision problem. The inclusion criteria table in the CS (Appendix D.1.3.3, Table 12) states that subgroups of interest were "disease stage, line of therapy, treatment setting, risk factors for progression" but does not list MMR status as a subgroup of interest here. The ERG noted that subgroup data based on MMR status are of particular interest in this population, particularly with regards immunologic treatments (see section 2.4 for details).
Screening and selection	Appendix D.1.3.3 and D.1.3.6	An additional study (the ECHO study[13]) was described in Document B, Section B.2.9.3 and used to confirm/validate the survival data for the comparator arm in KEYNOTE-775. This is a recent study by the Company and was not

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		identified by the SLR of RWE, as it is not published.
Data extraction	Appendix D.1.3.5	Standard accepted methods
Tool for quality assessment of included study or studies	Appendix D.1.3.5	Studies were assessed using the ROBINS-I.[14] The ERG noted that the ROBINS-I is best suited to evaluating non-randomised comparative studies. The ERG could not check how the ROBINS-I was applied to the included retrospective cohort studies because the assessments were not provided.

Abbreviations: CS, Company submission; ERG, Evidence Review Group; MMR, mismatch repair; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions; RWE, real-world evidence; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The company presented evidence from one pivotal Phase III trial of PEM+LEN against physician's choice (typically doxorubicin or paclitaxel monotherapy) in KEYNOTE-775.[5,15] This trial informs the company's economic model. One supportive Phase 1b/II dose-finding trial of PEM+LEN, KEYNOTE-146,[6] was used to validate model extrapolations. Limited information about KEYNOTE-146 was included in the CS. The ERG asked the company at the clarification call if further information about this study was available. The company indicated that only limited information was available as KEYNOTE-146 was not conducted by the submitting company and that CSR or further methodological information was available. Subsequently, the ERG identified that a protocol had been published as an appendix to a published results paper from the study.[6] Therefore, the ERG used information from the published protocol to provide additional information regarding the study methods.

A summary of the clinical evidence included in the CS is presented in Table 8 .

Table 8: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
KEYNOTE-775	Multi-centre, open-label, randomised Phase III trial	People with advanced (including metastatic) or recurrent EC who have disease progression following prior systematic therapy with platinum chemotherapy, and are not candidates for curative surgery or radiation.	PEM+LEN	Physician's choice, typically doxorubicin or paclitaxel monotherapy	Phase III
KEYNOTE-146	Multi-centre, open-label, single-assignment Phase Ib/II basket trial	Phase Ib: people with selected tumour types who have progressed after treatment with approved therapies or for whom there are no standard effective therapies available. Phase II: people with metastatic selected solid tumour types who have received 0−2 prior lines of systemic therapy.	PEM+LEN	None	Phase Ib/II

Abbreviations: CS, company submission; EC, endometrial cancer; PEM+LEN, pembrolizumab with lenvatinib

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The company's primary evidence for the combination of PEM+LEN comes from the KEYNOTE-775 study,[5,15,16] which was a global multi-centre, open-label, randomised Phase III trial of PEM+LEN against physician's choice, typically doxorubicin or paclitaxel in advanced or recurrent EC. This was the only trial of PEM+LEN that was used in the company economic model.

The study compromised a 28-day screening period followed by a period of treatment and finally a period of efficacy follow-up. Patients were enrolled using random assignment in a 1:1 ratio into one of two treatment arms: pembrolizumab 200 mg administered via IV every 3 weeks (Q3W) up to 35 cycles, plus lenvatinib 20 mg every day (QD); or treatment of physician's choice of either doxorubicin 60 mg/m2 Q3W up to a maximum cumulative dose of 500 mg/m2 or paclitaxel 80 mg/m2 every week (QW) on a 28 day cycle, 3 weeks on and 1 week off. The efficacy follow-up period was measured from the day after the end of treatment visit and continued for the duration of each patient's lifetime, or until the data cutoff date for the primary OS analysis if the participant was still alive.

A summary of the methodology of KEYNOTE-775 is provided in Table 9.

Table 9: Summary of KEYNOTE-775 trial methodology

Trial name	**KEYNOTE-775 (NCT03517449)**
Location	International, multi-centre trial with 167 sites across 21 countries, including nine sites in the United Kingdom (other sites were located in Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Ireland, Israel, Italy, Japan, Korea, Mexico, New Zealand, Poland, Russia, Spain, Taiwan, Turkey and US)
Trial design	Multi-centre, randomised, open-label, Phase III study
Method of randomisation	Patients were randomised in a 1:1 ratio to receive PEM+LEN or TPC. Randomisation followed a predefined randomisation scheme based on the following stratification factors: MMR status (pMMR or dMMR) ECOG performance status (0 or 1) Geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world) Prior history of pelvic radiation (yes or no)

Trial name	KEYNOTE-775 (NCT03517449)
	First, patients were stratified according to MMR status. Patients within the pMMR stratum were further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata were used for the study.
Eligibility criteria for patients	Key inclusion criteria: Female patients who were ≥18 years of age Histologically confirmed EC Documented evidence of advanced, recurrent, or metastatic EC Radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC (participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting) [a] Provided a fresh or archival tumour sample for determination of MMR status Had at least 1 measurable target lesion according to RECIST 1.1, including a non-nodal target lesion ≥1 cm in the longest diameter and lymph node lesion that measured ≥1.5 cm in the short axis ECOG Performance Status of 0 or 1 within 7 days of starting treatment Adequately controlled blood pressure with or without antihypertensive medications (defined as ≤150/90 mm Hg at screening) Key exclusion criteria: Had carcinosarcoma (malignant mixed Müllerian tumour), endometrial leiomyosarcoma and endometrial stromal sarcomas Had central nervous system metastases, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study Had gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib Had a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula Had significant cardiovascular impairment within 12 months of the first dose of study drug Full eligibility criteria are provided in Appendix N.1.
Trial drugs and method of administration	Intervention (n=411) Pembrolizumab (200 mg administered intravenously, every 3 weeks on Day 1 of a 21-day cycle; 35 doses maximum) plus lenvatinib (20 mg taken orally once daily) Comparator (n=416) Doxorubicin (60 mg/m2 administered intravenously, every 3 weeks on Day 1 of a 21-day cycle) or paclitaxel (80 mg/m2 administered intravenously, every week on Days 1, 8 and 15 of a 28-day cycle)[a] Participants continued to receive study treatment until disease progression was confirmed by BICR, development of unacceptable toxicity, withdrawal

Trial name	KEYNOTE-775 (NCT03517449)
	of consent, receipt of 35 administrations of pembrolizumab (approximately 2 years), or a lifetime cumulative dose of 500 mg/m² of doxorubicin Pembrolizumab and doxorubicin/paclitaxel were administered in the clinic by qualified site personnel, whilst lenvatinib was dispensed to patients for oral self-administration
Permitted and disallowed concomitant medication	Permitted concomitant medications: Hormone replacement therapy Thyroid hormone suppressive therapy Adjuvant hormonal therapy for history of definitively treated breast cancer Anticoagulants including low molecular weight heparin, warfarin, anti-Xa agents Anti-inflammatory agents Bisphosphonates or denosumab Antihypertensive therapy (including additional antihypertensive treatment as appropriate if blood pressure increases once the participant is enrolled) Palliative radiotherapy to non-target bone metastases or brain lesions may be permitted after consultation Disallowed concomitant medications: Concurrent anticancer therapies such as chemotherapy, targeted therapies, hormonal therapy directed at EC, radiotherapy, antitumour interventions, or cancer immunotherapy Other concurrent investigational drugs Live vaccines Systemic glucocorticoids for any purpose other than to modulate symptoms from an AR that is suspected to have immunologic aetiology
Primary endpoints	PFS, defined as the time from date of randomisation to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause, whichever occurs first OS, defined as the time from date of randomisation to date of death from any cause
Key secondary endpoints	ORR, defined as the proportion of patients who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1 HRQL, assessed using the global score of the EORTC QLQ-C30 The EORTC QLQ-C30 physical functioning score, EORTC QLQ EN24 urological symptoms score and the EQ-5D-5L VAS score were included as exploratory endpoints Incidence of treatment emergent AEs, SAEs, and immune-related AEs Proportion of patients discontinuing study treatment due to treatment emergent AEs Time to treatment failure due to toxicity, defined as the time from the date of randomisation to the date that a participant discontinues the study treatment due to treatment-emergent AEs[b]

Trial name	KEYNOTE-775 (NCT03517449)
	Plasma concentration vs. time, clearance and AUC for lenvatinib[b]
Subgroup analysis	Pre-specified subgroup analyses were performed in the all-comer population for PFS, OS and ORR. The subgroup analyses were conducted using the same methods described for the primary efficacy endpoints and were based on the following baseline demographic and disease characteristics: Age (<65, ≥65 years) Race (White, Asian, other) Region (Region 1, Region 2) MMR status (pMMR, dMMR) ECOG status (0, 1) Prior history of pelvic radiation (yes, no) Histology (endometrioid, non-endometrioid) Prior lines of therapy (1, 2, ≥3)

Key: AE: adverse event; AUC, area under the curve; BICR: Blinded Independent Central Review; CBR: clinical benefit rate; CR: complete response; CSR: clinical study report; DCR : disease control rate; dMMR: deficient mismatch repair; DOR: duration of response; ECOG : Eastern Cooperative Oncology Group; EORTC, European Organisation for the Research and Treatment of Cancer; HRQL: health-related quality of life; LVEF: Left ventricular ejection fraction; MMR: mismatch repair; ORR: overall response rate; OS: overall survival; PD: progressive disease; PEM+LEN, pembrolizumab with lenvatinib; PFS: progression free survival; PFS2: progression free survival on next line therapy; pMMR: proficient mismatch repair; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; SD: standard deviation; TTR: time to response; VAS, visual analogue scale.

Notes: [a], There was no restriction regarding prior hormonal therapy; [b], These endpoints have not been presented as part of this submission but are available in the CSR.

Source: CS, Table 4, pp.18-21, based on KEYNOTE-775 Clinical Study Report[15]

The company also presented supplementary evidence for the clinical effectiveness of PEM+LEN from the KEYNOTE-146 study.[6], which was a single-arm phase Ib/II trial of PEM+LEN. While limited information on this study was available in the CS, a study protocol was available as an appendix to the study results paper.[6] The ERG requested further information on KEYNOTE-146 via NICE, but the provision of this information was refused, inhibiting a full critique of this study which informs the model validation.

3.2.2.2. Population

In KEYNOTE-775, eligible participants were adult females aged at least 18 years with documented evidence of advanced, recurrent or metastatic endometrial cancer with completely resected Stage IB (tumours at least 4 cm) to Stage IIIA, who had an ECOG performance status 0-1 and who were able to receive cisplatin-based chemotherapy. Patients with carcinosarcoma

or sarcoma were excluded. Detailed inclusion and exclusion criteria were provided in the CS (Appendix N.1). These overall appeared reasonably aligned with the NICE scope and company decision problem.

There were a total of 827 participants, of whom 411 were randomised to the PEM+LEN arm and 416 were randomised to the comparator arm. The study recruited from 167 sites across 21 countries globally. Nine of the study sites were located in the United Kingdom (UK), no specific breakdown was provided for England and Wales, the UK nations for which this appraisal is applicable. Clinical advice to the ERG indicated that treatment pathways are unlikely to differ substantially between countries, but that the trial profile may underestimate the age and weight of patients encountered in routine clinical practice in the UK.

Baseline characteristics for KEYNOTE-775 are provided below as Table 10.

Table 10: Baseline characteristics for KEYNOTE-775

Characteristic	PEM+LEN (n=411)	TPC (n=416)
Sex, n (%)		
Female	411 (100)	416 (100)
Age in years, n (%)		
<65	206 (50.1)	204 (49.0)
≥65	205 (49.9)	212 (51.0)
Mean (SD)	63.2 (9.1)	63.8 (9.2)
Median (min, max)	64.0 (30, 82)	65.0 (35, 86)
Race, n (%)		
Asian	85 (20.7)	92 (22.1)
Black or African American	17 (4.1)	14 (3.4)
White	261 (63.5)	246 (59.1)
Other	12 (2.7)	20 (4.8)
Age in years at initial diagnosis, n (%)		
<65	253 (61.6)	255 (61.3)
≥65	158 (38.4)	161 (38.7)
Mean (SD)	61.3 (9.1)	61.5 (9.3)
Median (min, max)	62.4 (30, 81)	62.1 (27, 84)
Region,[a] n (%)		
Region 1	234 (56.9)	240 (57.7)

Characteristic	PEM+LEN (n=411)	TPC (n=416)
Region 2	177 (43.1)	176 (42.3)
MMR Status, n (%)		
pMMR	346 (84.2)	351 (84.4)
dMMR	65 (15.8)	65 (15.6)
ECOG, n (%)		
0	246 (59.9)	241 (57.9)
1	164 (39.9)	175 (42.1)
3	1 (0.2)	0 (0.0)
Prior history of pelvic radiation, n (%)		
Yes	168 (40.9)	173 (41.6)
No	243 (59.1)	243 (58.4)
Elapsed time in years from initial diagnosis		
Mean (SD)	2.4 (2.4)	2.9 (2.8)
Median (min, max)	1.7 (0, 21)	2.1 (0, 26)
Histology of initial diagnosis, n (%)		
Clear cell carcinoma	30 (7.3)	17 (4.1)
Endometrioid carcinoma	83 (20.2)	103 (24.8)
Endometrioid carcinoma with squamous differentiation	7 (1.7)	7 (1.7)
High grade endometrioid carcinoma	94 (22.9)	90 (21.6)
High grade mucinous carcinoma	0 (0.0)	1 (0.2)
High grade serous carcinoma	65 (15.8)	65 (15.6)
Low grade endometrioid carcinoma	59 (14.4)	54 (13.0)
Low grade mucinous carcinoma	1 (0.2)	0 (0.0)
Mixed	22 (5.4)	16 (3.8)
Neuroendocrine	2 (0.5)	0 (0.0)
Serous carcinoma	38 (9.2)	50 (12.0)
Unclassified	0 (0.0)	3 (0.7)
Undifferentiated histology	4 (1.0)	3 (0.7)
Other	6 (1.5)	7 (1.7)
FIGO stage at initial diagnosis, n (%)		
I	10 (2.4)	11 (2.6)

Characteristic	PEM+LEN (n=411)	TPC (n=416)
IA	54 (13.1)	64 (15.4)
IB	47 (11.4)	64 (15.4)
II	32 (7.8)	26 (6.3)
III	5 (1.2)	8 (1.9)
IIIA	28 (6.8)	33 (7.9)
IIIB	11 (2.7)	11 (2.6)
IIIC	30 (7.3)	24 (5.8)
IIIC1	17 (4.1)	25 (6.0)
IIIC2	27 (6.6)	27 (6.5)
IV	27 (6.6)	26 (6.3)
IVA	7 (1.7)	8 (1.9)
IVB	116 (28.2)	89 (21.4)
Brain metastasis,[c] n (%)		
Yes	2 (0.5)	2 (0.5)
No	409 (99.5)	414 (99.5)
Bone metastasis,[c] n (%)		
Yes	39 (9.5)	33 (7.9)
No	372 (90.5)	383 (92.1)
Liver metastasis,[c] n (%)		
Yes	101 (24.6)	98 (23.6)
No	310 (75.4)	318 (76.4)
Lung metastasis,[c] n (%)		
Yes	164 (39.9)	152 (36.5)
No	247 (60.1)	264 (63.5)
Intra-abdominal metastasis,[b,c] n (%)		
Yes	164 (39.9)	166 (39.9)
No	247 (60.1)	250 (60.1)
Lymph node metastasis,[c] n (%)		
Yes	224 (54.5)	225 (54.1)
No	187 (45.5)	191 (45.9)

Key: PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Notes: [a], Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World; [b], Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and

Characteristic	PEM+LEN (n=411)	TPC (n=416)
peritoneum. Does not include lymph nodes or other organs; [c], Lesion location as determined by investigator review.		

Source: CS, Table 5, pp. 21-23, based on KEYNOTE-775 CSR.[15]

In KEYNOTE-146, the participant profile was subdivided between two phases. In Phase Ib, participants were people with selected tumour types who have progressed after treatment with approved therapies or for whom there are no standard effective therapies available. In Phase II, participants were people with metastatic selected solid tumour types who had received up to two prior lines of systemic therapy. It is stated that 6 separate cohorts were enrolled into Phase II based on tumour location. A total of 125 participants were enrolled, of whom one was excluded due to leiomyosarcoma. Of the remaining 124 participants, nine were first line and 115 were second line. KEYNOTE-146 included up to 25 study sites from the United States and the European Union. There were no UK sites in KEYNOTE-146, which may limit generalisability to a UK decision-making context. Baseline characteristics for KEYNOTE-146 are shown in Table 11 below.

Table 11: Baseline characteristics for KEYNOTE-146

	Previously treated EC[a]			**All EC**
Characteristic	**MSS/pMMR (n = 94)**	**MSI-H/dMMR (n =11)**	**Total[b] (n = 108)**	**(n = 124)**
Age, years				
Mean	65.4	62.4	65.1	65.3
SD	7.42	9.45	7.60	7.83
Race, n (%)				
White	81 (86.2)	9 (81.8)	93 (86.1)	108 (87.1)
Black or African American	6 (6.4)	0	6 (5.6)	7 (5.6)
Asian	4 (4.3)	1 (9.1)	5 (4.6)	5 (4.0)
American Indian or Alaskan native	1 (1.1)	0	1 (0.9)	1 (0.8)
Native Hawaiian or other pacific islander	0	1 (9.1)	1 (0.9)	1 (0.8)
Other	2 (2.1)	0	2 (1.9)	2 (1.6)
ECOG PS, n (%)				
0	49 (52.1)	1 (9.1)	53 (49.1)	62 (50.0)

Characteristic	Previously treated EC[a]			All EC
	MSS/pMMR (n = 94)	MSI-H/dMMR (n =11)	Total[b] (n = 108)	(n = 124)
1	45 (47.9)	10 (90.9)	55 (50.9)	62 (50.0)
Histologic subtype, n (%)				
Endometrioid adenocarcinoma	46 (48.9)	8 (72.7)	55 (50.9)	67 (54.0)
FIGO grade I	10 (10.6)	2 (18.2)	12 (11.1)	15 (12.1)
FIGO grade 2	15 (16.0)	4 (36.4)	19 (17.6)	22 (17.7)
FIGO grade 3	21 (22.3)	2 (18.2)	24 (22.2)	30 (24.2)
Serous adenocarcinoma	33 (35.1)	0	35 (32.4)	39 (31.5)
Clear-cell adenocarcinoma	5 (5.3)	1 (9.1)	6 (5.6)	6 (4.8)
Dedifferentiated/ undifferentiated carcinoma	0	1 (9.1)	1 (0.9)	1 (0.8)
Adenocarcinoma, not otherwise specified	1 (1.1)	0	1 (0.9)	1 (0.8)
Other	1 (0.8)	1 (9.1)	10 (9.3)	10 (8.1)
PD-L1 status, n (%)				
Positive	46 (48.9)	7 (63.6)	53 (49.1)	60 (48.4)
Negative	39 (41.5)	4 (36.4)	43 (39.8)	52 (41.9)
Not available	9 (9.6)	0	12 (11.1)	12 (9.7)
Prior treatment regiments for EC, n (%)				
0	0	0	0	9 (7.3)
1	48 (51.1)	7 (63.6)	57 (52.8)	60 (48.4)
2	36 (38.3)	3 (27.3)	40 (37.0)	43 (34.7)
≥3	10 (10.6)	1 (9.1)	11 (10.2)	12 (9.7)
Prior treatment, n (%)				
Bevacizumab	5 (5.3)	1 (9.1)	6 (5.6)	7 (5.6)
Platinum + taxane combination (with or without other anticancer medication	92 (97.9)	11 (100.0)	106 (98.1)	113 (91.1)
Other anticancer combinations	9 (9.6)	1 (9.1	11 (10.2)	12 (9.7)

	Previously treated EC[a]			All EC
Characteristic	MSS/pMMR (n = 94)	MSI-H/dMMR (n =11)	Total[b] (n = 108)	(n = 124)
Monotherapy	33 (35.1)	3 (27.3)	36 (33.3)	37 (29.8)
Prior history of/ current hypertension, n (%)				
Yes	60 (63.8)	9 (81.8)	71 (65.7)	79 (63.7)

Key: CPS: combined positive score; dMMR: deficient mismatch-repair; EC: endometrial carcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; FIGO: International Federation of Gynecology and Obstetrics; MSI-H: microsatellite instability high; MSI/MMR: microsatellite instability/mismatch repair; PD-L1: programmed death-ligand 1; pMMR: mismatch-repair proficient; SD: standard deviation.

Notes: [a], Enrolled before July 1, 2018; [b], Three patients had an unknown MSI/MMR tumour status; c, Predominantly mixed histology; d, PD-L1 status is positive if CPS is ≥ 1 and negative if CPS is < 1; e, The majority of patients received therapies in the adjuvant or metastatic setting; 9 patients received therapy in the neoadjuvant setting; the setting for 2 patients was unknown; f, Patients may be counted in multiple categories.

Source: CS Appendix O.2, Table 55, based on Makker et al.[6,17]

3.2.2.3. Intervention

The intervention in KEYNOTE-775[15,16] was pembrolizumab 200 mg administered via IV every 3 weeks (Q3W) up to 35 cycles, plus lenvatinib 20 mg every day (QD). Phase Ib of KEYNOTE-146[6] sought to determine the maximum tolerated dose. Dosing began at the full dose of both PEM+LEN due to well-established safety profiles and non-overlapping mechanisms of action, with lower dose levels being explored as necessary based on observed toxicity. Phase Ib began with Dose Level 1; lenvatinib 24 mg/day orally and pembrolizumab 200 mg every 3 weeks IV were administered to participants with selected solid tumors on a 21-day treatment cycle. Two dose de-escalation steps were included: Dose Level 2 (lenvatinib 20 mg/day orally + pembrolizumab 200 mg Q3W, IV) and Dose Level 3 (lenvatinib 14 mg/day orally + pembrolizumab 200 mg Q3W, IV). In Phase II, following confirmation of the maximum tolerated dose, treatment proceeded at that dose.

3.2.2.4. Comparator

The comparator arm in KEYNOTE-775[15,16] was treatment of physician's choice of either doxorubicin 60 mg/m2 Q3W up to a maximum cumulative dose of 500 mg/m2 or paclitaxel 80 mg/m2 every week (QW) on a 28-day cycle, 3 weeks on and 1 week off. There was no comparator arm in KEYNOTE-146.

3.2.2.5. Outcomes

The outcomes covered in the KEYNOTE-775[15,16] study were summarised in the CS section B.2.3.1.

The primary efficacy outcome measures for this study were:

- Progression-free survival, defined as the time from date of randomisation to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause, whichever occurs first.
- Overall survival, defined as the time from date of randomisation to date of death from any cause.

The secondary efficacy outcome measures for this study were:

- Overall response rate, defined as the proportion of patients who have best overall response of either complete respond or partial response, as determined by BICR per RECIST 1.1.
- Health-related quality of life, assessed using the global score of the EORTC QLQ-C30.

Exploratory endpoints for this study were:

- Health-related quality of life, assessed using The EORTC QLQ-C30 physical functioning score, EORTC QLQ EN24 urological symptoms score and the EQ-5D-5L VAS score.

Safety outcome measures for this study were:

- Incidence of treatment emergent AEs, SAEs, and immune-related AEs
- Proportion of patients discontinuing study treatment due to treatment emergent AEs
- Time to treatment failure due to toxicity, defined as the time from the date of randomisation to the date that a participant discontinues the study treatment due to treatment-emergent AEs
- Plasma concentration vs. time, clearance and AUC for lenvatinib

The ERG considered that the outcomes presented in KEYNOTE-775[15,16] generally encompassed the outcomes from the NICE scope. Data were presented for duration of response, although it was not included in the list of outcomes in the company methods.

The ERG also noted that EQ-5D-5L was only an exploratory endpoint in KEYNOTE-775, despite being a key health-related quality of life outcome for health technology appraisals. EQ-5D-5L scores were mapped to EQ-5D-3L using the Van Hout algorithm.[18].

Information regarding outcomes is not presented in a clear list for KEYNOTE-146.[6] It seems that in addition to safety outcomes, the key effectiveness outcomes in this study were overall response rates and duration of response.

3.2.2.6. Critical appraisal of the design of the studies

Following clarification, the Company provided RoB2 assessments for KEYNOTE-775 (for PFS and OS).[16] The Company's broad RoB2 judgements are provided in Table 12, alongside ERG comments. The Company also provided the ERG with more detailed (item-by-item) RoB2 judgements, which the ERG mostly agreed with (minor disagreements did not alter the domain judgements provided in Table 12).

Table 12: Summary of the RoB2 assessments for KEYNOTE-775

Bias domain	Company RoB2 assessment		ERG Comment
	Makker et al (2022) PFS	Makker et al (2022) OS	
1. Bias arising from the randomisation process	Lower risk of bias	Lower risk of bias	Agree with domain judgements
2. Bias due to deviations from intended interventions	Some concerns	Some concerns	Low risk of bias (PFS and OS)
3. Bias due to missing outcome data	Lower risk of bias	Lower risk of bias	Agree with domain judgements
4. Bias in measurement of the outcome	Lower risk of bias	Lower risk of bias	Agree with domain judgements
5. Bias in selection of the reported result	Lower risk of bias	Lower risk of bias	Agree with domain judgements
Overall bias	Some concerns	Some concerns	Low risk of bias (PFS and OS)

Abbreviations: ERG, Evidence Review Group; RoB2, Cochrane Risk of Bias version 2; OS, overall survival; PFS, progression-free survival

The ERG agreed with the Company that the primary risk of bias in KEYNOTE-775[16] was from the open-label study design and the resultant lack of blinding of those delivering and undergoing treatment. The ERG agreed that there was no evidence to suggest that this lack of blinding led

to trial-contextual issues that would impact upon the delivery of the interventions (item 2.3 in the item-by-item RoB2 assessment supplied to the ERG was rated as 'probable no') or have a substantial impact on OS or PFS. However, according to the RoB2 judgement algorithm, this should lead to a domain 2 (and therefore overall bias) judgement of 'low' rather than 'some concerns' (see Table 12). However, if a 'no information' judgement had been given to item 2.3 (this was not the case, but would have been reasonable), domain 2 and overall bias judgements of 'some concerns' would be appropriate.

The company did not provide Newcastle-Ottawa scale assessment results for KEYNOTE-146.[6] The ERG was therefore unable to comment on the Company's risk of bias assessment of this study.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Progression-free survival

In KEYNOTE-775, median PFS was significantly improved with PEM+LEN compared with TPC; 7.2 and 3.8 months respectively, HR 0.56 (95% CI 0.47, 0.66; p< 0.0001). For KEYNOTE-146, median PFS was reported in the CS in (Table 11). For the PEM+LEN arm this was 7.4 months.

Overall survival

In KEYNOTE-775, Median OS was significantly longer in the PEM+LEN group compared with the control group; 18.3 and 11.4 months respectively, HR 0.62 (95% CI 0.51, 0.75; p< 0.0001) at interim assessment time point 1. For KEYNOTE-146, median OS was reported in the CS (Table 11). For the PEM+LEN arm this was 17.7 months.

Response rates

In KEYNOTE-775, overall response rate was 31.9% (95% CI 27.4, 36.6) in the PEM+LEN group compared to 14.7% (95% CI 11.4, 18.4) in the control arm, with an estimated difference of 17.2% (95% CI 11.5, 22.9%, p<0.0001). In KEYNOTE-146, overall response rate was 39.8% for pre-treated endometrial cancer patients.

Duration of response

Among patients achieving a response, the median duration of response was 14.4 months (range: 1.6, 23.7) in the PEM+LEN group compared to 5.7 months (range: 0.0, 24.2) for the

control group. In KEYNOTE-146, median duration of response was 22.9 months (95% CI: 10.2, not estimable) for pre-treated endometrial cancer participants.

Health-related quality of life

As described above (Section 3.2.2.5), quality of life in KEYNOTE-775 was assessed using several different scores. The scores from the EQ-5D-5L visual analogue scale results are presented here, as they informed the company's economic model, though in the trial this was only an exploratory endpoint. On this measure, both groups improved significantly over the 12-week follow-up period (PEM+LEN mean change -4.44, 95% CI -6.43, -2.46; control mean change -6.79, 95% CI -8.98, -4.60). However, there was no statistically significant difference between the two arms in terms of the extent of improvement over the 12-week period (difference in least squares mean change from baseline 2.35, 95% CI -0.44, 5,14, [redacted]). No health-related quality of life data were presented from KEYNOTE-146 in the CS, as this outcome was not assessed in this trial.

Subgroup analyses

Subgroup analyses were presented in the CS examining the differential effectiveness of PEM+LEN by age, race, region, MMR status, ECOG performance status, prior history of pelvic radiation, histology (endometrioid vs non-endometrioid) and prior lines of therapy (CS, Appendix E). Those considered by the ERG to be of greatest importance were MMR status and region. The region subgroup analysis divided the world into two regions: Region 1 being Europe, USA, Canada, Australia, New Zealand, and Israel; Region 2 being the rest of the world. There was no significant difference in OS or PFS between Regions 1 and 2 (CS Appendix E, Figure 5). The grouping is fairly broad and includes heterogeneous health systems and is therefore limited in its applicability to assessing the generalizability of the findings to a UK decision-making context.

There was a statistically significant difference in favour of PEM+LEN on both PFS and OS for both the pMMR and dMMR subgroups. However, the effect in favour of PEM+LEN was stronger in the dMMR subgroup for both PFS (dMMR HR 0.36, 95% CI 0.23-0.57; pMMR HR 0.60, 95% CI 0.50-0.72) and OS (dMMR HR 0.37, 95% CI 0.22-0.62; pMMR HR 0.68, 95% CI 0.56, 0.84). The trial was not powered specifically to explore differences between sub-groups, so these findings should be regarded as exploratory.

These findings were also evidence in median survival times, measured in months. Median PFS was 6.6 (95% CI 5.6, 7.4) months in the PEM+LEN group and 3.8 (95% CI 3.6, 5.0) months in

the control arm in the pMMR population and 10.7 (5.6, NR) months in the PEM+LEN group and 3.7 (3.1, 4.4) months in the control group in the dMMR population. Median OS was 17.4 (95% CI 14.2, 19.9) months in the PEM+LEN group and 12.0 (95% CI 10.8, 13.3) in the control group in the pMMR population and not reached in the PEM+LEN group and 8.6 (95% CI 5.5, 12.9) months in the control group in the dMMR population.

Finally, differences were also in evidence in survival proportions. Six-month OS was 82.9 (78.5, 86.5) in the PEM+LEN group and 77.9 (73.1, 81.9) in the control group in the pMMR population and 80.0 (68.1, 87.9) in the PEM+LEN group and 61.7 (48.5, 72.5) in the control group in the dMMR population. Twelve-month OS was 27.6 (22.5, 32.8) in the PEM+LEN group and 13.1 (8.9, 18.3) in the control group in the pMMR population and 67.2 (54.2, 77.2) in the PEM+LEN group and 39.1 (26.7, 51.3) in the control group in the dMMR population.

Adverse effects

Adverse events from KEYNOTE-775 were reported in section B.2.10 and Table 54, Appendix R.3 of the CS. These data were supplemented with adverse events data from KEYNOTE-146 (CS Appendix F).

Adverse effects: KEYNOTE-775

Adverse events in KEYNOTE-775 were provided for the safety population (n=406 for PEM+LEN; n=388 for TPC). Incidences of Grade 3 to 5 adverse events (AEs; 88.9% versus 72.7%), Grade 3 to 5 drug-related AEs (77.8% versus 59.0%), serious adverse events (SAEs; 52.7% versus 30.4%) and drug-related SAEs (52.7% versus 30.4%) were higher for treatment with PEM+LEN group compared with TPC. Likewise, dose interruptions (69.2% versus 27.1%), reductions (66.5% versus 12.9%) and discontinuations (33.0% versus 8%) due to AEs occurred more in the PEN+LEN arm than the TPC arm (CS B.2.10.1.2, Table 14), and discontinuations due to AEs were higher for lenvatinib (30.8%) than for pembrolizumab (18.7%).

Duration of exposure was longer in the PEM+LEN arm than the TPC arm; median (range) duration of exposure in days was 231.0 (1.0-817.0) for PEM+LEN and 104.5 (1.0-785.0) for TPC (see CS B.2.10.1.1, Table 13). Following adjustment for duration of exposure (see Table 13), lower rates of Grade 3 to 5 AEs and deaths were evident in the PEM+LEN arm compared with the TPC arm and SAEs were more similar between the two groups. Dose modifications, interruptions and reductions due to AEs remained higher in the PEM+LEN arm (Table 13).

There were more interruptions and discontinuations of treatment with LEN than PEM (see Table 15, section B.2.10.1.2 in the CS).

Table 13: Exposure-adjusted adverse event summary (KEYNOTE-775)

AE, event count rate (events/100 person-months)	PEM+LEN (n=406)	TPC (n=388)
Total exposure in person-months	3919.48	1765.17
One or more AE	9091 (231.94)	4526 (256.41)
No AE	1 (0.03)	2 (0.11)
Drug-related AEs	5221 (133.21)	2703 (153.13)
Toxicity grade 3-5 AEs	1216 (31.02)	861 (48.78)
Toxicity grade 3-5 drug-related AE	726 (18.52)	609 (34.50)
SAEs	398 (10.15)	178 (10.08)
Treatment-related SAEs	202 (5.15)	72 (4.08)
Dose modification due to and AE	1486 (37.91)	328 (18.58)
Dose interruption due to an AE	830 (21.18)	203 (11.50)
Dose reduction due to AE	594 (15.16)	84 (4.76)
Deaths	23 (0.59)	19 (1.08)
Deaths due to AEs	6 (0.15)	8 (0.45)
Discontinuations due to AEs	196 (5.00)	41 (2.32)
Discontinuation due to treatment-related AEs	156 (3.98)	31 (1.76)
Discontinuation due to SAE	95 (2.42)	15 (0.85)
Discontinuation due to a treatment-related SAE	64 (1.63)	8 (0.45)

Abbrevations: AE, adverse event; PEM+LEN, pembrolizumab with lenvatinib; SAE, serious adverse event TPC, treatment of physician's choice. Source: adapted from CS B.2.10.1.2, Table 15

The ERG agree that the specific adverse events from KEYNOTE-775 were consistent with what would be expected for the study treatments (see CS B.2.10.1.3, Table 16). Serious adverse events (SAEs) were also higher with PEM+LEN than with TPC (52.7% vs 30.4%; see CS B.2.10.1.7, Table 22).

The Company state that after adjusting for duration of exposure, most specific adverse events were lower or similar in the PEM+LEN arm compared with the TPC arm. The ERG noted that whilst this statement is not incorrect, there were some adverse events that remained higher with PEM+LEN than with TPC, including endocrine disorders, diarrhoea, decreased weight and appetite, hypertension and musculoskeletal and connective tissue disorders (CS Appendix R.3, Table 54).

AEs of special interest were provided in Tables 17 and 18, section B.2.10.1.3 of the CS, with the most common AEs of special interest in the PEM+LEN arm being hypothyroidism (57.6%), hyperthyroidism (11.6%), colitis (4.7%), skin reactions (3.2%) and infusion reactions (3.0%).

Treatment-related adverse events (TRAEs) are shown in Table 14, with hypertension, hypothyroidism, diarrhoea, nausea, and decreased appetite all reported in ≥ 30% of the PEM+LEN arm and nausea, anaemia, neutropenia and alopecia reported in ≥ 30% of the TPC arm. Grade 3 to 5 TRAEs (77.8% vs. 59.0%) and treatment-related SAEs (33.3% vs. 14.2%) were higher in the PEM+LEN than the TPC arm. There was a higher incidence of discontinuations due to TRAEs in the PEM+LEN compared with the TPC arm; discontinuations due to TRAEs were higher for lenvatinib than pembrolizumab (22.7% vs. 9.9%).

Table 14: Summary of treatment-related AEs (incidence ≥ 10% in one or more arms) in the KEYNOTE-775 trial (safety all-comer population)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
One or more treatment-related AE	395 (97.3)	364 (93.8)
Hypertension	248 (61.1)	4 (1.0)
Hypothyroidism	221 (54.4)	0 (0.0)
Diarrhoea	171 (42.1)	42 (10.8)
Nausea	158 (38.9)	157 (40.5)
Decreased appetite	149 (36.7)	64 (16.5)
Fatigue	113 (27.8)	92 (23.7)
Proteinuria	102 (25.1)	4 (1.0)
Vomiting	99 (24.4)	59 (15.2)
Weight decreased	90 (22.2)	7 (1.8)
Arthralgia	84 (20.7)	17 (4.4)
Palmar-plantar erythrodysaesthesia syndrome	84 (20.7)	3 (0.8)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
Dysphonia	76 (18.7)	2 (0.5)
Asthenia	75 (18.5)	76 (19.6)
Stomatitis	70 (17.2)	46 (11.9)
Alanine aminotransferase increased	63 (15.5)	14 (3.6)
Anaemia	58 (14.3)	150 (38.7)
Aspartate aminotransferase increased	58 (14.3)	12 (3.1)
Myalgia	54 (13.3)	13 (3.4)
Headache	53 (13.1)	14 (3.6)
Rash	47 (11.6)	6 (1.5)
Mucosal inflammation	45 (11.1)	35 (9.0)
Platelet count decreased	43 (10.6)	20 (5.2)
Blood thyroid stimulating hormone increased	40 (9.9)	1 (0.3)
Hyperthyroidism	39 (9.6)	1 (0.3)
Hypomagnesaemia	38 (9.4)	12 (3.1)
Constipation	36 (8.9)	51 (13.1)
Dry mouth	33 (8.1)	9 (2.3)
Dysgeusia	32 (7.9)	26 (6.7)
Lipase increased	32 (7.9)	2 (0.5)
Thrombocytopenia	31 (7.6)	22 (5.7)
Abdominal pain	30 (7.4)	13 (3.4)
Abdominal pain upper	28 (6.9)	28 (6.9)
Pruritus	27 (6.7)	7 (1.8)
Blood alkaline phosphatase increased	26 (6.4)	5 (1.3)
Pyrexia	26 (6.4)	26 (6.4)
Epistaxis	25 (6.2)	7 (1.8)
Hypertriglyceridaemia	24 (5.9)	1 (0.3)
Neutropenia	22 (5.4)	127 (32.7)
Blood creatinine increased	21 (5.2)	2 (0.5)
Leukopenia	20 (4.9)	47 (12.1)
Alopecia	17 (4.2)	117 (30.2)
Neutrophil count decreased	17 (4.2)	93 (24.0)
Lymphopenia	15 (3.7)	26 (6.7)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
White blood cell count decreased	15 (3.7)	58 (14.9)
Lymphocyte count decreased	10 (2.5)	22 (5.7)
Neuropathy peripheral	8 (2.0)	21 (5.4)
Febrile neutropenia	1 (0.2)	21 (5.4)

Abbreviations: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Source: CS B.2.10.1.4, Table 19

The most frequently reported Grade 3 to 5 TRAEs were hypertension, decreased weight, decreased appetite, and diarrhoea in the PEM+LEN arm and neutropenia, decreased neutrophil count, anaemia, decreased white blood cell count, leukopenia, and febrile neutropenia in the TPC arm (see CS, B.2.10.1.6, Table 21). The most frequently reported treatment-related SAEs (incidence ≥1%) for PEM+LEN were hypertension, colitis, decreased appetite, vomiting, diarrhoea, pyrexia, and acute kidney injury and the most frequently reported treatment-related SAEs for TPC were febrile neutropenia, neutropenia, and anaemia.

The Company state that deaths due to AEs were similar in the two trial arms and the ERG agrees with this: there were six deaths due to AEs in the PEM+LEN arm and eight in the TPC arm. The six deaths related to AEs in the PEM+LEN arm were considered to be treatment-related: one death was considered to be related to both pembrolizumab and lenvatinib (due to multiorgan dysfunction syndrome), three deaths were considered to be related to lenvatinib (one each due to cerebrovascular accident, right ventricular dysfunction and myelodysplastic syndrome), and one death was considered to be related to pembrolizumab (due to colitis). The eight deaths related to AEs in the TPC arm were considered to be related to doxorubicin (two due to pneumonia, and one each due to aspiration, pulmonary embolism, cardiogenic shock, toxic cardiomyopathy, cardiac failure, and sepsis).

Adverse events in KEYNOTE-146

Safety data from KEYNOTE-146 were provided in Appendix F of the CS (see CS Appendix F, Table 18 for a summary of all AEs up until Jan 10 2019 and CS Appendix F, Table 20 for a summary of all AEs up until Aug 18 2020). Table 15 provides a summary of TRAEs from this study. The ERG agrees that the data presented in Appendix F of the CS were broadly consistent with the safety data from KEYNOTE-775. The Company did not provide the CSR for

KEYNOTE-146. The ERG was unable, therefore, to verify the safety data provided for this study against the CSR.

Table 15: Overview of treatment-related adverse events in the KEYNOTE-146 trial (August 18, 2020)

Parameter, n (%)	Previously treated EC[a] (n = 108)
Patients with any treatment related AEs	104 (96.3)[a]
Patients with treatment related AEs leading to study-drug discontinuation[b]	23 (21.3)
Both lenvatinib and pembrolizumab	9 (8.3)
Lenvatinib[c]	19 (17.6)
Pembrolizumab[d]	17 (15.7)
Patients with treatment related AEs leading to study-drug dose reduction of lenvatinib	73 (67.6)
Patients with treatment related AEs leading to study-drug interruption[b]	80 (74.1)
Both lenvatinib and pembrolizumab	34 (31.5)
Lenvatinib[c]	77 (71.3)
Pembrolizumab[d]	47 (43.5)

Abbreviations: AE: adverse event; EC: endometrial cancer.

Notes: a, 94 (87.0%) and 10 (9.3%) patients experienced Grade ≤3 and Grade ≥4 treatment related AEs, respectively; b, Drug action taken is for lenvatinib or/and pembrolizumab; c, Drug action taken for lenvatinib, regardless of action taken for pembrolizumab; d, Drug action taken for pembrolizumab regardless of action taken for Lenvatinib.

Source: CS Apppendix F, Table 19

3.3. Additional clinical evidence submitted

No indirect treatment comparison or standard meta-analyses were presented. The ERG considered these decisions to be generally appropriate in light of the presence of relevant head-to-head data. The ERG agreed that it was not feasible to conduct a network meta-analysis due to the lack of connecting nodes. The ERG considered it could have been feasible to construct MAIC(s) between PEM+LEN and those comparators not trialled head to head e.g. paclitaxel monotherapy, but also noted significant uncertainty and limitations associated with bringing together data from a wide range of sources.

In considering the feasibility of conducting an indirect treatment comparison, the company discussed the Endometrial Cancer Health Outcomes – Europe (ECHO) study.[13] This is unpublished and as such was not identified through the SLR nor its methods and results included in the main clinical effectiveness section. This was a retrospective, multicentre chart review real-world evidence study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC patients previously treated with systemic therapy. Data from the UK cohort were presented. This comprised [redacted] eligible patients aged at least 18 years at the time of advanced or recurrent endometrial cancer diagnosis, who were not considered a candidate for curative-intent surgery, did not participate in any other endometrial cancer-related clinical trials during treatment and who had a known medical history from the date of advanced or recurrent endometrial cancer diagnosis. Eligible patients also did not have any prior malignancy active within the past three years, except from locally curable cancers that had been cured.

The majority of patients [redacted] were treated with [redacted] with the remainder [redacted] receiving [redacted] The data were re-weighted to exclude treatments considered to be investigative. Clinical advice to the ERG indicated that the proportion of patients with clear cell histology ([redacted] data provided in clarification response) was far in excess of what would be expected in a UK setting. The median OS from the start of second-line systemic therapy was [redacted] The company noted that the survival outcome in ECHO was comparable to the control group in the pivotal KEYNOTE-775 trial. The ERG noted that there was very limited methodological information available about the ECHO study.[13]

3.4. Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook additional searches (see Appendix A) to identify any evidence that had not been identified by the company. The ERG identified a small number of conference abstracts that had not been included by the company. However, the company did not provide a full list of excluded articles from the full-text screen of the interventional SLR, so the ERG was unable to comment on whether the company identified and excluded these abstracts or did not identify them. The ERG considered that the additional abstracts, while potentially eligible for the interventional SLR, did not provide additional data that would enhance the already identified clinical effectiveness evidence base.

3.5. Conclusions of the clinical effectiveness section

The ERG considered that the company's SLRs had identified the relevant evidence related to PEM+LEN and key comparators, except that the ECHO study on comparator treatments could not be identified through the SLR as it was unpublished. The ERG considered that the pivotal KEYNOTE-775 trial covered the relevant outcomes in the NICE final scope.[4] The ERG considered that generally the company's SLR and included trial were adequately described, although certain information was not described in sufficient detail. The ERG considered that the KEYNOTE-146 study which served as supplementary clinical evidence for model validation purposes was not well described in the CS, but further information was available through a published protocol identified by the ERG. The ERG requested further information on KEYNOTE-146 via NICE, but the provision of this information was refused, inhibiting a full critique of this study which informs the model validation. The ERG also considered that the unpublished ECHO study,[13] which also served for model validation purposes, was not described in adequate detail.

There was one pivotal clinical trial that informed the base case economic model – KEYNOTE-775. This was a multi-centre, open-label, randomised Phase III trial comparing PEM+LEN with treatment of physician's choice (paclitaxel or doxorubicin) for people with advanced, metastatic or recurrent endometrial cancer, previously treated with platinum-based therapy who are not able to receive curative surgery or radiation. The ERG was satisfied that all relevant studies were identified and that the pivotal KEYNOTE-775 trial was generally of high quality and well reported. The ERG was satisfied that the company's decision to not conduct an ITC was appropriate given the existence of a suitable directly comparative trial.

The ERG was satisfied that there was evidence for a statistically significant benefit in the KEYNOTE-775 trial for both OS and PFS for patients on PEM+LEN compared to patients on physician's choice of doxorubicin or paclitaxel. In the subgroup results, the ERG noted that the benefit of PEM+LEN, while statistically significant in both the pMMR and dMMR subgroups, was consistently greater in the dMMR subgroup.

The ERG considered that there were no key issues in the clinical effectiveness evidence base.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company conducted SLRs to identify existing cost-effectiveness evidence, health related quality of life (HRQoL) evidence, and cost and resource use evidence of PEM+LEN and comparator treatments, in adult patients (aged 18 years and older) with endometrial cancer limited to recurrent (Stage I and II), Stage III/IV, metastatic, irrespective of line of therapy.

In Appendix G, the company stated that an initial search was conducted on May 6, 2019, which included studies relevant to advanced/metastatic (stage III and IV) endometrial cancer between 1999 and 2019. An updated search was conducted on January 6 and November 8, 2021 which expanded the inclusion criteria to include recurrent early stage (stage I and II) endometrial cancer patients in addition to advanced/metastatic patients.

Table 16: Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix G.1.1 and Tables 25, 28.	The searches of bibliographic databases and grey literature sources are considered broadly appropriate.
Inclusion criteria	Appendix G.1.2 and Table 21	The company excluded studies prior to 1999, studies reporting clinical data only, simple costing studies, those studies that did not report model outputs and studies which included non-pharmaceutical interventions. The ERG considered the company's inclusion criteria to be broadly reasonable.
Screening	Appendix G.1.4	Studies (titles and abstracts) were independently assessed by two reviewers using the basic selection criteria. Eligible studies were screened at full text stage by two independent reviewers and any discrepancies were reconciled by a 3rd independent reviewer. The ERG considered the company's screening methods to be broadly reasonable.
Data extraction	Appendix G.1.4	The company state that data extraction was conducted systematically based on a predefined data extraction template in

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		line with standards required for HTA purposes. This appeared reasonable.
QA of included studies	Appendix G.1.5	QA was completed using the Drummond checklist, as recommended by NICE. The ERG considers the QA to be appropriate.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; QA, quality assessment

Table 17: Summary of ERG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix H.1.1 and Appendix G.1.1	The searches of bibliographic databases and grey literature sources are considered broadly appropriate.
Inclusion criteria	Appendix H.1.2 and Table 30	The inclusion criteria as outlined in Table 30 were considered to be mostly reasonable. The company stated that studies reporting HRQoL values only were excluded i.e. those reporting HRQoL scores without utility or disutility values.
Screening	Appendix H.1.4	The company stated that '*the same selection process as described in Appendix G.1.3 was used for the SLR conducted for utilities.*' The ERG assumed that the company used the same screening strategy as per G.1.4, which is considered appropriate.
Data extraction	Appendix H.1.4	It appeared that the company used the same data extraction approach as per G.1.4, which is considered appropriate.
QA of included studies	Appendix H.1.5	QA was completed using the Drummond checklist, as recommended by NICE. The ERG considers the QA to be appropriate.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; QA, quality assessment

Table 18: Summary of ERG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix I.1 and Table 37	The searches of bibliographic databases and grey literature sources are considered broadly appropriate.
Inclusion criteria	Appendix I and Table 35	The search for cost and healthcare resource use studies was restricted to those in a US and UK setting. The ERG considered this restriction to be reasonable.
Screening	Appendix I and I.1	The same independent two reviewer screening approach appeared to have been used for costs and healthcare resource use studies, as for economic evaluations. The ERG considered this to be reasonable.
Data extraction	Appendix I.1	The company identified 3 studies which were considered generalisable to the UK, however these were not used in the appraisal, as reporting of data were considered too limited. See section 4.2.9 for further commentary on the sources and modelled inputs used by the company for costs and healthcare resource use.
QA of included studies	Appendix I.1	Not mentioned by the company.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 19: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate, which captured the health benefit to patients. The company did not include carer disutility.

Attribute	Reference case	ERG comment on company's submission
Perspective on costs	NHS and PSS	NHS and PSS as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis and presented pairwise results.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A 40-year time horizon was used in the company's base case which was considered to be a lifetime horizon. The ERG considered this to be appropriate.
Synthesis of evidence on health effects	Based on systematic review	Clinical data used in the economic model was derived from the pivotal KEYNOTE-775 study. The ERG noted that median OS and PFS were reached. KEYNOTE-775 data were used to estimate modelled OS and PFS outcomes for both the intervention arm (PEM+LEN) and the comparator treatment arm (doxorubicin or paclitaxel) treatment. Information from KEYNOTE-146 and ECHO was provided as suporting data by the company to validate OS.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	QoL data were captured directly from patients in the KEYNOTE-775 study using the EQ-5D-5L. These values were then mapped to EQ-5D-3L values.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Utility values were estimated according to time to death. The company used a linear mixed effects regression model which was fitted to HRQoL data from KEYNOTE-775.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns.

Attribute	Reference case	ERG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use and costs were based on NHS reference costs and the 2019/20 PSSRU, as appropriate. The company also used prior NICE appraisals for ovarian, cervical and uterine cancers to estimate resource frequency.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5% as appropriate. However estimates of life years were discounted at 0%. The ERG did not consider this to be appropriate.

Abbreviations: EQ-5D-3L, EuroQol 5 dimension 3 level; EQ-5D-5L, EuroQol 5 dimension 5 level; ERG, Evidence Review Group; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal

4.2.2. Model structure

The model is a partitioned survival model (PSM; CS document B, section B.3.2.2) which is a common structure for modelling late stage cancer. Patients are defined as residing in one of three health states: progression-free (PF), progressed (PD) or dead, and the cycle length is 1 week. The advantage of partitioned survival models is that they are relatively simple and straightforward to implement, based on extrapolations of overall and progression-free survival curves from a clinical trial. Overall, the ERG considered the model structure to be appropriate for decision making.

As a general note, the key disadvantage of these models is that most implementations tend to draw on only one source of evidence (typically the key Phase III study for the product in question) for both baseline prognosis and treatment effect. NICE guidelines state that evidence on outcomes should be obtained from systematic review and meta-analysis provided there are sufficient relevant and valid data (NICE 2013; sections 5.2.2 and 5.2.8). As such it would have been preferable for the company to make use of a meta-analysis of appropriate data for baseline prognosis and/or treatment effect rather than the single KEYNOTE-775 study.

4.2.3. Population

The patient population within the company's economic analysis is adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and

who are not candidates for curative surgery or radiation. The ERG noted several points of uncertainty surrounding company's positioning and population.

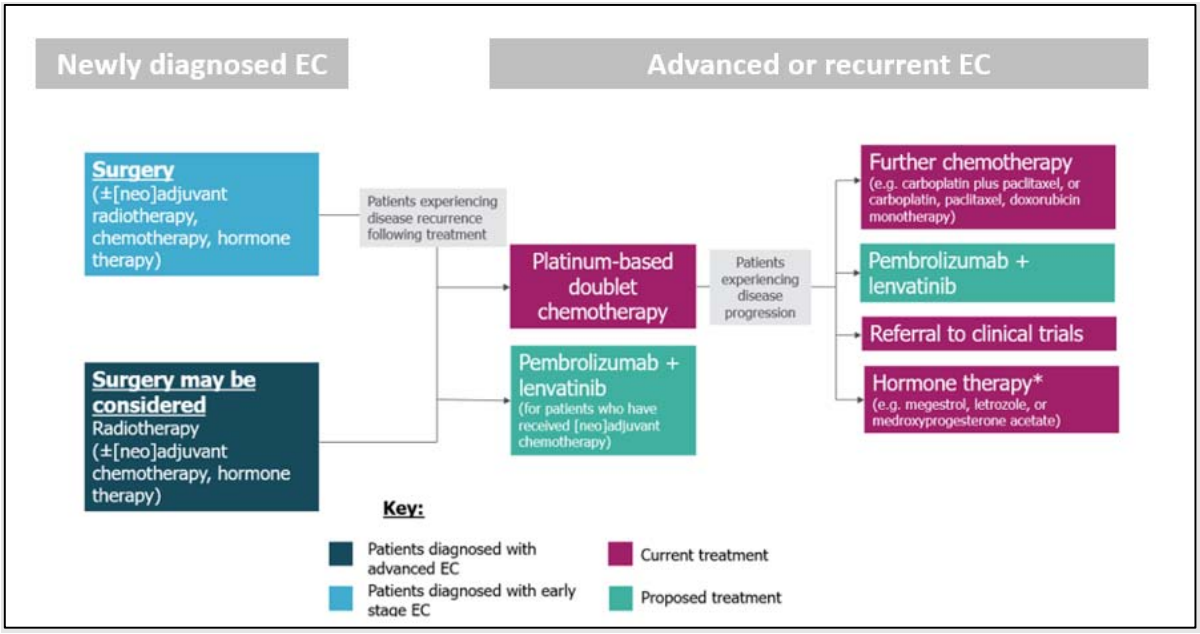
4.2.3.1. Modelled patient baseline characteristics

Modelled patient characteristics were based on patients from KEYNOTE-775. Within this pivotal study, average patient weight was 70.5 kg and median patient age was 63.5 years. The ERG noted KEYNOTE-775 was a multi-centre study, therefore patient characteristics used in the model were not specifically from a UK cohort. Due to generalisability concerns, the ERG asked clinical experts to comment on the appropriateness of the patient baseline characteristics. Based on responses, UK patients are likely to be heavier and older than the company's baseline characteristics. It was highlighted that endometrial cancer is most common amongst obese patients and that it usually affects older women i.e. between the ages of 75 and 79 years. In order to explore this uncertainty with respect to impact on cost effectiveness, the ERG conducted scenario analyses which used a higher weight and age (see Section 6.2.8 and 6.2.9). Whilst these scenario analyses did not have a meaningful effect on the ICER, they were included in the ERG's preferred base case as they were considered to better reflect UK patients.

4.2.3.2. Positioning

As noted in Section 2.4 and in Figure 1 below, the company appear to be positioning PEM+LEN as a treatment option following platinum-containing chemotherapy provided in the advanced/recurrent setting and secondly for those with recurrent, advanced or metastatic cancer who had received platinum-based chemotherapy in the (neo)adjuvant setting. The ERG noted that for the latter positioning, the most appropriate comparator is re-challenge with platinum-containing doublet chemotherapy and that the treatments provided in KEYNOTE-775 were primarily doxorubicin or paclitaxel (and not specifically platinum re-challenge). The company did provide a scenario analysis which assumed a proportion of patients received carboplatin in combination with paclitaxel as re-challenge (see p.65).

Figure 1: Positioning of PEM+LEN



Abbreviation: EC, endometrial cancer

4.2.3.3. Lack of subgroup analyses

Whilst the ERG noted the population to be consistent with the NICE final scope[4] and KEYNOTE-775 trial population, the appropriateness of assessing cost effectiveness in potentially clinically relevant subgroups was not explored. As noted in Section 3.2.3.1, the company conducted clinical subgroup analysis in dMMR and pMMR patients, however no cost effectiveness results were provided. During clarification with the company (B19), the ERG asked for further rationale as to why an economic analysis was not conducted based on MMR subgroups. The company stated that *'The indication covers the overall patient population irrespective of MMR status. As such the cost-effectiveness analyses focus on the overall patient population and such claim was not made by MSD as it would deviate from the final scope issued by NICE.'* Whilst the ERG agree that the overall population covered by the indication is in alignment with the NICE final scope, clinical opinion to the ERG suggested that prognosis and treatment options provided to patients may vary depending on MMR status.

As outlined in Section 4.2.4, clinical opinion to the ERG suggested that monotherapy immunotherapy treatments are currently used in patients with dMMR (due to high response to treatment). However, monotherapy appears to have limited efficacy in patients with pMMR. Clinical opinion to the ERG included interest in using PEM+LEN within the pMMR subgroup, as

the dual combination of PEM+LEN is likely to be more effective than single agent use. The ERG considered the lack of cost effectiveness results for MMR subgroups to be an area of uncertainty, particularly the lack of results for pMMR patients, as PEM+LEN is most likely to be used in this subgroup in practice.

4.2.4. Interventions and comparators

Pembrolizumab plus lenvatinib (dual therapy) is compared with a composite comparator of doxorubicin or paclitaxel, which the company state is reflective of physician's choice or TPC. This represents a blended comparator whereby the company assumed that 74.5% of patients received doxorubicin and 25.5% received paclitaxel. Based on clinical input to the ERG, doxorubicin or paclitaxel were considered appropriate comparators and were likely to be displaced by PEM+LEN, however choice of treatment varied, with most experts indicating that paclitaxel is used more than doxorubicin. In order to explore uncertainty surrounding the proportion of patients receiving doxorubicin or paclitaxel, the ERG conducted scenario analyses which varied proportions (see Section 6.2.2). Based on clinical input received, the ERG's preferred base case assumed 50% of patients received doxorubicin and 50% received paclitaxel.

Initially, the ERG had some concerns surrounding the company's assumption that doxorubicin and paclitaxel were comparable in terms of efficacy. Based on clinical input to the ERG, doxorubicin and paclitaxel were likely to be similarly '*effective or ineffective*', however choice between paclitaxel and doxorubicin would be based on the side-effect profile (cardiac vs renal).

The ERG noted that hormone therapy was not considered as an appropriate comparator within the company's economic analysis. The company justified the exclusion of hormone therapy on the basis that it is only used *'if all other treatment options are exhausted or patients cannot tolerate further lines of chemotherapy'*. Clinical opinion to the ERG, noted that hormone therapy is primarily given as a palliative treatment and therefore agreed with the company's decision to exclude it. The ERG are aware of a recent NICE appraisal for endometrial carcinoma dostarlimab (TA779),[3] which was recommended for patients with recurrent or advanced dMMR/MSIH EC who have progressed on or after platinum-based chemotherapy. Given that this is relatively recent guidance, published in March 2022, the ERG considered the exclusion of dostarlimab to be appropriate. Furthermore, dostarlimab is recommended for a subgroup of patients, which is narrower than the population for which pembrolizumab is indicated.

As noted on p. 70 of the CS (document B), the company conducted a scenario analysis, which compared PEM+LEN to a mixed chemotherapy arm. Treatment costs for this comparator were based on a weighted approach which used data from ECHO i.e. the mixed chemotherapy arm was assumed to consist of [redacted] % paclitaxel, [redacted] % doxorubicin, [redacted] % carboplatin, and [redacted] % carboplatin plus paclitaxel [as re-challenge]. Results were not sensitive to this analysis. The ERG noted that this analysis was subject to several simplifying assumptions, namely that the mixed chemotherapy arm was assumed to have equivalent efficacy to that of the TPC arm in KEYNOTE-775.

4.2.5. Perspective, time horizon and discounting

All costs and outcomes were estimated from a NHS and PSS perspective as appropriate. The time horizon used in the analysis was 40 years, which was considered by the company to be a lifetime horizon. The ERG noted that a 40 year time horizon had been used previously several ovarian cancer appraisals including niraparib (TA528)[19] and (TA673),[20] and a 30 year time horizon in others including rucaparib (TA611)[21] and olaparib (TA620).[22] Within the recent appraisal of dostarlimab (TA779),[3] for the treatment of patients with recurrent or advanced dMMR/MSI-H endometrial cancer, a 40 year time was used. Overall the ERG considered the time horizon was sufficiently long to adequately capture the differences in costs and outcomes between treatments and was broadly in line with appraisals for similar conditions. Furthermore, the company provided a scenario analysis which reduced the time horizon to 30 years, however this did not have a significant impact on results.

With respect to discounting used in the model, both costs and QALYs were discounted at 3.5%, in line with NICE guidance. However, estimates of life years were not discounted. NICE guidance states that "the same annual discount rate should be used for both costs and benefits (currently 3.5%)." [NICE 2013, paragraph 5.6.1].[23] The ERG conducted an analysis which discouted life years at 3.5%. This was included as part of the ERG's preferred base case (see Section 6.3).

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Critique of general modelling approach

The clinical data used to model PFS, OS and time-on-treatment (ToT) were taken from the phase III KEYNOTE-775 study (data cut 26 October 2020). Due to the lack of long-term data

from this trial (and to assess the cost effectiveness of PEM+LEN over a lifetime horizon), the company extrapolated OS and PFS beyond the clinical trial's last follow-up.

The company considered several modelling approaches, including a 'one-piece' approach (standard parametric) and 'two-piece' (piecewise KM followed by parametric) approach independently fitted to each treatment arm. As noted in Appendix P of the CS, propotional hazards-based methods were not considered to be a viable means to estimate OS, citing Schoenfeld residuals and proportional hazard plots. The ERG agreed that a proportional hazards modelling approach was not justifiable on the basis of log-cumulative hazard plots (Document B Appendix, figures 26 and 30). The company considered modelling OS or PFS using a one-piece parametric survival curve; however, the company considered these fits implausible/inappropriate (sections B.3.3.3 and B.3.3.4). The ERG agreed that the one-piece approach appeared not to fit the hazard function well, most notably for OS (CS document B, figures 13 and 14).

In the base case analysis the company opted for the two-piece approach to estimate both OS and PFS in the trial period of both arms of KEYNOTE-775. The company argued (document B section 3.3.3.1; clarifications to B9, B11, B13) that the two-piece approach provided a good visual fit (adequate internal validity) and plausible extrapolated survival (adequate external validity).

The CS supplied plots of the modelled hazards for the one- and two-piece approaches in CS document B (figures 13, 14, 17, 18) for OS but not PFS. Within these figures was a curve labelled 'smooth spline estimate'. This was clarified by the company (responding to clarification questions B10 and B12) as a representation of the hazard function using many-knot (31) basis splines, as opposed to a flexible modelling approach of the type outlined in TSD 21 (e.g. restricted cubic spline). The ERG hereon terms the former the empirical hazard function. 'Zoomed-in' versions of some of these plots were supplied in clarification response section C. PFS hazard function plots for the two-piece approach were not provided in the CS but obtained in clarification response to B12 (figures 9 and 10).

The 'two-piece' approach used by the company uses an initial nonparametric (KM) fit followed by standard parametric fits to later data points. The ERG acknowledges that the two-piece or 'Liverpool approach' has been used in previous appraisals and is one possibility outlined in TSDs 14 and 21.[24,25] A criticism of the two-piece approach is that placement of the breakpoint (between KM and parametric) can be arbitrary. In the CS, the results of a Chow test to more

objectively set the breakpoint were cited, though these were only supplied after clarification (B6).

The ERG noted a range of issues with the two-piece approach. When comparing the two-piece fitted hazard to the empirical hazard (labelled 'smooth spline fit'), a failure to track the hazard function closely is apparent in all fitted two-piece models see (e.g. clarification response figure 8). Sudden changes in hazard at the breakpoint, mentioned in TSD21[25] as potentially implausible and a drawback of the two-piece approach, are apparent with some parametric model choices in the two-piece approach (see e.g. doc B figs 17 and 18). A 26-week breakpoint was selected for OS and 10-week breakpoint for PFS on the basis of Chow test results, visual inspection of the hazard function and a preference for earlier breakpoints, thereby providing more data for parametric fitting in the second piece (doc B p80). Taking the Chow test at face value, the plots supplied at clarification (B6) do not appear to clearly support the 10-week breakpoint selection for PFS (clarification figs 4 and 5), nor the 26-week OS breakpoint in the TPC arm (clarification fig 3). Moreover, the ERG believes the Chow test to be an invalid approach because it is inappropriate to use a 'test statistic surface' to determine relevant breakpoints, and in the event Chow test statistics revealed a range of plausible breakpoints.

The company chose not to use other flexible fitting approaches outlined in TSD 21[25] in the CS, and declined to do so for clarification (see e.g. clarification responses B9, B11). It is not possible therefore to assess any improvement in fit over the two-piece approach, nor the plausibility of any extrapolations under an improved fit. The ERG recommends restricted cubic splines are applied and assessed as these are the best combination of flexibility and generalisability given the hazard functions in evidence.

The company introduced further constraints to survival modelling in the form of capping to ensure that PFS and ToT never exceed OS, and to ensure OS is capped to general mortality (further discussed in section 4.2.6.2).

Validation of extrapolations

The company appeared to have presented its selected fits to clinicians who indicated that they were plausible (CS document B section 3.3.3.1). The CS indicates that 'All participants were more comfortable predicting plausible extrapolations for the TPC arm, given their experience in treating patients with chemotherapy regimens in this treatment area'. In the TPC arm clinicians to the company favoured certain extrapolations (the 'bottom group of curves in figure 16'

representing Weibull, Gompertz and exponential; see clarification response C2). It is not clear to the ERG from the CS that clinicians *selected* from the extrapolating model(s) in the PEM+LEN arm, though it appears they accepted the company's choice (log-logistic) was plausible.

The company attempted to validate the extrapolated curves with the use of longer-term information. The company marshalled information from other studies (KEYNOTE-146 for PEM+LEN and ECHO for TPC) to validate its extrapolations. This aspect is discussed in more detail in section 4.2.6.4 . For the TPC arm the ERG found reporting to be inadequate for the purpose, and there were marked discrepancies in patient characteristics between the ECHO and KEYNOTE-775 TPC arm. For the PEM+LEN arm, the supporting study (KEYNOTE-146) was comparable in many ways to the KEYNOTE-775 arm, though some information remained unavailable (e.g. time since diagnosis).

Specific issues with base case extrapolations

Turning to the choice of parametric model under the two-piece approach (but noting the ERG's preference for a restricted cubic spline approach as discussed above), the ERG disagreed with the company base-case choice for OS in the TPC arm.

For OS, the empirical hazard function declines at later follow-up times in both TPC and PEM+LEN arms (clarification figs 7 and 8). The company selected a model to track this decline in the PEM+LEN arm (log-logistic selected), but not so the in the TPC arm (exponential selected). This is depicted in Figure 2 below. The company argued (CS document B, p. 85) that 'the hazards in the PEM+LEN arm have a strong decreasing trend after 26 weeks, which does not occur in the TPC arm'. However, the ERG noted a decline in hazards from about 60 weeks in the TPC arm, albeit delayed compared to PEM+LEN and with less precision, and in this context questions the selection of a uniform hazard (exponential model).

Extrapolated OS (up to 10 years) for ERG and company curve fit selections is shown in

Figure 3. In the TPC arm, higher survival is predicted in the longer term by the ERG choice (log-logistic) than the company (exponential). The ERG choice responds to clinicians advising the ERG: there was some variation in responses, however on balance long-term OS extrapolation under the company choice in the TPC arm was considered an underestimate. The estimates of OS within and beyond the trial period at 1, 2, 5 and 10 years are shown in Table 20.

Based on the supplied survival curves for PFS (CS document B figures 21 and 22), there is less divergence between models and the ERG has not altered the company's base case choices as these were viewed to be reasonable. The ERG noticed (but could not explain) the relatively jagged form of the empirical hazard supplied for PFS in the TPC arm (clarification response figure 10).

Figure 2: Company and ERG base-case model choices (after 26-week breakpoint) with empirical hazard (black line) for OS (ERG-constructed figure)

Abbreviations: CS, company submission; ERG, Evidence Review Group; KN, KEYNOTE (trial); OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treating physician's choice

Source: company-supplied survival data and parameter estimates

Figure 3. Fitted OS models with CS and ERG selections, extrapolated to 10 years

[redacted]

Abbreviations: CS, company submission; ERG, Evidence Review Group; KN, KEYNOTE (trial); OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; TPC, treating physician's choice

Table 20: Survival estimates from the main trial (KEYNOTE-775) and base case extrapolations by ERG and company

Years		1	2	5	10
PEM+LEN	KEYNOTE-775	[redacted]	[redacted]	-	-
	ERG/CS model (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]
	KEYNOTE-146	[redacted]	[redacted]	[redacted]	-
TPC	KEYNOTE-775	[redacted]	[redacted]	-	-

Years		1	2	5	10
	CS base case (exponential)	[redacted]	[redacted]	[redacted]	[redacted]
	ERG base case (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company submission; ERG, Evidence Review Group; PEM+LEN, pembrolizumab with lenvatinib; TPC, treating physician's choice

4.2.6.2. Capping of OS and PFS

As OS, PFS and ToT are modelled independently, the spreadsheet model implements capping to ensure that PFS and ToT never exceed OS. Furthermore OS is capped to general population mortality (CS document B, Section 3.2.2, p. 66). This is implemented in a 'hybrid' fashion. For example, overall survival at time t is set to be the minumum of the predicted overall survival at time t from the chosen OS model, and the overall survival at t-1 multiplied by 1-hazard of death in the general population:

$OS(t) = \min[OS_{pred}(t), OS(t-1)*(1-h_{pop}(t)]$

where $OS_{pred}(t)$ is the overall survival at time t predicted by the chosen survival function, and $h_{pop}(t)$ is the hazard of death in the general popuation at time t (i.e. for the age and gender of the subject patient).

Likewise, PFS is calculated in the same manner:

$PFS(t) = \min[PFS_{pred}(t), PFS(t-1)*(1-h_{OS}(t)]$

where $PFS_{pred}(t)$ is the PFS at t predicted by the chosen function, and $h_{OS}(t)$ is the hazard of overall survival at t, after adjusting for overall population mortality.

This hybrid approach is somewhat inconsistent. For example, in the latter case it mixes together the 'stock' of PFS survival as predicted by the chosen survival function, which is itself a function of the 'flows' of hazards predicted purely by the chosen survival function and the 'flows' of hazards capped for OS and population mortality. A simpler approach would be to cap OS at the minimum of OSpred and general population mortality, and to cap PFS at the minimum of PFS_{pred} and OS:

$OS(t) = \min[OS_{pred}(t), OS_{pop}(t)]$

$PFS(t) = \min[PFS_{pred}(t), OS(t)]$

where $OS_{pop}(t)$ is general population survival at t. We describe this as the 'simple' approach.

Alternatively, perhaps more plausibly, it could be argued that the *risk* (hazard) of death in patients with advanced EC each period should be the greater of that predicted by the chosen survival function and that experienced in the general population:

$OS(t) = OS(t-1) * (1 - \max[h_{OS,pred}(t), h_{pop}(t)])$

And likewise the hazard of progression or death should be the greater of that predicted by the chosen PFS survival function and that for overall survival (and by definition from the equation above, greater than the hazard of death for the general population):

$PFS(t) = PFS(t-1) * (1 - \max[h_{PFS,pred}(t), h_{OS,pred}(t), h_{pop}(t)])$

We describe this as the 'hazards' approach.

It should be noted that these alternative approaches were applied to both the PEN+LEN arm and the TPC (and mixed chemotherapy arms), as part of ERG scenario analyses. The impact of these alternative approaches is explored in the ERG's scenario analyses (see Section 6.2.10).

4.2.6.3. Treatment waning

The company did not include treatment waning in their economic model, on the basis of precendent and stated this was 'validated by long-term KN-146 data'. The appraisals described in the CS (document B, Table 24) to demonstrate non-applicability of treatment waning were for PARP inhibitors in ovarian cancer. During clarification, the ERG asked the company to provide additional rationale for excluding exploration of a waning in treatment effect. In clarification response B18, the company cited two additional pembrolizumab appraisals which did not use a treatment waning assumption (TA531:[26] untreated PD-L1-positive metastatic non-small-cell lung and TA357:[27] advanced melanoma after disease progression with ipilimumab). The company stated that as longer-term immunotherapeutic effects were demonstrated after stopping treatment in these appraisals, it could be expected that PEM+LEN would offer a sustained treatment effect. The ERG noted that it may not be appropriate to assume that PEM+LEN would mirror the treatment effect seen in these appraisals, on the basis that there would be differences across patient populations with respect to baseline characteristics, drug mechanisms, disease

type and treatments received. Furthermore, based on a review of dostarlimab TA779,[3] the ERG noted that treatment waning was considered as part of the company's base case.

In order to validate the company's decision to exlcude treatment waning, the ERG sought clinical expert opinion. Responses to the ERG were somewhat mixed and noted there to be a lack of data surrounding waning of effect. However on balance clinicians considered that after stopping treatment with PEM+LEN, there may be gradual waning. It was also noted that there would be patients who will relapse/experience disease progression. In order to explore uncertainty surrounding treatment waning, the ERG conducted a scenario analysis which included a treatment waning assumption. Results were highly sensitive to this analysis (see Section 6.2.10).

The company also stated (clarification B18) that treatment waning was not explored on the basis that long-term OS data from KEYNOTE-146 showed a durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN i.e. sustained OS in the form of a plateau (with 30% of patients alive at 5 years). However, the ERG noted that the latter part of the KM curve shown (CS document B, figure 9) is still subject to considerable censoring with small numbers at risk after 28 months, and confidence intervals may be wide. The confidence intervals were not shown and the company informed the ERG that the underlying data were not available (clarification response B7). Furthermore, based on clinical opinion to the ERG, 30% survival at 5 years is likely higher than in UK clinical practice. On the other hand in case of sufficient support for the notion that some patients are cured (best demonstrated through sufficient maturity and precision in survival curves), survival modelling may need to incorporate a cure fraction (TSD21 section 3.6).[25]

4.2.6.4. Validation of extrapolations

The population characteristics of the KEYNOTE-146 study, used to validate extrapolation in the KEYNOTE-775 PEM+LEN arm, are shown in Table 21, derived by the ERG from the CS. The ERG interpretation is that many characteristics are well-matched when available, but on the other hand the ERG observes the CS statement (Document B p.37) that 'KEYNOTE-146 and KEYNOTE-775 are heterogeneous in terms of study design and population'. Information is sometimes limited (see also section 3.2.1), and the ERG noted in particular that the time since diagnosis has not been supplied for KEYNOTE-146 (despite a request in clarification A13) and that the distribution of stages is only available for endometrioid cancers. This significantly limits the value of KEYNOTE-146 for validation of extrapolations.

Table 21: Comparison of baseline characteristics for PEM+LEN arms of KEYNOTE-775 and KEYNOTE-146 (EC subgroup).

Baseline characteristics		**KEYNOTE-775: PEM+LEN arm**	**KEYNOTE-146: endometrial cancer subgroup**	
			Previously treated	All
Age (mean)		63.2	65.1	65.3
Ethnicity (%)	Asian	20.7	4.6	4.0
	Black	4.1	5.6	5.6
	White	63.5	86.1	87.1
	Other [a]	2.7	3.7	3.2
ECOG status (%)	0	59.9	49.1	50
	1	39.9	50.9	50
	2	-	-	-
	3	0.2	-	-
MMR (%)	pMMR	84.2	87	-
	dMMR	15.8	13	-
PD-L1 (%)	+	-	49.1	48.4
	-	-	39.8	41.9
	N/A	-	11.1	9.7
FIGO grading (%) [b,c]	I	27	11.1	12.1
	II	7.8	17.6	17.7
	III	29	22.2	24.2
	IV	36	-	-
Histology (%)[d]	Clear cell	7.3	5.6	4.8
	Endometrioid [2]	59.2	50.9	54
	Serous [1]	25	32.4	31.5
Time since diagnosis (mean, years)		2.4	-	-
Prior treatment with (%)	monotherapy	-	33.3	29.8
	Platinum+taxane	-	98.1	91.1
Patients		Advanced recurrent or metastatic EC, progression after 1 prior systemic platinum-based chemo	No more than 2 previous systemic therapies	

Abbreviations: dMMR, deficient mismatch repair; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; N/A, not applicable; PD-L1, programmed death-ligand 1; PEM+LEN, pembrolizumab with lenvatinib; pMMR, proficient mismatch repair

Sources : Doc B Table 5 , Doc B Appendices Table 55

Notes:[a] pooled over small categories for 'Other' by ERG; [b] pooled over subcategories by ERG; [c] in KN146 for endometrioid cancers only – see clarification response A14; [d] pooled over subcategories by ERG. 1: serous + high-grade serous ; 2: endometrioid + endometrioid with squamous differentiation + high grade endometrioid + low grade endometrioid

The population characteristics of the ECHO study,[13] used to validate extrapolation of the KEYNOTE-775 TPC arm, are shown in Table 22, derived by the ERG from the CS. There are numerous characteristics that differ markedly between the cohorts, including [redacted]. There are further discrepancies e.g. proportion of dMMR patients.

The ERG has further concerns about the use of ECHO :

- limited information presented by the company to support its suitability for validation, and no study report, no protocol, no peer-reviewed publication available;
- offers only a short extrapolation period of [redacted] (updated from [redacted] in the CS – see clarification A15) even though it represents standard treatment; and
- [redacted] of patients in ECHO are on doxorubicin or paclitaxel.

A clinician advising the ERG indicated that in the UK population performance status was roughly in the proportions (0=10%, 1=50%, 2=30%, 3=10%), MMR status in the proportions (dMMR=30%, pMMR=70%) and in the relapsed setting histology of (endometrioid=40%, serous=40%, clear-cell=15-20% and mucinous= <5%). Comparing the supporting study (ECHO, KEYNOTE-146) characteristics to the routine UK population, the ERG noted:

- low proportion of performance status (as measured by ECOG) grades 2 or 3 in ECHO (compared to 30% and 10% respectively in the UK);
- a smaller proportion of MMRd (around [redacted]) in ECHO and a larger proportion (around [redacted]) in KN-146 compared to the UK (approximately 30%); and
- differences in the proportions of serous or endometrioid cancers in both studies compared to the UK.

The company further informs of the following difference (CS document B, p. 83): 'ECHO included some patients who received investigational treatments not routinely available in UK clinical practice as a subsequent treatment (such as PD-1/PD-L1 and VEGF/VEGFR inhibitors).

In order to obtain the fullest information for extrapolating the TPC arm, the ERG recommends extending the search for RWE on survival to include web searches for grey literature sources not included in bibliographic databases (e.g., UK cancer registries or reports derived from electronic health records). Searches for the company's RWE SLR were conducted in July 2020 and updating these searches may also identify additional evidence. Paclitaxel or doxorubicin in combination or alone could be informative. The ERG noted that the dostarlimab appraisal (TA779)[3] provided results on what may be a relevant cohort, but the information is confidential.

Should further external sources for validation be obtained, the ERG recommends carrying out a comparison of the population characteristics of any extrapolating studies to those of the target population (UK clinical practice), and consideration of adjusted extrapolations by standardising to the target population.

Table 22: Comparison of baseline characteristics for TPC arm of KEYNOTE-775 and RWE study ECHO.

Baseline characteristics		**KEYNOTE-775 : doxorubicin or paclitaxel arm**	**ECHO**
Age in years at initial diagnosis (mean)		61.5	[redacted]
Ethnicity (%)	White	59.1	[redacted]
	Black or African/ Caribbean-origin	3.4	[redacted]
	Middle Eastern/ North-African	-	[redacted]
	Asian	22.1	[redacted]
	Other	4.8	[redacted]
MMR Status (%)	dMMR	15.6	[redacted]
	pMMR	84.4	[redacted]
MSI status (%)	MSI-H/dMMR	-	[redacted]
	Non-MSI-H/pMMR	-	[redacted]
	Mixed	-	[redacted]
ECOG at recurrent or advanced diagnosis (%)	0	57.9	[redacted]
	1	42.1	[redacted]

Baseline characteristics		KEYNOTE-775 : doxorubicin or paclitaxel arm	ECHO
	2	-	[redacted]
	3	0.0	[redacted]
Radiation (%)		41.6	[redacted]
Histology [a] (%)	Clear cell	4.1	[redacted]
	Endometrioid [2]	61.1	[redacted]
	Serous [1]	27.6	[redacted]
	Mucinous [3]	0.2	[redacted]
Elapsed time in years from initial diagnosis (years, mean)		2.9	[redacted] [e]
Staging at initial diagnosis [b] (%)	I	33.4	[redacted]
	II	6.3	[redacted]
	III	30.7	[redacted]
	IV	29.6	[redacted]
Metastatic site(s) at diagnosis (%)		-	[redacted]
	Liver metastasis	23.6	[redacted]
	Distant [c] lymph node(s)	54.1	[redacted]
	Lung metastasis	36.5	[redacted]
	Bone metastasis	7.9	[redacted]
	Brain metastasis	0.5	[redacted]
	Pancreas	-	[redacted]
	Kidney	-	[redacted]
Treatment with doxorubicin or paclitaxel [d]	Yes	100%	[redacted]

Abbreviations: dMMR, deficient mismatch repair; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; pMMR, proficient mismatch repair; RWE, real-world evidence; TPC, treating physician's choice

Sources: Doc B table 5; clarification question response A11

Notes:[a] pooled over subcategories by ERG : 1: serous + high-grade serous ; 2: endometrioid + endometrioid with squamous differentiation + high grade endometrioid + low grade endometrioid; 3: low-grade mucinous + high-grade mucinous; [b] pooled over subcategories by ERG; [c] described as 'distant' in ECHO but not in KN775; [d] inferred from text; [e] ERG conversion from presumed reported months

4.2.7. Time-on-treatment and stopping rules

For ToT, the company investigated one-piece parametric survival models and applied stopping rules, derived from dosage/cycle limits for doxorubicin and pembrolizumab, to each selected

model. The company's base case analysis included a 24 month stopping rule for pembrolizumab and assumed that treatment with doxorubicin would be limited to a maximum lifetime cumulative dose of 500 mg/m². Based on clinical expert opinion to the ERG, these assumptions were considered to be reasonable. For completeness, the company conducted scenario analyses which assumed no maximum dosing rule for doxorubicin and which assumed a maximum duration of 6 months for paclitaxel. Results were not sensitve to these analyses.

Long term drug acquisition costs for lenvatinib, pembrolizumab and TPC were modelled using a generalised gamma curve. The ERG noted that pembrolizumab and lenvatinib were modelled seperately to account for the costs associated with each treatment, however ToT for doxorubicin and paclitaxel were not modelled separately, but rather as a sigle arm 'TPC' (see **Figure 4**). The company stated that this was due to the short duration of treatment and low costs associated with the treatments.

For pembrolizimab, lenvatinib and TPC, the company stated that the generalised gamma provided a plausible fit to the observed data from KEYNOTE-775. The company provided some scenario analyses to test the impact of alternative ToT assumptions on the ICER, which included the the use of an alternative parametric function (Weibull) for both arms, the assumption that ToT cannot exceed PFS (in both arms) and estimating ToT based on KM data, see Table 52, Section B.3.8.3 of the CS. The ICER was not sensitive to these analyses. The ERG considered that the most appropriate method of estimating drug costs was to cap ToT by PFS, as ToT should be largely coterminous with PFS i.e. progression would often trigger a change or desistance in treatment. The ERG conducted a scenario analysis based on this approach (and considered this as part of the ERG preferred base case). Results were not especially sensitive to this (see Section 6.2.7 and 6.2.10).

Figure 4: ToT extrapolation used in the company's base case

[redacted]

Abbreviations: KN, KEYNOTE (trial); OS, overall survival; LEN, lenvatinib; PEM, pembrolizumab; PEM+LEN, pembrolizumab with lenvatinib; ToT, time-on-treatment; TPC, treating physician's choice

4.2.8. Health-related quality of life

Quality of life data collected directly from patients in KEYNOTE-775 were used to derive health state utilities in the model. In KEYNOTE-775, patients were given the EQ-5D-5L to complete on day 1 of each cycle, for the equivalent of four cycle lengths and the end of treatment visit. On CS document B p. 101, the company stated that completion of HRQoL questionnaires following the end of treatment visit i.e. post treatment discontinuation, was not mandatory. The ERG noted that the EQ-5D-5L values were mapped to EQ-5D-3L values using the Van Hout cross walk method (as per NICE's position statement). In the base case analysis the company opted to use a time to death (TTD) approach to derive base case utilities (utilities presented in Table 23 below), as opposed to a progression status approach whereby values are presented based on whether patients are progression-free (PF) or have progressed diseased (PD).

Table 23: Time to death utility values used in the company's base case analysis

Time to death	Mean utility value
≥360 days	[redacted]
270 - 359 days	[redacted]
180 - 269 days	[redacted]
90 - 179 days	[redacted]
30 - 89 days	[redacted]
<30 days	[redacted]

To estimate TTD utility values for the six time-based modelled health states, the company used a linear mixed effects regression model which was fitted to HRQoL data from KEYNOTE-775. Explanatory variables were dummy variables for time to death less than 30 days, 30-90, 90-180, 270-360, greater than 360 and absence of AEs (grade 3 and above). (Note 180-270 days to death is therefore the default.)

Health state utilities were estimated assuming no AEs. The manufacturer did not use the estimated coefficient to estimate disutility of AEs from the model, opting instead to estimate a sum of disutilities for each grade 3/4 AE individually, weighted for the probability and duration to estimate a QALY penalty per cycle. The ERG assessed that this was reasonable to account for the duration of adverse events.

On p.102 of the CS, the company justified the TTD approach to estimating health state utility on the basis that it captures *'the decrease in utility as patients move closer to death, driven by the underlying impact of the disease over time, removing the dependence on clinical assessment of progression status.'* The company further stated that this approach has been used in previous oncology appraisals including TA531[26] and TA357.[27]. Whilst the ERG acknowledged that time to death had been used previously, the approach does not adequately account for progression status i.e. utilities based on time to death rather than progression status divorced health related quality of life from disease status in the model. Furthermore, the ERG noted that changing the PFS curve whilst holding OS the same made no difference to QALYs gained (only costs). This appeared somewhat counterintuitive.

Based on a review of the dostarlimab (TA779)[3] committee papers, the company used a regression equation which estimated utility based on time to death, but also included progression status as a covariate. Utility values were therefore estimated for pre progression (> 5 cycles from death and ≤5 cycles from death) and post progression (> 5 cycles from death and

≤5 cycles from death). The ERG considered this approach, which also captured progression status, to be more appropriate.

The company did conduct a scenario analysis whereby health state utilities were estimated based on progression status. Using this approach, the mean utility value for PF was estimated to be [redacted] and the mean utility for PD was [redacted]. Results were sensitive to this analysis, resulting in a moderate upward impact in the ICER (See Section 5.2.3). Overall, the ERG preferred utility estimation according to progression status, therefore this approach has been used in the ERG's preferred base case (see Section 6.2.6).

4.2.9. Resources and costs

The company's model included drug acquisition costs, administration and monitoring costs, adverse event costs, subsequent treatment costs and end of life care costs.

4.2.9.1. Drug acquisition costs

Drug costs were included for the intervention (PEM+LEN) and comparator treatment arms (doxorubicin or paclitaxel). The dosing regimen for PEM+LEN was based on the EMA and MHRA marketing authorisation and the KEYNOTE-775 protocol. For pembrolizumab, patients received 200mg every 3 weeks and for lenvatinib patients received 20mg every day. For doxorubicin and paclitaxel, dosing was based on KEYNOTE-775 protocol (see table 42, p.112 of the CS). Based on clinical opinion to the ERG, the dosing schedule used appeared to be appropriate.

Unit costs were derived from MIMS and the drugs and pharmaceutical electronic tool kit (eMIT). The ERG noted some uncertainty surrouding costs and sources for several drugs i.e. the incorrect cost appeared to have been used for medroxyprogesterone and doxorubicin. The company were asked to comment on these during the clarification stage and acknowleged the incorrect costs had been used. The company confirmed that when the correct prices were used for these treatments, this had minimal impact on the ICER. The ERG's preferred base case uses the correct prices for these treatments (see Section 6.1).

The ERG noted that for lenvatinib, the company used the relative dosing intensity (RDI) from the KEYNOTE-775 study, which was estimated to be [redacted]. The company's base case approach therefore assumed that a proportion of patients do not remain on lenvatinib 20mg, but experience dose reduction over time (dropping to 14mg, 10mg, 8mg and 4mg). The ERG noted that the cost of lenvatinib 10mg and 4mg is equivalent (£1,437). Overall, the ERG considered

that the use of dosing data from KEYNOTE-775 may be appropriate (if reflective of clinical practice). For completeness, the ERG sought further clinical expert opinion in order to determine whether dose reduction in clinical practice is likely. Based on feedback received, most patients are likely to receive dose reduction with lenvatinib (approximately 66%). As an exploratory analysis, the ERG conducted a scenario analysis which assumed no dose reduction for lenvatinib. Results were not overly sensitive to this (see Section 6.2.10).

Finally, the company has excluded pre-medication costs for paclitaxel for simplicity i.e. as per the SmPC for paclitaxel patients should receive steroids, antihistamines and H2-receptor antagonists. The company further noted that this is a conservative asssumption as this underestimates the costs of TPC. Due to the relatively small costs associated with these pre-medications, the ERG did not consider this to be an issue and found the company's approach to be reasonable.

4.2.9.2. Health state, monitoring and administration costs

Disease management costs (including monitoring costs) were included in the model and estimated for each health state i.e. PF or PD (see Table 44 on p.117 of the CS for a full list). Health state costs were calculated according to time spent in each state and specific healthcare resources used in that state. The company derived healthcare resource use estimates from previous NICE TA's including TA620[22] and ID1547,[28] which the ERG considered to be reasonable. The total weekly cost (cost per model cycle) associated with the PF and PD health states was estimated to be £43.06 and £35.08 respectively. Unit costs taken from the Personal Social Services Research Unit (PSSRU) and 2019/20 NHS reference costs as appropriate. In order to explore the impact of health state costs on the ICER, the ERG varied the cost per model cycle in the PF and PD health states by +/- 50%, however this did not have a meaningful impact on the ICER. With respect to administration costs, the company assumed no administration cost for lenvatinib, on the basis that it it an oral treatment. For pembrolizumab, paclitaxel and doxorubicin, the cost of intravenous administration were sourced from 2019/20 NHS reference costs (see Table 43, p.115 of the CS). The ERG considered the company's handling of administration costs to be reasonable.

4.2.9.3. Subsequent treatment costs

The model incorporated subsequent treatment costs (see Table 24 for subsequent treatments and proportions used in the base case). Subsequent treatments were based on those given in KEYNOTE-775 (excluding treatments that are not provided in the UK setting) and were

modelled as a one-off cost, applied at point of treatment discontinuation. Overall, based on clinical opinion to the ERG, the list of subsequent treatments and proportions used by the company were largely appropriate. For completeness the company conducted a scenario analysis which assumed subsequent treatments to be reflective of those received by patients in ECHO (see Table 46, p. 123 of the CS). However results were not sensitive to this analysis.

Unit costs for subsequent treatments were derived from eMIT and MIMS, which are considered to be appropriate sources (see Table 47, on p. 124 of the CS for full list of subsequent treatment costs). The ERG noted that MIMS provided a range of prices for bevacizumab i.e. £205.55 to 242.66 for 100mg/4ml and £810.10 to 924.40 for 400mg/16ml, and that the company used the cheapest price in their analysis (without providing justification). However, the ERG did not consider this to be an issue as bevacizumab is included at 0%.

Table 24: Modelled subsequent treatments

Subsequent treatments	After PEM+LEN	After TPC
Paclitaxel	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]

Abbreviations: PEM+LEN, pembrolizumab with lenvatinib; TPC, treating physician's choice

The company stated that PD-L1 regiments are currently not available in the UK for use as subsequent treatment, however clinical opinion to the ERG noted that recently there had been some immunotherapy use during the Covid 19 pandemic, particularly nivolumab. As per advice from NHS England regarding the use of interim treatment options during the Covid 19 pandemic, dostarlimab has recently displaced nivolumab as a viable subsequent treatment option for patients with previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.

4.2.9.4. Adverse event costs

The manufacturer estimated the cost of AEs based on incidence, recurrence and duration of Grade 3+ AEs that were observed in more than 5% of patients in KEYNOTE-775. The ERG noted that the AE cost per cycle in the TPC arm was around 4 times higher than in the PEM+LEN arm (£42.19 vs £10.74). This is driven primarily by the incidences of neutropenia and febrile neutropenia in TPC versus a higher incidence of hypertension in PEM+LEN. This is reasonable as hypertension is less costly to treat than (febrile) neutropenia.

Unit costs for each adverse event were mostly taken from NHS reference costs 2019/20, as appropriate, however serveral costs including hypokalaemia and proteinuria were assumed to be £0. Adverse events were not considerd to be a key driver of cost effectiveness within this appraisal. Based on one-way sensitivity analysis conducted by the company which excluded AE costs from the model, the ICER increased by approximately 1%.

4.2.9.5. End of life costs

End of life costs were applied as a one off cost when a patient entered the death health state. The company derived the cost from a published study by Georghiou et al. (2014),[29] which was a Nuffield Trust report that explored care costs towards the end of life. This was estimated to be £6,015, however the company inflated this to the current year using PSSRU inflation indices, resulting in a cost of £6,520.55. The ERG identified various end of life costs in the report i.e. hospital care costs for those patients diagnosed with cancer in the final 2 years of life (£4,580), however the ERG were not able to identify the £6,015 figure from the report. Therefore there is some uncertainty as to what this cost consists of i.e. care setting (hospital or hospice) and resource use involved.

Based on a review of olaparib TA598,[30] end of life costs were derived from an alternative source i.e. Guest et al. (2006),[31] which assessed palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. The cost was reported to be £7,638.51. Whilst the ERG noted some variation in end of life case costs depending on the source used, overall end of life care costs were not considered to be a key driver of cost effectiveness. Varying the cost by +/- 50% did not have a meaningful impact on the ICER.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1.1. Base case results

The company submitted base case results are in Table 25. [redacted]. It should be noted that these results do not include the PAS for lenvatinib. CMU prices were also not included (see the cPAS Appendix for results relevant to decision making).

Based on the company's base case analysis, PEM+LEN resulted a deterministic and probabilistic ICER of [redacted] and [redacted] respectively, compared to doxorubicin or paclitaxel. The ERG noted the primary driver of incremental costs to be the drug acquisition costs associated with pembrolizumab and lenvatinib (in the progression-free health state), whilst the incremental QALY gain was primarily driven by an increase in life years i.e. due to the company's OS extrapolation approach patients receiving PEM+LEN lived longer and therefore accrued more QALYs than those in the comparator arm.

Table 25: Company base case results (with pembrolizumab PAS)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
PEM+LEN	[redacted]	[redacted]	-	-	-
Doxorubicin or paclitaxel	[redacted]	[redacted]	[redacted]	1.75	[redacted]
Company probabilistic base case					
PEM+LEN	[redacted]	[redacted]			
Doxorubicin or paclitaxel	[redacted]	[redacted]	[redacted]	1.77	[redacted]

Abbreviations: PAS, patient access scheme; PEM+LEN, pembrolizumab with lenvatinib; QALYs, quality adjusted life years.

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis

The company provided one-way sensitivity analyses which tested several clinical, QoL and cost variables (see Section B.3.8.2 of the CS for results). The company stated that parameters were

varied by the upper and lower limits of the confidence intervals reported in Appendix P. Results were most sensitive to variation in OS, utility and ToT parameters. Overall, the ERG considered the OWSA to be of limited use for decision making, as the relevant confidential price discounts for lenvatinib (and CMU prices for other treatments) were not incorporated. Furthermore, all the OWSAs considered are based on the deterministic results, not the probabilistic. This yields a biased estimate of the expected incremental costs and outcomes.

5.2.2. Probabilistic sensitivity analysis

The company conducted probabilistic sensitivity analysis which varied multiple model parameters simultaneously over 1000 iterations (see Table 25, for the company's base case probabilistic results). The ERG repeated the PSA multiple times generating a coefficient of variation of the ICER of approximately 0.5%, suggesting 1000 simulations are sufficient to minimise Monte Carlo error (a general rule of >2% implies insufficient simulations). Results were also presented in the form of a scatter plot and CEAC (see p. 131 and p. 132 of the CS). Based on the CEAC results (list prices), PEM+LEN had a [redacted] and [redacted] probability of being cost effective at a willingness to pay threshold of £30,000 and £50,000 respectively. Overall, the ERG considered the company's handling of the PSA to be appropriate and did not identify any errors.

As a general observation, on p. 131 of the CS, the company stated agreement between probabilistic analysis and deterministic analysis as evidence of robustness of the model, *"Therefore, the outcomes from the cost-effectiveness model are considered robust to uncertainty from parameter distributions."* The ERG do not consider this statement to be true, because the agreement between probabilistic and deterministic analyses depends on the degree of 'non-linearity' in the model and not robustness.

5.2.3. Scenario analyses

The company conducted a range of scenario analyses whereby alternative assumptions were used in the model (for the full list see p. 169, Appendix Q). Table 26 below presents five scenarios which had the largest impact on the company's base case ICER. Overall, results were not especially sensitive to changes in key model assumptions, however it should be noted that these results include the PAS for pembrolizumab (and list price for lenvatinib and comparator treatments).

Table 26: Company scenario analyses

Parameter	ICER	% change from company base case
Discount rate (1.5% for both costs and utilities)	[redacted]	[redacted]
Lenvatinib weekly dosing (full 20mg)	[redacted]	[redacted]
Health state utilities based on progression status	[redacted]	[redacted]
Use Caelyx® cost for doxorubicin	[redacted]	[redacted]
ToT cannot exceed PFS (both arms)	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; ToT, time-on-treatment

5.3. Model validation and face validity check

The company stated that the model was quality assured by the economists who constructed the model and an external economist (not involved in the model's construction) reviewed the technical implemetation of calculations and coding. A checklist was used to document the list of inconsistencies and errors. Overall, the ERG considered the company's model to be valid i.e. no major coding errors were identified. However, several minor errors were found and amended by the ERG (see Section 6.1).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified a number of limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the ERG believes are more plausible. This section is organised as follows:

- Section 6.1 outlines the errors identified by the ERG in the company's model.
- Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the ERG corrected company base case analysis.
- Results for all scenario analyses are presented in Section 6.2.10.
- In Section 6.3, the ERG base case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

The ERG noted a number of minor errors and typographical errors in the company's submitted model. These were:

- Typographical error in cost of doxorubicin (£20.20 corrected to £20.02)
- Error in cost of medroxyprogesterone (£1.84 corrected to £58.67)
- Life years discounting default set to 0% not 3.5%.

The company submitted a revised version of the model with the typographical errors corrected. These made no material difference to the results (Table 27). The ERG edited the default discount rate for life years to 3.5%. [redacted] The results below include this revised PAS for pembrolizumab and list price for lenvatinib.

Table 27: ERG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG corrected company deterministic base case					
PEM+LEN	[redacted]	[redacted]	-	-	-
Doxorubicin or paclitaxel	[redacted]	[redacted]	[redacted]	1.75	[redacted]
ERG corrected company probabilistic base case					
PEM+LEN	[redacted]	[redacted]	-	-	-
Doxorubicin or paclitaxel	[redacted]	[redacted]	[redacted]	1.76	[redacted]

Abbreviations: ERG, Evidence Review Group; PEM+LEN, pembrolizumab with lenvatinib; QALY, quality-adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the ERG

6.2.1. Survival function capping

As described in Section 4.2.6.2, the company used a 'hybrid' approach to capping overall survival to general population survival and PFS to OS (

Figure 5). In this scenario the ERG have explored two alternative approaches to capping overall survival, a ‘simple’ approach (Figure 6) and a ‘hazards’ approach (

Figure 7). The ERG's preference is for the hazards-based approach as this generates more plausible estimates of survival. For example, this ensures the hazard of death in the patient population increases in line with that of the general population at older ages, avoiding a plateau of mortality under the simple approach. Results were insensitive to this adjustment under the company's base case, but may be sensitive to this under alternative survival functions. See Section 6.2.10 for results.

Figure 5: Company's base case approach to capping survival

Abbreviations: GenPopOS, general population overall survival; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival

Figure 6: Survival function capped via 'simple' approach

Abbreviations: GenPopOS, general population overall survival; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival

Figure 7: Survival function capped by hazards ('hazards' approach)

Abbreviations: GenPopOS, general population overall survival; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival

6.2.2. Comparator weighting

For these scenarios, the ERG explored the impact of altering the proportion of patients receiving doxorubicin or paclitaxel. Scenario a) assumed that 100% patients receive doxorubicin, scenario b) assumed that 100% of patients receive paclitaxel and scenario c) assumed that 50% of patients will receive doxorubicin and 50% will receive paclitaxel. Based on clinical advice received, the ERG have opted to use scenario c) as part of the ERG preferred base case. Results were not sensitive to these analyses. See Section 6.2.10 for results.

6.2.3. Treatment waning

As noted in Section 4.2.6.3, there is some uncertainty surrounding the long-term treatment effect of PEM+LEN. For this scenario the ERG implemented a waning treatment effect between years 2 and 5. This was implemented by substituting the hazard of OS and PFS in the PEM+LEN arm for a weighted average of the predicted OS and PFS in the PEM+LEN and TPC arms, with the weight increasing linearly between years 2 and 5, such that by year 5, the hazard in the PEM+LEN arm was equal to the hazard in the TPC arm. Under some model extrapolations, the predicted hazard at later time points in PEM+LEN exceeded that in the TPC arm. Thus to prevent a 'treatment waxing' effect, the hazard was set at the maximum of the

predicted hazard in PEM+LEN and the weighted average. Results were highly sensitive to this analysis (and to the start and stop timings of the waning). See Section 6.2.10 for results.

6.2.4. No dose reduction for lenvatinib

In the base case analysis, the dose for lenvatinib was based on the dosing observed in the KEYNOTE-775 study i.e. a dose reduction was observed, with relative dose intensity estimated to be [redacted]. The ERG has asked clinical experts to comment on whether dose reduction (as witnessed in KEYNOTE-775 is likely to occur in clinical practice. Based on the response received, most patients are likely to receive dose reduction with lenvatinib (approximately [redacted]). However, in order to explore uncertainty surrounding lenvatinib dosing, the ERG have conducted a scenario analysis which assumes no dose reduction i.e. patients receive 20mg weekly. Results were mildly sensitive to the analysis. See Section 6.2.10 for results.

6.2.5. OS extrapolation

The ERG conducted three scenario analyses to examine the impact of alternative OS modelling assumptions on the ICER. These are as follows:

- **Extrapolate OS using a one-piece model:** The company did not provide an analysis using a one-piece model to extrapolate OS in the PEN+LEN arm, on the basis that this modelling approach produced implausible OS estimates, when compared to longer term data in KEYNOTE-146 (See Section 4.2.6 for further discussion). Given that the company provided scenario analysis using a one-piece modelling approach for PFS (in both treatment arms), the ERG considered that for consistency it would be useful to have a scenario analysis which estimated OS based on this alternative modelling approach. For this scenario, OS in both arms was extrapolated using the best fitting curves based on AIC and BIC (Log-Normal for PEM+LEN and Log-Logistic for the TPC arm). Results were highly sensitive to the analysis. See Section 6.2.10 for results.
- **Two-piece modelling approach using alternative parametric distribution for OS in the PEM+LEN arm:** Given that the Weibull was the best fitting curve (based on AIC/BIC scores), the ERG explored the impact of KM+Weibull in place of the company base case of KM+Log-Logistic. During clarification (B5), the company was asked to explain why the Weibull was not used in the base case to extrapolate OS in the PEN+LEN arm. The company acknowledged, that whilst the Weibull (and exponential) curves provided a good statistical fit, they provided an insufficient fit to decreasing hazards in KEYNOTE-775 (as

per Fig 17 in the CS) and long term KM data from KEYNOTE-146. The company further stated the extrapolated OS estimates from these models were clinically implausible and underestimated long-term survival. Results were highly sensitive to the analysis. See Section 6.2.10 for results.

- **Two-piece modelling approach using alternative parametric distribution for OS in the TPC arm:** As noted in Section 4.2.6.1, clinical opinion to the ERG noted that modelled OS in the TPC arm was considered to be underestimated. In this scenario analysis the ERG explored the impact of using KM+Log-Logistic in place of the company base case of KM+Exponential. This analysis has been included as part of the ERG's preferred base case. Results were moderately sensitive to the analysis. See Section 6.2.10 for results.
- As an exploratory analysis, the ERG tested the impact of reducing the OS gap between the PEM+LEN arm and TPC arm. This scenario analysis combines the prior two options. It should be noted that this analysis is considered to be highly exploratory. Results were highly sensitive to this analysis. See Section 6.2.10 for results.

6.2.6. Health state utilities based on progression status

As noted in Section 4.2.8, the ERG identified several concerns surrounding the appropriateness of using time to death utilities within the base case. For this scenario, health state utilities were estimated on a health state basis i.e. progression-free, progression and dead, in place of the proximity to death approach. This analysis has been considered as part of the ERG's preferred base case. The results were mildly sensitive to the analysis. See Section 6.2.10 for results.

6.2.7. ToT capped by PFS

In the company base case, ToT was modelled independently from health state, allowing patients to continue treatment post progression. As noted in section 4.2.7, the ERG considered that ToT is more appropriately estimated by capping ToT by PFS. This analysis has been considered as part of the ERG's base case. The results were mildly sensitive to the analysis. See Section 6.2.10 for results.

6.2.8. Patient weight increased to 85kg / Body Surface Area to 1.96m^2

According to the clinical advice received by the ERG, patients enrolled in the clinical trial were of a lower mean weight than those typically seen in UK clinical practice (company base case: 70kg). The ERG therefore conducted a scenario analysis at a patient mass of 85kg.

In the company's model, dosing of paclitaxel, doxorubicin, gemcitabine and cisplatin is set according to body surface area (company base case: 1.77m^2). Bevacizumab is dosed according the body mass (company base case: 70kg). Body surface area is a function of height and weight, for which a number of alternative formulae exist.[32] However, the company's model does not explicitly link the two. Therefore, the ERG conducted a scenario analysis setting patient mass to 85kg and body surface area to 1.96m^2. (In 2019, the average height of a woman in England was 162cm.[33] Using the average weight of a patient in KM-775 of 70kg, the Mosteller formula[34] generates a BSA equal to the company base case of 1.77m^2. Using the same formula with a mass of 85kg yields an estimated BSA of 1.96m^2.) The results were insensitive to the analysis. See section 6.2.10 for results.

6.2.9. Patient age increased to 75

According to clinical advice received by the ERG, patients enrolled in the clinical trial were of a lower age than those typically seen in UK clinical practice. Supporting evidence was provided to the ERG, which highlighted that incidence rates for uterine cancer are highest amongst females aged 75-79 years.[35] For this scenario the ERG explored set the mean age of patients to be 75 (which was also used in the ERG's preferred base case). This had a relatively minor upward impact on the ICER. See Section 6.2.10 for results.

6.2.10. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG made the changes described in Sections 6.2.1 to 6.2.9. Each change has been made individually. The results of the ERG's exploratory analyses are provided in Table 28 and Table 29 below. All results are based on the updated pembrolizumab PAS and lenvatinib list price.

Table 28: ERG's exploratory analyses (deterministic)

Exploratory scenarios	Section in ERG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- company base case
Company base case	5.1.1.1	[redacted]	1.75	[redacted]	---
Approach to capping the survival function					
a. Simple capping method	4.2.6.2 and 6.2.1	[redacted]	1.82	[redacted]	[redacted]
b. Hazards capping method	4.2.6.2 and 6.2.1	[redacted]	1.77	[redacted]	[redacted]
Comparator					

Exploratory scenarios	Section in ERG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- company base case
a. 100% of patients receive doxorubicin	4.2.4 and 6.2.2	[redacted]	1.75	[redacted]	[redacted]
b. 100% of patients receive paclitaxel	4.2.4 and 6.2.2	[redacted]	1.75	[redacted]	[redacted]
c. 50% of pts receive doxorubicin and 50% receive paclitaxel	4.2.4 and 6.2.2	[redacted]	1.75	[redacted]	[redacted]
Treatment waning assumed for PEM+LEN (waning from year 2 to 5)	4.2.6.3 and 6.2.3	[redacted]	0.56	[redacted]	[redacted]
No dose reduction for lenvatinib (20mg weekly assumed to be maintained)	4.2.9.1 and 6.2.4	[redacted]	1.75	[redacted]	[redacted]
Overall survival					
a. OS extrapolated using best-fitting one-piece model for both treatment arms (Log-Normal curve used for the PEM+LEN arm and Log-logistic curve used for the doxorubicin or paclitaxel arm)	4.2.6 and 6.2.5	[redacted]	0.85	[redacted]	[redacted]
b. OS for PEM+LEN (KM+Weibull)	4.2.6 and 6.2.5	[redacted]	0.81	[redacted]	[redacted]
c. OS for doxorubicin or paclitaxel (KM +Log logistic)	4.2.6 and 6.2.5	[redacted]	1.31	[redacted]	[redacted]
d. (b) & (c) combined	6.2.5	[redacted]	0.37	[redacted]	[redacted]
Health state utilities based on progression status	4.2.8 and 6.2.6	[redacted]	1.59	[redacted]	[redacted]

Exploratory scenarios	Section in ERG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- company base case
ToT capped by PFS	4.2.7 and 6.2.7	[redacted]	1.76	[redacted]	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	4.2.3 and 6.2.8	[redacted]	1.75	[redacted]	[redacted]
Patient age increased to 75 years	4.2.3 and 6.2.9	[redacted]	1.55	[redacted]	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

Table 29: ERG's exploratory analyses (probabilistic)

Exploratory scenarios	Section in ERG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- company base case
Company base case	5.1.1.1	[redacted]	1.77	[redacted]	---
Approach to capping the survival function					
a. Simple capping method	4.2.6.2 and 6.2.1	[redacted]	1.83	[redacted]	[redacted]
b. Hazards capping method	4.2.6.2 and 6.2.1	[redacted]	1.77	[redacted]	[redacted]
Comparator					
a. 100% of patients receive doxorubicin	4.2.4 and 6.2.2	[redacted]	1.77	[redacted]	[redacted]
b. 100% of patients receive paclitaxel	4.2.4 and 6.2.2	[redacted]	1.76	[redacted]	[redacted]
c. 50% of pts receive doxorubicin and 50% receive paclitaxel	4.2.4 and 6.2.2	[redacted]	1.75	[redacted]	[redacted]
Treatment waning assumed for PEM+LEN (waning from year 2 to 5)	4.2.6.3 and 6.2.3	[redacted]	0.57	[redacted]	[redacted]
No dose reduction for lenvatinib (20mg weekly assumed to be maintained)	4.2.9.1 and 6.2.4	[redacted]	1.77	[redacted]	[redacted]
Overall survival					

Exploratory scenarios	Section in ERG report	Incremental discounted costs	Incremental discounted QALYs	ICER £/QALY	+/- company base case
a. OS extrapolated using best-fitting one-piece model for both treatment arms (Log-Normal curve used for the PEM+LEN arm and Log-logistic curve used for the doxorubicin or paclitaxel arm)	4.2.6 and 6.2.5	[redacted]	0.86	[redacted]	[redacted]
b. OS for PEM+LEN (KM+Weibull)	4.2.6 and 6.2.5	[redacted]	0.85	[redacted]	[redacted]
c. OS for doxorubicin or paclitaxel (KM +Log logistic)	4.2.6 and 6.2.5	[redacted]	1.32	[redacted]	[redacted]
d. b) & (c) combined	6.2.5	[redacted]	0.38	[redacted]	[redacted]
Health state utilities based on progression status	4.2.8 and 6.2.6	[redacted]	1.61	[redacted]	[redacted]
ToT capped by PFS	4.2.7 and 6.2.7	[redacted]	1.76	[redacted]	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	4.2.3 and 6.2.8	[redacted]	1.76	[redacted]	[redacted]
Patient age increased to 75 years	4.2.3 and 6.2.9	[redacted]	1.56	[redacted]	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PEM+LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

6.3. ERG's preferred assumptions

The ERG's preferred base case results are presented below. All results are based on the updated pembrolizumab PAS and lenvatinib list price.

Table 30: ERG preferred assumptions (deterministic)

	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	5.1.1.1	[redacted]	1.75	[redacted]
ERG corrected company base case				
Drug costs corrected + additional PAS	6.1	[redacted]	1.75	[redacted]
ERG Preferred base case assumptions (applied individually)				
Survival capped by hazards	6.2.1 and 6.2.10	[redacted]	1.77	[redacted]
50% of patients receive doxorubicin and 50% receive paclitaxel	6.2.2 and 6.2.10	[redacted]	1.75	[redacted]
ToT capped by PFS	6.2.7 and 6.2.10	[redacted]	1.76	[redacted]
Health state utilities based on progression status	6.2.6 and 6.2.10	[redacted]	1.76	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	6.2.8 and 6.2.10	[redacted]	1.75	[redacted]
Patient age increased to 75 years	6.2.9 and 6.2.10	[redacted]	1.55	[redacted]
OS for doxorubicin or paclitaxel (KM +Log logistic)	6.2.5 and 6.2.10	[redacted]	1.31	[redacted]
Cumulative impact of ERG's preferences	1.7 and 6.3	[redacted]	1.07	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

Table 31: ERG preferred assumptions (probabilistic)

	ERG report section	Incremental cost	Incremental QALYs	ICER
Company's base case	5.1.1.1	[redacted]	1.77	[redacted]
ERG corrected company base case				
Drug costs corrected + additional PAS	6.1	[redacted]	1.76	[redacted]
ERG Preferred base case assumptions (applied incrementally)				
Survival capped by hazards	6.2.1 and 6.2.10	[redacted]	1.77	[redacted]
50% of patients receive doxorubicin and 50% receive paclitaxel	6.2.2 and 6.2.10	[redacted]	1.75	[redacted]

	ERG report section	Incremental cost	Incremental QALYs	ICER
ToT capped by PFS	6.2.7 and 6.2.10	[redacted]	1.76	[redacted]
Health state utilities based on progression status	6.2.6 and 6.2.10	[redacted]	1.61	[redacted]
Patient weight increased to 85 kg (and BSA to 1.96 m^2)	6.2.8 and 6.2.10	[redacted]	1.76	[redacted]
Patient age increased to 75 years	6.2.9 and 6.2.10	[redacted]	1.56	[redacted]
OS for doxorubicin or paclitaxel (KM +Log logistic)	6.2.5 and 6.2.10	[redacted]	1.32	[redacted]
Cumulative impact of ERG's preferences	1.7 and 6.3	[redacted]	1.05	[redacted]

Abbreviations: BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; ToT, time-on-treatment

6.4. Conclusions of the cost-effectiveness section

Overall, the company's model was of good quality. The company's base case yielded a deterministic ICER of [redacted] and a probabilistic ICER of [redacted] (based on the original pembrolizumab PAS as per Section 5.1.1.1). The ERG disagreed with a number of the company's base case assumptions, most of which had a minor impact on the ICER with the exception of the overall survival function for the comparator arm (TPC).

Based on clinical opinion to the ERG, the modelled long-term survival gap between PEM+LEN and TPC appeared to lack clinical plausibility. In particular, modelled OS for the TPC arm was considered to underestimate the proportion of patients alive at 5 years. In order to estimate more clinically plausible overall survival estimates, the ERG opted to use an alternative parametric curve for extrapolation (see Sections 4.2.6 and 6.2.5). In isolation, this increased the deterministic ICER by [redacted] to [redacted] (Table 28) and increased the probabilistic ICER by [redacted] to [redacted] (Table 29).

It should be noted that the results are much more sensitive to the survival function selected for the PEM+LEN arm; when KM+Weibull is assigned, the ICER increased by [redacted] to [redacted] (deterministic) and by [redacted] to [redacted] (probabilistic). Furthermore, the results are highly sensitive to a number of other scenarios the ERG explored, in particular the impact of treatment waning, which increased the deterministic ICER by [redacted] to [redacted] (Table 28) and increased the probabilistic ICER by [redacted] to [redacted] (Table 29).

However, the cumulative impact of the ERG's preferred scenario yields a deterministic ICER of [redacted] and a probabilistic ICER of [redacted].

7. END OF LIFE

The company provided several data sources to support the application of NICE end of life criteria. The ERG noted NICE end of life criteria to be as follows;

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months, and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

As noted in Section B.2.13.4 of the CS, the company refer to results from KEYNOTE-775 which reported median survival (for patients receiving current standard of care) to be 11.4 months. In the company's base case, mean survival in TPC as estimated by the company's model was [redacted] months, though the ERG's base case estimated this as [redacted] years in both deterministic and probabilistic analyses . The company further outlined survival results from ECHO, a retrospective UK chart review (note: full study details were not available to the ERG and were stated to be on file). In this study, median survival was reported to be [redacted] months for standard of care. Based on survival data from these sources, the ERG agreed that that life expectancy for the patient population under review could be plausibly less than 24 months.

Furthermore, based on overall survival data from KEYNOTE-775, median overall survival was significantly longer in the PEM+LEN group compared with the control group; 18.3 and 11.4 months respectively (demonstrating an extension of life of approximately 6.9 months).

The ERG sought further clinical opinion to determine whether end of life criteria would be met if separate subgroups were to be considered i.e. according to dMMR and pMMR status. Clinical opinion noted that average life expectancy is likely to be less than 24 months for each subpopulation, PEM+LEN would result in an extension of life of at least an additional 3 months and that patient numbers are sufficiently small.

Based on the evidence provided by the company and clinical opinion received, the ERG considered that it may be appropriate to consider NICE end of life criteria for this appraisal, though the choice of extrapolation in the TPC arm is potentially dispositive.

References

1. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. BGCS uterine cancer guidelines: Recommendations for practice, 2021: British Gynaecological Cancer Society. Available from: https://www.bgcs.org.uk/wp-content/uploads/2021/11/British-Gynaecological-Cancer-Society-v13-for-website-with-figure1.pdf.
2. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022;399(10333):1412-28.
3. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779], 2022. Available from: https://www.nice.org.uk/guidance/ta779.
4. National Institute for Health and Care Excellence (NICE). Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer. Final scope, 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10692/documents/final-scope.
5. Makker V, Colombo N, Casado Herráez A, Santin A, Colomba E, Miller D, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer. Gynecologic Oncology. 2021;162:S4.
6. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. Journal of Clinical Oncology. 2020;38(26):2981-92.
7. Julius JM, Tanyi JL, Nogueras-Gonzalez GM, Watkins JL, Coleman RL, Wolf JK, et al. Evaluation of pegylated liposomal doxorubicin dose on the adverse drug event profile and outcomes in treatment of recurrent endometrial cancer. International Journal of Gynecological Cancer. 2013;23(2):348-54.
8. Moreira E, Paulino E, Ingles Garces Á H, Fontes Dias MS, Saramago M, de Moraes Lino da Silva F, et al. Efficacy of doxorubicin after progression on carboplatin and paclitaxel in advanced or recurrent endometrial cancer: a retrospective analysis of patients treated at the Brazilian National Cancer Institute (INCA). Medical Oncology. 2018;35(3):20.
9. Nagao S, Nishio S, Michimae H, Tanabe H, Okada S, Otsuki T, et al. Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study. Gynecologic Oncology. 2013;131(3):567-73.
10. Rubinstein M, Halpenny D, Makker V, Grisham RN, Aghajanian C, Cadoo K. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. Gynecologic Oncology Reports. 2019;28:120-3.
11. Sovak MA, Dupont J, Hensley ML, Ishill N, Gerst S, Abu-Rustum N, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. International Journal of Gynecological Cancer. 2007;17(1):197-203.
12. Ueda Y, Miyake T, Egawa-Takata T, Miyatake T, Matsuzaki S, Yokoyama T, et al. Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. Cancer Chemotherapy and Pharmacology. 2011;67(4):829-35.
13. Endometrial Cancer Health Outcomes. Europe (ECHO EU5): A retrospective, multicenter chart review study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC (aEC) patients previously treated with systemic therapy in United Kingdom. Unpublished. 2021.

14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
15. Merck Sharp Dohme. 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. Clinical Study Report. 2021.
16. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. New England Journal of Medicine. 2022;386(5):437-48.
17. Makker V, Aghajanian C, Cohn AL, Romeo M, Bratos R, Brose MS, et al. Lenvatinib and pembrolizumab in advanced endometrial carcinoma (EC): long-term efficacy and safety update from a phase 1b/2 study. Journal for ImmunoTherapy of Cancer. 2021;9(354):A381.
18. Van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.
19. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA528], 2018. Available from: https://www.nice.org.uk/guidance/TA528.
20. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [TA673], 2021. Available from: https://www.nice.org.uk/guidance/TA673.
21. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [TA611], 2019. Available from: https://www.nice.org.uk/guidance/ta611.
22. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [TA620], 2020. Available from: https://www.nice.org.uk/guidance/ta620.
23. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Processes and methods, 2013. Available from: https://www.nice.org.uk/process/pmg9.
24. NICE DSU. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient level data, 2013: Decision Support Unit, ScHARR, University of Sheffield. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.
25. NICE DSU. NICE DSU Technical Support Document 21: Flexible methods for survival analysis, 2020: Decision Support Unit, ScHARR, University of Sheffield. Available from: http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf.
26. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531], 2018. Available from: https://www.nice.org.uk/guidance/ta531.
27. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab [TA357], 2017. Available from: https://www.nice.org.uk/guidance/ta357.

28. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [TA645], 2020. Available from: https://www.nice.org.uk/guidance/ta645/.
29. Georghiou T, Bardsley M. Exploring the cost of care at the end of life, 2014: Nuffield Trust. Available from: https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf.
30. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [TA598], 2019. Available from: https://www.nice.org.uk/guidance/ta598.
31. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. European Journal of Cancer. 2006;15(1):65-73.
32. Calculator.net. Body surface calculator, 2022. Available from: https://www.calculator.net/body-surface-area-calculator.html.
33. NHS Digital. Health Survey for England 2019. Overweight and obesity in adults and children, 2020. Available from: https://files.digital.nhs.uk/9D/4195D5/HSE19-Overweight-obesity-rep.pdf.
34. Mosteller RD. Simplified calculation of body-surface area. New England Journal of Medicine. 1987;317(17):1098.
35. Cancer Research UK. Uterine cancer incidence statistics, 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence.

Appendix A: Additional searches conducted by ERG

Additional searches conducted by ERG

The ERG conducted an additional search to test the impact of the exclusion of conference abstracts in Ovid Embase in the SLR of interventional evidence. This search retrieved 454 results, and these were single screened by the Information Specialist, with 38 records selected for further consideration. Two reviewers independently screened the 38 records. The ERG considered that the additional abstracts, while potentially eligible for the interventional SLR, did not provide additional data that would enhance the already identified clinical effectiveness evidence base.

The search strategy for Ovid Embase is provided below:

Embase <1974 to 2022 May 06>

1	exp *endometrium carcinoma/	14269
2	exp *endometrium cancer/	32580
3	((endometrium or endometrial) adj1 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti.	24628
4	((endometrium or endometr.ial) adj1 adenocarcinoma*).ti.	1711
5	((endometrium or endometrial) adj1 (metastasis or metastatic*)).ti.	246
6	or/1-5	35843
7	Clinical Trial/	1033747
8	Randomised Controlled Trial/	707273
9	controlled clinical trial/	465536
10	multicenter study/	322509
11	Phase 3 clinical trial/	60337
12	Phase 4 clinical trial/	4742
13	exp RANDOMISATION/	94020
14	Single Blind Procedure/	46022
15	Double Blind Procedure/	194618
16	Crossover Procedure/	70225
17	PLACEBO/	379874
18	randomi?ed controlled trial$.tw.	284401
19	rct.tw.	46580
20	(random$ adj2 allocat$).tw.	49830
21	single blind$.tw.	28771
22	double blind$.tw.	229762
23	((treble or triple) adj blind$).tw.	1547
24	placebo$.tw.	342325
25	Prospective Study/	763144
26	(single-arm or single arm).tw.	22768
27	(Phase II or Phase 2).tw.	148543
28	Phase 2 clinical trial/	96477
29	or/7-28	2762428

30	Case Study/	85034
31	case report.tw.	484899
32	letter/	1147956
33	Editorial.pt.	725072
34	Letter.pt.	1222404
35	Note.pt.	892557
36	or/30-35	3398463
37	29 not 36	2629509
38	6 and 37	3605
39	exp endometrium carcinoma/	22335
40	exp endometrium cancer/	55826
41	((endometrium or endometrial) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	46815
42	((endometrium or endometrial) adj3 adenocarcinoma*).ti,ab.	6030
43	((endometrium or endometrial) adj3 (metastasis or metastatic*)).ti,ab.	1566
44	or/39-43	66646
45	Clinical Trial/	1033747
46	Randomised Controlled Trial/	707273
47	controlled clinical trial/	465536
48	multicenter study/	322509
49	Phase 3 clinical trial/	60337
50	Phase 4 clinical trial/	4742
51	exp RANDOMISATION/	94020
52	Single Blind Procedure/	46022
53	Double Blind Procedure/	194618
54	Crossover Procedure/	70225
55	PLACEBO/	379874
56	randomi?ed controlled trial$.tw.	284401
57	rct.tw.	46580
58	(random$ adj2 allocat$).tw.	49830
59	single blind$.tw.	28771
60	double blind$.tw.	229762
61	((treble or triple) adj blind$).tw.	1547
62	placebo$.tw.	342325
63	Prospective Study/	763144
64	(single-arm or single arm).tw.	22768
65	(Phase II or Phase 2).tw.	148543
66	Phase 2 clinical trial/	96477
67	or/45-66	2762428
68	Case Study/	85034
69	case report.tw.	484899
70	abstract report/ or letter/	1237405
71	Conference proceeding.pt.	0
72	Conference abstract.pt.	4389743
73	Editorial.pt.	725072
74	Letter.pt.	1222404
75	Note.pt.	892557
76	or/68-75	7738096
77	67 not 76	1998071
78	44 and 77	6279
79	38 not 78	1227

80	(advanced or recurrent or metastatic or inoperable or irresectable or unresectable or resistant or progressive).ti,ab.	2479879
81	79 and 80	454

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

[ID3811] Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

The ERG response to the issues raised by the company during the factual accuracy check is provided in the Tables below

Section 1: Factual inaccuracies

Issue 1 Publishing pembrolizumab PAS across the report and CEM

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Disclosed PAS across the document • Pg 20 – All of the ERG's analyses therefore include the PAS of [redacted] • [redacted] Pg 84 – [redacted] • Pg 87 – [redacted] • CEM remove PAS info To reduce probability of disclosing/providing highly sensitive	Please remove any reference to the PAS discount through the document and refer as the "*latest PAS*"	In order to reduce probability of disclosing information about any confidential pricing agreements we request to remove pembrolizumab agreed PAS from this report and CEM [**we have noted to NICE that the ERG has included the value of the latest PAS within the landing page of the economic model shared – please be sure to redact this information from the Excel files**]. We remind reviewers that this treatment combination and all involved parties have to stay blinded to the confidential pricing agreements.	This is not a factual inaccuracy. Standard NICE STA process is that the PAS would be included in the ERG report but marked in blue as CIC. However, upon special request, and with the guidance of NICE, the ERG has removed reference to the pembrolizumab PAS discount. See p.18, p.85 and p.88.

commercial information about the confidential information related to pembrolizumab PAS we request that all instances in the ERG report of the PAS value are replaced with "latest PAS".			

Issue 2 Decision problem: Missing descriptions/details that could cause a misrepresentation of the treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We are concerned at potentially misleading statements regarding the recent recommendation for dostarlimab, of which there are multiple instances throughout the report: Pg 21 – Recently, a clear difference in the treatment pathway has emerged for people with dMMR EC compared to those with pMMR EC: those with advanced or recurrent previously treated EC displaying dMMR are now able to access dostarlimab as monotherapy Pg 23 – The ERG highlights that although the treatment and population in the company's decision problem are reasonably consistent with the NICE scope, the treatment is likely more appropriate for people with pMMR EC than for those with dMMR	Please review concerns regarding the considerations of dostarlimab and discussion in the ERG report. We would welcome further clarifications to the text to align with the NICE reference case.	These statements are misleading as the ERG suggests the subgroup analysis leads to uncertainty in the decision problem for the overall population, the population relevant to the decision problem set out in the final scope from NICE. It is important to note: • Our license is "advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation". This includes both pMMR and dMMR patients • Dostarlimab was approved for use within the CDF based	The ERG disagree that these statements are misleading – they represent the current clinical picture/treatment pathway in England and Wales. The ERG has made some minor changes to the text to ensure clarity: Pg 23 The wording has been slightly updated to ensure that it is clear that, with regards dostarlimab, the Company's decision problem is consistent with the NICE scope, but the fact remains that the dMMR subgroup

EC. Those with EC displaying MSI/dMMR can now access dostarlimab monotherapy (TA779).[1] Clinical advice to the ERG indicated that immunohistochemistry was more accurate for identifying MMR status where available compared to MSI. Appropriate comparators for PEM+LEN in this subgroup is, therefore, immune checkpoint inhibitors as monotherapy. Pg 24 – The ERG noted that people with dMMR EC now have access to dostarlimab (TA779), as monotherapy. Therefore, PEM+LEN may be most appropriately positioned for people with pMMR EC. Pg 25 – However, if the committee considered the subgroup analyses to be appropriate for decision making then comparators in the dMMR subpopulation are likely to be immune checkpoint inhibitors as monotherapy. Pg 27 – PEM+LEN may be expected to perform better in people with dMMR EC but be most appropriately positioned for people with pMMR EC (those with dMMR EC now have access to dostarlimab as monotherapy). Pg 63 – As outlined in Section **Error! Reference source not found.**, clinical opinion to the ERG suggested		on a phase 1 single-arm study, after the company submission for PEM+LEN in endometrial cancer, therefore, it was not appropriate or possible for the company to comment at the time of writing [1, 2]. • Dostarlimab was approved very recently and only within the CDF [1, 2]. Therefore, it cannot be considered routine practice within the NHS and, as it is only being available in the CDF, it is not an appropriate comparator in the decision problem for pembrolizumab, per the NICE reference case guidance. • There are multiple instances where the ERG refers to "monotherapy immunotherapy treatments… currently used in patients with dMMR". For transparency, this only refers to a single treatment, dostarlimab. Furthermore, dostarlimab is only recommended for a subgroup of patients with endometrial cancer, which is narrower than the population	now have another treatment option available to them. Pg 25/26 A statement has been added here to clarify that studies using dostarlimab as a comparator would not be expected yet in the UK population, due to the recency of the avalability of dostarlimab via the CDF. In the cost effectiveness section of the ERG report, it is clearly stated that dostarlimab is not considered an appropriate comparator due the recency of guidance (p.65). The ERG has however made reference to dostarlimab (TA779) in the report, given that it has been approved by NICE. The ERG also felt that it would be useful for the committee to understand the model assumptions that

that monotherapy immunotherapy treatments are currently used in patients with dMMR (due to high response to treatment). However, monotherapy appears to have limited efficacy in patients with pMMR. Clinical opinion to the ERG included interest in using PEM+LEN within the pMMR subgroup, as the dual combination of PEM+LEN is likely to be more effective than single agent use. The ERG considered the lack of cost effectiveness results for MMR subgroups to be an area of uncertainty, particularly the lack of results for pMMR patients, as PEM+LEN is most likely to be used in this subgroup in practice Pg 63-64 – The ERG are aware of a recent NICE appraisal for endometrial carcinoma dostarlimab (TA779), which was recommended for patients with recurrent or advanced dMMR/MSIH EC who have progressed on or after platinum-based chemotherapy. Given that this is relatively recent guidance, published in March 2022, the ERG considered the exclusion of dostarlimab to be appropriate Pg 71 – Furthermore, based on a review of dostarlimab TA779,[1] the ERG noted that treatment waning was		for which pembrolizumab is indicated, and this is not always clear in the ERG report. We welcome clarifications to the text to align with the NICE reference case.	were used in the dostarlimab (TA779) appraisal. For transparency, the ERG has added the following additional sentence to p.65 *'Furthermore, dostarlimab is recommended for a subgroup of patients, which is narrower than the population for which pembrolizumab is indicated.'*

considered as part of the company's base case.			

Issue 3 Misrepresentation of potential impact of additional data in KEYNOTE-775

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 11 – The ERG report notes that the technology is modelled to affect QALYs by "time spent in the PD health state, as most of the PEM+LEN incremental QALY gain ([redacted]) is accrued in the PD health state". This is slightly misleading as the conclusion is only appropriate when using an assumption in the company's scenario analysis; the company's base case models the impact on QALYs via proximity in time to end of life. Pg 11 – The value of [redacted] is only applicable when using the company's scenario analysis; it would be incorrect to associate the value with the base case analysis using a different utility approach.	We suggest correcting the sentence to: "The impact of the treatment on the patient's quality of life based on the proximity to death, or the time spent in the PD health state, where most of the PEM+LEN incremental QALY gain ([redacted]) is accrued in the PD health state"	The value mentioned is specifically only applicable to one approach to the utility analysis, which was used as the company's scenario option.	The ERG has modified the sentence to include the TTD utilities as a driver of QALY gains: "Time spent in the PD health state ***and use of time-to-death*** to estimate utilities…". See p.11 of the ERG report.
Pg 12 – It is stated in the report that "Patients in the dMMR subgroup performed significantly better than patients in the pMMR subgroup on both OS and PFS outcomes, although it should be noted that the study was not specifically powered	The following amendment is more accurate: "…the study was not specifically powered to explore the impact of MMR status on survival outcomes and the follow-up period of KEYNOTE-775 was limited, leading to uncertainty **in any subgroup analysis**."	The uncertainty mentioned in the original sentence relates to uncertainty in the subgroup analysis, and it would not affect uncertainty in the survival outcomes	The ERG has edited the text to: "Point estimate results suggested patients in the dMMR subgroup may have performed better than patients in the pMMR subgroup on both OS and PFS outcomes,

to explore the impact of MMR status on survival outcomes and the follow-up period of KEYNOTE-775 was limited, leading to uncertainty."		of the overall population from KEYNOTE-775. There is no statistical comparison of the subgroups of pMMR vs dMMR. The company considers it is inappropriate to compare the two subgroups directly and to draw inferences from the comparison. Both pMMR and dMMR subgroups demonstrated statistically significant benefits in both PFS and OS. Additionally, the marketing authorisations issued by the MHRA and EMA both include those subgroups within the license.	although it should be noted that the study was not specifically powered to explore the impact of MMR status on survival outcomes and the follow-up period of KEYNOTE-775 was limited." See p.12 of the ERG report.
Pg 13 – The ERG's statement that "The expected impact on cost effectiveness remains unclear" is misleading. The question is: "What is the expected effect on the cost-effectiveness estimates?" Without further clarification the report suggests that the subgroup analysis could have an impact on the cost-effectiveness analysis submitted by the company, which relates to the overall population. There is no impact on the results for the targeted population based on the company position.	Amend the statement: "The subgroup analyses have no impact on the results for the company's targeted population. The expected impact on cost effectiveness within subgroups remains unclear."	The original response is misleading in context of the question asked.	Whilst not a factual inaccuracy, the ERG has clarified the text to read "The expected impact on cost effectiveness ***of each subgroup*** remains unclear." See p.14 in the ERG report.

Pg 13 – It is incorrect to suggest that the ICER can be predicted only by comparing OS estimates. The report does not acknowledge that ICERs are a result of several modelled inputs including PFS, ToT and HRQL. Without understanding each of these factors associated with the subgroup analysis, it is, in fact, not possible to predict ICERs: "However, due to improved OS in the dMMR subgroup, compared to the pMMR subgroup, the ICER for PEM+LEN is likely to be lower in this subgroup."	We suggest the following amendment to the ERG's opinion: "However, due to improved OS in the dMMR subgroup, compared to the pMMR subgroup, the ICER for PEM+LEN is likely to be lower in this subgroup if all other features of the model remained constant, including PFS, ToT and HRQL."	The original response is misleading in context of the question asked.	Whilst not a factual inaccuracy, the ERG has clarified the text to read "…lower in this subgroup, ***all else remaining equal.***" See p.14 of the ERG report.
Pg 34 – This was the only trial of PEM+LEN that was used in the company economic model. The ERG statement is misleading that more data are available but were not used.	We ask that the ERG amends the relevant text to reflect the actual reason to use KN775 study data. "It was the only trial for which IPD was available to the company, and the only Phase III trial for PEM+LEN in this indication"	The ERG statement is misleading that more data are available but were not used. We propose the edit that reflects data availability.	No factual error. The ERG statement solely states that there was one trial of PEM+LEN that was used in the economic model. It does not imply anything about the presence or absence of other potential data sources. No edits made.
Pg 47 – However, the effect in favour of PEM+LEN was stronger in the dMMR subgroup for both PFS (dMMR HR 0.36, 95% CI 0.23-0.57; pMMR HR 0.60, 95% CI 0.50-0.72) and OS (dMMR HR 0.37, 95% CI 0.22-0.62; pMMR HR 0.68, 95% CI 0.56, 0.84).	We ask that the ERG add additional information to the statement: *"*Note that KEYONOTE-775 study was not powered to explore these differences. These findings should be interpreted with caution due to small number of patients in each group.*"*	Proposed amendment adds clarity around the interpretation of subgroup results. Considering the study design claims around performance of subgroups should be made with caution. Considering the study design MSD is requesting	No factual error. However, the ERG has added a note of clarification (on p.49) that the trial was not powered to address subgroups and that these findings should be regarded as exploratory.

The proposed statement implies that there is enough evidence to analyse as two separate subgroups without outlining limitations.		a recommendation for the overall licensed population.	

Issue 4 Incorrect descriptions related to KEYNOTE-146

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 14 – "The ERG did not have access to the KEYNOTE-146 CSR, which introduced further uncertainty." This suggests that the company may have had access to the KEYNOTE-146 CSR, when in fact it did not. As discussed in response to ERG clarification question A12, the sponsor and the owner of the KEYNOTE-146 CSR is another company. Although we understand that there are questions that cannot be answered, the absence of this document also does not *introduce* uncertainty to the reported data or the resulting analysis.	The following suggestion provides transparency around the owner of the KEYNOTE-146 CSR: "The ERG did not have access to the KEYNOTE-146 CSR, which meant the ERG could not explore its queries further. The company is unable to provide the document as the sponsor and the owner of the KEYNOTE-146 CSR is another company."	The original statements may mistakenly cause the perception that the company did not provide the CSR, when it could not, as it does not own KEYNOTE-146.	No factual error. The ERG was correct to point out that the non-provision of a CSR for a trial included in the submission introduced further uncertainty. It is the submitting company's choice which trials to include. The ERG would expect full access to information on these trials in order to provide a full critique. However, the ERG has clarified that the company included a trial for which it did not own the CSR. See p.14/15 of the ERG report.
Pg 32 – The terminology used by the ERG to describe the primary objective of KEYNOTE-146 is ambiguous: "One supportive Phase 1b/II dose-finding trial of PEM+LEN, KEYNOTE-146, was	We would appreciate the following amendment to the ERG's description of KEYNOTE-146: "One supportive Phase 1b/II trial of PEM+LEN that was designed to determine the maximum tolerated dose for the combination treatment,	The terminology used to describe the objective of KEYNOTE-146 is ambiguous.	No factual error. The ERG's phrasing was taken from the company submission. No edits made.

used to validate model extrapolations." KEYNOTE-146 was designed to determine the maximum tolerated dose for lenvatinib in combination with 200 mg intravenous pembrolizumab every 3 weeks.	KEYNOTE-146, was used to validate model extrapolations"		
Pg 41 – No further information was available about the geographical distribution including the number of UK sites KEYNOTE-146 does not have any UK sites i.e. no UK patients. Clinicaltrials.gov list Norway and Spain as only European locations (last update March 7, 2022). [3]	We ask that the ERG amends the relevant text to clarify the statement: "No UK sites were reported for the KEYNOTE-146"	Proposed amendment adds clarity around the available data for the UK population.	The ERG has added clarification. See p.42 in the ERG report.
Pg 47 – No health-related quality of life data were presented from KEYNOTE-146 in the CS. The health-related quality of life data were not presented as it was not collected at the Phase 1b/2 KEYNOTE-146 study.	We ask that the ERG to edit the statement: "Health-related quality of life data were not collected in the Phase 1b/2KEYNOTE-146 study"	This statement can be misleading and imply that more data are available. Please omit or edit the highlighted statement to clarify the available evidence. The company provided phase 3 KEYNOTE 775 EQ-5D as per NICE reference case requirements.	No factual error. But the ERG has clarified that the reason was that the outcome was not collected rather than solely not reported. See p.48 of the report.

Issue 5 Clinical and RWE SLRs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 29 – Table 6 Line "Searches" "Hand searching and database searches of known conference	We ask that the ERG amends the relevant text to reflect that the company's SLR included manual searching of conference proceedings.	Proposed amendment adds clarity around the used methodology and reported outcomes.	The ERG has edited the text to reflect that the company's SLR included manual

proceedings may have mitigated this issue" Company submission clinical SLR Methods section outlines four conferences that were manually searched (CS Appendices D.1.1.1). The suggested edit reflects the methodology applied for SLR searches.			searching of four conference proceedings.
Pg 54 – However, the company did not provide a full list of excluded articles from the full-text screen of the interventional SLR so the ERG was unable to comment on whether the company identified and excluded these abstracts or did not identify them. The list of excluded studies was provided as part of the Clinical SLR report table 40.	We ask that the ERG omits this sentence.	The proposed edits reflect methods followed by the company and the information detailed within the company submission.	The ERG are unable to find the Table (list of excluded studies) referred to by the company in the CS or in the appendices provided by the company. As such, the sentence should remain in the ERG report.
Pg 30-31 – Table 7 Line "Screening and selection" "An additional study (the ECHO study) was described in Document B, Section B.2.9.3 and used to confirm/validate the survival data for the comparator arm in KEYNOTE-775. This is a recent study by the Company and was not identified by the SLR of RWE"	We ask that the ERG amends the relevant text to clarify why the highlighted study was not part of the RWE SLR: "… This is a recent **unpublished** study by the Company and was not identified by the SLR of RWE"	The proposed edits clarify why the RWE study was identified manually rather than being retrieved in the RWE SLR.	No factual error. It is already stated elsewhere in the ERG report that the reason the SLR did not capture the totality of the evidence base was that the ECHO study had not been published. However, the ERG has added clarification. See p.33 of the ERG report.

This statement requires clarification on how this study was added to the submission.			
Pg 56 – Table 16 Line “Searches” “The searches of bibliographic databases and grey literature sources are considered broadly appropriate. The ERG noted an error in the final line combination of the January 2021 update search in Embase.com (NOT was used instead of OR), however, searches of additional bibliographic databases and grey literature sources are likely to have mitigated the impact of this error.” NOT is the correct word by design, it’s not an error. In table 1 of January 2021 search strategies, the new and upgraded ‘advanced disease’ filter (line 14) was applied to comprehensively identify evidence from 1999 to 2021, while the old filter (line 8) was also used from 1999 to 2018 to identify the studies that existed in duplicate via use of the already existing filter. A ‘NOT’ in table 1 removed duplicate hits included by use of both the filters, while unique studies identified from	We ask that the ERG to omit this statement.	The proposed edits reflect methods followed by the company and the information detailed within the company submission..	The ERG have checked the search strategy and removed this statement from the ERG report.

1999 to January 2021 were still included in the final number of hits. Since the searches in November 2021 utilized the same new and upgraded filter (line 8) as used in January 2021 (line 14), thus the use of 'NOT' to remove duplicates was not necessary.			

Issue 6 Clinical effectiveness: Meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 61 – As such it would have been preferable for the company to make use of a meta-analysis of appropriate data for baseline prognosis and/or treatment effect rather than the single KEYNOTE-775 study.	We ask that the ERG to omit this statement.	KEYNOTE-775 is the pivotal phase 3 study informing this submission and contributes evidence for efficacy and safety for the intervention of interest. Therefore, a meta-analysis is neither relevant nor necessary to inform the HTA submission.	This is not a factual error and the ERG's recommendation is in line with TSD1 and TSD5. No edit made.

Issue 7 Patient characteristics - Age

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 17 – Based on clinical input, patients in the UK are likely to be heavier and older than those in KEYNOTE-775 (see section **Error! Reference source not found.** for further discussion). Pg 61 – The ERG noted KEYNOTE-775 was a multi-centre	We ask that the ERG remove the increased age scenario from the report.	Statements about average patient age misleads stakeholders about the patients' characteristics and real impact on the cost-effectiveness analysis. Company provided KEYNOTE-775 median age 63.5, KEYNOTE-775 UK specific patient – [redacted]	This is not a factual inaccuracy. Our clinical experts suggested the age profile of patients in KEYNOTE775 was younger than those seen in clinical practice. Furthermore, the ERG base case assumes a

study, therefore patient characteristics used in the model were not specifically from a UK cohort. Due to generalisability concerns, the ERG asked clinical experts to comment on the appropriateness of the patient baseline characteristics. Based on responses, UK patients are likely to be heavier and older than the company's baseline characteristics. It was highlighted that endometrial cancer is most common amongst obese patients and that it usually affects older women i.e. between the ages of 75 and 79 years. ERG interviewed KOLs (n=?) provided feedback that patients are much older than in the study and was not followed with any evidence or references to support the statement.		[redacted]). These values are consistent and should be generalisable for the UK population and are in line with clinical input sought during the submission development process. Furthermore, mean/median age from the KN775 is similar to values published in clinical and RWE SLRs. Patients' characteristics were validated with clinicians and no concerns were raised about patients age or generalisability to UK population. Proposed amendments ensure correct patients characteristics are used and are applicable to the UK population.	higher patient age (as per clinical advice). It is not appropriate to simply remove this from our analysis. No edit made.

Issue 8 Patient characteristics – Weight and BSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 61 – Modelled patient characteristics were based on patients from KEYNOTE-775. Within this pivotal study, average patient weight was 70.5 kg and	We ask that the ERG remove the weights and BSA edits from the report.	Statements about average patient weights and BSA misleads stakeholders about the patients' characteristics and real impact on the cost-effectiveness analysis.	This is not a factual inaccuracy. Our clinical experts suggested the BMI/weight profile of patients in KEYNOTE-775 was lower

median patient age was 63.5 years Pg 92 – According to the clinical advice received by the ERG, patients enrolled in the clinical trial were of a lower mean weight than those typically seen in UK clinical practice (company base case: 70kg). The ERG therefore conducted a scenario analysis at a patient mass of 85kg. ERG interviewed KOLs (n=?) provided feedback that patients are much heavier than in the study and was not followed with any evidence or references to support the statement.		Company provided KN775 (70kg) and KEYNOTE-775 UK patient weights ([redacted]). These values are consistent and should be generalisable for the UK population. Furthermore, mean/median weight/BSA from the KN775 is similar to values published in clinical and RWE SLRs. Patients' characteristics were validated with clinicians and no concerns were raised about patients' weight/BSA or generalisability to UK population. Proposed amendments ensure correct patients characteristics are used and are applicable to the UK population.	than those seen in clinical practice. No edit made.
Page 92 – Incorrect value for body surface area noted	The value investigated by the ERG in scenario analysis was 1.96m^2. Body surface area "1.91m^2" should be corrected to "1.96m^2"	Incorrect value noted.	The ERG has corrected this typo in the section heading. See p.93 of the ERG report.

Issue 9 Incorrect elucidation of PEM+LEN and comparator positioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 22 – Whilst both carboplatin and doxorubicin are included as comparators, the key trial in the company submission does not use this doublet as a comparator	We would appreciate if the ERG amended this statement to: "Whilst both carboplatin and doxorubicin are included as comparators, the company provided an exploratory scenario which incorporated carboplatin in combination with paclitaxel (as re-challenge) and carboplatin monotherapy – in addition to paclitaxel and doxorubicin. Due to data limitations this scenario is only addressed from a costing perspective with efficacy being derived from the TCP arm of KEYNOTE-775."	As mentioned in CS Document B Section B.3.2.3.2 and B.3.8.3 a 'mixed chemotherapy' comparator scenario was investigated in which the impact of including different chemotherapies (paclitaxel, doxorubicin, carboplatin and carboplatin in combination with paclitaxel [as re-challenge]) was tested. Furthermore, as there are no robust data for these treatments in previously treated advanced EC, it was necessary and appropriate to assume equivalent efficacy between the mixed chemotherapy options and TPC arm of KEYNOTE-775. This approach was also validated by expert clinicians.	This is not a factual inaccuracy. On p.65 of the ERG report, the ERG mention the scenario analysis conducted by the company which compared PEM+LEN to mixed chemotherapy (including carboplatin in combination with paclitaxel). For completeness the ERG has added *'as re-challenge'* on p.65.
Pg 61-62 – The ERG noted that for the latter positioning, the most appropriate comparator is re-challenge with platinum-containing doublet chemotherapy. Given that the treatments provided in KEYNOTE-775 were primarily doxorubicin or paclitaxel (and not specifically platinum re-challenge), the clinical data provided by the company does not appear to support the use of PEM+LEN in this positioning.	We would appreciate if the ERG amended this statement to: "The company included a 'mixed chemotherapy' comparator scenario in which the impact of including different chemotherapies (paclitaxel, doxorubicin, carboplatin and carboplatin in combination with paclitaxel [as re-challenge]) was tested." Please delete the concluding remarks of the statement "the clinical data provided by the company does not appear to support the use of PEM+LEN in this positioning." KEYNOTE-775 does support the use of PEM+LEN in its		For clarity, the ERG has edited the text on p.62 and p.63 of the ERG report.

	full positioning as it this is currently the licensed population.		

Issue 10 Critique of general modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 66 – A 26-week breakpoint was selected for OS and 10-week breakpoint for PFS on the basis of Chow test results (not supplied in CS). Taking the Chow test at face value, the plots supplied at clarification (B6) do not appear to support the 10-week breakpoint selection for PFS (clarification figs 4 and 5), nor the 26-week OS breakpoint in the TPC arm (clarification fig 3).	Proposed phrasing: "A 26-week breakpoint was selected for OS and 10-week breakpoint for PFS based on multiple criteria, including on the basis of Chow test results (not supplied in CS). Using the Chow test and other criteria, the CS included a 10-week breakpoint selection for PFS (clarification figs 4 and 5) and a 26-week OS breakpoint in the TPC arm (clarification fig 3)."	Chow test is just one of the criteria we exam to verify the cut-off for two-piece extrapolations. Other important criteria include the **tail performance of the hazard estimates**, **robustness of extrapolations**, number of events after cut-off, and visual inspection as well. Chow tests were performed on a sequence of F-tests for a sequence of cut-off point candidates (usually starting from week 3 and proceeding at weekly intervals until the end of the trial). The F-tests were based on the null hypothesis (the whole survival curve fit one-piece exponential curve) versus the alternative hypothesis (the survival curve is fitted by a two-piece exponential curve with the specific cut-off point). For PFS and OS, the corresponding selected cut-points, respectively, demonstrated the most pronounced structural change to the slope of the cumulative hazard curve and selected as the cut point. The 26-week breakpoint in OS is clear within the Chow test plot pem+len arm while the Chow test plot for TPC OS also suggests a break point around 13 weeks. The 26-week breakpoint for OS has improved performance for the hazard estimates compared with the 1-piece parameterisations and provides robust external validation. As mentioned above, the Chow test results were not the only criteria for cut-off selection. The cumulative hazard plots were also used to confirm the selections, and the plausibility of the long-term projection based on these cut-off points was validated. This method utilises the majority of the Kaplan Meier data whilst at the same time there are sufficient remaining patients to fit parametric curves. We make sure there are sufficient amount patients alive in both arms. With regards to PFS, the first tumour assessment is at 8 weeks which is also close to the 10-week break point for PFS.	The ERG maintains that clarification fig 3 does not clearly support a 26 week breakpoint in the OS TPC arm, nor does the empirical hazard curve (shown in clarification fig 8). Similarly for the 10-week choice of breakpoint in PFS (see clarification figs 4,5,9,10). The ERG acknowledges that the company choice was dependent on several criteria, and has amended the sentences as follows on p.67 of the ERG report: "A 26-week breakpoint was selected for OS and 10-week breakpoint for PFS on the basis of Chow test results, visual inspection of the hazard function and a preference for earlier breakpoints, thereby providing more data for parametric fitting in the second piece (doc B p80). Taking the Chow test at face value, the plots supplied at clarification (B6) do not appear to clearly support the 10-week breakpoint selection for PFS (clarification figs. 4 and 5), nor the 26-week OS breakpoint in the TPC arm (clarification fig. 3)."

Issue 11 RWE ECHO study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 67 – For the TPC arm the ERG found reporting to be inadequate for the purpose, and there were marked discrepancies in patient characteristics between the ECHO and KEYNOTE-775 TPC arm. RCTS are the highest quality study a company can conduct to provide high quality evidence. RWE studies provide additional information but cannot match the quality of the RCT. RWE has multiple confounders and was never designed to be like the KN775 study.	We ask that the ERG edits the proposed sentence: "Company provided data from the RWE ECHO retrospective study, which was designed to review patient records to evaluate treatment patterns and clinical outcomes. The population characteristics did not exactly match the KEYNOTE-775 patients as this was RWE study ([redacted]) with patients receiving any treatment options."	The proposed amendment provides clarification on why differences were observed between the KN775 and ECHO.	Not a factual inaccuracy. The ERG highlighted details of the differences in baseline characteristics between ECHO and KEYNOTE-775 in its report (section 4.2.6.4, including Table 22). These differences reduce the value of ECHO as a validating study for extrapolations from KEYNOTE-775.

Issue 12 Discounting LYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 60 – However estimates of life years were discounted at 0%. The ERG did not consider this to be appropriate. Pg 64 – However, estimates of life years were not discounted. NICE guidance states that "the same annual discount rate should be used for both costs and	We ask that the ERG remove the outlined sentences	The proposed amendment removes confusion of what the company was required to submit as per NICE Guide 2013 (agreed process with NICE) [5].	This is not a factual inaccuracy. We refer the committee and company to the NICE methods guide, section 5.6.1 as stated in the ERG's report. No edit made.

benefits (currently 3.5%).” [NICE 2013, paragraph 5.6.1].[4] The ERG conducted an analysis which discounted life years at 3.5%. This was included as part of the ERG’s preferred base case (see Section **Error! Reference source not found.**). In the response to ERG questions (C5) company explained that life years specifically are not discounted in the base case, in accordance with the applicable NICE reference case at the time of the company submission [5]. So the discount rate of 0% for life years is correct (not a typographical error) and does not need updating.			

Issue 13 Cost-effectiveness: One-way and probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85, section 5.2.2 “Furthermore, all the OWSAs considered are based on the deterministic results, not the probabilistic. This yields a biased estimate of the expected incremental costs and outcomes.”	We ask that the ERG to edit the paragraph: “The OWSA was based on the deterministic results and the bias is unknown”	The proposed amendment removes confusion of what company was required to submit as per NICE Guide 2013 (agreed process with NICE) [5].	This is not a factual inaccuracy. No edit made.

This is a misleading statement. The submission followed NICE Guide to the methods of technology appraisal 2013 [5]. According to the guide the recommendation was "One-way simple sensitivity analysis (univariate analysis): Each parameter is varied individually to isolate the consequences of the parameter on the results of the study." Company submission had PAS included where all inputs were varied simultaneously – which is a realistic test to include all variation – robustly demonstrated no-low impact of joint variability in the inputs i.e. high consistency in DSA and PSA results with a difference of only £40.0			
Page 85 – Based on the CEAC results, PEM+LEN had a [redacted] and [redacted] probability of being cost effective at a willingness to pay threshold of £30,000 and £50,000 respectively. The company proposes that the ERG's text could be confusing as the ICERs reported throughout the document incorporate the pembrolizumab discount, whereas the results for the probability of being cost effective at a	We suggest amending the text to read: "Based on the CEAC results (list prices), PEM+LEN had a [redacted] and [redacted]" OR "Based on the CEAC results (including PAS for pembrolizumab), PEM+LEN had a [redacted] and [redacted]"	The proposed amendments ensure consistency across the document.	This is not a factual inaccuracy, however the ERG agree with the company's suggestion of adding clarity. See p.86 of the ERG report.

willingness to pay threshold of £30,000 and £50,000 are those in which with the list price of treatments was applied.			
Pg 85 – As a general observation, on p. 131 of the CS, the company stated agreement between probabilistic analysis and deterministic analysis as evidence of robustness of the model, *"Therefore, the outcomes from the cost-effectiveness model are considered robust to uncertainty from parameter distributions."* The ERG do not consider this statement to be true, because the agreement between probabilistic and deterministic analyses depends on the degree of 'non-linearity' in the model and not robustness. Company submitted model did employ PSA methodology as per NICE 2013 guide requirements. Non-linearity is addressed in the probabalistic analysis and the mean PA says the result is still consistent with the deterministic analysis.	We ask that the ERG to remove statement . "The ERG do not consider this statement to be true, because the agreement between probabilistic and deterministic analyses depends on the degree of 'non-linearity' in the model and not robustness."	The proposed amendments ensure consistency with the NICE Guide requirements	This is not a factual inaccuracy. No edits made.

Issue 14 Cost-effectiveness: Exploratory and sensitivity analyses undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 15/79 – the ERG noted that in the company's base case TTD approach, varying the PFS curve (whilst keeping OS unchanged) did not have an impact on QALYs, but did impact costs.	TTD utility estimates are dependent on mortality and not progression. It is important to note that this case is not unique to the company model and is a result of using a TTD utility approach in oncology modelling. We would appreciate if the ERG could add that "When selecting the health state utilities approach in scenario analysis, QALYs were only impacted by </>0.01 when PFS curve was varied (and the OS curve was held the same)."	The original statements may mistakenly cause the perception that, in taking the health state approach, varying the PFS curve (whilst keeping OS unchanged) may have a significant impact on QALYs.	This is not a factual inaccuracy, however the company's suggestion appears reasonable. The ERG has edited text on p.79 to reflect the company's comment.
Pg 17 and 88 – The ERG explored two alternative approaches to capping overall survival, a 'simple' approach and a 'hazards' approach. In the model, these two alternative approaches were only applied to the PEM+LEN arm, not the TPC arm (or mixed chemotherapy [MC] arm). Specifically, these approaches were not accounted for in 'PFS' sheet columns AZ and BA, and 'OS' sheet columns AZ and BA. Therefore, this analysis performed by the ERG is incomplete.	We request that the two alternative approaches to survival capping are also applied to TPC and MC treatment arms in the model and that results presented in Tables 28-31 for 'approach to capping the survival function' and 'survival capped by hazards' are updated accordingly.	Without applying the highlighted approaches to the TPC and MC arms, there is a technical inconsistency that is otherwise omitted by the ERG report.	We thank the company for pointing out this issue. We have now applied the two approaches to the TPC and MC arms and updated the results in our report and confidential appendix. An additional sentence has also been added to p.72 of the ERG report.

Issue 15 Misrepresentation of company approach to exclude treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 71 – The ERG noted that the company did not include treatment waning in their economic model, on the basis of precedent. The appraisals described in the CS (document B, Table 24) to demonstrate precedent for lack of treatment waning were for PARP inhibitors in ovarian cancer.	In CS (Document B, Table 24) treatment waning was noted as "not applicable as with previous appraisals; validated by long-term KN-146 data". We wish to clarify that this table summarises key features of the economic analysis, alongside corresponding features of completed appraisals in other gynaecological cancers. Thus, the table itself merely presented similarities and differences between these appraisals. As recognised by the ERG, company justification for not including treatment waning in the economic analysis was provided in response to ERG CQ B18. We would appreciate if the ERG removed the following sentences as they misrepresent the company approach: "The company did not include treatment waning in their economic model, on the basis of precedent. The appraisals described in the CS (document B, Table 24) to demonstrate precedent for lack of treatment waning were for PARP inhibitors in ovarian cancer."	The original statements omit elements of the company's justification and is a misrepresentation of company approach to the exclusion of treatment waning, as clarified in response to ERG CQ B18.	Not a factual inaccuracy. The CS mentions treatment waning once (doc B table 24). It stated that treatment waning is 'Not applicable as with previous appraisals; validated by long-term KN-146 data' and listed 6 appraisals of PARP inhibitors in ovarian cancer. The ERG does acknowledge that the CS table also mentions validation by long-term data, and has therefore made minor amendments to the paragraph. See p.72 of the ERG report. The company's further justifications for not including waning (CQ B18) were repeated and discussed in ERG report section 4.2.6.3.

Issue 16 Minor erroneous data values in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 45 – Median PFS and OS from KEYNOTE-146 are erroneously described in the ERG report as not being provided in the company submission: • "PFS for KEYNOTE-146 was not reported in the CS." • "OS was not reported in the CS in KEYNOTE-146." These are both provided in Table 11 of the company submission.	Amend the statement to include the correct figures provided in the company submission: • Median PFS of PEM+LEN for KEYNOTE-146 was reported in the CS in Table 11 of 7.4 months • Median OS was reported in Table 11 of the CS in KEYNOTE-146, 17.7 months in the PEM+LEN arm.	Erroneous statements regarding the provision of data in the company submission. Company provided both mPFS and mOS from KN-146 study in CS Document B Table 11.	The ERG considered the company's submission contained inadequate signposting, particularly with respect to clinical trial information. However, the ERG agree with the company that Table 11 provided median PFS data and OS data for KEYNOTE-146. The report has been edited to reflect this. See p.47.
Table 20 – Minor rounding errors in the values reported in the table.	We believe there are minor rounding errors in Table 20 based on the version of the ERG model we were provided; correct values are provided below: • ERG/CS model (log-logistic), at 1, 2 and 5 years: [redacted] respectively (instead of [redacted]) • CS base case (exponential), at 2 years: [redacted] (instead of [redacted]) • ERG base case (log-logistic), at 5 years: [redacted] (instead of [redacted])	Minor rounding errors to the data values in Table 20.	The ERG accept the company's rounded figures. The difference is considered very minor. See p.70/71 of the ERG report.
Pg 67 – The company attempted to validate the extrapolated curves with the use of longer-term information	Recommendation to edit the sentence to reflect the provided exploratory scenario	It is misleading to stakeholders to imply that the provided data might not be good enough. It is	This is not a factual inaccuracy, No change recommended.

	"For the validation the company **provided** extrapolated curves with the use of longer-term information"	suggested to keep the statement neutral.	
Pg 74 – a smaller proportion of MMRd (around 15%) in ECHO and a larger proportion (around 44%) in KN-146 compared to the UK (30%)…	We ask that the ERG to edit the sentence "a smaller proportion of dMMR (around 15%) in ECHO and a larger proportion (around 44%) in KN-146 compared to the UK (20-25%)"	MSD discussion with clinicians points that 20-25% of all patients would are dMMR. This is in line with the TA779 -23% ("Around 23% of people with endometrial cancer have the subtype with high microsatellite instability (MSI) or DNA mismatch repair (MMR) deficiency biomarkers.")	Not a factual inaccuracy. 30% was based on clinical opinion to the ERG. However, the ERG have added the word 'approximately'. See p75 of the ERG report.
Page 75-76 – Table 22 Incorrect value for age in years at initial diagnosis (mean) in KEYNOTE-775 TPC arm. This value is also currently not marked AIC while it is marked AIC in the company submission.	The correct value is [redacted] not [redacted] which is currently reported. This value should also be marked AIC.	Incorrect value – should also be highlighted as AIC.	The ERG has corrected this and have underlined AIC, as per the company's request. See p.76 of the report.

Issue 17 Other minor labelling or typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 12 “The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issue for the committee’s consideration”	Spelling corrected: “The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issues for the committee’s consideration.”	Minor typographical error.	The ERG have corrected this minor typographical error. See p.12 of the ERG report.
Pg 18 – Table 3 title “Table 3: ERG preferred assumptions (deterministic)” Pg 18 – Table 4 title “Table 4: ERG preferred assumptions (probabilistic)” Pg. 88 Table 27 “ERG-corrected company base case results” It is not clear what pembrolizumab price was used – list or with applied PAS. Due to the nature of the submission with multiple products having various pricing agreements and submission/ERG report reporting both list and PAS applied results, there is potential for confusion as to the object of each statement. Adding “including PAS for pembrolizumab” will clarify the statement.	Please add that “including PAS for pembrolizumab (lenvatinib at list price)”	Please add the clarification that only pembrolizumab PAS was applied i.e., lenvatinib still has list price.	This is not a factual inaccuracy, however the ERG agree with the company’s comment that this will provide clarity. The ERG has added sentences to p.18, p.88, p.94 and p.97 stating that the results include the updated pembrolizumab PAS and list price for lenvatinib.
Pg 21 “In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Merck,	Spelling corrected (please check all legends/keys as we spotted a few instances): lenvatinib	Minor typographical error.	The typographical error on p.21 has been corrected. The ERG has also corrected the spelling

Sharp and Dohme (MSD) in support of pembrolizumab with levatinib (PEM+LEN) for previously treated advanced, metastatic or recurrent endometrial cancer (EC)." The incorrect spelling for lenvatinib occurs a few times in tables, legends, etc.			of lenvatinib throughout the report.
Pg 23 "MSI" to be corrected to "MSI-H": "Those with EC displaying MSI/dMMR can now access dostarlimab monotherapy (TA779)."	Spelling corrected: MSI-H	Minor typographical error.	This has been corrected as per the company request. See p.23 of the ERG report.
Table 59 – "maped" to be corrected to "mapped".	Spelling corrected: mapped	Minor typographical error.	The ERG assume the company is referring to Table 19. This minor typographical error has been corrected.
Pg 75 Table 22 header – "KEYNOTE-755" to be corrected to "KEYNOTE-775".	Spelling corrected: KEYNOTE-775	Minor typographical error.	The ERG has corrected minor typographical errors on p.75 and p.76 of the ERG report.
Pg 81 "…the ERG did not consider this to be an issue and foud the company's approach to be reasonable."	Spelling corrected: found	Minor typographical error.	The ERG have corrected this minor typographical error. See p.81 of the ERG report.
Pg 80 For pembrolizumab, patients received 100mg every 3 weeks. For doxorubicin and paclitaxel, dosing was based on KEYNOTE-775 protocol (see table 42, p.112 of the CS)	Correction to reported dose of pembrolizumab For pembrolizumab, patients received **2**00mg every 3 weeks plus lenvatinib 20 mg every day.	Please edit to correct dosing and add lenvatinib dosing to the sentence	The ERG has corrected the pembrolizumab dose and amended the text slightly to reflect lenvatinib dosing. See p.81 of the ERG report.

Page 73 – Table 21 title line "KEYNOTE-146: endometrial cancer subgroup	Please merge the title "KEYNOTE-146: endometrial cancer subgroup" for the "Previously treated" and "All" columns	Minor formatting error.	This has been amended as per the company's request. See p.73 (Table21) in the ERG report.
Pg 74 - Very little performance status (as measured by ECOG) grades 2 or 3 in ECHO (compared to 30% and 10% respectively in the UK)	Please edit "*Low proportion of* performance status (as measured by ECOG) grades 2 or 3 in ECHO (compared to 30% and 10% respectively in the UK);"	The terminology as "very little" is not appropriate to describe performance status or proportion of patients. Please clarify accordingly.	The ERG agree with the company and have therefore made the change as requested. See p.75.
Pg 37 – …hyperthyroidism (57.6%), hyperthyroidism (11.6%). Hyperthyroidism as an AESI duplicated	Should state hypothyroidism (57.6%) and hyperthyroidism (11.6%)	Minor ty.pographical error.	The ERG assume the company is referring to p.51. The ERG have amended to 'hypothyroidism (57.6%)'.
Pg 38-39 – Table 14 Summary of treatment-related AEs (incidence ≥ 5%)	Should read ' Summary of treatment related AEs (incidence of ≥ 10%)	Minor typographical error.	The ERG assume the company is referring to p.51. The ERG have made the amendment as requested by the company.

References

1. National Institute for Health and Care Excellence (NICE). *Technology appraisal guidance. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779], 2022*. Available from: https://www.nice.org.uk/guidance/ta779.
2. NHS England. *National Cancer Drugs Fund List (ver1.214 06-Jun-22)*. 2022 [cited 2022 2022-06-14]; Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/cdf-list-v1.214.pdf.
3. ClinicalTrials.gov. *A Trial of Lenvatinib (E7080) Plus Pembrolizumab in Participants With Selected Solid Tumors (KEYNOTE-146)*. 2022 [cited 2022 2022-06-14]; Available from: https://www.clinicaltrials.gov/ct2/show/NCT02501096.
4. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013. Processes and methods, 2013*. Available from: https://www.nice.org.uk/process/pmg9.

5. National Institute for Health and Care Excellence (NICE), *Guide to the methods of technology appraisal 2013.* 2013.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1 and sections 1.3 – 1.6).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 8 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Clinically distinct subgroups in the evidence base - deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). Are there difference in the clinical effectiveness of the dMMR and pMMR subgroups? Should they be considered separately?	No	**The co-primary objectives of KEYNOTE-775 were met by demonstrating pembrolizumab plus lenvatinib resulted in significantly longer and consistent clinical benefit in progression-free survival and overall survival versus chemotherapy across all subgroups as per trial statistical analysis plan. This included pMMR followed by the overall population. Since the study was not powered to ascertain differences across subgroups MSD disagrees with these populations being considered separately for decision making purposes.** More evidence is provided below to support the focus of decision making on the overall trial population. <u>KEYNOTE-775 demonstrates clinical effectiveness across all patient subgroups</u> In all three populations (pMMR, dMMR, all-comer), the combination of pembrolizumab plus lenvatinib demonstrated consistent improvements in ORR, PFS, and OS. This was the first phase III study to show benefit of a

		new therapy against a widely used standard of care regardless of biomarker status. The MHRA approved pembrolizumab in combination with lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation. (1) Therefore not limiting the use of the combination to a specific subgroup. **Based on the clinical study design and marketing authorisation the full population should be considered.** <u>Unmet need for pMMR patients:</u> MSD notes that very little progress has been made in endometrial cancer (EC) management over the past years. There is no agreed standard of care beyond platinum-based chemotherapy for advanced or recurrent EC, as acknowledged in the British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines, published in 2021 (2-4). Additional options include hormone therapy, which has no survival benefit, rechallenge with chemotherapy or enrolment into clinical trials. (4) The recent NICE recommendation for TA779 to enter the Cancer Drugs Fund for further data collection, provides an option for the 23% of patients with EC who have dMMR status (5). The approval was based upon a phase I single-arm study. **For pMMR patients, current treatment options remain very limited and patients have a poor prognosis**. <u>KEYNOTE-775 was not powered to test differences between subgroups:</u>

		KEYNOTE-775 was not designed or powered to compare pembrolizumab plus lenvatinib with chemotherapy in the dMMR population. The study was not designed or powered for subgroups MMR status but employed a hierarchical testing approach (pMMR→ITT) with dMMR being explored as a subgroup. Improvement was observed across efficacy end points in the dMMR population for pembrolizumab plus lenvatinib compared with chemotherapy. (6) There is no statistically meaningful comparison of the subgroups of pMMR vs dMMR. The company considers it is inappropriate to compare the two subgroups directly and to draw inferences from the comparison. **Both pMMR and dMMR subgroups demonstrated statistically significant benefits in both PFS and OS compared with the control arm.** **Pembrolizumab plus lenvatinib is an effective and safe therapy in the overall patient population having demonstrated clinically significant PFS and OS benefit from a phase III RCT for endometrial cancer which does not require patient MMR testing.** **MSD does not support the separation of the trial population by MMR status for decision making purposes as this could artificially lead to the introduction of uncertainty in the economic modelling and cost-effectiveness conclusions.**
2. Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of pembrolizumab with lenvatinib in the dMMR and pMMR subgroups.	No	**Whilst MSD recognises there appears to be a differential response across the two subgroups mentioned, the trial was not powered to detect it. Therefore it is not clear if it is clinically or statistically meaningful. The uncertainty surrounding the cost effectiveness of this combination within the dMMR and pMMR subgroups increases due to study design limitations.**

		MSD considers appropriate that the cost-effectiveness analyses are focused on the overall patient population, in line with the final scope issued by NICE and following the best available evidence base for pembrolizumab plus lenvatinib. The population for this appraisal aligns with the marketing authorisation (MA). The Final Scope did not specify any subgroups. As described in the response to Issue 1 (above), there is an unmet need for effective and safe treatment options in all eligible patients. In KEYNOTE-775, efficacy benefits were observed in the entire intention-to-treat population, a phase III RCT. As this indication is MMR agnostic i.e. eligibility for treatment with PEM+LEN is not based on the outcome of an MMR status test. This is beneficial in the real-world where patients with disease may not be biopsied or tested in a timely manner.
3. Uncertainty surrounding extrapolation of overall survival (OS) and: - use of ECHO study to validate OS in doxorubicin or paclitaxel arms - unavailable clinical study report (CSR) for KEYNOTE-146 because it is an Eisai study. - dismissal of restricted cubic splines	Yes	**KEYNOTE-775 is a phase III RCT study, which provides the highest level of data for this indication. Supporting RWE studies provide some insights; however they do have limitations and are likely to be more optimistic compared to the TPC arm in the cost-effectiveness model. To reduce uncertainty surrounding the OS and PFS extrapolations a summary of the final analysis results from KEYNOTE-775 is shared as an addendum. Also, the KEYNOTE-146 CSR is shared as part of this response (Appendix A).** Treating Physicians Choice (TPC) arm OS validation Randomized control trials are viewed as the highest level of evidence as they are designed to be unbiased and have less risk of systematic errors. (7) KEYNOTE-775 is the only phase III study that has approved marketing authorization for previously treated advanced, metastatic or recurrent endometrial cancer. This multi-centre open-label trial has months median

		duration of follow-up (at the time of IA1). The Final Analysis shared with the response document has 14.7 months follow up data in the all-comer population. The model extrapolations for the TPC arm were validated using ECHO RWE UK study and clinicians' inputs. An additional RWE study became available during the TE process included the Heffernan et al UK RWE study. (8) Summary of both UK RWE studies: 1. ECHO is a retrospective, multicentre chart review study evaluating treatment patterns and clinical outcomes in advanced or recurrent EC patients (n=101) who received at least one prior systemic therapy (data on file). Physicians provided data obtained from medical records of adults diagnosed with advanced or recurrent EC between 1 July 2016 – 31 December 2018, and who had disease progression after a prior systemic therapy during 1 July 2016 – 30 June 2019. Understandably it has some limitations: • Small sample size • Treatment options received in first and/or subsequent lines: chemotherapy as per NICE Scope but also off license use of other treatments like bevacizumab, nivolumab, everolimus and other. 2. Since the Heffernan UK RWE study was published recently the company was not able to incorporate the evidence into this submission. However a brief discussion around its suitability for external validation of the SoC TPC arm is offered in this response. This non-interventional study used routine, administrative health data from the National Cancer Registration and Analysis Service in England to identify patients diagnosed with recurrent/advanced

		endometrial cancer between 1 January 2013 and 31 December 2018, inclusive. A cohort (n=999) of patients who progressed to second line treatment were identified as the 'immune checkpoint inhibitor-eligible second-line' cohort. (8) It should be noted that this study has multiple limitations to be comparable with the KEYNOTE-775 TPC arm data: • This study analysed only second line EC patients while 28% patients in KN775 had 2 prior platinum-based treatments • The ECOG PS was only reported for 50% of the RWE study • 24% of records are missing disease grade data • Uncertainty on the breakdown of pMMR and dMMR patients within the study • Difference in patient histology proportions • No clear mention of previous pelvic irradiation • KN775 patients required to have histologically/cytologically proven recurrent solid tumour with measurable lesion per RECIST • No Progression Free Survival or Overall Response Rate data reported for study comparisons. All discrepancies between evidence from the clinical trial compared with RWE can have an impact on the observed efficacy for a wide range of reasons. **The aforementioned limitations potentially overestimate the SoC arm compared to the KEYNOTE-775 TPC extrapolations**. The lower hierarchy level of evidence such as RWE studies could provide additional insights and help to validate TPC OS but should be viewed with caution due to the high risk of bias.

Please see the table below with the key summary data of the KEYNOTE-775 and RWE studies.

Table 1: Comparison of RWE studies versus KEYNOTE-775 TCP arm.

	KN775 All comer TPC (n=351)	**KN775 UK TPC (n=20)**	**ECHO UK SoC (n=101)**	**Heffernan (SoC n=999)**
Cohort I/E	Phase 3 RCT trial Patients with advanced endometrial cancer who had previously received at least one platinum-based chemotherapy Region: multi centre country	Same as per KN775 study column Region: UK	Adult women diagnosed with aEC who received at least one prior systemic therapy and progressed between July 1, 2016 – June 30, 2019, were included Region: UK	Pts with 1+ EC diagnosis between Jan 1, 2013, and Dec 31, 2018 Pts with recurrent or advanced (stage III, IV) EC Received a platinum-doublet regimen after the earliest diagnosis of recurrent or adv disease (index date) Received 2L treatment Region: UK
Age at initial diagnosis	66 (median) 61.3 (mean)	[redacted]	[redacted]	NA (median) 65 (mean)
Follow-up/median	10.7 (0.3-26.3) month > From randomization	NA	24 month > From aEC diagnosis	27.4 (3.5–91.1) month > From recurrent or advanced disease diagnosis
Disease stage N(%) I II	 114 (32.4) 22 (6.3) 103 (29.3)	[redacted]	[redacted]	 183 (18) 38 (4) 415 (42)

III IV	112(32)			363 (36)
Histology Endometrioid Serous Clear cell carcinoma Other	 151 (43) inc. HG 112 (31.9) inc. HG serous 17 (4.8) 71 (20.3)	[redacted]	[redacted]	 424 (42) 401 (40) 46 (5) 128 (13)
ECOG 0 1 2-4 Unknown	 207 (59.0) 144 (41.0) 0 0	[redacted]	[redacted]	 320 (64) 181 (36) 0 498 (50)

Key: aEC, advanced endometrial cancer; HG, high grade; pts, patients

The table below presents an updated CS Table 53 with median OS and PFS estimates extracted from the cost-effectiveness model alongside median OS and PFS extracted from KEYNOTE-775, KEYNOTE-146, ECHO UK RWE and Heffernan RWE data. There are some differences between the modelled and observed values. Results for the OS from both RWE studies are similar with the TPC arm but should be considered with a caution due to the risk of potentially overestimating the benefit in the short and long term.

Table 2 (Updated CS Table 53): Comparison between reported and modelled median survival

	PEM+LEN		TPC	
Health State	**PFS (months)**	**OS (months)**	**PFS (months)**	**OS (months)**
Modelled (KN-775 informed)	6.67	18.63	3.91	11.27

Observed (KN-775)	7.23	18.3	3.78	11.43
Observed (KN-146)	7.5	16.7	NA	NA
ECHO UK SoC*	NA	NA	NA	11
Heffernan UK SoC**	NA	NA	NA	10.3

Key: KN-146, KEYNOTE-146; KN-775, KEYNOTE-775; OS, overall survival; PEM+LEN, pembrolizumab in combination with lenvatinib; PFS, progression-free survival; SoC, standard of care; TPC, treatment of physician's choice.
*Patients received other treatments that are off license (bevacizumab, everolimus, nivolumab and etc) this potentially has impact on the measured outcome**;** **Only patients progressed to receive a second-line therapy

In addition to the validation process outlined above, UK clinical experts consulted by MSD provided clinical validation to confirm curve selection for OS and PFS extrapolations. This ensured consistency of the modelled population with the UK decision problem.

CSR for KEYNOTE-146

The KN146 CSR is provided as a separate document to this response as per the ERG's request.

Restricted cubic splines

As detailed in Document B Section B.3.3.3 and in response to ERG clarification question B19, the two-piece modelling approach for OS in the company base case provides a sufficiently good fit to the data and adequately reflects the underlying hazards. The company has not dismissed cubic splines as a potential alternative, it is simply that no other types of flexible parametric models were explored in addition to the numerous modelling approaches already included in the submission. In total, the company explored 18 models for OS for each treatment arm (six standard distributions for one-piece parametric models, and two-piece models with a 26-week and 52-week cut-off point).

		In a comprehensive assessment of the fitted curves, the two-piece approach demonstrated a good visual and statistical fit to trial outcomes and underlying hazards. In addition they provided a clinically plausible estimate of the long term extrapolation validated by clinical expert opinion and longer-term follow-up from KEYNOTE-146 (in the case of PEM+LEN OS). Overall, internal and external validity were sufficiently met by two-piece models, and, following NICE DSU TSD 21, further exploration of alternative methods was not deemed necessary in this case. (9) The company approach also aligns with previous appraisals of pembrolizumab treatment in advanced malignancies in which two-piece models have been deemed appropriate to model survival by the ERG.(10, 11) However, the company acknowledge the ERGs comments on the two-piece approach and understand the possible benefits of utilising restricted spline models to explore uncertainty. It is further appreciated that such models may have the potential to better capture the complex trend of the empirical hazard in evidence. **Please note that since the company submission KEYNOTE-775 has had a final analysis (FA) read out. Appendix A provides a summary of the clinical data update.** Unfortunately, due to the short period of time between availability of the patient-level data and the deadline for the response to technical engagement, there has been insufficient time to introduce into the model and re-run the cost-effectiveness analysis.
4. Uncertainty surrounding the company's time to death utility approach	No	**MSD considers that TTD approach is more suitable for the base case of this evaluation. This approach captures patients' HRQoL over time, which is clinically appropriate as time states closer to death are likely to be associated with worse HRQoL and a lower utility value. Utilising a TTD approach can remove the dependence on subjective clinical assessment of progression status.**

		A number of published economic evaluations of IO treatments have used the TTD-based utility approach, noting that such an approach avoids a number of issues typically attributed to progression-based analyses. (12-14) TTD-based utility values are becoming a more common approach for economic evaluations of IO treatments. A recent review of IO appraisals performed by NICE found that of the 21 identified company submissions, 11 used health states by progression status, seven by TTD, and three by using a model that had aspects of both utilities' elements approach. (15) There are some advantages to using TTD utilities relative to a progression-based approach: Progression-based utilities distinguish between 2 health states while TDD utilities distinguish between 4 health states, which can allow for finer gradations in utility across patients. Limited utility assessments are typically available in IO trials following disease progression (e.g., at treatment discontinuation and a 30-day post-treatment safety visit only) for being able fully model the trajectory of health utility for this health state. Instead, time-to-death utility data are captured for at least a subset of patients across the full spectrum of possible health states (e.g., to within 30 days from death) which allows for the imputation of lower utility values near the point of death for patients for whom a death event utility was not assessed during the trial due to a lack of utility assessment post-progression. **The company provided both TTD as a base case to account for the limitations stated above. Scenario for utilities by disease progression status was explored as a scenario since it cannot fully capture the value of PEM+LEN in the HRQoL of patients.**
5. There is uncertainty around the maintenance of the treatment effect for	No	**We acknowledge that the ERG explored Issue 5 only within scenario analysis owing to the lack of robust clinical data to model otherwise.**

pembrolizumab with lenvatinib. No treatment waning assumed in company base case (and results highly sensitive to this assumption)		**MSD wanted to take opportunity to note that there is critical evidence (from KEYNOTE-775, KEYNOTE-146 and other advanced cancer indications) and clinical expert opinion to substantiate a long-term treatment effect of pembrolizumab and that there is none to substantiate an assumption of treatment waning.** As noted in response to ERG clarification question B18 and throughout Document B, long-term OS data after 5 years of follow-up are available from KEYNOTE-146. The observed data proved durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN. This is corroborated by data from KEYNOTE-775 (Document B Figure 9), which details distinct evidence of sustained OS for PEM+LEN in the form of a plateau with 30% of patients alive at 5 years. Thus, in the absence of evidence of a waning treatment effect, this was not explored further in the company model. Pembrolizumab is a type of checkpoint inhibitor immunotherapy. Immunotherapies act by activating and enhancing the ability of the patient's immune system to recognise cancerous cells. (16) The potential for immune memory enables the activated immune system to continue to identify and fight off cancer cells after stopping pembrolizumab immunotherapy. In KEYNOTE-775 patients received 35 cycles of pembrolizumab, and therefore this 'immune surveillance' effect of pembrolizumab is expected to be maintained after pembrolizumab cessation which is referred to as ongoing "immunotherapeutic effect". For KEYNOTE-775 in particular, it is also worth noting that Lenvatinib is treat to progression. The ongoing treatment benefit experienced by patients is supported also across with other checkpoint inhibitors agents across a number of tumours with longer follow up data including NSCLS, melanoma and head & neck, whereby a proportion of patients achieves long term survival due to the

		unique mode of action of IO agents. (17-19) Additional evidence of long term benefit are also provided from KEYNOTE-146 (34.7 months follow up data) specific to advanced endometrial cancer. Additional empirical evidence still exists for longer term follow up on pembrolizumab in advanced malignancies outside EC, which demonstrates no waning effect. (18, 20-24) This aligns with the expectation that PEM+LEN is highly likely to have a sustained treatment effect that is distinct from conventional chemotherapy options in EC, in direct contrast to the fundamental rationale behind the application of treatment-effect waning. Furthermore, clinical experts consulted for this appraisal confirmed the plausibility of long-term OS projections, supporting the long-term immunotherapeutic effect PEM+LEN in this patient population. To conclude, considering the evidence described and clinical expert opinion to substantiate a long-term treatment effect, and the absence of evidence to support or quantify an assumption of treatment waning, it was not deemed appropriate to explore treatment waning in the company model.
6a. Time on treatment: continuous vs capping by progression-free survival	No	**The resource implications of time on treatment (up to 35 cycles) vs time on treatment capped by PFS in the UK practice are minimal. However, the ERG provided alternative approach is reasonable.** Although the impact of Issue 6a is minimal (ToT capped by PFS reduces the ICER £3,869 (company base case)), the company accept the ERG's preference to cap ToT by PFS in the model. In accordance with this, the company has revised its base-case, with cost-effectiveness estimates presented in Table 4.
6b. Percentage of patients receiving doxorubicin or paclitaxel: 75%/25% split or 50%/50% split	No	Given that there is still no standard of care beyond platinum-based chemotherapy for advanced or recurrent EC, it is unsurprising that the split of patients receiving doxorubicin or paclitaxel varied greatly between clinicians consulted by the company and the ERG for this appraisal. In the KEYNOTE-775 study the TPC arm treatment (doxorubicin or paclitaxel) was chosen at the clinician's discretion and reflect their clinical practice.

		The ERG proposed 50%/50% split has minimal impact on the ICER (reduces company base case by £681). **MSD prefers to keep the base case as per KEYNOTE-775 study where doxorubicin or paclitaxel has 75%/25% split.**
6c. Modelled baseline patient characteristics (weight and age) from KEYNOTE-775 may not be generalisable to patients in UK practice.	No	**MSD do not agree with inflated age and weigh patient characteristics as it does not follow the available evidence. The ERG's preference is in contrast KEYNOTE-775 which is deemed as fully generalisable in the UK setting for decision making purposes and potentially disadvantages the technology under assessment as well as RWE studies.** The ERG and the clinicians referenced in the report suggested that UK patient population for this indication are much older and heavier than what is observed in KEYNOTE-775 and therefore the study is not representative of the intended population. Please note that KEYNOTE-775 ITT median age was 63.5, KEYNOTE-775 UK specific patient – [redacted]), ECHO UK – [redacted], Heffernan UK (only second line eligible patients) – 65.5. These values are consistent and should be generalisable for the UK population and are in line with clinical input sought during the submission development process. Furthermore, mean/median age from the KN775 is similar to values published in literature (please see two SLRs (interventional and observational) CS Appendix D). Patients' characteristics were validated with clinicians and no concerns were raised about patients age or generalisability to UK population. Similarly the company does not agree with a patient weight increase in the base case. MSD provided KN775 (70kg) and KEYNOTE-775 UK patient weights ([redacted]). Furthermore, mean/median weight/BSA/BMI from the KN775 is similar to values published in clinical SLRs (please see two SLRs (interventional and observational) CS Appendix D). Values from the KEYNOTE-775 are consistent with the literature and should be generalisable

		for the UK population. Patients' characteristics were validated with clinicians and no concerns were raised about patients' weight or generalisability to UK population.
6d. Capping of overall survival: hybrid vs hazards-based approach	No	In the company submission, a 'hybrid' approach was initially used to cap overall survival to general population survival and PFS to OS. **In the revised base case, the company has included the ERG's preference of applying a hazards-based approach**. The revised cost-effectiveness estimates are presented in Table 4. We wish to note that the company base case ICER in the final ERG model differs from the submitted company base case ICER and the first ERG model. The ICER (at pembrolizumab list price) in the company base case is £65,110 and reported in the final ERG model as £65,265. This minor error arises from the formulae in columns AZ in both the 'OS' and 'PFS' sheets (where 'capping' occurs) which contain external links (also seen in columns BA of both sheets). Removing these external links and correcting the CHOOSE function returns the company base case ICER. Changes to the company's cost effectiveness estimate (Table 4) were performed after this correction was made to the final ERG model.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: ***Uncaptured value***	General	No	When assessing the cost-effectiveness of this intervention, we hope the NICE committee will take into account the comments of consultees who have illustrated that there is no standard of care and very few treatment options for these patients. There have been no NICE Technology Appraisals in endometrial cancer until very recently. Even then just a proportion of patients gained an interim approved treatment option. Incidence of endometrial cancer has been on the rise, increasing by 15.4% since 2010 (25) and deaths have also increased since 2013 by 33.8%. (26) Whilst it is most prevalent in an older population, many women are still of a working age. (27) Unfortunately, the majority of patients with advanced or recurrent endometrial cancer have an expected survival of approximately 12 months after diagnosis. (28, 29) The Women's Health Strategy for England, is a central government policy which has prioritised endometrial cancer as one of the gynaecological cancers in which to improve screening, access to treatment and increase survival rates for at least 5 years after diagnosis.(30)

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 6a: Time on treatment: continuous vs capping by progression-free survival	ToT was modelled independently from health state, allowing patients to continue treatment post progression	Following the ERG report, modelled ToT has been capped by PFS (please also see note in response to Issue 6d, above)	ICER resulting from the change described (on its own): £59,202 Change from the company's original base-case ICER: -£5,909 (-9%)
Key issue 6d: Capping of overall survival: hybrid vs hazards-based approach	A 'hybrid' approach was used to cap overall survival to general population survival and PFS to OS	Following the ERG report, a hazards-based approach has been applied to cap overall survival general population survival (please also see note in response to Issue 6d, above)	ICER resulting from the change described (on its own): £64,677 Change from the company's original base-case ICER: -£434 (-1%)
Company's revised base case following technical engagement			Company revised base-case (list price): • Incremental costs: £[redacted] • Incremental QALYs: 1.77

			• ICER: £58,810 Company revised base-case (pembrolizumab PAS applied): • Incremental costs: [redacted] • Incremental QALYs: [redacted] • ICER: £[redacted]

Sensitivity analyses around revised base case

Table 5 Mean probabilistic base case results, pairwise analysis – List prices

	Total costs	Total life years	Total QALYs	Incremental, PEM+LEN versus TPC			ICER
				Costs	Life years	QALYs	
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.82	£57,016

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

Table 6 Mean probabilistic base case results, pairwise analysis – pembrolizumab price with PAS applied

	Total costs	Total life years	Total QALYs	Incremental, PEM+LEN versus TPC			ICER
				Costs	Life years	QALYs	
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

References

1. Merck Sharp & Dohme (UK) Limited. Keytruda® (pembrolizumab) 25 mg/mL concentrate for solution for infusion, Prescribing Information for GB 2022 [Available from: https://www.emcpi.com/pi/33162.
2. Bradford LS, Rauh-Hain JA, Schorge J, Birrer MJ, Dizon DS. Advances in the management of recurrent endometrial cancer. American journal of clinical oncology. 2015;38(2):206-12.
3. Merck Sharp and Dohme (MSD) UK Ltd. Clinical Expert Consultation. 2021.
4. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. BGCS uterine cancer guidelines: Recommendations for practice 2021 [Available from: https://www.bgcs.org.uk/wp-content/uploads/2021/11/British-Gynaecological-Cancer-Society-v13-for-website-with-figure1.pdf.
5. NICE. TA779 Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency 2022 [Available from: https://www.nice.org.uk/guidance/ta779.
6. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. New England Journal of Medicine. 2022.
7. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305-10.
8. Heffernan K, Nikitas FS, Shukla U, Camejo HS, Knott C. Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis. Gynecologic oncology. 2022;166(2):317-25.
9. NICE Decision Support Unit. Technical Support Document 21: Flexible Methods for Survival Analysis. 2020.
10. NICE. TA357 Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab 2017 [Available from: https://www.nice.org.uk/guidance/ta357.
11. NICE. TA531 Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer 2018 [Available from: https://www.nice.org.uk/guidance/ta531.
12. Chang C, Park S, Choi YR, Tan SC, Kang SH, Back HJ, et al. Measurement of Utilities by Time to Death Related to Advanced Non-Small Cell Lung Cancer in South Korea. Value in Health. 2016;19(7):A744-A.
13. Harvey RC, Tolley K, Cranmer HL. Estimation of Health-Related Quality of Life (Hrqol) in Cancer Patients Utilising a Time-to-Death Analysis. Value in Health. 2017;20(9):A767-A.
14. Wang XF, Wang XY, Hodgson L, George SL, Sargent DJ, Foster NR, et al. Validation of Progression-Free Survival as a Surrogate Endpoint for Overall Survival in Malignant Mesothelioma: Analysis of Cancer and Leukemia Group B and North Central Cancer Treatment Group (Alliance) Trials. Oncologist. 2017;22(2):189-98.
15. Hatswell AJ, Bullement A, Schlichting M, Bharmal M. What is the Impact of the Analysis Method Used for Health State Utility Values on QALYs in Oncology? A Simulation Study Comparing Progression-Based and Time-to-Death Approaches. Appl Health Econ Hea. 2021;19(3):389-401.
16. McDermott J, Jimeno A. Pembrolizumab: Pd-1 Inhibition as a Therapeutic Strategy in Cancer. Drug Today. 2015;51(1):7-20.
17. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced Non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. Journal of Clinical Oncology. 2019;37(28):2518-+.
18. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncology. 2019;20(9):1239-51.

19. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. Journal of Clinical Oncology. 2015;33(17):1889-U48.
20. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.
21. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol. 2021;16(10):1718-32.
22. Reck M, Rodriguez-Abreu D, Robinson AG, Hui RN, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2016;375(19):1823-33.
23. Reck M, Rodriguez-Abreu D, Robinson AG, Hui RN, Csoszi T, Fulop A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score >= 50%. Journal of Clinical Oncology. 2021;39(21):2339-+.
24. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. New England Journal of Medicine. 2015;372(26):2521-32.
25. NHS Digital. Cancer Registration Statistics, England 2019 2021 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2019.
26. Office for National Statistics (ONS). Mortality statistics - underlying cause, sex and age 2022 [Available from: https://www.nomisweb.co.uk/datasets/mortsa.
27. NICE. TA772 Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies 2022 [Available from: https://www.nice.org.uk/guidance/ta772.
28. McMeekin S, Dizon D, Barter J, Scambia G, Manzyuk L, Lisyanskaya A, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecologic oncology. 2015;138(1):18-23.
29. Rubinstein M, Halpenny D, Makker V, Grisham RN, Aghajanian C, Cadoo K. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. Gynecologic oncology reports. 2019;28:120-3.
30. Department of Health & Social Care. Women's Health Strategy for England 2022 [Available from: https://www.gov.uk/government/publications/womens-health-strategy-for-england/womens-health-strategy-for-england.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Technical Engagement Clinical Addendum

August 2022

Contents

Tables and figures

Overview

Efficacy

- PEM+LEN is superior to TPC with respect to progression-free survival and overall survival in patients with advanced EC who have failed prior therapy
- Final analyses of the pivotal KEYNOTE-775 trial estimates that PEM+LEN:
  - Reduces risk of progression or death by 44% (median PFS: 7.3 vs 3.8 months; HR: 0.56 [95% CI: 0.48, 0.66]; P <0.0001)
  - Reduces risk of death by 35% (median OS: 18.7 vs 11.9 months; HR: 0.65 [95% CI: 0.55, 0.77]; P <0.0001)
  - More than doubles the ORR (34% vs 15%; P <0.001) and extends median DOR by 7.5 months (12.9 vs 5.4 months)

Safety

- No new safety signals were observed with the KEYNOTE-775 trial continuing to demonstrate a safety profile consistent with the known safety profile of PEM+LEN

Clinical effectiveness summary

The final analysis database lock for KEYNOTE-775 occurred on 1 March 2022, at which time the median duration of follow-up was 14.7 months in the all-comer population. These data therefore provide an additional [redacted] months median duration of follow-up compared with the interim analysis 1 (IA1) data.

A clinical effectiveness summary table is provided in Table 1.

Table 1: Clinical Effectiveness Summary (ITT all-comer population)

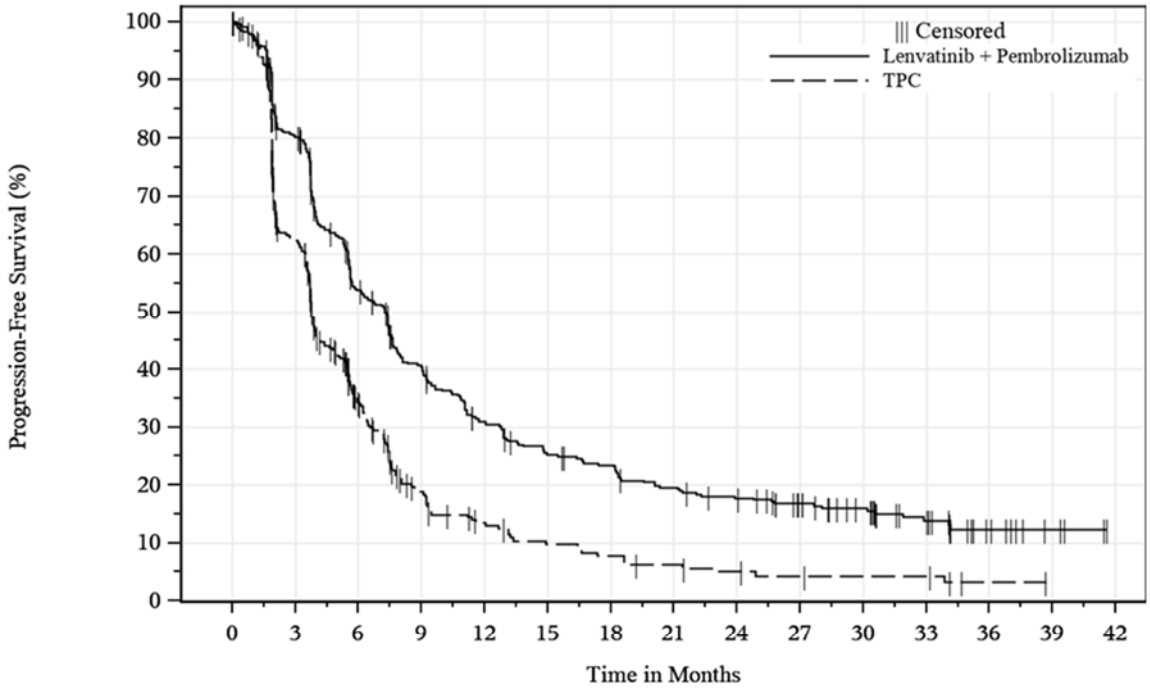
	Interim Analysis 1		Final Analysis	
	PEM+LEN (n=411)	**TPC (n=416)**	**PEM+LEN (n=411)**	**TPC (n=416)**
Progression-free survival				
Median months (95% CI)	7.2 (5.7-7.6)	3.8 (3.6-4.2)	7.3 (5.7-7.6)	3.8 (3.6-4.2)
HR (95% CI)	0.56 (0.47-0.66)		0.56 (0.48-0.66)	
P-value	P <0.0001		*P* <0.0001	
Overall survival				
Median months (95% CI)	18.3 (15.2-20.5)	11.4 (10.5-12.9)	18.7 (15.6-21.3)	11.9 (10.7-13.3)
HR (95% CI)	0.62 (0.51-0.75)		0.65 (0.55-0.77)	
P-value	*P* <0.0001		*P* <0.0001	
Response rates				
ORR, % (95%)	31.9 (27.4-36.6)	14.7 (11.4-18.4)	33.8 (29.3-38.6)	14.7 (11.4-18.4)
P-value	< 0.0001		< 0.0001	
CRR, %	6.6	2.6	7.5	2.6
Duration of response				
Median months (range)	14.4 (1.6-23.7)	5.7 (0-24.2)	12.9 (1.6-39.5)	5.4 (0.0-37.1)
Key: CI: confidence interval; HR: hazard ratio; ITT, intention-to-treat; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.				

Progression-free survival (primary endpoint)

The median progression-free survival (PFS) (per RECIST 1.1 by blinded independent central review [BICR]) remained significantly improved with pembrolizumab with lenvatinib (PEM+LEN) with a hazard ratio (HR) of 0.56 (95% confidence interval [CI]: 0.48, 0.66; p<0.0001) (Table 1).

The Kaplan–Meier curves for PFS remained consistently separated throughout the longer duration of follow-up, as depicted in Figure 1.

Figure 1: Kaplan–Meier estimates of PFS in KEYNOTE-775 trial (ITT all-comer population; Final analysis)



n at risk

Lenvatinib + Pembrolizumab	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
TPC	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V01MK3475: adam-adsl; adtte]

Key: ITT, intention-to-treat; PFS, progression-free survival; TPC: treatment of physician's choice.

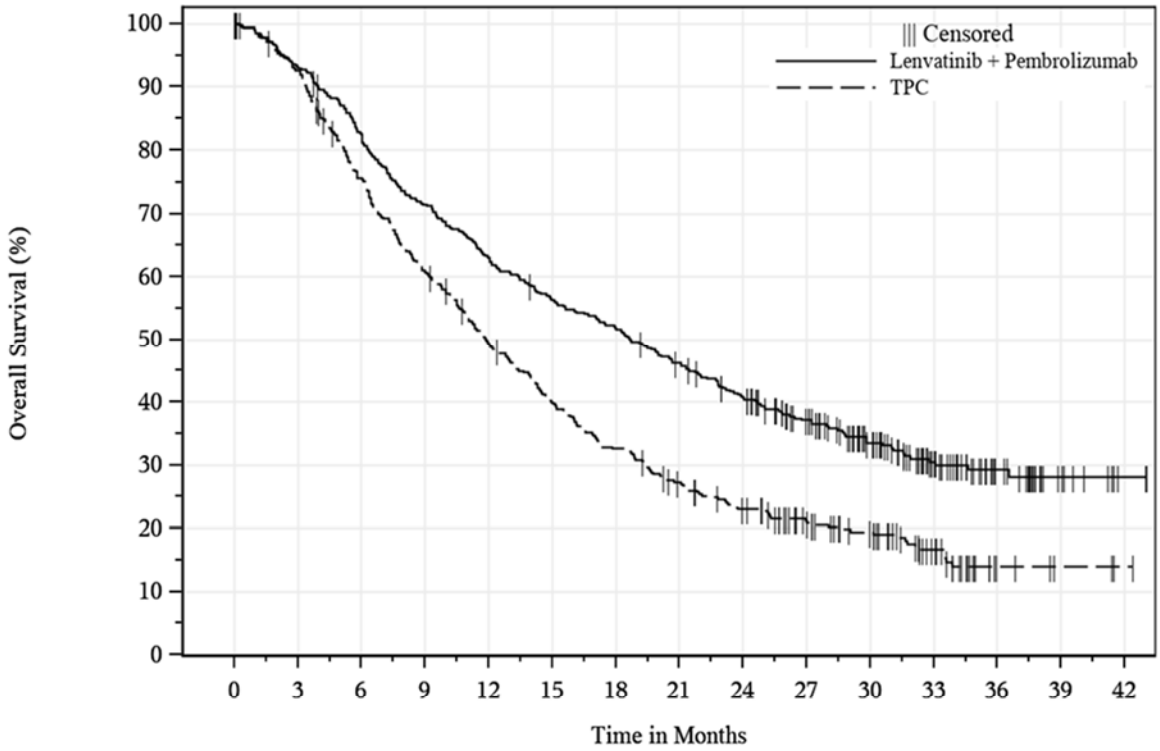
Overall survival (primary endpoint)

The median overall survival (OS) remained significantly improved with pembrolizumab with lenvatinib (PEM+LEN) with a HR of 0.65 (95% CI: 0.55, 0.77; p<0.0001) (Table 1).

The Kaplan-Meier curves for OS remained consistently separated throughout the longer duration of follow up, as depicted in Figure 2.

When interpreting survival data, it is important to acknowledge that at the time of final analysis, over half of patients in the TPC arm ([redacted]) had received subsequent anticancer treatment including subsequent PD1/PDL1 treatment for [redacted]% of patients that are not currently available in the UK.

Figure 2: Kaplan–Meier estimates of OS in KEYNOTE-775 trial (ITT all-comer population; Final analysis)



n at risk

Lenvatinib + Pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
TPC	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V01MK3475: adam-adsl; adtte]

Key: ITT, intention-to-treat; OS, overall survival; TPC: treatment of physician's choice.

Objective response rate

Objective response rate (ORR) (per RECIST 1.1 by BICR) increased in the PEM+LEN arm from IA1 to final analysis and the estimated difference compared with the TPC arm increased to 19.1% (33.8% vs 14.7%) (Table 1). The proportion of patients who achieved a complete response (CR) also increased to 7.5% (Table 1).

Duration of response

The median duration of response (DOR) was 12.9 months at the time of final analysis. This is a shorter median than observed at the time of IA1, but the longest DOR observed to date extended to 39.5 months (Table 1).

Safety summary

Adverse events Grade 3+

The incidence of Grade 3+ adverse events (AEs) in the PEM+LEN group remained higher compared with the TPC group ([redacted] vs [redacted]), but no new safety signals were observed with frequently reported AEs continuing to show consistency with the known safety profile of PEM+LEN.

The most frequently reported Grade 3+ AEs (incidence ≥5%) were hypertension, diarrhoea and decreased appetite for the PEM+LEN group and neutropenia, anaemia and fatigue for the TPC group, as summarized in Table 2.

Table 2: Summary of Grade 3 to 5 AEs (Incidence ≥5% in one or more arms) in the KEYNOTE-775 trial (Safety all-comer population; Final analysis)

AE, n (%)	PEM+LEN (n=406)	TPC (n=388)
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]

Aspartate aminotransferase increase	[redacted]	[redacted]
Lipase increase	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Key: AE: adverse event; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.		

Subsequent anticancer therapy

At the time of final analysis, [redacted] of patients in the TPC group and [redacted] of patients in the PEM+LEN group had received at least one subsequent anticancer therapy.

The most common subsequent anticancer therapy type in both groups was chemotherapy (Table 3) and the most common chemotherapy regimens used were paclitaxel ([redacted] of all patients), doxorubicin ([redacted] of all patients), carboplatin ([redacted]of all patients) and gemcitabine ([redacted] of all patients). [redacted] of patients in the TPC group went onto receive subsequent PD1/PDL1 treatments that are not currently available in the UK (versus [redacted] of patients in the PEM+LEN group).

Table 3: Summary of subsequent anticancer therapy (ITT all-comer population; Final analysis)

Subsequent therapy, n (%)	**PEM+LEN (n=411)**	**TPC (n=416)**
Any anticancer therapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Hormonal therapy	[redacted]	[redacted]
PD1/PD-L1 checkpoint therapy	[redacted]	[redacted]
Other I-O therapy	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]
VEGF/VEGFR inhibitor	[redacted]	[redacted]
Other	[redacted]	[redacted]
Subsequent therapy by lines 1 subsequent line 2 subsequent lines ≥3 subsequent lines	[redacted]	[redacted]
Key: I-O, immune-oncology; ITT, intention-to-treat; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.		

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1 and sections 1.3 – 1.6). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **Friday 29 July 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating previously treated advanced, metastatic or recurrent endometrial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Clare Green
2. Name of organisation	Southampton University NHS Trust
3. Job title or position	Medical Oncology Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with previously treated advanced, metastatic or recurrent endometrial cancer? ☒ A specialist in the clinical evidence base for previously treated advanced, metastatic or recurrent endometrial cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
8. What is the main aim of treatment for previously treated advanced, metastatic or recurrent endometrial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To shrink the tumour, delay progression, improve symptoms and quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any reduction or stabilisation of disease such that disease progression is delayed and there is improvement in symptoms.
10. In your view, is there an unmet need for patients and healthcare professionals in previously treated advanced, metastatic or recurrent endometrial cancer?	Absolutely yes. There is just a 10-15% response rate to available second line chemotherapy. There was no other realistic options aside from palliative care
11. How is previously treated advanced, metastatic or recurrent endometrial cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	We follow the ESMO guidelines. The guidelines are however fairly loose as second line chemotherapy can be offered if the patient is fit enough, albeit with a low response rate, but the chemo given will depend on time interval since primary chemo, previous response and toxicities, as well as patient preference so may be: Carboplatin and paclitaxel as a retreatment Caelyx (most commonly) Weekly paclitaxel

	Patients who are more unwell / less fit may be offered high dose progesterone treatment as a “holding measure” and to improve their appetite and general wellbeing, or just best supportive / palliative care.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The new treatment combination will provide a new standard of care in second line treatment for relapsed endometrial cancer. It is a “game changer”. The response rate is around 40%, so, far superior (4 times more effective) than alternative chemotherapy treatment and it is extremely well tolerated. Even patients who would not tolerate conventional chemo will be able to tolerate this treatment – it will mean far more patients who would have previously been referred for palliative care, will have access to a well tolerated treatment regime with a high chance of significant benefit and additional survival time – not only time alive, but alive and well, continuing to work and spending quality time with family and friends. This technology / treatment should be used in secondary care and specialist oncology centres. The treatment regime is already in use via a compassionate access programme and nurses and physicians are gaining experience with its use / managing potential toxicities etc, so additional facilities / training will not be needed.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, this treatment will potentially significantly extend length and quality of life for our patients. In the clinic we will be able to change our dialogue from a conversation whereby patients with relapsed endometrial cancer are facing very poor treatment options alongside a poor prognosis, to being able to offer patients a meaningful treatment which will lengthen their life without detriment in its quality.

	I can't stress enough how much of a "game changer" this new treatment is for this group of previously poor prognostic patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. It may be more effective "on paper" from a scientific point of view in MMRd patients, but my observations as well as the results of the KEYNOTE 775 study suggest benefit in both groups. It is certainly more suitable than chemotherapy for the elderly and poorer PS patients too.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Much easier to use. From a patient point of view - Few, manageable toxicities, shorter treatment duration, ongoing benefit beyond end of treatment course From a Healthcare perspective – significantly better response rates, shorter treatment time – saving capacity resources, very little monitoring, no additional testing, no unusual concomitant medication required, patients staying well for longer. Treatment pathway not as intense.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, MMR testing is already carried out as a reflex test at diagnosis and if licence is for both MMRd and MMRp this won't be a "rule" to allow initiation of therapy. Treatment would be stopped at clinical or radiological progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Patients will certainly benefit in terms of QALY. Not only will they feel physically better with reduced tumour related side effects, and few treatment associated toxicity, but they will spend more time out of hospital, are more likely to be able to continue to work and safely go away on holidays. One of the treatments in the regime is given orally which makes things even easier for the patient. The IV part of the regime is a short infusion every 3 weeks.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The treatment is an immunotherapy, which in itself is innovative within this tumour type. It also addresses an area of unmet need – currently this group of patients faces a poor prognosis with response rates of 10-15% to current second line chemo, with typically just a few months of progression free time. This new treatment increases response rates to 40% with a durable response -a real tenable, meaningful difference. This is certainly a huge step change in the management of this condition.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are few and very manageable. Patients sometime suffer with a skin rash / dry/ peeling skin, fatigue, thyroid function issues and diarrhoea. Compared to those of chemotherapy, these side effects in the majority are mild and more manageable.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Results of the KEYNOTE 775 trial reflect current UK practice. Response rates and PFS are the most important outcomes, both of which were measured in the trial. There are no additional adverse events to my knowledge that were not in the trial but have come to light subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	In my experience, response in the "real world", in the cases I have seen in my clinic, is even better than in the trials. ALL the patients I have treated have responded – 12 patients, a number of those dramatically so with heavy burden

	of disease pre-treatment now not visible on CT scans. Their responses are also seemingly very durable. One patient who prior to treatment had lung and liver metastatic disease is still in CR with no disease visible on scans 18 months after completing treatment.
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	None. As this treatment is effected and well tolerated even in poorer prognostic patients and the elderly, all comers can benefit.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise (NB: we have emboldened the items which we are particularly interested in your feedback on, if you are able to answer). If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. Clinically distinct subgroups in the evidence base - deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). Are there difference in the clinical effectiveness of the dMMR and pMMR subgroups? Should they be considered separately?	No. It may be more effective “on paper” from a scientific point of view in MMRd patients, but my observations as well as the results of the KEYNOTE 775 study suggest benefit in both groups. The KEYNOTE 775 study enrolled patients regardless of MMR status and as such showed improvement in both groups. The study was not powered to show a particular benefit in one subgroup over another.
2. Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of	If subgroup data analysis does subsequently show a difference in response in the 2 subgroups then inevitable there will be cost effectiveness difference. I am unaware of any robust data that is powered to make this differentiation.

pembrolizumab with lenvatinib in the dMMR and pMMR subgroups. **- Are the current treatment options in the UK the same for people with dMMR and pMMR endometrial cancer?** **- Is there a different prognosis for dMMR and pMMR endometrial cancer?**	Currently the same second line chemo / hormone therapy / best supportive care options are offered to all patients regardless of MMR status. Of late we have been able to offer Dostartimab to MMRd patients via the CDF and pembrolizumab and Lenvatinib as combination treatment via the Patient access programme for MMRp patients. I am not aware of a different prognosis for MMRp and MMRd patients with endometrial cancer.
3. Uncertainty surrounding extrapolation of overall survival (OS) and: - use of ECHO study to validate OS in doxorubicin or paclitaxel arms - unavailable clinical study report (CSR) for KEYNOTE-146 because it is an Eisal study. - dismissal of restricted cubic splines	
4. Uncertainty surrounding the company's time to death utility approach	
5. There is uncertainty around the maintenance of the treatment effect for pembrolizumab with lenvatinib. No treatment waning assumed in company base case (and results highly sensitive to this assumption)	A number of patients completed the full 2 year protocol of treatment on the KEYNOTE 775 study and a minority had another year of compassionate treatment at relapse. I have no doubt the treatment effect is durable, but it must be assumed there would eventually be some treatment waning effect.
6a. Time on treatment: continuous vs capping by progression-free survival	

6b. Percentage of patients receiving doxorubicin or paclitaxel: 75%/25% split or 50%/50% split	As first line treatment is carboplatin and paclitaxel, at relapse, the majority of patients will be offered doxorubicin (or pegylated doxorubicin to be more precise), so I would say the split is 75%/25%.
6c. Modelled baseline patient characteristics (weight and age) from KEYNOTE-775 may not be generalisable to patients in UK practice.	I think the patients were perhaps slightly younger and fitter in the KEYNOTE 775 study compared with the average patient we see in clinic, but as the treatment is well tolerated and suitable for poorer performance status and older patients, this will not effect its translatability into clinical practice.
6d. Capping of overall survival: hybrid vs hazards-based approach	
Additional questions: - **For what reasons would patients not be considered candidates for surgery and radiotherapy? (required in the license for pembrolizumab with lenvantinib) Would prior surgery and radiotherapy be a reason why they would not be candidates?** - **Related to the above point, is the company's proposed placement of pembrolizumab with lenvantinib in the treatment pathway appropriate for patients who are not candidates for surgery and radiotherapy? (i.e. is placement after surgery or radiotherapy for newly diagnosed patients appropriate / make sense given patients for pembrolizumab**	If patients have widespread recurrence / metastatic disease they would not be suitable for surgery and / or radiotherapy. These modalities of treatment are used in localised recurrences. Prior surgery would not preclude further surgery if recurrent disease was localised, but previous maximum dose radiotherapy would render a patient unsuitable for further treatment (due to risk of damage to bladder / bowel etc) At present we do not have the data to support first line use of pembrolizumab and Lenvatinib, however, it would be extremely useful to have the combination as an option for patients presenting with metastatic disease who may not be suitable for local surgical / radiotherapy treatment and who are too frail / unwell for combination carboplatin and paclitaxel chemotherapy.

with lenvatinib are not candidates for surgery or radiotherapy?) (see section B1.3.2 and figure 1 of company submission) - **Company states hormone therapy not relevant comparator to pembrolizumab with lenvantinib as typically used later in the pathway after – do you agree?** - **Company use generic doxorubicin price, not pegylated (Caelyx) price noting it has the same effectiveness and less toxicity so the use by the company is conservative. Would you agree? Would you expect it to differ in effectiveness?**	Yes, I agree, hormone therapy is really part of a palliative approach and would not be considered on a level, as a comparator with pembolizumab/ Lenvatinib No difference in effectiveness between generic doxorubicin and Caelyx. Caelyx is definitely is less toxic.
Are there any important issues that have been missed in ERG report?	None I can think of.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1.Effective treatments in the relapsed setting in endometrial cancer is an area of unmet need.
2.The combination of Pembrolizumab and Lenvatinib is 4 times more effective in terms of response rates than conventional chemotherapy and response is duarable.
3. Pembrolizumab and Lenvatinib are well tolerated and any toxicities well managed. As a result the patient experience and QOL is far better than on conventional chemo.
4.Time in hospital is greatly reduced with relatively low monitoring requirements– aiding NHS capacity issues
5. This treatment combination is certainly a step change in the treatment pathway of these patients

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with previously treated advanced, metastatic or recurrent endometrial cancer or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1 and sections 1.3 – 1.6).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 29 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with previously treated advanced, metastatic or recurrent endometrial cancer

Table 1 About you, previously treated advanced, metastatic or recurrent endometrial cancer, current treatments and equality

1. Your name	Helen White
2. Are you (please tick all that apply)	☐ A patient with previously treated advanced, metastatic or recurrent endometrial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with previously treated advanced, metastatic or recurrent endometrial cancer? ☒ A patient organisation employee or volunteer? ☒ Other (please specify): A patient with experience of endometrial cancer
3. Name of your nominating organisation	Peaches Womb Cancer Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I founded and run Peaches Patient Voices, a group of 57 people with lived experience of womb cancer as a patient or carer. Through this, I regularly get to hear about the experiences and views of a wide range of people whose lives have been affected by endometrial cancer and understand what is important to them. I was closely involved in obtaining patient and carer feedback for Peaches Womb Cancer Trust's submission via focus group interviews and questionnaires. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with previously treated advanced, metastatic or recurrent endometrial cancer? **If you are a carer (for someone with previously treated advanced, metastatic or recurrent endometrial cancer) please share your experience of caring for them**	Not applicable
7a. What do you think of the current treatments and care available for previously treated advanced, metastatic or recurrent endometrial cancer on the NHS? (note that pembrolizumab with lenvantinib is licensed for people 'who are not candidates for curative surgery or radiation' so please bear in mind that the guidance will apply to these patients when answering this and the following questions.)	a. Despite being the fourth most common cancer in women, current treatments for previously treated advanced, metastatic or recurrent endometrial cancer are woefully lacking. For those who can tolerate it, further chemotherapy is an option, but debilitating side effects severely impact quality of life. Furthermore, chemotherapy offers little hope of keeping the cancer at bay or improving survival, causing emotional distress to both patients and their carers and further impact on quality of life.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	b. I believe my views are closely aligned with those of others.
8. If there are disadvantages for patients of current NHS treatments for previously treated advanced, metastatic or recurrent endometrial cancer (for example, how pembrolizumab with lenvatinib is given or taken, side effects of treatment, and any others) please describe these	Previous treatments for endometrial cancer already cause myriad long-term side effects that affect day-to-day living, and are detailed in Peaches Womb Cancer Trust's submission. Any further chemotherapy following diagnosis with advanced, metastatic or recurrent endometrial cancer causes added side effects that have far-reaching impact on quality of life whilst offering little promise of effectiveness. This is a cause of great despair for patients diagnosed with advanced, metastatic or recurrent endometrial cancer faced with the dire prospect of limited survival, and provokes feelings of abandonment and hopelessness.
9a. If there are advantages of pembrolizumab with lenvatinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab with lenvatinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Real world patient experience suggests pembrolizumab and lenvatinib is a kinder treatment than chemotherapy and offers improved quality of life with respect to both physical and mental health, enabling patients to live with cancer and flourish. The combination of 3-weekly pembrolizumab 30-minute infusions and daily oral lenvatinib is also appealing to patients as it is less burdensome than chemotherapy regimens.
10. If there are disadvantages of pembrolizumab with lenvatinib over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab with lenvatinib? If you are concerned about any potential side	

effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from pembrolizumab with lenvatinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The majority of patients with endometrial cancer are postmenopausal older women, many of whom live with obesity, which may be associated with comorbidity and disability. Pembrolizumab and lenvatinib offers these women access to an effective and kinder treatment. The 30-minute duration of pembrolizumab infusion also makes this treatment more accessible to people who may not tolerate a longer duration infusion.
12. Are there any potential equality issues that should be taken into account when considering previously treated advanced, metastatic or recurrent endometrial cancer and pembrolizumab with lenvatinib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	There are two distinct groups of people disadvantaged by age and sex: First, as above, the majority of patients with endometrial cancer are postmenopausal older women who may have comorbidities and or are disabled. Pembrolizumab and lenvatinib offer this group of women access to a treatment that is both effective and kinder than chemotherapy. Second, premenopausal women often find themselves diagnosed with endometrial cancer at an advanced stage due to healthcare professionals' failure to recognise symptoms of endometrial cancer in younger people and or lack of explicit guidance on referring symptomatic women under 55. These women are disadvantaged by age, have been let down by health services, and deserve access to the best available treatments.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

1. Clinically distinct subgroups in the evidence base: deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). The clinical effectiveness of pembrolizumab with lenvatinib appears to be different in the dMMR and pMMR subgroups. Should they be considered separately?	See question 2.
2. Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of pembrolizumab	Treatment options for people with both dMMR and pMMR endometrial cancers are currently limited. Notwithstanding NICE's recommendation to use dostarlimab for advanced endometrial cancer within the Cancer Drugs Fund, few patients with dMMR tumours currently get access to

with lenvatinib in the dMMR and pMMR subgroups. - Are the current treatment options in the UK the same for people with dMMR and pMMR endometrial cancer? - Is there a different prognosis for dMMR and pMMR endometrial cancer?	this, and there remains an urgent unmet need for all patients to access the widest range of effective treatments, regardless of MMR proficiency/deficiency.
3. Uncertainty surrounding extrapolation of overall survival (OS) and: - use of ECHO study to validate OS in doxorubicin or paclitaxel arms - unavailable clinical study report (CSR) for KEYNOTE-146 because it is an Eisai study. - dismissal of restricted cubic splines	Unable to answer
4. Uncertainty surrounding the company's time to death utility approach	Unable to answer
5. No treatment waning assumed in company base case (and results highly sensitive to this assumption)	Unable to answer
6a. Time on treatment: continuous vs capping by progression-free survival	Unable to answer
6b. Percentage of patients receiving doxorubicin or paclitaxel: 75%/25% split or 50%/50% split	Unable to answer
6c. Modelled baseline patient characteristics (weight and age) from KEYNOTE-775 may not be generalisable to patients in UK practice.	Unable to answer

Patient expert statement

6d. Capping of overall survival: hybrid vs hazards-based approach	Unable to answer
Are there any important issues that have been missed in ERG report?	Not aware of any

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Despite being the fourth most common cancer in women, current treatments for previously treated advanced, metastatic or recurrent endometrial cancer are woefully lacking, provoking feelings of abandonment and despair in patients.
- Current treatment (further chemotherapy) has limited effectiveness, is not suitable for many people due to comorbidity, and severely impacts quality of life due to the impact of side effects on both physical and mental health.
- Pembrolizumab and lenvatinib is a step change in terms of effectiveness and also promises to be a kinder treatment that will improve quality of life and enable patients with endometrial cancer to flourish.
- As a kinder treatment, pembrolizumab and lenvatinib will improve equity of access to treatment for advanced, metastatic or recurrent endometrial cancer, including older people and those with comorbidities and or disability.
- Having access to an effective treatment brings much needed hope to all patients regardless of tumour type, age and comorbidity and or disability.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with previously treated advanced, metastatic or recurrent endometrial cancer or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1 and sections 1.3 – 1.6).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 29 July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with previously treated advanced, metastatic or recurrent endometrial cancer

Table 1 About you, previously treated advanced, metastatic or recurrent endometrial cancer, current treatments and equality

1. Your name	Gracey Remmington Teeling
2. Are you (please tick all that apply)	☒ A patient with previously treated advanced, metastatic or recurrent endometrial cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with previously treated advanced, metastatic or recurrent endometrial cancer? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Peaches Womb Cancer Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with previously treated advanced, metastatic or recurrent endometrial cancer? **If you are a carer (for someone with previously treated advanced, metastatic or recurrent endometrial cancer) please share your experience of caring for them**	I was originally diagnosed with stage 3c, grade 3 endometrial cancer in December 2019 – for which I received a hysterectomy, 4 rounds of chemotherapy (paclitaxel and carboplatin), 25 rounds of radiotherapy and 3 rounds of brachytherapy. My cancer returned May 2021 (only 8 months after finishing treatment). Scans showed tumours in my bowel and locally in my pelvis and I was given surgery (Hartmann's procedure and tumour resection) which removed all visible tumours. After a baseline scan, there was another small tumour identified near to my liver. I have been on pembrolizumab for a year (as of 28th July 2022) and several of my most recent scans are clear and show no evidence of disease. Note: I am on pembrolizumab as a monotherapy and not levantinib. I cannot comment on levantinib.
7a. What do you think of the current treatments and care available for previously treated advanced, metastatic or recurrent endometrial cancer on the NHS? (note that pembrolizumab with lenvantinib is licensed for people 'who are not candidates for curative surgery or radiation' so please bear in mind that the guidance will apply to these patients when answering this and the following questions.)	1a. have been through 4 rounds of paclitaxel/carboplatin, 25 radiotherapy and 3 brachytherapy when I was first diagnosed. I found chemotherapy quite difficult physically and mentally. Physically, I struggled with debilitating fatigue – and also had a minor allergic reaction which meant my medical team decided to double my steroids for the days after chemotherapy. I have outlined further size effects under question 8. The options for advanced, metastatic or recurrent endometrial cancer are very limited. If I did not have access to pembrolizumab, at the point at which I was diagnosed with recurrence (May 2021), there were very few options available for me

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	as I had not responded well to chemotherapy. What is very scary is that, at the age of 32, I may have been having very difficult conversations with my oncologist. One of the big impacts of pembrolizumab is on my hope for the future. Despite living with advanced, recurrent cancer, I have hopes and plans for the future: career goals, a desire to travel and to spend as much time as I can with my loved ones. My access to immunotherapy has given me so much hope for the future – either through pembrolizumab keeping the cancer at bay for as long as possible, or even long enough to bridge to other treatments. By contrast, the current treatment options do not offer this hope for the future. Beyond hope for my survival and quality of life, the current options also present a much bleaker vision for the future than immunotherapies, such as pembrolizumab. The idea that I may have to spend a significant portion of my life on chemotherapies feels incredibly difficult and pessimistic about the future. 7b. Most of my friends and acquaintances in the 'cancer world' (I am involved in several support groups) see chemotherapy as 'belts and braces' – something to just get through and accept that your quality of life won't be great for the duration. When facing an incurable diagnosis, chemotherapy feels like a poor option to many of us. I don't know anyone else on immunotherapy, but I do feel like I am living life and thriving on pembrolizumab in a way I wouldn't be able to, based on my experience of chemotherapy. I also have friends who are missing out on immunotherapy, and rely on chemotherapy, and their outlook on life is not as positive.
8. If there are disadvantages for patients of current NHS treatments for previously treated advanced, metastatic or recurrent endometrial cancer (for example, how pembrolizumab with lenvatinib is given or taken, side effects of treatment, and any others) please describe these	For me, the most challenging side effect of chemotherapy was (at least) 4 days of debilitating fatigue followed by a week of moderate (and still unpleasant) fatigue. During the debilitating fatigue 'phase' of each cycle, I found it very challenging to do simple tasks such as showering and dressing. Even lying on the bed or sitting on the sofa felt exhausting. Due to the steroids, I also couldn't sleep, and I felt as though I was in a state of suspended animation in which time passed very slowly. I cannot understate how physically and psychologically difficult this was as a side effect. I still get flashbacks two years later, despite psychological support.

	I also needed to take two different anti-emetics to manage nausea – though these did prevent most of the nausea. I did have a reduced appetite for the first few days. I also had quite bad diarrhoea around 4-5 days after each cycle. Psychologically, I also really struggled with anxiety related to my white blood cells dipping in the middle of each cycle. This was to the extent that I had panic attacks and some days I felt too scared to go to sleep in case I had an infection which might lead to neutropenic sepsis. Prior to COVID-19, I was also advised to avoid crowds at certain periods which meant missing important activities for my wellbeing, such as going to choir or having an active social life. I also struggled with intense hot flushes for the first few days after treatment. I also experienced myoclonic jerks which made it difficult to sleep (though this could've been due to anxiety around my immune system). I was unable to work due to fatigue and brain fog. I was unable to be as active as I would like due to fatigue. I also had to change plans and limit my social life to avoid infection in the middle of each cycle (even for the first two cycles prior to COVID-19 pandemic). By the end of all of my initial treatment, I felt as though I had to climb a mountain to recover: it took almost a year to even feel even halfway back to my normal self (at which point, I relapsed). And I feel lucky to have escaped without long-term side effects such as pelvic radiation disease or peripheral neuropathy. With pembrolizumab, whilst there are some side effects (discussed below), I generally feel like I am more well than I have been in years. As I had severe symptoms before diagnosis, I would say this is, by far, the best that I have felt in over three years!
9a. If there are advantages of pembrolizumab with lenvatinib over current treatments on the NHS please describe these. For example, the effect on your	9a. Overall, my perspective of pembrolizumab has been that it has really improved my quality of life: to the extent that I feel that I have thriving whilst on active treatment. I have found the treatment to be much kinder and more manageable than

quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab with lenvatinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	any others that I have had and I experience far fewer side effects. It has also meant there is currently no evidence of cancer on my CT scans. I am honestly grateful every day that I am able to live my life fully and without many of the side effects of previous treatments. With pembrolizumab, I have been able to be active (taking part in outdoor swimming, climbing, paddleboarding, cycling, hill walking and daily dog walking), continue to work and actively develop a career which I thought was over (I have recently received a promotion!), and live a fulfilling and happy life. I would say that I am able to thrive despite my advanced endometrial cancer diagnosis. Sometimes I even forget that I have incurable cancer! I do not feel that there would have been many options available to me, had immunotherapy not been available, and that the conversations with my doctors would have been very different had my recurrence happened before it was available – particularly as I did not respond well to chemotherapy resulting in a relapse shortly after finishing treatment. From conversations with my oncologist, it seems as though there would be few available options which is not a conversation that I wanted to have at 32. Instead, I am currently 'cancer-free' and living a healthy and full life and believe I will have a much longer lifespan than would have otherwise been possible. At 32, it has been so important to me that treatment options are available that mean I am able to live an active and healthy life for as long as possible. I also have faith that it may extend my life long enough for other treatment options to become more available. From a care perspective, the trips to the oncology centre are still every 3 weeks (as with chemotherapy) but it is a much shorter infusion: 30 minutes instead of 8 hours! I don't need to have pre-meds or take steroids – I needed a double dose of steroids for chemo which came with many unpleasant side effects including changes to mood and insomnia. I also have much less contact with my GP as I haven't had any

	acute side effects – with chemo, I did need to get in contact for issues related to diarrhoea/indigestion and sore mouth. As mentioned, I found the period where my blood count during chemotherapy dropped incredibly stressful. With pembrolizumab, I feel much more relaxed and able to live a normal life – even with COVID issues – and am able to go to the office, meet friends, occasionally go out dancing and attend social and family events. 9b. My priorities for my life, as someone living with advanced and recurrent cancer, is to live a full life, where I don't constantly feel like a cancer patient, and I am able to thrive for as long as possible. Over the past year, I have been able to live a nearly normal life – with the exception of needing to rest more and not 'over-do' it. I cannot understate the positive impact that the treatment has had on my life – or the gratitude I feel for being able to do most of the things that I want to. 9c. My experience of pembrolizumab is that it is much kinder and more tolerable than any precious treatments (chemotherapy, radiotherapy and brachytherapy) with fewer side effects and less of an impact on my quality of life. During my first phase of treatment, I needed help from my wife for cooking and cleaning, as well as psychological support as I was very anxious about both cancer and the risk of getting COVID. On pembrolizumab, I am much more independent – for example, I find it easier to drive myself to and from treatment; attend work and appointments; manage more of the housework and cooking. This means that there is less of a burden on her, as I am fairly self-sufficient apart from a few days when I feel really tired (which is usually when I have overdone it).

10. If there are disadvantages of pembrolizumab with lenvatinib over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab with lenvatinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I do need to more actively manage tiredness and fatigue to make sure that I don't overdo it – this usually means arranging rest days and not taking on too many things at once (which is often easier said than done). I did have issues with an underactive thyroid as a result of treatment that led to more extreme tiredness. Combined with a viral infection that caused some inflammation of lung (consistent with symptoms of pleurisy), it meant I needed a month off work, but once the levothyroxine started to work, I felt I had got back to my baseline level of wellbeing. However, these are much less than any previous treatment. For example, on chemotherapy, I had days of really awful fatigue that was psychologically incredibly difficult. I also needed to take a lot more medication (e.g., anti-emetics and steroids) and the steroids made me feel pretty awful. I also had diarrhoea on chemotherapy which I no longer have. On pembrolizumab, I am not on any other medication apart from levothyroxine – and usually send my anti-emetics back to the pharmacy as I don't need them. I have also learned how to manage my tiredness (and prevent other side effects) on the whole – through a combination of rest, stress management, nutrition and exercise. Keeping healthy and active has improved my experience of having treatment and meant that I am able to maximise my energy levels and support my immune system to tolerate the treatment. I would also like to highlight that there is a significant difference between fatigue on chemotherapy and tiredness/fatigue on pembrolizumab which may not be easily captured, without the qualitative input of patient experts. My experience of fatigue during chemotherapy was that it was debilitating for at least the first week. Towards the end of treatment, I was also completely exhausted all the time. By contrast, whilst I do get more tired on immunotherapy when compared to my peers, this is something that can be managed to enable me to live my life: to work, socialise, volunteer and exercise.

	There has been some cumulative impacts of treatment on my energy levels and I would say that I am more tired now than I am at the beginning or middle of treatment. Again, this is not comparable to the debilitating fatigue I had on chemotherapy but it is a factor. Again, my active management of my activity, and building in rest, are key to managing this side effect.
11. Are there any groups of patients who might benefit more from pembrolizumab with lenvatinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I cannot comment on this point comprehensively. However, the majority of people with endometrial cancer are postmenopausal women who may have other health conditions or disabilities that may chemotherapy more difficult. As (a much younger) person on pembrolizumab, I have found it a much kinder treatment and I would imagine that it would benefit women who would struggle with conventional therapies. As a younger person with endometrial cancer, I am also aware that many premenopausal women get diagnosed at more advanced stages as a result of doctors failing to identify the possibility of cancer. I saw at least three gynaecologists – all of whom missed my advanced cancer diagnosis, despite having most of the common symptoms and being very unwell with pain and PV bleeding. I wasn't diagnosed until I was admitted to A and E with a life-threatening PV bleed. I have found that I am able to thrive on pembrolizumab in a way that I haven't on current treatments and live a relatively normal life for someone of my age. I feel I was let down by the healthcare system, resulting in a late diagnosis reducing my likelihood of a 'treatment to cure'. Instead, I am living with recurrent cancer which is life-limiting at the age of 32. I feel that pembrolizumab is one of the best possible treatments to extend my life for as long as possible, despite late diagnosis.
12. Are there any potential equality issues that should be taken into account when considering previously treated advanced, metastatic or recurrent endometrial cancer and pembrolizumab with lenvatinib? Please explain if you think any groups of people with this condition are particularly disadvantaged	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

1. Clinically distinct subgroups in the evidence base: deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). The clinical effectiveness of pembrolizumab with lenvatinib appears to be different in the dMMR and pMMR subgroups. Should they be considered separately?	I can't give an opinion on whether they should be considered separately or cost effectiveness. My comments and insights are instead reflective of my lived experience. I have dMMR, as a result of Lynch Syndrome. For me, personally, what would bring me hope for the future would be the availability of options for the future and for my medical team to have access to treatment options that would enable them to be flexible in offering me the best possible treatment. This might mean access to pembrolizumab with options for dostarlimab/lenvatinib in future, if they are viable options for me. I would also like to highlight that this drug has been truly life-changing for me and my quality of life and life expectancy has been transformed as a result. The reason that I wanted to take part in the NICE appraisal is because I feel that people with advanced endometrial cancer deserve access to treatment options that enable them to live longer and fuller lives and even thrive with a cancer diagnosis. I would like to see this option offered to as many people as possible.

2. Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of pembrolizumab with lenvatinib in the dMMR and pMMR subgroups. - Are the current treatment options in the UK the same for people with dMMR and pMMR endometrial cancer? - Is there a different prognosis for dMMR and pMMR endometrial cancer?	We consider patient perspectives may particularly help to address this issue (See above)
3. Uncertainty surrounding extrapolation of overall survival (OS) and: - use of ECHO study to validate OS in doxorubicin or paclitaxel arms - unavailable clinical study report (CSR) for KEYNOTE-146 because it is an Eisal study. - dismissal of restricted cubic splines	Not answered
4. Uncertainty surrounding the company's time to death utility approach	Not answered
5. No treatment waning assumed in company base case (and results highly sensitive to this assumption)	Not answered
6a. Time on treatment: continuous vs capping by progression-free survival	Not answered

Patient expert statement

6b. Percentage of patients receiving doxorubicin or paclitaxel: 75%/25% split or 50%/50% split	We consider patient perspectives may particularly help to address this issue Please see above regarding my personal experience of paclitaxel and carboplatin
6c. Modelled baseline patient characteristics (weight and age) from KEYNOTE-775 may not be generalisable to patients in UK practice.	I would like to highlight that I am atypical as an otherwise healthy, 32-year-old (with a healthy weight) with endometrial cancer. The KEYNOTE 775 study is based on a much older age group – with an average age of 64 years (median) and the youngest patient being 46 years – which means that there is a data gap, particularly for younger patients. I am aware that younger patients with endometrial cancer are rare but I am concerned that the implications of this could mean that clinical decisions may be made for patients based on data of a much older sample of patients. This could lead to decisions on treatment that may not result in the best outcomes for younger patients.
6d. Capping of overall survival: hybrid vs hazards-based approach	Not answered
Are there any important issues that have been missed in ERG report?	Not answered

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Pembrolizumab has been life-changing for me in terms of quality of life and impact of my survival. Despite living with recurrent, advanced endometrial cancer, I am currently no evidence of disease.
- In my experience, pembrolizumab is a much kinder treatment, with fewer debilitating side effects, which has enabled me to thrive and live my life fully.
- My experience of current treatments has been that they have a significant impact on quality of life and are a ‘belts and braces’ treatment which are physically and psychologically difficult to manage.
- Pembrolizumab has given me hope and offers the potential to provide hope to so many patients in terms of their ability to live longer and fuller lives and even thrive with a cancer diagnosis.
- People with advanced, recurrent or metastatic endometrial cancer diagnosis deserve to ‘live with cancer’ – and to be able to live fully and well – rather than be faced with a lack of options which make us feel abandoned and hopeless.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

NICE National Institute for Health and Care Excellence

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1 and sections 1.3 – 1.6).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 29 July 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Eisai
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Eisai is the marketing authorisation holder for lenvatinib

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Clinically distinct subgroups in the evidence base - deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). Are there difference in the clinical effectiveness of the dMMR and pMMR subgroups? Should they be considered separately?	No	PEM+LEN was effective in the ITT population of KEYNOTE-775 (previously treated EC), with a statistically significant treatment effect of 0.56 (95% CI 0.47, 0.66; p< 0.0001) on PFS, and 0.62 (95% CI 0.51, 0.75; p< 0.0001) on OS compared to chemotherapy. Based on these data, the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) granted PEM+LEN marketing authorisations on 26th November 2021 and 29th November 2021 respectively for patients with advanced or recurrent endometrial EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation. [1,2,3] This is reflected in the population in the final scope for this appraisal, where no subgroups were listed. The ESMO Clinical Practice Guideline for endometrial carcinoma also recommends PEM+LEN in pMMR and dMMR patients [4]. Therefore, we disagree with the ERG's suggestion that PEM+LEN may be most appropriately positioned in the subgroup of patients with pMMR EC. Moreover, no clinical rationale was provided in the ERG report and the only justification provided is that patients with dMMR disease now have the option to be treated with dostarlimab. However, this treatment option is

		only available via the CDF [TA779] based on immature survival data from the single arm phase I GARNET study, which resulted in a high level of uncertainty. Comparisons for dostarlimab against chemotherapy relied on a MAIC involving data from a real-world study [5]. In contrast, KEYNOTE-775 is a randomised phase 3 study of 827 patients comparing PEM+LEN with current standard of care treatments. If reimbursed, PEM+LEN would be the first treatment for previously treated EC with a direct head-to-head comparison with current standard of care treatments. The restricted positioning of PEM+LEN to the pMMR subgroup based on the availability of dostarlimab, as proposed by the ERG, is therefore unjustified and may ultimately disadvantage patients whose treatment options are already limited. Consequently, we believe that PEM+LEN should be recommended for routine commissioning in all previously treated patients, as per the final scope, regardless of MMR status. References: 1. European Medicines Agency (EMA). LENVIMA (lenvatinib) Summary of Product Characteristics. 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/lenvima 2. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of product characteristics. Kisplyx 4 mg hard capsules. Available at: https://products.mhra.gov.uk/product/?product=LENVIMA%204MG%20HARD%20CAPSULES 3.Medicines and Healthcare products Regulatory Agency (MHRA). Summary of product characteristics. LENVIMA 10 mg hard capsules. Available at: https://products.mhra.gov.uk/product/?product=LENVIMA%2010MG%20HARD%20CAPSULES 4. A. Oaknin, T.J. Bosse, C.L. Creutzberg, G. Giornelli, P. Harter, F. Joly, D. Lorusso, C. Marth, V. Makker, M.R. Mirza, J.A. Ledermann, N. Colombo, Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, Annals of Oncology, 2022, ISSN 0923-7534, https://doi.org/10.1016/j.annonc.2022.05.009. 5. National Institute for Health and Care Excellence (NICE). Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair

		deficiency. Technology appraisal guidance [TA779]. Available at: https://www.nice.org.uk/guidance/ta779 . 2022.
2. Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of pembrolizumab with lenvatinib in the dMMR and pMMR subgroups.	No	While we acknowledge the rationale to explore cost-effectiveness in relevant subgroups, it is unclear what uncertainty will be resolved by exploring the cost effectiveness of PEM+LEN in the MMR subgroups when the licensed indication is for the entire previously treated EC population, regardless of MMR status. The ERG states that "due to improved OS in the dMMR subgroup, compared to the pMMR subgroup, the ICER for PEM+LEN is likely to be lower in this subgroup, all else remaining equal". In contrast, the ERG has suggested that PEM+LEN should be positioned in the pMMR subgroup. It is therefore unclear how this subgroup analysis will help the committee in their decision making. As stated in response to issue 1, we believe that PEM+LEN should be recommended for routine commissioning in all previously treated patients, as per the final scope, regardless of MMR status.
3. Uncertainty surrounding extrapolation of overall survival (OS) and: - use of ECHO study to validate OS in doxorubicin or paclitaxel arms - unavailable clinical study report (CSR) for KEYNOTE-146 because it is an Esal study. - dismissal of restricted cubic splines	No	Please provide your response to this key issue, including any new evidence, data or analyses

4. Uncertainty surrounding the company's time to death utility approach	No	Please provide your response to this key issue, including any new evidence, data or analyses
5. There is uncertainty around the maintenance of the treatment effect for pembrolizumab with lenvatinib. No treatment waning assumed in company base case (and results highly sensitive to this assumption)	No	Please provide your response to this key issue, including any new evidence, data or analyses
6a. Time on treatment: continuous vs capping by progression-free survival	No	Please provide your response to this key issue, including any new evidence, data or analyses
6b. Percentage of patients receiving doxorubicin or paclitaxel: 75%/25% split or 50%/50% split	No	Please provide your response to this key issue, including any new evidence, data or analyses
6c. Modelled baseline patient characteristics (weight and age) from KEYNOTE-775 may not be generalisable to patients in UK practice.	No	
6d. Capping of overall survival: hybrid vs hazards-based approach	No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]:

ERG Review of Company's Response to Technical Engagement Response

---

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter.
EX1 2LU

Authors

Brian O'Toole[1]
Maxwell S Barnish[1]
Edward CF Wilson[1]
Justin Matthews[1]
Helen Coelho[1]
Naomi Shaw[1]
Melanie Powell[2]
Neil Ryan[3]
Emma Crosbie[4]
Alexandra Taylor[5]
Louise Crathorne[1]
G.J. Melendez-Torres[1]

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter.
EX1 2LU

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter

[2] Consultant Clinical Oncologist, St Bartholomew's Hospital, London

[3] Specialty Registrar in Obstetrics and Gynaecology, Severn Deanery

[4] NIHR Advanced Fellow, Professor and Honorary Consultant in Gynaecological Oncology, Manchester

[5] Consultant in Clinical Oncology, The Royal Marsden NHS Foundation Trust

Correspondence to

Brian O'Toole
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; b.otoole@exeter.ac.uk

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement (TE) report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811].

As part of their Technical Engagement response, the company has;

- responded to the key issues raised by the ERG
- provided the ERG with the final data cut for KEYNOTE-775, as a means of addressing uncertainty surrounding overall survival (OS) and progression free (PFS) extrapolation. However, it should be noted that the company has not incorporated these data into the economic model.
- provided the ERG with the CSR for KEYNOTE-146
- provided summary data from a real world evidence (RWE) study by Heffernan et al. (2022) to support long term extrapolation of the physician's choice (TPC) OS (1)
- provided revised base case results which incorporate two of the ERG's preferred assumptions i.e. time on treatment (ToT) capped by PFS and a hazards-based approach used to cap OS

The ERG response is structured as follows;

- Section 2: ERG response to company's Technical Engagement response form
- Section 3: ERG response to changes to the company's cost effectiveness estimates
- Section 4: ERG response to issues raised by stakeholders

2. ERG RESPONSE TO COMPANY'S TECHNICAL ENGAGEMENT RESPONSE FORM

2.1. Key issue 1: Clinically distinct subgroups in the evidence base - deficient mismatch repair (dMMR) and proficient mismatch repair (pMMR). Are there difference in the clinical effectiveness of the dMMR and pMMR subgroups? Should they be considered separately?

The ERG considered that dMMR and pMMR are clinically relevant distinct subgroups in the evidence base. This was supported by clinical advice regarding differential prognosis in these two subgroups. The ERG also noted that point estimate results suggested patients in the dMMR subgroup may have performed better on both OS and PFS than patients in the pMMR subgroup.

The ERG do however acknowledge the company's concerns surrounding the consideration of dMMR and pMMR patients within separate subgroups, noting that the marketing authorisation for pembrolizumab plus lenvatinib is for the full population (as per the NICE scope). Furthermore, as the trial (KEYNOTE-775) was not specifically powered to assess subgroups, using subgroup results in the cost effectiveness analysis may introduce additional uncertainty.

2.2. Key issue 2: Uncertainty surrounding the cost effectiveness of pembrolizumab with lenvatinib within dMMR and pMMR subgroups. There is likely to be a difference in the cost effectiveness of pembrolizumab with lenvatinib in the dMMR and pMMR subgroups.

The company did not provide a subgroup analysis. In their TE response the company reiterate that it is appropriate to focus on an overall patient population, as this is in line with the final scope issued by NICE. The company also agreed that there is differential response across subgroups, however the trial was not powered to detect this. Therefore it is not clear if the response is clinically or statistically meaningful. The ERG consider the company's points to be valid, however consider that an exploratory subgroup analysis would have been helpful for decision making (albeit subject to limitation).

2.3. Key issue 3: Uncertainty surrounding extrapolation of overall survival (OS)

The ERG noted that with the TE response the company provided the CSR for KEYNOTE-146, which addresses the ERG's earlier concern about reporting of study methods. The company also provided clinical data from the KEYNOTE-775 final data cut, extending median duration of follow-up [redacted] months. The updated data were not incorporated in the economic model. The ERG considered that median survival data and the overall shape of the K-M curves were sufficiently similar for the interim and final analyses that the failure to update the model is not a key issue. In the final analysis, PEM+LEN reduced risk of progression or death by 44% (median PFS: 7.3 vs 3.8 months; HR: 0.56 [95% CI: 0.48, 0.66]; p <0.0001), reduced risk of death by 35% (median OS: 18.7 vs 11.9 months; HR: 0.65 [95% CI: 0.55, 0.77]; p <0.0001), more than doubled the ORR (34% vs 15%; p <0.001) and extends median DOR by 7.5 months (12.9 vs 5.4 months). The company reported that no new safety signals were identified in the final analysis.

Additionally, the company provided clinical data from the Heffernan et al (2022) UK real-world evidence (RWE) study as an additional source of data for model validation purposes for the TPC arm (1). As a validation source this study has some advantages over the original study presented in the CS, ECHO (2): the study sample size was larger (n=999) than ECHO (UK) (n=101) and is now formally published, with an associated protocol and more detailed results.

On the other hand, there are several limitations associated with this study, many of which the company noted in its TE response. The study was conducted solely in the second line, whereas in KEYNOTE-775, 28% of patients had received two prior platinum-based treatments. The second-line treatments in Heffernan et al. (2022) were carboplatin, paclitaxel and doxorubicin monotherapy as well as doublet therapies of these, whereas KEYNOTE-775 TPC arm is of paclitaxel or doxorubicin monotherapy. KEYNOTE-775 required participants to have histologically or cytologically proven recurrent solid tumour with measurable lesion per RECIST (3), whereas these requirements did not apply to Heffernan et al (2022) (1). There are also missing data for ECOG PS scores (for 50% of participants), and disease grade scores (for 24% of participants); and missing information (dMMR and pMMR, previous pelvic irradiation, overall response rate, PFS).

The intended purpose of the ECHO and Heffernan et al studies is as validation of the extrapolation carried out for the TPC arm of KEYNOTE-775. Apart from study differences, noted

above for Heffernan et al. and set out in ERG report section 4.2.6.4 for ECHO, a major weakness of the two as validation studies is that follow-up in both is not very long (median 27.4 and 24 months).

Nevertheless the Heffernan et al. observational study appears methodologically sound and in the appropriate setting (recent UK clinical practice), and does provide some appropriate subgroup information, set out further in Table 1. The ERG notes the considerable difference between the doxorubicin/paclitaxel monotherapy median OS in KEYNOTE-775 (11.9 (10.7 to 13.3), TE Addendum Table 1) compared with Heffernan (6.6 and 4.9). The Heffernan et al. data suggest survival with paclitaxel or doxorubicin monotherapy in the 'real world' is approximately half that observed in KN775. The ERG believes this is likely due to either patients enrolled in a trial receiving protocol-driven monitoring and/or treatment over and above routine care, or inclusion criteria for the trial recruiting a cohort of patients with a longer life expectancy than the broader patient population.

If survival in the control arm (of KEYNOTE-775) is greater than observed in real life and this is driven by the clinical trial design, then it is reasonable that survival in the intervention arm is also overestimated. However, the impact on incremental QALYs and thus the ICER is uncertain as the area between the survival curves in each arm (representing the difference in life expectancy) may increase or decrease were the curves to be rescaled. Analysing this is not straightforward as survival curves were all modelled independently.

Table 1: Estimates of median OS from KEYNOTE-775 TPC arm and ECHO and Heffernan validation studies (including subgroups)

Study	2nd line treatment	Median OS (95% CI [a])	# patients
KN 775	TPC (doxorubicin or paclitaxel monotherapy)	11.9 (10.7 to 13.3)	416
ECHO (UK)	60% doxorubicin or paclitaxel; 40% platinum-based chemotherapy	[redacted]	101
Heffernan et al. 2022	carboplatin	8.3 (6.7 to 11.4)	93
	paclitaxel mono	6.6 (5.7 to 8.0)	116
	doxorubicin mono	4.9 (4.2 to 6.0)	130
	doxorubicin + carboplatin	13.9 (11.2 to 15.7)	141
	paclitaxel + carboplatin	14.2 (12.4 to 16.1)	279
	aggregate	10.3 (9.2 to 11.1)	999

Sources: TE Addendum Table 1, CS doc B and Heffernan et al. Table 3. a confidence level not reported in Heffernan et al.

The ERG made some criticism of the company's two piece approach (ERG report section 4.2.6.1), including ambiguity around the choice of breakpoints. The company has not responded to these in TE. The ERG also encouraged the use of survival modelling with cubic splines, which the company indicated has not been possible in the TE timeframe.

2.4. Key issue 4: Uncertainty surrounding the company's time to death (TTD) utility approach

The ERG acknowledges the company's comments surrounding the appropriateness of using a TTD approach to model utility values, namely that this approach has been used in the assessment of several immunotherapy treatments and that it provides additional/finer granularity in utility. However, the ERG maintain that a progression based utility approach better reflects the company's model structure, which is characterised by the progression free (PF) and progressed disease (PD) health states i.e. using TTD approach divorces health related quality of life from disease status in the model. Although a TTD approach is not necessarily invalid, the ERG considers that it is more methodologically robust for the company to align their utility approach with the model structure.

Overall, the ERG found that the company's approach to estimating model utility was not a key driver of cost effectiveness, as this was largely driven by assumptions with respect to OS extrapolation and treatment waning.

2.5. Key issue 5: There is uncertainty around the maintenance of the treatment effect for pembrolizumab with lenvatinib. No treatment waning assumed in company base case (and results highly sensitive to this assumption)

The company has not presented additional data to support maintenance of a long-term PEM+LEN treatment effect. The ERG's critique as outlined in the ERG report therefore remains relevant for consideration (see p.72 of the ERG report). In their TE response, the company reiterate the following points to support their case for a maintained treatment effect.

- KEYNOTE-775, which details evidence of a sustained OS for PEM+LEN via a plateau with 30% of patients at 5 years (see company CS, Fig 9)

- Long term OS data after 5 years from KEYNOTE 146. The company states these data show a durable and sustained treatment response beyond 2 years in the PEM+LEN arm
- Mechanism of action associated with pembrolizumab. The company state that treatment with pembrolizumab potentially allows for 'immune memories' which enables the activated immune system to continue to identify and fight off cancer cells after stopping pembrolizumab immunotherapy. The company state that the 'immune surveillance' effect is likely to be maintained after pembrolizumab is stopped.
- Evidence from immunotherapy use in other indications (NSCLS, melanoma and head and neck cancer)

As a general comment the ERG noted that in NICE TA779 for dostarlimab (for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency), the committee preferred and accepted the ERG's more conservative approach to modelling the long-term treatment effect (4). This involved the application of a treatment waning effect immediately after discontinuation, with a declining effect over a long period of time until the chance of dying was the same between arms. The ERG also noted that treatment waning assumptions have been used and accepted in previous appraisals for medicines with similar mechanism of action.

The ERG conducted scenario analysis which included a treatment waning assumption (see p.91 and p.95 of the ERG report). Results were highly sensitive to this assumption.

2.6. Key issue 6: Model assumptions and inputs

6a) Time on Treatment. ERG and Company are in agreement. No further comment required.

6b) Paclitaxel / Doxorubicin split. We note the disagreement between the ERG's preferred 50/50 split between Pac/Dox and the company's preference for 25.5/74.5 as observed in the KEYNOTE-775. We note that the impact on the ICER is trivial ([redacted]), and therefore we prefer to keep to our own base case (50/50 split).

6c) Baseline age and weight. Clinical advice received by the ERG was unambiguous that typical patients would be older and heavier than suggested in the KEYNOTE-775 data. Whilst weight makes very little difference to the ICER ([redacted]), increasing age is associated with a deterioration in the ICER of [redacted]. The ERG prefers to keep the older and heavier assumptions for its base case.

6d) Capping overall survival. Company and ERG are in agreement on the approach to capping OS. No further comment required. We thank the Company for correcting the links in the model we supplied. We confirm our base case now agrees with the company's.

3. ERG RESPONSE TO CHANGES TO THE COMPANY'S COST EFFECTIVENESS ESTIMATES

In response to the ERG report, the company subsequently made two revisions to their base case analysis. These were as follows;

- capping ToT by PFS (initially the company modelled ToT independently of health state)
- applying a hazards based approach to cap OS (a hybrid approach was initially used to cap overall survival to general population survival and PFS to OS)

The ERG considered the company's revisions to be largely reasonable and these were appropriately modelled. Furthermore, the impact of incorporating these changes resulted in a reduced ICER. The company's revised deterministic and probabilistic base case results (list prices and PAS for pembrolizumab) are presented in Table 2 to Table 4 below.

Table 2: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 6a: Time on treatment: continuous vs capping by progression-free survival	ToT was modelled independently from health state, allowing patients to continue treatment post progression	Following the ERG report, modelled ToT has been capped by PFS (please also see note in response to Issue 6d, above)	ICER resulting from the change described (on its own): [redacted] Change from the company's original base-case ICER: [redacted]
Key issue 6d: Capping of overall survival: hybrid vs hazards-based approach	A 'hybrid' approach was used to cap overall survival to general population survival and PFS to OS	Following the ERG report, a hazards-based approach has been applied to cap overall survival general population survival (please also see note in response to Issue 6d, above)	ICER resulting from the change described (on its own): [redacted] Change from the company's original base-case ICER: [redacted]

Company's revised base case following technical engagement			Company revised base-case (list price): Incremental costs: £[redacted] Incremental QALYs: 1.77 ICER: £58,810 Company revised base-case (pembrolizumab PAS applied): Incremental costs: [redacted] Incremental QALYs: 1.77 ICER: £[redacted]

Table 3: Mean probabilistic base case results, pairwise analysis – List prices

	Total costs	Total life years	Total QALYs	Incremental, PEM+LEN versus TPC			ICER
				Costs	Life years	QALYs	
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	2.60	1.82	£57,016

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

Table 4: Mean probabilistic base case results, pairwise analysis – pembrolizumab price with PAS applied

	Total costs	Total life years	Total QALYs	Incremental, PEM+LEN versus TPC			ICER
				Costs	Life years	QALYs	
PEM+LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; PAS, patient access scheme; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

4. ERG RESPONSE TO ISSUES RAISED BY STAKEHOLDERS.

The ERG thank EISAI for their comments.

In their response, EISAI state that the ERG have proposed a restricted positioning to the pMMR subgroup, based on the availability of dostarlimab. However, this is not the case. The ERG have simply reported the availability of dostarlimab for the treatment of dMMR patients and noted clinical expert opinion to the ERG surrounding potential use of PEM+LEN in practice (see p.63 and p.64 of the ERG report). On p.24 of the ERG report, the ERG stated the following *'The ERG noted that people with dMMR EC now have access to dostarlimab (TA779), as monotherapy. Therefore, PEM+LEN may be most appropriately positioned for people with pMMR EC.'* This does not constitute a recommendation and is rather the opinion of the ERG.

Finally, the ERG acknowledges that the population presented by the company in their base case matches the NICE final scope. The ERG raised the notion of distinct subgroups based on clinical opinion received (surrounding differences in prognosis).

5. REFERENCES

1. Heffernan K, Nikitas FS, Shukla U, Camejo HS, Knott C. Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis. Gynecol Oncol. 2022;166(2):317-25.
2. Corman S, Kelkar S, Odak S, Zhang J, Prabhu VS, Rusibamayila N, et al. Treatment patterns and outcomes among patients with microsatellite stable (MSS) advanced endometrial cancer in the United States: Endometrial Cancer Health Outcomes (ECHO) retrospective chart review Study. Journal of Clinical Oncology. 2021;39(15_suppl):5581-.
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
4. National Institute for Health and Care Excellece (NICE). Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency 2021 [Available from: https://www.nice.org.uk/guidance/ta779/documents/final-appraisal-determination-document.