Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission from Merck Sharp & Dohme:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. a. Peaches Womb Cancer Trust

4. **Expert personal perspectives** from:
   a. Grace Remmington Teeling, Peaches Patient Voices Lead, patient expert nominated by Peaches Womb Cancer Trust
   b. Dr Gemma Eminowicz, Consultant Clinical Oncologist, clinical expert nominated by Merck Sharp & Dohme

5. **External Assessment Report** prepared by Warwick Evidence

6. **External Assessment Report – factual accuracy check**

7. **External Assessment Group - supplementary report – subgroup analyses**
   This report was prepared after the meeting and did not form part of the Committee papers

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 platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381]

Document B

Company evidence submission

September 2024

File name	Version	Contains confidential information	Date
ID6381_Pembro_1L_EC_DocumentB_v1.1 [redacted]	1.1	No	7th March 2025

Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
1L	First-line
AE	Adverse event
BGCS	British Gynaecological Cancer Society
CCC	Clear cell carcinoma
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Carcinosarcoma
CT	Chemotherapy
dMMR	Mismatch repair deficient
DOR	Duration of response
EC	Endometrial cancer
ECOG	Eastern Cooperative Oncology Group
EEC	Endometrioid adenocarcinoma
EPAR	European Public Assessment Report
ESGO	European Society of Gynaecological Oncology
ESMO	European Society of Medical Oncology
FACT-En-TOI	Functional Assessment of Cancer Therapy–Endometrial
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity
FIGO	International Federation of Gynecology and Obstetrics
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
ITT	Intention-to-treat
IV	Intravenous
MMR	Mismatch repair
MSI-H	High microsatellite instability
NHS	National Health Service
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival on next-line therapy
pMMR	Mismatch repair proficient

Abbreviation	Definition
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PS	Performance status
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RECIST	RECIST – Response Evaluation Criteria in Solid Tumours
RWE	Real-world evidence
SAE	Serious adverse event
SC	Serous adenocarcinoma
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
UC	Uterine cancer

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

B.1.1. Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication:

"KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults."

The decision problem addressed in this submission is presented 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 primary advanced or recurrent endometrial cancer	As per NICE scope	N/A
Intervention	Pembrolizumab in combination with platinum-based chemotherapy followed by pembrolizumab maintenance treatment	As per NICE scope	N/A
Comparator(s)	Following treatment options, followed by routine surveillance: • Platinum-based chemotherapy (such as paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide) • Hormone therapy (such as medroxyprogesterone acetate and megestrol)	Carboplatin + paclitaxel	Platinum-based chemotherapy specifically refers to carboplatin + paclitaxel to align with the BGCS Endometrial Cancer Guidelines.[1] Hormone therapy is typically used when all other treatment options are exhausted, or if chemotherapy is not suitable for patients. In this setting, it has a palliative intent rather than clinical response, i.e. it would not be a comparator for pembrolizumab or any other active treatment, and there is no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival.[1] [2] Clinical advisors highlighted that while a small proportion of low-grade, low-volume, hormone-receptor positive patients may receive hormone therapy over chemotherapy, the evidence base is lacking, and they did not consider hormone therapy a comparator in this population [3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Progression-free survival • Response rates • Duration of response • Overall survival • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Progression-free survival • Response rates • Duration of response • Overall survival • Adverse effects of treatment • Health-related quality of life	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an 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.	As per NICE scope	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	• MMR immunohistochemistry status	Information concerning site of recurrence was not systematically collected in the KEYNOTE-868 (NRG-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Molecular subgroups, such as MMR status • Local versus metastatic recurrence • People who have had primary debulking surgery versus those who have not had surgery		GY018) trial. Forest plots available in the CSR make a distinction between subgroups based on whether patients had recurrent or primary advanced disease at the start of the trial, but not explicitly based on site of recurrence (local versus metastatic). Although the CSR for KEYNOTE-868 (NRG-GY018) does have indirect data points with regards to details about the site of recurrence, identification and prior therapies, which could potentially be used to assess some of the site-relevant information for recurrent patients, more detailed data may have gaps and will likely be subject to limitations when attempting to interpret the data. Therefore, evidence does not allow for the consideration of the local versus metastatic recurrence subgroups. Information concerning proportion of people who had primary debulking surgery versus those who have not had surgery was also not systematically collected in the KEYNOTE-868 (NRG-GY018) trial.

Key: BGCS, British Gynaecological Cancer Society; CSR, clinical study report; DFS, disease-free survival; MMR, mismatch repair; NHS, National Health Service.

B.1.2. Description of the technology being evaluated

Pembrolizumab (KEYTRUDA®, MSD) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor, thereby blocking its interaction with ligands programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2).[4] The programmed cell death protein (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. PD-L1 and PD-L2 are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

The draft Summary of Product Characteristics (SmPC) is provided in Appendix C. As the regulatory submission is currently ongoing, please note this draft SmPC is subject to change.

Table 2: Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA ®)
Mechanism of action	KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumour cells. KEYTRUDA is a humanised monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumour cells and healthy cells.[5]
Marketing authorisation/CE mark status	The application for marketing authorisation was submitted to the MHRA through the Project Orbis programme in May 2024. Marketing authorisation was granted by the MHRA in February 2025.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication under appraisal is: "KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults." Pembrolizumab, as monotherapy or in combination with other agents, is also licensed for the management of: • Melanoma • Non-small-cell lung cancer • Classical Hodgkin's lymphoma • Urothelial carcinoma • Head and neck squamous cell carcinoma • Renal cell carcinoma • Colorectal cancer • Oesophageal cancer • Triple-negative breast cancer • Endometrial cancer

	• Cervical cancer • Gastric or GEJ adenocarcinoma • MSI-H or dMMR cancer • Biliary tract cancer
Method of administration and dosage	The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an IV infusion over 30 minutes. Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. In KEYNOTE-868 (NRG-GY018), patients received paclitaxel + carboplatin along with either 200 mg pembrolizumab or placebo administered intravenously in a 30-minute infusion every 3 weeks for 6 cycles, which was followed by 400 mg pembrolizumab or placebo maintenance administered intravenously in a 30-minute infusion every 6 weeks for up to 14 cycles; a maximum of 20 cycles (6 x 200 mg Q3W followed by 14 x 400 mg Q6W) of pembrolizumab or placebo could be administered.[6]
Additional tests or investigations	No additional tests, in addition to those currently conducted as part of clinical practice, would be needed to identify patients for treatment.
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial.
Patient access scheme (if applicable)	A commercial access agreement is in place; details are provided in Appendix K.

Key: dMMR, mismatch repair deficient; GEJ, gastroesophageal junction; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; MSI-H, high microsatellite instability; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

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

Summary of key points:

Advanced or recurrent endometrial cancer

- Endometrial cancer (EC) is a cancer of the inner lining of the uterus (womb) called the endometrium, and is the fourth most common cancer affecting females in the UK.[7]
- Four main molecular subgroups of EC have been identified: *POLE*-ultramutated (*POLE*mut), mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and p53-abnormal (p53abn). Each have distinct molecular landscapes and effects on prognosis. The POLEmut subgroup is associated with a very favourable prognosis, while the p53abn subgroup has poor prognosis; and the dMMR and NSMP subgroups have an intermediate prognosis.[8-11]
- The majority of cases of EC are diagnosed in the early stages, however, for patients diagnosed at the later stage (Stage IV), the 5-year survival rate is only 15%.[12-14]
- In addition, approximately 18% of early-stage cases of EC recur. Recurrent disease is associated with poor prognosis; with a 5-year survival rate of 20%.[15]
- EC patients are frequently shown to have a poor health-related quality of life (HRQoL), and with advanced disease or disease recurrence, HRQoL is reported to decrease, with an increase in anxiety and depression.[16,17]

Current clinical pathway of care

- The current standard of care (SoC) for the first-line (1L) systemic treatment of patients with advanced or recurrent EC is platinum-based chemotherapy (CT) (carboplatin and paclitaxel) regardless of histological or molecular subtype, as recommended by the BGCS guidelines.[1]
- Pembrolizumab + CT will be positioned as a new 1L treatment in the systemic setting, followed by pembrolizumab as 1L maintenance.

Unmet need

- Unlike many other solid tumours, survival for women with EC has not improved over the past four decades.[18,19] Although recently there has been progress in the

clinical treatment landscape, particularly in second-line (2L) treatments, CT remains the standard of care for 1L treatment of advanced/recurrent patients with EC.

- Women with advanced or recurrent EC face a poor prognosis, with high symptom burden and decreased HRQoL. Only about 47% of patients diagnosed at stage IV survive for one year or more, compared to approximately 99% for those diagnosed at stage I. Additionally, for patients that experience recurrence (approximately 18%), the median survival is 23 months after recurrence.[20,21]
- ECs are a prime candidate for immune checkpoint inhibitors (ICIs), which can be utilised in combination with CT to improve the durability of the antitumour immune response.[22]
- In England, black women and women from deprived backgrounds face higher incidence rates, advanced stage at diagnosis and poorer outcomes. This underscores the urgent need to provide effective treatments for EC, particularly for those most at risk and underserved.[23,24]

B.1.3.1. Disease background

Endometrial cancer (EC) is a cancer of the inner lining of the uterus (womb) called the endometrium.[7] It is the most common type of uterine cancer (UC), making up approximately 95% of cases; therefore, EC and UC terminology are often used interchangeably.[23,25] Risk factors for EC include obesity, hormone levels, increased age and family history.[26] Hormonal changes may be due to an external influence, such as contraceptive pills, or can vary with the number of menstrual cycles over a woman's life, pregnancy and diagnosis of ovarian tumours or polycystic ovarian syndrome.[26]

EC is graded by FIGO criteria.[9] Typically, Grade 1 and 2 are combined and referred to as low grade, and Grade 3 is referred to as high grade.[9,27] Tumours of a higher grade are poorly differentiated from normal cells, grow more rapidly and are more likely to metastasise than lower grade tumours.[27]

EC can be classified into the following histological subtypes:[28]

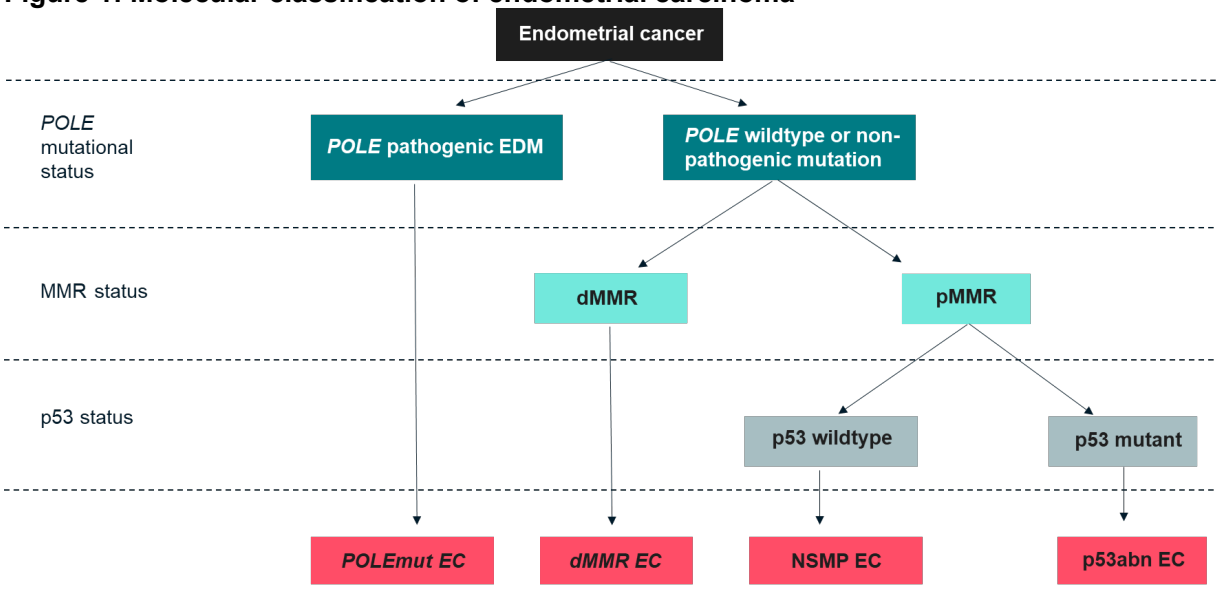
- Endometrioid adenocarcinoma (EEC)
- Serous carcinoma (SC)
- Clear cell carcinoma (CCC)

- Mixed carcinoma (MC)
- Undifferentiated carcinoma
- Carcinosarcoma (CS)
- Other

Most EC cases are classified as either EEC or SC (80%–90%), with CS accounting for approximately 5% of all ECs.[29,30] These different histological types have different molecular features, microscopic appearance, precursor lesions prognosis, and natural history.[28] EC is historically divided into two types.[7] Type 1 cancers are the most common; these are usually EECs, linked to excess oestrogen, slow growing and less likely to spread. Type 2 cancers are not linked to excess oestrogen; these are typically SCs and CCCs and are faster growing.[7]

EC is a molecularly heterogeneous disease, particularly high-grade EECs. Molecular profiling of these tumours enables distinct prognosis groups to be identified.[28,31] Figure 1 presents the four main molecular subgroups that have been identified in clinical practice, according to The Cancer Genome Atlas, including *POLE*mut, dMMR, NSMP, and p53abn.[11,28] NSMP and p53abn are collectively considered mismatch repair proficient (pMMR). These subgroups have distinct molecular landscapes and significant differences in their clinical outcomes.[11] The subgroup with the highest prevalence in The Cancer Genome Atlas is NSMP (30-40%), followed by dMMR (25-30%), *POLE*mut (5-15%) and p53abn (5-15%). ECs of the *POLE*mut subgroup have a very favourable prognosis, whereas p53abn ECs have poor clinical outcomes; and dMMR and NSMP ECs have an intermediate prognosis.[9,11]

Figure 1: Molecular classification of endometrial carcinoma



Key: dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain mutations; MMR, mismatch repair; NSMP, no specific molecular profile; POLE, DNA polymerase epsilon; pMMR, mismatch repair proficient.

Source: Adapted from Leon-Castillo. 2023[11]

EC is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[28,31] The latest FIGO staging system was published in 2023, nearly 14 years after its last update in 2009.[28] The 2023 update introduced a move from anatomy-based staging into a prognosis-based staging system and is based on new molecular stratification.

Staging is based on tumour size and the degree of spread from the endometrium to other tissues (i.e. myometrial invasion) and organs. Broadly, EC is split into four stages with increasing severity, with each stage also being divided into sub-stages[28]:

- Stage I disease is confined to the uterine corpus and ovary
- Stage II disease shows invasion of cervical stroma
- Stage III disease shows local/regional spread
- Stage IV disease has spread to the bladder, intestinal mucosa or other distant metastasis

KEYNOTE-868 (NRG-GY018), the pivotal trial supporting pembrolizumab in the patient population outlined by the decision problem (Table 1), enrolled patients with Stage III, IVA or IVB EC based on the FIGO 2009 criteria.[32] UK clinical experts have indicated that FIGO 2009 criteria is still used in UK clinical practice, and the adoption of the FIGO 2023 guidelines is limited. Clinicians confirmed that the differences between the 2009 and 2023

guidelines do not have a practical impact on the management and treatment of patients with EC.[3]

As the most common symptom of EC (abnormal bleeding from the vagina) is easily identifiable, the majority of cases of EC are diagnosed in the early stages, with only 16% of patients diagnosed with advanced EC (Stage III/IV).[12,13,33] Whilst the prognosis for EC diagnosed in the early-stages is relatively good, with a one-year survival rate of 99% (Stage I), for those diagnosed at the latest stage (Stage IV), the 1-year survival rate is only 47%.[14] In addition, approximately 18% of EC patients experience recurrence, with a higher risk in those who are diagnosed with later-stage disease (Stage IIB-IV), who have Type 2 histology, who are older, or who have positive progesterone receptor expression.[15,34,35] 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).[15 1]

B.1.3.2. Epidemiology

EC is the fourth most common cancer affecting females in the UK, with approximately 9,700* new cases each year.[7] Recent data shows that in England in 2021, the age-standardised rate of EC was 28.8* per 100,000 people; with a rate of 18.8* per 100,000 for Stage I/II at diagnosis and 5.0* per 100,000 for Stage III/IV at diagnosis.[36]

EC predominantly affects older women. Age-specific incidence rates increase sharply starting around ages 45-49, then decline in the oldest age groups, which is a somewhat unique pattern compared to most other cancers.[23] In 2021, approximately 60%* of cases in England were diagnosed in females between the ages of 55 and 79.[36] The highest rates are in the 70 to 74 age group, with 1,282* new cases diagnosed in England in 2021.[36] Incidence is also linked with deprivation in England; data shows higher incidence rates for females in the most deprived quintile compared to the least.[23]

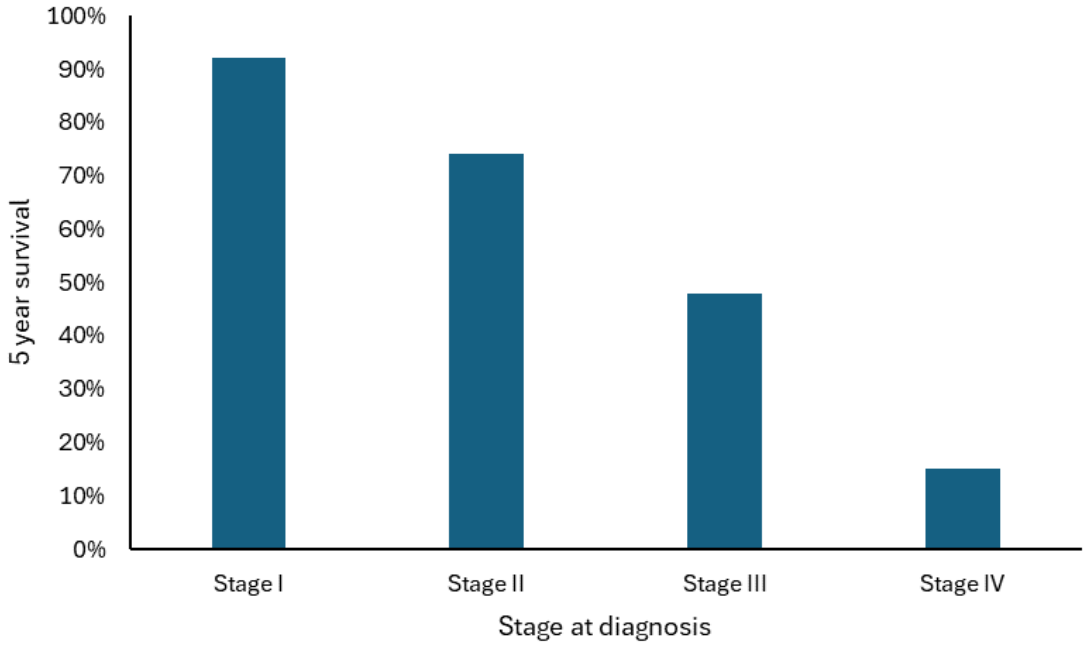
The incidence of EC in the UK has increased approximately 59%* between 1993-1995 and 2016-2018, and between 2006-2008 and 2016-2018, incidence rates increased by 12%*.[23] Incidence is still increasing; projections calculated by the Cancer Intelligence Team at Cancer Research UK using the age-period-cohort modelling approach, suggest that by 2038-2040 there will be approximately 11,800* new cases of EC annually in the UK.[23]

Approximately 2,500* people die from EC in the UK each year, accounting for 3% of all female cancer deaths.[23] Around 76% of people diagnosed with EC (any stage) survive ≥ 5 years.[37] However, as discussed in Section B.1.3.1, the majority of patients are diagnosed

with early-stage disease, and survival in EC is heavily influenced by disease stage at diagnosis. Figure 2 presents the 5-year survival by stage at EC diagnosis for women in England. For patients diagnosed with stage I disease, prognosis is good, with a 5-year survival of over 90%; however, this falls to 50% for people diagnosed with stage III disease and 15% for people diagnosed with Stage IV disease.[21] Therefore, early diagnosis and treatment of patients is critical to patient outcomes.[38] In addition, EC mortality rates are increasing; projections calculated by the Cancer Intelligence Team at Cancer Research UK show rates rising by 12%* between present day and 2038-2040, which would account for around 4,200* yearly deaths.[23]

**Statistics shared are for uterine cancer. EC is the most common type of uterine cancer, accounting for approximately 95% of diagnoses. Therefore, these statistics are referred to as EC for simplicity.[23,25]*

Figure 2: 5-year survival by stage at EC diagnosis for England



Notes: The statistics reported are for net survival for women diagnosed in England between 2013 and 2017.
Source: Office for National Statistics[21]

B.1.3.3. Burden of disease

Patients with EC experience a high symptom burden. Abnormal vaginal bleeding (which may include heavy bleeding, or persistent bleeding between periods) is the most common symptom of EC, especially in post-menopausal women.[12] Other symptoms include abnormal vaginal discharge, pelvic pain, blood in urine, or unintended weight loss.[39,40] EC patients are

frequently shown to have decreased health-related quality of life (HRQoL) with higher levels of anxiety, depression, pain, fatigue, and impaired physical and emotional functioning compared with the general population.[41,42] Multiple case reports indicate that patients often struggle with the symptoms of EC and its treatments, which can significantly impact their mental health.[43] In one study, the prevalence of depression in gynaecological cancer patients was 23%, which was higher than for many other cancer diagnoses such as breast (11%) and respiratory tract (3%).[44]

Studies have found that factors associated with poor HRQoL include higher tumour stage, severity of surgery, comorbidities, lower socioeconomic status and living alone.[42,45] Patients with advanced EC are more likely to have more comorbidities than patients with earlier stage disease, and therefore are more likely to have a poorer HRQoL. Additionally, with disease recurrence, patient HRQoL is reported to decrease, with an increase in anxiety and depression, and 'more threatening illness perceptions' reported after diagnosis of relapse.[16,17]

The current standard of care (SoC) for advanced/recurrent EC is typically a combination of surgery, chemotherapy (CT) and/or radiotherapy. Surgical removal of the uterus and affected tissues, as well as treatment with CT and radiotherapy, can damage sex organs and impair sexual function. A study found that 68.6% of patients experienced sexual dysfunction following treatment. Following surgery, patients may also face pain during intercourse, impaired physical functioning and mobility, and difficulty with daily activities.[17]

B.1.3.4. Clinical care pathway and proposed positioning of pembrolizumab + chemotherapy

Currently, there is no screening programme for EC in the UK. As per the NICE guidelines for suspected cancer (NG12), women who present with signs and symptoms of EC may be referred for further investigation by their GP using the suspected cancer referral pathway.[46] Women aged ≥ 55 years who present with post-menopausal bleeding (i.e. unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause) are referred for urgent investigation, whereas women under 55 years who present with signs and symptoms that warrant investigation are considered for referral.[46]

Following referral, women should undergo a full abdominal and pelvic examination, which involves speculum examination of the cervix, a transvaginal ultrasound to measure endometrial thickness, and additional imaging tests, including X-rays, computed tomography scans and magnetic resonance imaging (MRI) scans where appropriate.[1,9,47] The combination of examination methods is used to assess the tumour location, volume and

potential spread to another pelvic organ. Histopathological examinations using a biopsy are performed to determine the histological type, grade, and molecular status.[1,9,47]

The key guidelines for clinical care of EC include the British Gynaecological Cancer Society (BGCS), the European Society of Medical Oncology (ESMO) and the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) (ESGO/ESTRO/ESP) guidelines.[1,9,10] There are currently no NICE guidelines for the management of EC, apart from guidelines for laparoscopic hysterectomy for EC, and the testing strategies for Lynch syndrome in people with EC.[48,49]

The goal of currently available treatments for patients with non-curative, advanced (Stage III or IVA) or recurrent EC is to provide relief from symptoms, maintain quality of life, prevent disease progression, delay time to next treatment, and extend life. This differs from early-stage disease, where the intent is usually curative. The treatment of patients with advanced or recurrent EC is dependent on the patient's condition, extent of the disease, previous treatment received, suitability for surgery and the patient's wishes.[1,9]

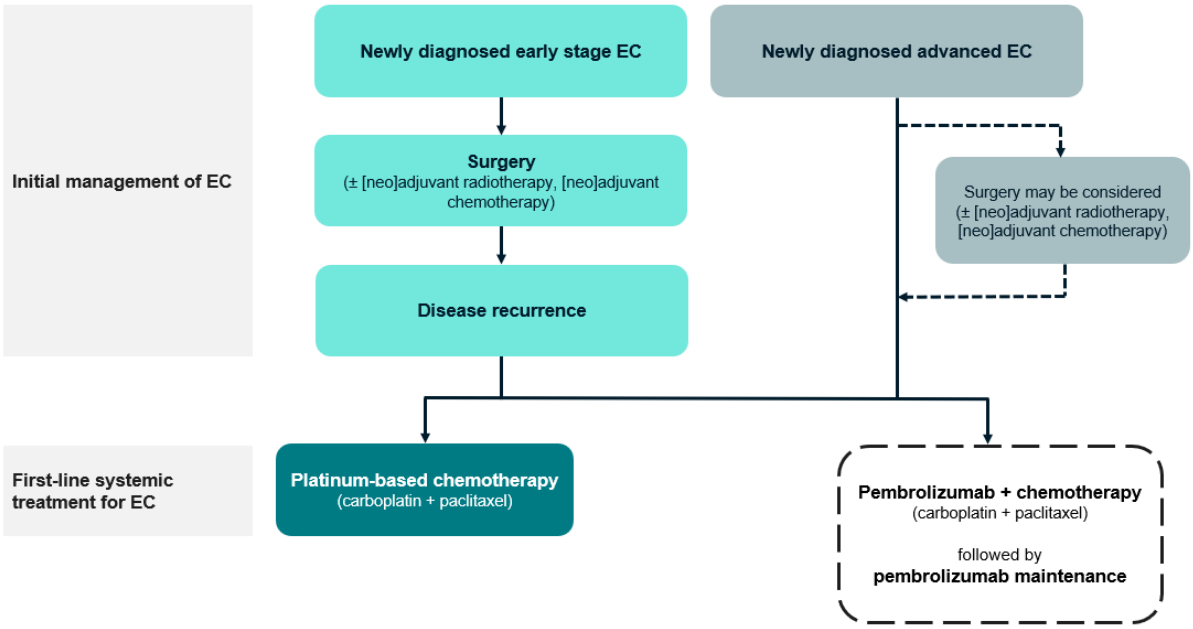
Patients who are newly diagnosed with early-stage EC are typically treated with surgery.[1] Radiation therapy and chemotherapy are often used alongside surgery. As recommended by the BGCS guidelines, surgery may be an option for some patients with recurrent disease, although the standard 1L systemic treatment for patients with recurrent disease is platinum-based CT, specifically carboplatin and paclitaxel, regardless of histological subtypes.[1] Patients who are not suitable for carboplatin and paclitaxel due to Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities or patient preference, may be offered hormone therapy, or other chemotherapy options.[1] Patients who are diagnosed with advanced EC may be considered for surgery as the initial management of EC, however many patients are not suitable. Similar to patients who have disease recurrence following surgery for early-stage EC, the 1L treatment option for advanced EC is chemotherapy (carboplatin and paclitaxel).[1] UK clinical experts have confirmed that this treatment pathway aligns with that currently seen in UK clinical practice (see Section B.3.14.2 for further information on the clinical advisory board).[3]

Patients who progress after 1L treatment are recommended to receive pembrolizumab with lenvatinib or to be rechallenged with platinum-based CT. Additionally, for patients with dMMR tumours, pembrolizumab monotherapy is recommended and dostarlimab monotherapy is also available via the CDF.[1,50-52]

Pembrolizumab + CT, followed by pembrolizumab maintenance, is intended as a new 1L treatment option for adults with primary advanced or recurrent EC. Therefore, the comparator for this intervention will be platinum-based CT (carboplatin + paclitaxel), the SoC in current practice.

Figure 3 presents the 1L treatment pathway, based on the BGCS guidelines, and the proposed placement of pembrolizumab + CT.

Figure 3: Treatment pathway of primary advanced or recurrent EC with the proposed positioning of pembrolizumab plus chemotherapy



Key: EC, endometrial carcinoma.

Notes: Proposed treatment positioning is indicated by the dashed box.

Source: British Gynaecological Cancer Society guidelines.[1]

Dostarlimab + CT is available via the Cancer Drugs Fund (CDF) as an option for treating primary advanced or recurrent EC with MSI-H or dMMR in adults who are candidates for systemic therapy (TA963; dostarlimab dMMR/MSI-H).[53] In line with NICE process, technologies recommended with managed access are not considered established practice in the National Health Service (NHS) and are not considered suitable comparators for NICE appraisals.[54]

In patients treated with platinum-based CT (carboplatin and paclitaxel) in the early-stage setting, retreatment may be considered as a treatment option for selected patients who relapse more than 6 months after the last dose of platinum-based CT.[9] In KEYNOTE-868 (NRG-GY018), the pivotal trial supporting pembrolizumab in the patient population outlined

by the decision problem (Table 1), prior adjuvant CT (carboplatin and paclitaxel) had to have been completed at least 12 months prior to trial registration for patients to be included in the trial; this ensured that prior adjuvant CT was not a confounding factor in the KEYNOTE-868 (NRG-GY018) trial.[55] UK clinical experts confirmed that a 6−12 month disease-free interval before retreating with CT is aligned with clinical practice.[3]

B.1.3.5. Unmet need

For women with advanced or recurrent EC, prognosis is much worse than for women with early-stage EC, with a high symptom burden, poor HRQoL, and an average 5-year survival less than 20%.[20] Approximately 47% of EC patients diagnosed at the most advanced stage (Stage IV) survive for one year or more, compared to approximately 99% for those diagnosed at the earliest stage (Stage I).[21] In addition, about 18% of endometrial cancer patients experience recurrence, the majority during the first two years after primary surgical treatment.[35] Median survival after recurrence is 23 months.[35]

Unlike many other solid tumours, survival for women with ECs has not improved over the past four decades. Although there have been a few recent innovations, particularly in the 2L setting, overall, advancements in the treatment options for EC have been very limited for a long time, and SoC for the 1L treatment of advanced/recurrent patients with EC remains as CT. This further highlights the urgent need for improvement in this area.[18,19]

As discussed in Section B.1.3.1 the molecular subgroups of EC have varying prognoses: the *POLE*mut subgroup has a very favourable prognosis, dMMR and NSMP have an intermediate prognosis, and p53abn ECs have a poor prognosis. Notably, the NSMP and p53 tumours, which are associated with less favourable outcomes, are pMMR, which highlights the particular need for treatments effective in the pMMR population. There has been a growing focus on developing targeted treatments in EC, with the funding of dostarlimab + CT with platinum-based chemotherapy by the CDF; however this treatment is only available for the dMMR population.[53] Additional treatments are needed to provide effective first-line treatment options for patients with advanced or recurrent pMMR tumours (approximately 70%),[11] and effective alternative treatment options for the advanced or recurrent dMMR population (pending a decision on the appropriateness of routine commissioning for dostarlimab + CT following assessment after the duration of their managed access period).

Combining immune-oncology therapies with platinum-containing CT is an area of growing interest. Emerging evidence suggests that, in addition to the cytotoxic and cytostatic effects

of CT, the mode of action of conventional chemotherapies may involve activation of tumour-targeted immune responses.[56-61]

Until recently there has been a lack of therapeutic advancements in EC, highlighting the urgent need for new effective treatments in the first line advanced or recurrent EC treatment pathway. The addition of pembrolizumab + CT followed by pembrolizumab maintenance to this pathway offers patients a promising new targeted treatment option, with a proven survival benefit.

B.1.4. Equality considerations

EC only affects women, and unlike many other solid tumours, survival for women with EC has not improved over the past four decades.[18,19] Improvements in access to effective treatment options are needed in EC to ensure equality in access to medicines compared to other cancers.

EC incidence rates in England are 17% higher in the most deprived quintile compared with the least, and around 640 cases of EC each year in England are linked with deprivation.[23] Socio-demographic differences drive differences in exposure to theoretically avoidable risk factors, such as obesity, a major risk factor for EC.[62] Furthermore, low socioeconomic status is associated with advanced stage at diagnosis. Whilst the association between socioeconomic deprivation and cancer is complex and multifaceted, it may be that patients with higher socioeconomic status are more aware of symptoms and promptly seek medical attention, while patients with low socioeconomic status tend to ignore early symptoms of disease.[63] Patients with EC who have multiple comorbidities experience decreased survival. Since the prevalence of comorbidities tend to be higher among patients with higher levels of deprivation, this could also affect survival.[63] In addition, one study found that socio-economically deprived women with EC were more likely to develop fatal recurrence.[64] There is a need to ensure the most deprived in society are not restricted from access to effective treatment options for diseases that disproportionately affect them.

Incidence rates for EC are higher in the Black ethnic group compared with the White ethnic group, in women in England (2013–2017).[24] EC was in the 10 most common cancers for the Asian, Black and Mixed/Multiple ethnic groups but only 14th most common for the White ethnic group.[24] Black women are more likely to be diagnosed with the higher-risk, non-endometrioid EC subtypes (38% of Black women with EC were diagnosed with non-endometrioid cancer, compared to 20% of women of other ethnic groups).[65] They also are more likely to have molecular tumour alterations associated with worse outcomes (p53abn),

while the *POLE*mut alteration, which is associated with the best outcomes, is rare in black women.[65]

Black women are more likely to receive a late-stage diagnosis of EC compared to women from other ethnic groups.[24] Early detection of EC relies on patients recognising symptoms and seeking medical help.[65] Delays in this can result in more advanced disease at diagnosis. Studies have shown that cancer symptom awareness is generally lower among black and ethnic minority women, and black women face additional barriers, such as lack of confidence in discussing symptoms, embarrassment about gynaecological symptoms, and reliance on traditional remedies, which can further delay diagnosis.[65]

The diagnostic method for EC, transvaginal ultrasound, is less reliable when fibroids are present and for high-risk, non-endometrioid EC tumours, both of which are more common in black women, potentially leading to missed or delayed diagnoses in black women.[65] Additionally, a UK study found that black patients have a higher likelihood of needing three or more GP consultations before being referred to a hospital for cancer symptoms indicating a provider-driven diagnostic delay for these patients.[65]

Women from deprived backgrounds and black women face higher incidence rates, advanced stage diagnosis and poorer outcomes. This underscores the urgent need to provide effective treatments for EC. Access to new efficacious treatment options for EC can help to address the significant disparities in survival rates among patients of different socio-economic status or ethnic backgrounds.

B.2. Clinical effectiveness

Summary of key points:

Study identification

- A clinical systematic literature review (SLR) identified one published study (KEYNOTE-868 [NRG-GY018]; 5 publications) that provided direct efficacy and safety evidence for pembrolizumab + chemotherapy followed by pembrolizumab maintenance in the first-line treatment of advanced or recurrent EC
- KEYNOTE-868 (NRG-GY018) is an ongoing Phase III, global, double-blind, randomised, placebo-controlled trial investigating the efficacy and safety of treatment with pembrolizumab + CT compared with placebo + CT in patients with advanced or recurrent EC, and is the pivotal trial providing evidence in this submission[6,66]

KEYNOTE-868 (NRG-GY018)

Efficacy

- At the Interim Analysis (IA; December 2022 data-cut), pembrolizumab + CT demonstrated a statistically significant improvement in progression-free survival (PFS) in both dMMR and pMMR cohorts (dMMR hazard ratio [HR] 0.34 [95% CI: 0.22, 0.53]; pMMR HR: 0.57 [95% CI: 0.44, 0.74]).[6]
- At the August 2023 data cut-off (9 months of additional follow-up; median duration of follow-up [redacted]), pembrolizumab + CT demonstrated superior efficacy when compared with placebo + CT in the all-comer population[67]
    - An improvement of [redacted] in PFS: [redacted] versus [redacted] (hazard ratio [HR]: [redacted]; 95% confidence interval [CI]: [redacted]), representing a [redacted] reduction in the risk of disease progression or death, supporting the results observed at the IA
    - OS HR: 0.74 (95% CI: 0.57, 0.97; one-sided nominal p = 0.0153) in favour of pembrolizumab + CT, representing a 26% reduction in the risk of death
    - Objective response rate (ORR): 75.2% versus 62.6%, with an estimated treatment difference of 12.4% (95% CI: 5.4, 19.4; nominal one-sided p = 0.00029)
    - Median duration of response (DOR): 12.1 months versus 6.2 months

- The results from subgroup analyses were generally consistent with the primary analysis across key demographic subgroups for pembrolizumab + CT compared to placebo + CT[67]

HRQoL

- Overall, [redacted][66]

Safety

- As of the August 2023 data cut-off, the types and incidences of adverse events (AEs) and serious AEs were generally consistent with the established individual safety profiles of pembrolizumab monotherapy and the CT regimen.[66] No new safety concerns were identified

B.2.1. Identification and selection of relevant studies

An SLR was conducted to identify and select evidence of the efficacy and safety of interventions used in the UK for the first-line treatment of advanced or recurrent EC.

The searches were executed on 02 April 2024 with predefined search strategies. A total of 13,644 potentially relevant papers or abstracts were identified through database searches. Only one published study (5 publications) was deemed relevant to this submission based on the criteria defined in the NICE scope, aligning to the patient population outlined by the anticipated marketing authorisation (Table 1). The study identified was the KEYNOTE-868 (NRG-GY018) trial. Full details on the SLR are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

Details of the pembrolizumab + CT clinical effectiveness evidence are provided in Table 3.

The KEYNOTE-868 (NRG-GY018) trial (ClinicalTrials.gov number: NCT03914612) is the pivotal trial providing evidence of the clinical benefits of pembrolizumab + CT in this submission.[55] KEYNOTE-868 (NRG-GY018) is a Phase III trial comparing the efficacy and safety of pembrolizumab + CT followed by pembrolizumab maintenance versus placebo + CT in adults with advanced or recurrent EC.

Table 3: Clinical effectiveness evidence

Trial	KEYNOTE-868 (NRG-GY018)
Trial title	A Phase III Randomized, Placebo-controlled Study of Pembrolizumab in Addition to Paclitaxel and Carboplatin for

	Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer
Trial number	NCT03914612
Study design	Phase III, randomised, placebo-controlled, multicentre
Population	Patients with advanced or recurrent endometrial cancer
Intervention(s)	Pembrolizumab + CT (paclitaxel + carboplatin) and pembrolizumab maintenance
Comparator(s)	Paclitaxel + carboplatin
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	The following outcomes are reported: • **PFS** • ORR • DOR • **OS** • HRQoL • Safety The hypotheses for each of the outcomes were duplicated to cover the two cohorts (dMMR and pMMR).
All other reported outcomes	• PFS2

Key: CSR, clinical study report; CT, chemotherapy; dMMR, mismatch repair deficient; DOR, duration of response; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient.

Notes: Bolded outcomes represent those incorporated in the model.

Source: Eskander et al. 2023[6]; KEYNOTE-868 (NRG-GY018) CSR.[66]

The trial was designed to assess treatment outcomes in the all-comer population as two separate cohorts depending on MMR status: patients with dMMR disease and patients with pMMR disease (refer to Section B.2.3). The data for the key primary and secondary endpoints for the pMMR and dMMR cohorts from the pre-specified interim analysis (data-cut dated December 2022) is presented in Appendix E. An Efficacy and Safety Update was generated based on an August 2023 data cut, which includes approximately 9 months of additional follow-up data since the interim analysis. Post-hoc analyses were conducted to

analyse the all-comer population (comprising both cohorts of dMMR and pMMR patients). MSD consider this to be the appropriate population to reflect the decision problem, aligning with the anticipated marketing authorisation.

Table 4 summarises the analyses of KEYNOTE-868 (NRG-GY018), the data reported for each analysis, and the location in the submission. In section B.2 all tables (with the exception of HRQoL) present data from the Efficacy and Safety Update (August 2023 data-cut) for the all-comer population. The subgroup data for the pMMR and dMMR cohorts, from the Efficacy and Safety Update (August 2023 data cut) are presented in Appendix E.

Table 4: KEYNOTE (NRG-GY018) analyses and data reported

Analysis	Population	Data cut-off dates	Outcomes reported in this submission	Location
Efficacy and Safety Update	All-comer population	18 August 2023	PFS	B.2.6.1
			OS	B.2.6.2
			ORR	B.2.6.2
			DOR	B.2.6.2
			Safety	B.2.10
	pMMR cohort	18 August 2023	PFS	Appendix E
			OS	Appendix E
			ORR	Appendix E
			DOR	Appendix E
			Safety	Appendix E
	dMMR cohort	18 August 2023	PFS	Appendix E
			OS	Appendix E
			ORR	Appendix E
			DOR	Appendix E
			Safety	Appendix E
Interim Analysis	pMMR cohort	16 December 2022	HRQoL	B.2.6.4
			PFS	Appendix E
			OS	Appendix E
	dMMR cohort	6 December 2022	PFS	Appendix E
			OS	Appendix E

Key: dMMR, mismatch repair deficient; DOR, duration of response; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient.

B.2.3. Summary of methodology of KEYNOTE-868 (NRG-GY018)

B.2.3.1. Trial design

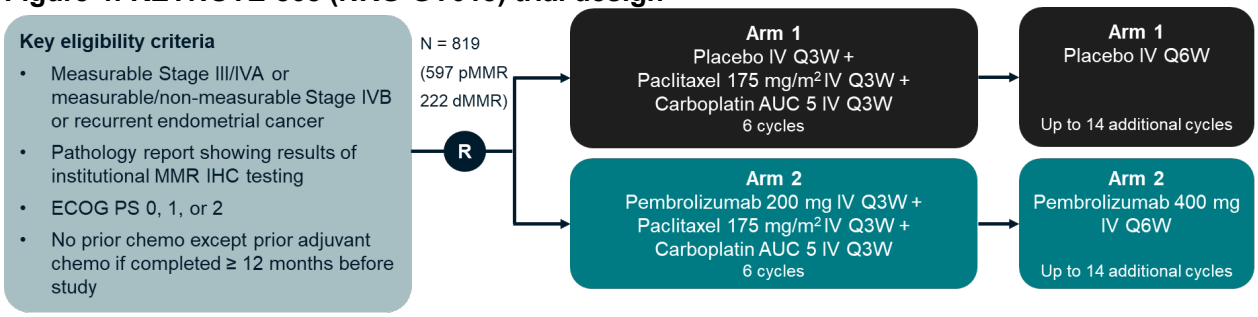
A summary of the trial methodology for KEYNOTE-868 (NRG-GY018) is presented in Table 5.

KEYNOTE-868 (NRG-GY018) is an ongoing Phase III, international, double-blind, randomised, placebo-controlled trial investigating the efficacy and safety of treatment with pembrolizumab + CT compared with placebo + CT in patients with advanced or recurrent EC.[6,66] The treatments were analysed in two independent cohorts: patients with dMMR disease and patients with pMMR disease. The population of the decision problem, outlined in Table 1, is the all-comer population, in line with the anticipated marketing authorisation. Therefore, post-hoc analyses were conducted to analyse the all-comer population to support the submission.

The primary objective/hypothesis was to demonstrate that treatment with pembrolizumab + CT is superior to placebo + CT in improving progression-free survival (PFS). The study is being conducted at 217 centres in four countries (the US, Canada, Japan and South Korea).[6]

A schematic of the trial design is presented in Figure 4.

Figure 4: KEYNOTE-868 (NRG-GY018) trial design



Key: AUC, area under the curve; CSR, clinical study report; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; pMMR, mismatch repair proficient; PS, performance status; Q3W, every 3 weeks; Q6W, every 6 weeks.

Source: Eskander et al. 2023[6] and KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update.[68]

To be eligible for the trial, patients had to have confirmed MMR status through the submission of the results of institutional or local immunohistochemical analysis of MMR status for examination in a central laboratory.[6,66] An inconclusive test would require repeat testing. The test results determined which cohort the patients were in; either the dMMR or pMMR cohort. The focus of this submission is the all-comer population, as per the NICE decision problem; outcomes for the separate cohorts are available in Appendix E. In addition, to be eligible for the trial, patients had to have measurable Stage III/IVA EC or measurable/non-measurable Stage IVB or recurrent EC, ECOG PS 0, 1 or 2, and no prior CT except prior adjuvant CT if completed ≥ 12 months before the study.[6,66] Full details of the inclusion/exclusion criteria of KEYNOTE-868 (NRG-GY018) can be found in Appendix M.

Eligible patients were stratified by MMR status (dMMR yes or no), ECOG PS (0 or 1 versus 2), and receipt of prior CT (yes or no), and were randomly assigned in a 1:1 ratio to receive one of the following treatment arms:

- Placebo + CT (paclitaxel + carboplatin) combination phase followed by placebo monotherapy maintenance phase
- Pembrolizumab + CT (paclitaxel + carboplatin) combination phase followed by pembrolizumab monotherapy maintenance phase

In the combination phase, patients in the placebo + CT treatment group received placebo intravenous (IV) over 30 minutes on Day 1 of each cycle, paclitaxel IV over 3 hours on Day 1 of each cycle, and carboplatin IV over 30–60 minutes on Day 1 of each cycle.[6,66] Patients in the pembrolizumab + CT treatment arm received 200 mg pembrolizumab IV over 30 minutes on Day 1 of each cycle, paclitaxel IV over 3 hours on Day 1 of each cycle, and carboplatin IV over 30-60 minutes on Day 1 of each cycle. For both treatment arms, the treatment was repeated every 3 weeks for six cycles in the absence of disease progression or unacceptable toxicity. Patients with stable disease or partial response who still had measurable disease could continue treatment for up to a total of 10 cycles (if deemed necessary by the treating physician) in the absence of disease progression or unacceptable toxicity.[6,66]

In the maintenance phase, patients in the placebo + CT treatment group received placebo IV over 30 minutes on Day 1 of each cycle, and patients in the pembrolizumab + CT treatment arm received 400 mg pembrolizumab IV over 30 minutes on Day 1 of each cycle.[66] For both treatment groups, the maintenance treatment was initiated 3 weeks after the last chemotherapy dose and was repeated every 6 weeks for up to 14 cycles in the absence of disease progression or unacceptable toxicity.

For simplicity, throughout the submission the study arms are referred to as pembrolizumab + CT and placebo + CT. This is intended to be reflective of the study design which includes the optional maintenance phase per study arm, as described above.

Table 5 presents an overview of the methodology of the KEYNOTE-868 (NRG-GY018) trial.

Table 5: Summary of the KEYNOTE-868 (NRG-GY018) trial methodology

Study name	KEYNOTE-868 (NRG-GY018)
Trial design	Phase III, international, double-blind, randomised, placebo-controlled trial
Eligibility criteria for participants	**Key eligibility criteria:** Eligible patients were female, at least 18 years of age, with an ECOG PS of 0, 1 or 2 and adequate organ function as defined

	in Section 3 of the study protocol, who had EC with protocol-specified disease characteristics and met testing requirements for tumour specimens at baseline, as follows: • Stage III or Stage IVA EC, each with measurable disease per RECIST Version 1.1 or Stage IVB or recurrent EC, each with or without measurable disease[a] • Pathology report confirming one of the following histologic subtypes for the original primary tumour: ECC, SC, dedifferentiated/undifferentiated carcinoma, CCC, mixed epithelial carcinoma, or adenocarcinoma not otherwise specified • Pathology report with results of institutional (local) MMR IHC testing • Submission of tumour tissue for centralised MMR IHC testing and PD-L1 IHC testing Patients may have received: • No prior chemotherapy for treatment of EC or • Prior adjuvant chemotherapy (e.g. paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥12 months prior to trial registration Prior radiation therapy for treatment of EC (including pelvic radiation therapy, extended field pelvic/para aortic radiation therapy, and/or intravaginal brachytherapy) provided it was completed ≥4 weeks prior to trial registration
Settings and locations where the data were collected	The trial was conducted at 217 sites in four countries (the US, Canada, Japan and South Korea)
Trial drugs	**Intervention** • Six cycles: pembrolizumab 200 mg IV Q3W + paclitaxel 175 mg/m^2 IV Q3W + carboplatin AUC 5 IV Q3W. Followed by up to 14 additional cycles: pembrolizumab 400 mg IV Q6W **Comparator** • Six cycles: placebo IV Q3W + paclitaxel 175 mg/m^2 IV Q3W + carboplatin AUC 5 IV Q3W. Followed by up to 14 additional cycles: placebo IV Q6W
Primary outcome	PFS, assessed by investigators according to RECIST Version 1.1
Key secondary outcomes	• OS • ORR • DOR • Concordance between institutional versus central MMR IHC testing results • Safety • HRQoL

Other outcomes used in the economic model/specified in the scope	• Time to treatment discontinuation (TTD)
Pre-planned subgroups	• Age • Race • ECOG PS • Histology • Prior CT • Prior radiation therapy • Measurable disease at baseline • Status of disease

Key: AUC, area under the curve; CCC, clear cell carcinoma; CSR, clinical study report; CT, chemotherapy; DOR, duration of response; EC, endometrial cancer; ECC, endometrioid carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST Version 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; SC, serous adenocarcinoma.

Notes: [a] Measurable disease was defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by computed tomography or magnetic resonance imaging. Lymph nodes must be ≥ 15 mm in short axis when measured by either diagnostic imaging procedure.

Source : Eskander et al. 2023[6] ; KEYNOTE-868 (NRG-GY018) CSR.[66]

B.2.3.2. Outcomes assessed

The primary outcome was PFS, assessed by investigators according to the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria. Key secondary outcomes included safety, overall survival (OS), objective response rate (ORR) assessed by RECIST Version 1.1 criteria, duration of response (DOR), concordance between institutional versus central MMR immunohistochemistry testing, and HRQoL.[6,66] HRQoL was measured by the Trial Outcome Index of the Functional Assessment of Cancer Therapy–Endometrial (FACT-En-TOI), the short form of the Patient-Reported Outcomes Measurement Information System (PROMIS)–Fatigue, and the short form of the PROMIS–Physical Function. PFS on next-line therapy (PFS2), was analysed as an exploratory endpoint to support the efficacy results.

As discussed in Section B.2.2, the trial was designed to assess treatment outcomes in two separate cohorts (dMMR and pMMR). In the interim analysis (data cut December 2022) all outcomes were examined and reported separately as the dMMR and pMMR cohorts, apart from HRQoL assessments which were performed only in the pMMR cohort. Post-hoc analyses, based on data from the Efficacy and Safety Update (August 2023 data cut) were conducted to analyse the all-comer population. This is the appropriate analysis that reflects the decision problem, as presented in Table 1. In Section B.2, all tables (with the exception

of HRQoL) present data from the Efficacy and Safety Update (August 2023 data-cut) for the all-comer population. The subgroup data for the pMMR and dMMR cohorts, from both the Efficacy and Safety Update (August 2023 data cut) and the interim analysis (December 2022 data cut) are presented in Appendix E.

B.2.3.3. Baseline demographics and disease characteristics of trial participants

The baseline demographics and disease characteristics for the all-comer population of the KEYNOTE-868 (NRG-GY018) trial are presented in Table 6.

The demographic characteristics, along with clinical and pathological factors, were well balanced between patients in the pembrolizumab + CT and placebo + CT groups. All patients were female, with a median age of 66.1 years, and most patients were White, non-Hispanic or Latino, and had an ECOG PS of 0 or 1. Additionally, the majority of patients had no prior CT, but had prior surgery. The most common histologic subtypes of EC in both treatment arms were endometrioid adenocarcinoma (Grades 1–3) and serous adenocarcinoma (note patients with carcinosarcomas were not eligible for the trial). UK clinical experts have confirmed that the KEYNOTE-868 (NRG-GY018) trial population is broadly similar to the patients seen in real-world clinical practice.[3]

Table 6: Baseline demographics and disease characteristics (Efficacy and Safety Update, data cut: August 2023)

Characteristic	All-comer population		
	Pembrolizumab + CT (n = 408)	Placebo + CT (n = 411)	Total (n = 819)
Age, median (range), years	66.3 (31 to 94)	66.0 (29 to 91)	66.1 (29 to 94)
Race, n (%)			
White	307 (75.2)	300 (73.0)	607 (74.1)
Black or African American	56 (13.7)	60 (14.6)	116 (14.2)
Asian	20 (4.9)	19 (4.6)	39 (4.8)
Other	4 (0.9)	8 (1.9)	12 (2.8)
Missing	21 (5.1)	24 (5.8)	45 (5.5)
Ethnicity, n (%)			
Non-Hispanic/non-Latino	371 (90.9)	375 (91.2)	746 (91.1)
Hispanic/Latino	27 (6.6)	22 (5.4)	49 (6.0)
Not reported	5 (1.2)	7 (1.7)	12 (1.5)
Unknown	5 (1.2)	7 (1.7)	12 (1.5)
ECOG PS, n (%)			
0	270 (66.2)	273 (66.4)	543 (66.3)
1	128 (31.4)	124 (30.2)	252 (30.8)
2	10 (2.5)	14 (3.4)	24 (2.9)
Histology			

Characteristic	All-comer population		
	Pembrolizumab + CT (n = 408)	Placebo + CT (n = 411)	Total (n = 819)
Adenocarcinoma, NOS	36 (8.8)	47 (11.4)	83 (10.1)
Clear cell	19 (4.7)	20 (4.9)	39 (4.8)
Dedifferentiated/ undifferentiated	11 (2.7)	10 (2.4)	21 (2.6)
Endometrioid, G1	76 (18.6)	80 (19.5)	156 (19.0)
Endometrioid, G2	104 (25.5)	102 (24.8)	206 (25.2)
Endometrioid, G3	68 (16.7)	61 (14.8)	126 (15.8)
Mixed epithelial	9 (2.2)	12 (2.9)	21 (2.6)
Serous	85 (20.8)	78 (19.0)	163 (19.9)
MMR status, n (%)			
pMMR	291 (71.3)	295 (71.8)	586 (71.6)
dMMR	111 (27.2)	112 (27.3)	223 (27.2)
No prior chemotherapy, n (%)	329 (80.6)	326 (79.3)	665 (80.0)
No prior radiotherapy, n (%)	246 (60.3)	231 (56.2)	477 (58.2)

Key: CT, chemotherapy; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; MMR, mismatch repair; NOS, not otherwise specified; pMMR, mismatch repair proficient.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (All-comer Disposition, Demographics and Concomitant Medications).[68]

B.2.4. Statistical analysis and definition of study groups in KEYNOTE-868 (NRG-GY018)

B.2.4.1. Analysis populations

The analysis population sets in the KEYNOTE-868 (NRG-GY018) trial are presented and defined in Table 7. Efficacy analyses were based on the Intention-to-Treat (ITT) population for the overall trial population (all-comer patients), including all patients who were randomised before the data cut-off dates.[68] Safety analyses were based on the All-Participants-as-Treated (APaT) population for the overall trial population, including all randomised patients who received at least one dose of study treatment.[68] The patient-reported outcomes (PRO) analyses were based on the pMMR Full Analysis Set (FAS) population, defined as pMMR patients including all randomised patients who received at least one dose of study treatment and who provided a valid baseline PRO assessment and at least one follow-up PRO assessment.[68]

Table 7: KEYNOTE-868 (NRG-GY018) analysis sets

	Definition		Number of patients

Analysis set		Outcome	Pembrolizumab + CT	Placebo + CT	Total
ITT	All randomised patients are included in this population	Efficacy	408	411	819
ApaT	All randomised patients who received at least one dose of study treatment are included in this population	Safety	391	388	779
pMMR FAS	pMMR patients who received at least one dose of study treatment, and provided a valid baseline PRO assessment and at least one follow-up PRO assessment	HRQoL	268	266	534

Key: ApaT, All-Participants-as-Treated; CT, chemotherapy; FAS, full analysis set; HRQoL, health-related quality of life; ITT, Intention-to-Treat.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (All-comer Disposition, Demographics and Concomitant Medications).[68]

B.2.4.2. Statistical methods

A summary of statistical analyses conducted for the KEYNOTE-868 (NRG-GY018) trial is presented in Table 8.

Interim analysis of KEYNOTE-868 (NRG-GY018) occurred after accrual of the study participants was complete and at least 50% information fraction of target final PFS events were observed. In the interim analysis (December 2022 data cut) efficacy and safety were analysed and reported separately for the pMMR and dMMR cohorts. Statistical considerations related to KEYNOTE-868 (NRG-GY018) are summarised in Table 8.

Details of the methods presented here are for the Efficacy and Safety Update analyses (August 2023 data cut) for the all-comer population. Additional details on the statistical methods used for the interim analyses of the dMMR and pMMR cohorts are available in the statistical analysis plan.[69]

Table 8: Summary of statistical analyses

Hypothesis (primary) objective	To evaluate the efficacy of pembrolizumab in combination with paclitaxel and carboplatin in patients with advanced stage (measurable Stage III or IVA), Stage IVB and recurrent endometrial cancer. Efficacy will be determined via investigator assessed progression free survival (PFS) as assessed by RECIST 1.1 in two distinct populations referred to as proficient and deficient mismatch repair (pMMR and dMMR).
Statistical analysis	For time-to-event endpoints (OS, PFS and PFS2), the Kaplan–Meier method was used to estimate the survival curves. To assess treatment difference (HR), a Cox proportional hazard model was applied, with treatment as covariate, and stratified by MMR status (pMMR versus dMMR) and prior CT (yes versus no). One-sided p-values were based on a stratified log-rank test. Since the analysis includes both dMMR and pMMR populations, the Cox

	model is stratified by MMR status and prior CT. The ECOG PS was not included as a stratification factor due to the low number of participants with ECOG PS 2 (2.9% of all comer population). The Stratified Miettinen and Nurminen method was used to compare the ORRs between the treatment arms, stratified by MMR status and prior CT. A 95% CI for the difference in response rates and a one-sided p-value for testing that the risk difference is equal to zero are provided. Time to response is summarised descriptively using mean and median times for each treatment group. DOR is summarised descriptively using Kaplan–Meier medians and quartiles by treatment and graphically by Kaplan–Meier plots For the safety data, no formal testing is done, only frequencies and percentages are provided for Aes. Aes are summarised according to category of AE (any AE, adverse event of special interest) and Grade 3–5. To account for the potential difference in follow-up time and duration of exposure between treatment arms, AE incidence adjusted for treatment exposure analyses are provided, based on the total number of events (recurrent event is also counted) ×100/person-months exposure
Sample size, power calculation	As the Efficacy and Safety Update analyses was a post-hoc analyses; the sample size power calculation is relevant to the interim analysis. Approximately 590 patients were planned to be enrolled in the pMMR cohort and 220 were planned to be enrolled in the dMMR cohort. In the control arm, PFS and OS in both MMR populations are assumed to follow the survival models below: $S_{PFS}(t) = 0.9 \times e^{-0.07t} + 0.1$ $S_{OS}(t) = 0.9 \times e^{-0.003244t} + 0.1$ The numerical model corresponds to a median survival of 11.6 months for PFS and 25 months for OS. Proportional treatment hazards are assumed. A HR of PFS is assumed to be 0.7 in the treatment arm relative to the control arm for the pMMR population, and 0.6 in the dMMR population. HR of OS is assumed to be 0.7 in both MMR populations. With initial alpha allocation, 394 PFS events in the pMMR population provide 90% power. A total of 168 PFS events in the dMMR population provide 85% power. At interim efficacy analysis, power was expected to be 58% and 50% for pMMR and dMMR populations, respectively. No dropout was assumed for the power calculation for each MMR population
Data management, patient withdrawals	Patients who discontinued treatment for unacceptable AE(s) were followed until resolution or stabilisation of the AE. In the case that protocol-directed therapy was discontinued for reasons other than disease progression, the radiographic tumour measurement schedule as defined under Assessments During Treatment was followed (until disease progression documented by RECIST Version 1.1, or until the patient initiated a subsequent cancer therapy)

Key: AE, adverse event; CI, confidence interval; CT, chemotherapy; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MMR, mismatch repair; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on next-line therapy; pMMR, mismatch repair proficient; RECIST Version 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer efficacy).[68]

B.2.4.3. Patient flow

A summary of the patient disposition data for all-comer patients is presented in Table 9. The trial enrolled 819 patients, of which 408 were randomly assigned to receive pembrolizumab + CT, and 411 to receive placebo + CT. Note that nine of these patients from the pMMR group who were enrolled on or before the enrolment closing date (6 December 2022) were randomised after the IA data cut-off date and are therefore not included in the IA results. At the Efficacy and Safety Update analyses (August 2023 data cut), of the randomised patients, [redacted] patients in the pembrolizumab + CT arm, and [redacted] patients in the placebo + CT arm had discontinued the trial; and [redacted] patients in the pembrolizumab + CT arm, and [redacted] patients in the placebo + CT arm are ongoing in the study.

For the Efficacy and Safety Update analysis, at the time of data cut-off (August 2023), [redacted] patients in the pembrolizumab + CT arm, and [redacted] patients in the placebo + CT arm, received the study intervention, of which: [redacted] patients in the pembrolizumab + CT arm and six patients in the placebo + CT arm completed the study intervention; [redacted] patients in the pembrolizumab + CT arm and [redacted] patients in the placebo + CT arm discontinued; and [redacted] patients in the pembrolizumab + CT arm and three patients in the placebo + CT arm are continuing to receive the study treatment. The primary reason for discontinuation of treatment was disease progression ([redacted] patients in the pembrolizumab + CT arm and [redacted] patients in the placebo + CT arm). In the placebo + CT arm, another major reason for discontinuation was due to unblinding of trial participants after PFS was met at the interim analysis. A large number of patients ([redacted]) listed 'other' as the reason for discontinuation and the majority of patients in this category discontinued as a result of unblinding ([redacted] in total; [redacted] in the pMMR cohort and [redacted] in the dMMR cohort).[68]

The patient disposition data at the interim analysis of the separate dMMR and pMMR cohorts is presented in Appendix E.

Table 9: Disposition of all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Status for trial		
Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Subject decision to withdraw from study	[redacted]	[redacted]
Other	[redacted]	[redacted]

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Ongoing	[redacted]	[redacted]
Status for study medication in trial		
Started	[redacted]	[redacted]
Completed	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]
AE/complication	[redacted]	[redacted]
Agent not given, no sensitivity to paclitaxel	[redacted]	[redacted]
Alternative therapy (in absence of progression)	[redacted]	[redacted]
Death on study	[redacted]	[redacted]
Disease progression, relapse during active treatment	[redacted]	[redacted]
Patient off-treatment for other complicating disease	[redacted]	[redacted]
Patient withdrawal/refusal after beginning protocol therapy	[redacted]	[redacted]
Symptomatic deterioration	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]

Key: AE, adverse event; CT, chemotherapy; ITT, Intention-to-Treat.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (All-comer Disposition, Demographics and Concomitant Medications)[68]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The Cochrane collaboration's risk of bias tool version 2 was used to assess the risk of bias for KEYNOTE-868 (NRG-GY018). The trial has low risks of bias across the five domains of the Cochrane risk of bias assessment, and therefore is assessed to have an overall low risk of bias.

Full details are provided in Appendix D.

B.2.6. Clinical effectiveness results of the KEYNOTE-868 (NRG-GY018) trial

The efficacy results presented are from the Efficacy and Safety Update based on an August 2023 data cut, unless stated otherwise.[67] The results presented are for the all-comer

population; data for the separate pMMR/dMMR cohorts from the Efficacy and Safety Update and the interim analysis are presented in Appendix E.

B.2.6.1. Primary endpoint: Progression-free survival

At the Interim Analysis (December 2022 data-cut), pembrolizumab + CT provided a statistically significant improvement in PFS in both dMMR and pMMR cohorts. In the pMMR cohort, the hazard ratio (HR) was 0.57 (95% CI: 0.44, 0.74) in favour of pembrolizumab + CT, representing a 43% reduction in the risk of disease progression or death.[6] In the dMMR cohort, the HR was 0.34 (95% CI: 0.22, 0.53) in favour of pembrolizumab + CT, representing a 66% reduction in the risk of disease progression or death.[6] The full PFS results from the interim analysis can be found in Appendix E.

This was further supported by the additional analysis of the all-comer population from the Efficacy and Safety Update (August 2023 data-cut). As statistical significance was met at the IA, no formal hypothesis testing was conducted for the PFS results in the Efficacy and Safety Update and therefore p-values are nominal. Table 10 presents the results for PFS for the all-comer population ITT analysis set of the KEYNOTE-868 (NRG-GY018) trial from the Efficacy and Safety Update. Progression-free survival determined by investigator review is defined as the time from the date of randomisation to the date of the first disease progression or death (whichever occurs first).

Pembrolizumab + CT continued to demonstrate an improvement in PFS compared with placebo + CT.[67] The median PFS was [redacted] in the pembrolizumab + CT group and [redacted] in the placebo + CT group. The PFS HR of [redacted], represents a [redacted] relative reduction in the risk of disease progression or death when treated with pembrolizumab + CT compared to placebo + CT. PFS rates were higher in the pembrolizumab + CT group compared with the placebo + CT group at 12 months [redacted] and 36 months [redacted].[67]

Table 10: Analysis of PFS based on investigator assessment per RECIST 1.1 (primary protocol censoring rule) in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)[a]	[redacted]	[redacted]
PFS HR (95% CI)[b]	[redacted]	
Nominal p-value[c]	[redacted]	
PFS rate at month 6, % (95% CI)	[redacted]	[redacted]
PFS rate at month 12, % (95% CI)	[redacted]	[redacted]

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	Placebo + CT (n = 411)
PFS rate at month 18, % (95% CI)	[redacted]	[redacted]
PFS rate at month 24, % (95% CI)	[redacted]	[redacted]
PFS rate at month 30, % (95% CI)	[redacted]	[redacted]
PFS rate at month 36, % (95% CI)	[redacted]	[redacted]

Key: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, Intention-to-Treat; PFS, progression-free survival.

Notes: a From product-limit (Kaplan–Meier) method for censored data.

B Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status and prior chemotherapy.

C One-sided p-value based on log-rank test stratified by MMR status and prior chemotherapy.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer efficacy).[67]

As presented in Figure 5, the Kaplan–Meier curves for pembrolizumab + CT and placebo + CT separated at [redacted] and remained separated over time in favour of pembrolizumab + CT. PFS in both arms begins to plateau at approximately [redacted].

Figure 5: PFS based on investigator assessment per RECIST Version 1.1 (primary protocol censoring rule) (in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

[redacted]**Key:** ITT, Intention-to-Treat; PFS, progression-free survival; RECIST Version 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer efficacy).[67]

As the trial met the pre-specified endpoint at the interim analysis, all patients were unblinded in [redacted] and were able to switch from their assigned treatment. Therefore, almost all patients in the placebo + CT arm who remained progression-free discontinued from study treatment. A total of [redacted] patients in the placebo + CT arm received subsequent treatment of some kind prior to progression, of which [redacted] patients received a pembrolizumab-based treatment. It is therefore possible that the PFS for the placebo + CT arm is slightly overestimated which may introduce bias in favour of the CT arm.

B.2.6.2. Secondary efficacy endpoints

Overall survival

Table 11 presents the results for OS for the all-comer population ITT analysis. The OS HR was 0.74 (95% CI: 0.57, 0.97; one-sided nominal p = 0.0153) in favour of pembrolizumab + CT, representing a 26% reduction in the risk of death.

As presented in Figure 6, the Kaplan–Meier OS curves for pembrolizumab + CT and placebo + CT separated early before Month 6, and remained separated over time in favour of pembrolizumab + CT.

The median OS by Kaplan–Meier estimation was not reached for pembrolizumab + CT. OS rates were higher in the pembrolizumab + CT group compared with the placebo + CT group at 18 months (75.8% versus 69.2%) and 42 months (59.8% versus 36.7%).

Table 11: Analysis of OS in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Number of events, n (%)	94 (23.0)	119 (29.0)
Median OS, months (95% CI)[a]	NR (NR, NR)	32.2 (27.4, 42.7)
OS HR (95% CI)[b]	0.74 (0.57, 0.97)	
Nominal p-value[c]	0.0153	
OS rate at month 6, % (95% CI)	95.2 (92.6, 96.9)	93.7 (90.8, 95.7)
OS rate at month 12, % (95% CI)	86.1 (82.1, 89.2)	82.5 (78.2, 86.0)
OS rate at month 18, % (95% CI)	75.8 (70.3, 80.4)	69.2 (63.4, 74.2)
OS rate at month 24, % (95% CI)	68.9 (62.4, 74.5)	62.3 (55.8, 68.1)
OS rate at month 30, % (95% CI)	59.8 (50.9, 67.6)	51.7 (42.1, 60.4)
OS rate at month 36, % (95% CI)	59.8 (50.9, 67.6)	45.9 (34.6, 56.5)
OS Rate at month 42 (%) (95% CI)	59.8 (50.9, 67.6)	36.7 (19.2, 54.5)

Key: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, Intention-to-Treat; NR, not reached; OS, overall survival.

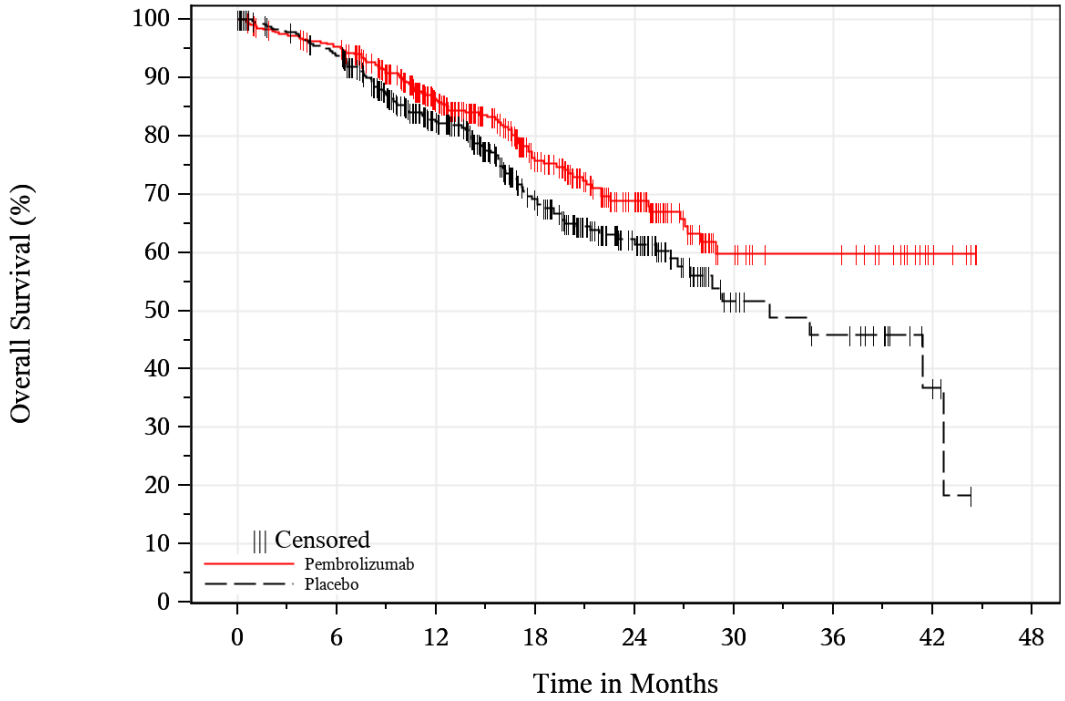
a From product-limit (Kaplan-Meier) method for censored data.

b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status and prior chemotherapy.

c One-sided p-value based on log-rank test stratified by MMR status and prior chemotherapy.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

Figure 6: OS in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)



Number of Participants at Risk

Pembrolizumab	408	377	262	147	84	28	21	7	0
Placebo	411	368	241	139	71	21	15	4	0

Key: ITT, Intention-to-Treat; OS, overall survival.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

Objective response rate

The results for ORR and best overall response per RECIST Version 1.1 by investigator assessment for the all-comer population ITT analysis set of the KEYNOTE-868 (NRG-GY018) trial are presented in Table 12 and Table 13, respectively. Patients with measurable disease at baseline were included in the ORR analysis: 319 patients in the pembrolizumab + CT group and 334 patients in the placebo + CT group.

In patients with measurable disease at baseline pembrolizumab + CT provided an improvement in ORR compared with placebo + CT. The ORR was higher in the pembrolizumab + CT group (75.2%) compared with the placebo + CT group (62.6%), with an estimated treatment difference of 12.4% (95% CI: 5.4, 19.4; nominal one-sided p = 0.00029). Most of this increase in ORR was driven by the higher proportion of complete responders with pembrolizumab + CT, as the number of partial responders is similar between the pembrolizumab + CT and placebo + CT treatment groups (55.8% and 52.7%, respectively).

Most responses were a partial response, with a complete response of 19.4% in the pembrolizumab + CT group and 9.9% in the placebo + CT group.

Table 12: Analysis of ORR in all-comers population (ITT population with measurable disease at baseline; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 653)	
	Pembrolizumab + CT (n = 319)	**Placebo + CT (n = 334)**
Number of objective responses	240	209
ORR, % (95% CI)	75.2 (70.1, 79.9)	62.6 (57.1, 67.8)
Difference (pembrolizumab + CT versus placebo + CT), %		
Estimate (95% CI)[a]	12.4 (5.4, 19.4)	
Nominal p-value[b]	0.00029	

Key: CI, confidence interval; CT, chemotherapy; ITT, Intention-to-Treat; ORR, objective response rate; OS, overall survival.

Note: Patients who enter the study with no measurable disease are excluded from the ORR calculation.

A Based on Miettinen & Nurminen method by MMR status and prior chemotherapy.

B One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

Table 13: Summary of best overall response in all-comers population (ITT population with measurable disease at baseline; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 653)	
	Pembrolizumab + CT (n = 319)	**Placebo + CT (n = 334)**
CR, n (%)	62 (19.4)	33 (9.9)
Partial response, n (%)	178 (55.8)	176 (52.7)
Overall response, n (%)	240 (75.2)	209 (62.6)
Stable disease n (%)	33 (10.3)	71 (21.3)
Disease control rate (CR + PR + SD ≥ 8 weeks), n (%)	268 (84.0)	273 (81.7)
95% CI	(79.5, 87.9)	(77.2, 85.7)
Clinical benefit (CR + PR + SD ≥ 23 weeks), n (%)	253 (79.3)	231 (69.2)
95% CI	(74.4, 83.6)	(63.9, 74.1)
Progressive disease, n (%)	20 (6.3)	22 (6.6)
Non-evaluable	2 (0.6)	3 (0.9)
No assessment	24 (7.5)	29 (8.7)

Key: CI, confidence interval; CR, complete response; CT, chemotherapy; ITT, Intention-to-Treat; NE, non-evaluable; NR, not reported; PR, partial response; SD, stable disease.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

Duration of response

Table 14 presents the results for DOR and time to response determined by the investigator per RECIST Version 1.1 in all-comer patients with measurable disease at baseline. The median DOR, by Kaplan–Meier estimation, was 5.9 months longer in the pembrolizumab + CT group compared with the placebo + CT group (12.1 months versus 6.2 months). More patients in the pembrolizumab + CT group compared with the placebo + CT group had responses lasting ≥ 6 months (80.7% versus 53.0%, respectively) and ≥ 12 months (50.7% versus 20.8%, respectively) based on Kaplan–Meier estimation. The median time to response was 2.3 months in both treatment groups.

Table 14: Analysis of TTR and DOR in all-comer population with a response (ITT population with measurable disease at baseline; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 653)	
	Pembrolizumab + CT (n = 319)	**Placebo + CT (n = 334)**
Number of patients with response[a]	240	209
Time to response (months)		
Mean (SD)	3.0 (2.0)	2.9 (1.4)
Median (range)	2.3 (1.6–19.6)	2.3 (1.0–14.5)
Response duration[b] (months)		
Median (range)	12.1 (0.0+ - 41.8+)	6.2 (0.0+ - 42.2+)
Number (%[b]) of patients with extended response		
≥ 6 months	168 (80.7)	79 (53.0)
≥ 12 months	66 (50.7)	18 (20.8)
≥ 18 months	38 (44.6)	11 (17.9)
≥ 24 months	15 (41.4)	2 (14.0)

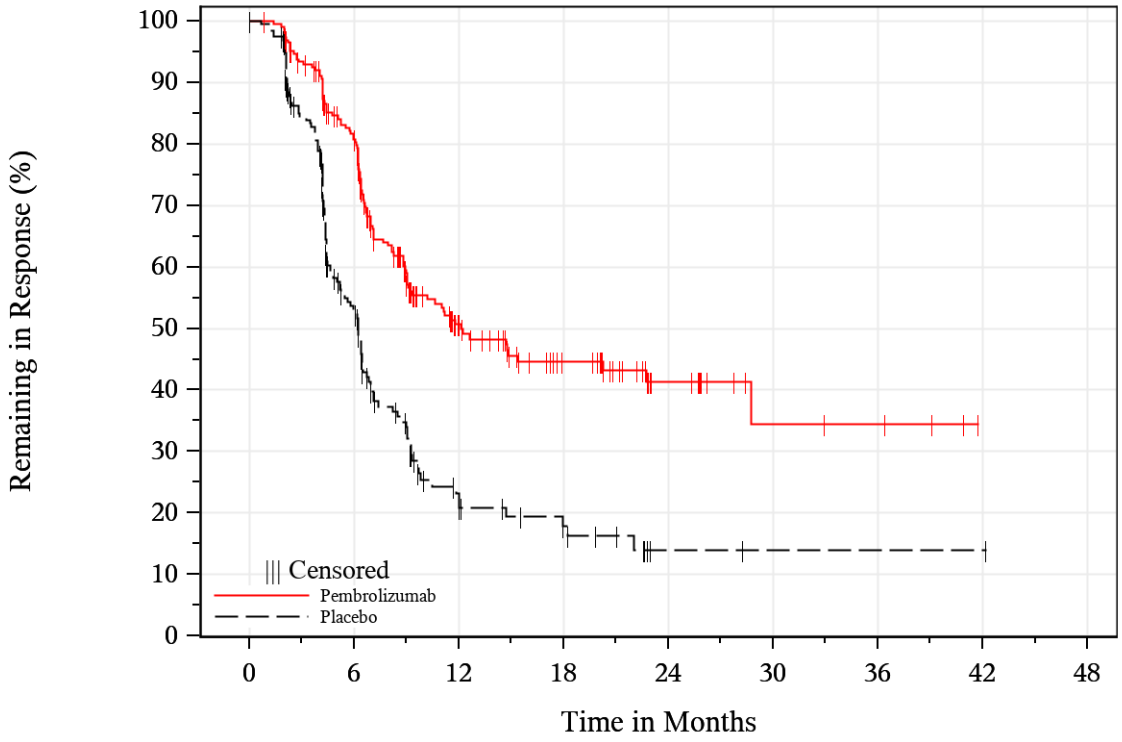
Key: CT, chemotherapy; DOR, duration of response; ITT, Intention-to-Treat; NR, not reported; SD, standard deviation; TTR, time to response.

Notes: [a] Includes patients with complete response or partial response. [b] From product-limit (Kaplan–Meier) method for censored data. "+" indicates there is no progressive disease by the time of last disease assessment.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

As presented in Figure 7, the Kaplan–Meier DOR curves for pembrolizumab + CT and placebo + CT separated early (before month 3), and remained separated over time in favour of pembrolizumab + CT. In both arms, the curves appeared to plateau at around 12 months.

Figure 7: DOR per RECIST Version 1.1 in all-comer patient population (ITT population with measurable disease at baseline; Efficacy and Safety Update; August 2023 data cut)



Number of Participants at Risk

Pembrolizumab	240	168	66	38	15	5	4	0	0
Placebo	209	79	18	11	2	1	1	1	0

Key: DOR, duration of response; ITT, Intention-to-Treat; RECIST Version 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

B.2.6.3. Exploratory endpoints

Progression-free survival on next-line therapy (PFS2), defined as the time from randomisation to disease progression by investigator assessment or death (whichever occurs first) on subsequent anticancer therapy, was analysed as an exploratory endpoint to support the efficacy results. There was an improvement in PFS2 between the pembrolizumab + CT group compared with the placebo + CT group.

Table 15 presents the results for PFS2 for the all-comer population ITT analysis set of the KEYNOTE-868 (NRG-GY018) trial. The HR for PFS2 based on investigator assessment was [redacted], favouring the pembrolizumab + CT group, representing a [redacted] reduction in the risk of progression or death on subsequent anticancer therapy.

Table 15: Analysis of PFS2 based on investigator assessment in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Number of events, n (%)	[redacted]	[redacted]
Median PFS2, months (95% CI)[a]	[redacted]	[redacted]
PFS HR (95% CI)[b]	[redacted]	
Nominal p-value[c]	[redacted]	
PFS rate at month 6, % (95% CI)	[redacted]	[redacted]
PFS rate at month 12, % (95% CI)	[redacted]	[redacted]
PFS rate at month 18, % (95% CI)	[redacted]	[redacted]
PFS rate at month 24, % (95% CI)	[redacted]	[redacted]
PFS rate at month 30, % (95% CI)	[redacted]	[redacted]
PFS rate at month 36, % (95% CI)	[redacted]	[redacted]
PFS rate at month 42, % (95% CI)	[redacted]	[redacted]

Key: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, Intention-to-Treat; NR, not reached; PFS, progression-free survival; PFS2, progression-free survival on next-line therapy.

Notes: a From product-limit (Kaplan–Meier) method for censored data.

b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status and prior chemotherapy.

c One-sided p-value based on log-rank test stratified by MMR status and prior chemotherapy.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

As presented in Figure 8, Kaplan–Meier curves for PSF2 separated at approximately [redacted]

Figure 8: PFS2 per RECIST Version 1.1 in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

[redacted]**Key:** ITT, Intention-to-Treat; PFS2, progression-free survival on next-line therapy; RECIST Version 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy).[67]

B.2.6.4. Patient-reported outcomes in the pMMR population

The PRO analyses presented are from the interim analysis data cut (December 2022). Change from baseline PRO data were collected using both disease-specific and generic instruments, including FACT-En-TOI, FACT/Gynecologic Oncology Group-Neurotoxicity (GOG-NTX), and PROMIS-Fatigue Scale (short form), and PROMIS-Physical Function Scale (short form). These PROs were collected from only pMMR patients at Week 0, 6, 18, 30, and 54. The choice of these time points allow for collection of PROs to reflect key trial landmarks, as presented in Table 16.

Table 16: Rationale for PRO collection time points

Time points	Rationale for time points
Week 0	Baseline measurement to assess status pre-treatment
Week 6	Examine active treatment differences, in which patients may start to respond to treatment, and AEs may or may not differ between arms yet
Week 18	Start of maintenance phase
Week 30	May indicate chemotherapy recovery phase since patients would have been 15 weeks from the last cytotoxic therapy
Week 54	May represent expected median PFS

Key: AE, adverse event; PFS, progression-free survival; PRO, patient-reported outcome.

There were high completion rates for all the PRO instruments at baseline to Week 54 across both groups (range: 84.9–97.0%). In both arms, completion rates decreased over time due to discontinuations from study. However, compliance rates (a measure of completion rates amongst patients who were expected to complete the questionnaire at a given timepoint) remained consistently high (>80%) over time, ranging from 84.9-98.5% in the pembrolizumab + CT group and 88.4-98.8% in the placebo + CT group.

Both treatment groups had [redacted] in the FACT-En-TOI, PROMIS-Physical Function Scale (short form) score, and PROMIS-Fatigue Scale (short form) score. Overall, [redacted] in overall quality of life (QoL), physical function, and fatigue were observed between groups. Table 17 presents the change from baseline to Week 18 in FACT-En-TOI, PROMIS-Physical Function Scale, and PROMIS-Fatigue Scale.

Table 17: Change from baseline to week 18 in FACT-En-TOI, PROMIS-Physical Function Scale, and PROMIS-Fatigue Scale (PRO pMMR population; interim analysis; December 2022 data cut)

	Pembrolizumab + CT	Placebo + CT
FACT-En-TOI		
N, baseline	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Week 18, mean (SD)	[redacted]	[redacted]
Change from baseline to week 18, LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means[a]	[redacted]	
p value	[redacted]	
PROMIS-Physical Function Scale (short form)		
N, baseline	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Week 18, mean (SD)	[redacted]	[redacted]
Change from baseline to week 18, LS mean (95% CI)	[redacted]	[redacted]

	Pembrolizumab + CT	Placebo + CT
Difference in LS means[a]	[redacted]	
p value	[redacted]	
PROMIS-Fatigue Scale (short form)		
N, baseline	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Week 18, mean (SD)	[redacted]	[redacted]
Change from baseline to week 18, LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means[a]	[redacted]	
p value	[redacted]	

Key: CSR, clinical study report; FACT-En-TOI, Functional Assessment of Cancer Therapy-Endometrial Trial Outcome Index; LS, least-square; pMMR, proficient mismatch repair; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.

Notes: [a] Repeated measures model based on the missing at random assumption. Model covariates included treatment, age at enrolment onto the study, pre-treatment QoL/PRO score, assessment time and treatment-by-time interaction.

Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[66]

PROMIS-Fatigue Scale (short form)

Baseline scores for fatigue in the pMMR population were [redacted] (Table 17). At Week 18, both treatment groups had [redacted] in the PROMIS-Fatigue Scale (short form) score. [redacted] occurred in the pembrolizumab + CT group compared with the placebo CT group [redacted], as presented in Figure 9. In both treatment groups, mean fatigue scores [redacted]

Figure 9: Mean change from baselines for the PROMIS-Fatigue Scale (short form) over time (PRO pMMR population; interim analysis; December 2022 data cut)

[redacted]**Key:** CI, confidence interval; CSR, clinical study report; pMMR, proficient mismatch repair; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System.

Note: A higher score on the PROMIS-Fatigue Scale indicates greater fatigue, which corresponds to a worse HRQoL. A lower score indicates less fatigue and a better HRQoL

Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[66]

PROMIS-Physical Function Scale (short form)

Baseline scores for physical function in the pMMR population were [redacted] (Table 17). At Week 18, both treatment groups had [redacted] of approximately [redacted] in the mean PROMIS-Physical Function Scale (short form) score, with [redacted]. Both treatment groups showed a [redacted]Figure 10.

Figure 10: Mean change from baselines for the PROMIS-Physical Function Scale (short form) over time (PRO pMMR population; interim analysis; December 2022 data cut)

[redacted]**Key:** CI, confidence interval; CSR, clinical study report; pMMR, proficient mismatch repair; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System.

Note: A higher score on the PROMIS-Physical Function Scale indicates better physical function, which corresponds to a better HRQoL. A lower score indicates worse physical function and a lower HRQoL.

Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[66]

FACT-En-TOI

Baseline scores for FACT-En-TOI in the pMMR population were [redacted] (Table 17). At Week 18, both treatment groups had [redacted] in the FACT-En-TOI, as presented in Figure 11. [redacted] occurred in the placebo + CT group compared with the pembrolizumab + CT group (last square mean change: [redacted] versus [redacted]). However, the [redacted].[66]

Figure 11: Mean change from baseline for the FACT-en-TOI over time (PRO pMMR population; interim analysis; December 2022 data cut)

[redacted]**Key:** CI, confidence interval; CSR, clinical study report; FACT-En-TOI, Functional Assessment of Cancer Therapy–Endometrial; pMMR, proficient mismatch repair; PRO, patient-reported outcome.

Notes: A higher score on the FACT-en-TOI indicates a better HRQoL. A lower score indicates a worse HRQoL

Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[66]

Exploratory PRO endpoints

Baseline FACT/GOG-Ntx subscale scores in the pMMR population [redacted]. At Week 18, FACT/GOG-Ntx subscale scores [redacted] in the pembrolizumab + CT group and the placebo + CT [redacted] FACT/GOG-Ntx subscale scores were [redacted] during the evaluation period. The figure presenting mean change from baseline for FACT GOG-NTX over time is presented in Appendix M.2.1.

B.2.6.5. Subsequent therapies

Table 18 presents a summary of the subsequent systemic anti-cancer treatment in the all-comer population for both treatment arms. A wide range of subsequent treatments were received by patients following study treatment discontinuation. Discussions with UK clinical experts indicated that, as with many international trials, certain treatments are not approved or used within UK clinical practice. [3] Consequently, the subsequent treatments utilised in the model were adjusted and validated to exclude those not used in England and Wales or not representative of clinical practice. For detailed information on how these adjustments were made, refer to Section B.3.5.2.

Table 18: Summary of subsequent systemic anti-cancer treatment in the all-comer population (ITT population)

	Pembrolizumab + CT (n=408)	Placebo + CT (n=411)	Total (n=819)
Started study treatment	391 (95.8)	388 (94.4)	779 (95.1)
Discontinued study treatment	271 (66.4)	379 (92.2)	650 (79.4)

	Pembrolizumab + CT (n=408)	Placebo + CT (n=411)	Total (n=819)
Received any subsequent systemic anti-cancer therapy	146 (35.8)	248 (60.3)	394 (48.1)
Subsequent systemic therapy by type			
Any anti-PD-1/PD-L1	61 (15.0)	176 (42.8)	237 (28.9)
atezolizumab	0 (0.0)	3 (0.7)	3 (0.4)
durvalumab	3 (0.7)	7 (1.7)	10 (1.2)
nivolumab	0 (0.0)	3 (0.7)	3 (0.4)
pembrolizumab	58 (14.2)	165 (40.1)	223 (27.2)
retifanlimab	0 (0.0)	1 (0.2)	1 (0.1)
Any anti-angiogenic	60 (14.7)	123 (29.9)	183 (22.3)
bevacizumab	17 (4.2)	24 (5.8)	41 (5.0)
bevacizumab awwb	2 (0.5)	1 (0.2)	3 (0.4)
bevacizumab bvzr	0 (0.0)	1 (0.2)	1 (0.1)
cediranib	4 (1.0)	4 (1.0)	8 (1.0)
lenvatinib	38 (9.3)	88 (21.4)	126 (15.4)
lenvatinib mesylate	2 (0.5)	10 (2.4)	12 (1.5)
Any chemotherapy	64 (15.7)	67 (16.3)	131 (16.0)
carboplatin	23 (5.6)	30 (7.3)	53 (6.5)
cisplatin	5 (1.2)	5 (1.2)	10 (1.2)
cyclophosphamide	2 (0.5)	1 (0.2)	3 (0.4)
docetaxel	1 (0.2)	3 (0.7)	4 (0.5)
doxorubicin	16 (3.9)	12 (2.9)	28 (3.4)
gemcitabine	3 (0.7)	2 (0.5)	5 (0.6)
liposomal doxorubicin	11 (2.7)	9 (2.2)	20 (2.4)
liposomal doxorubicin hydrochloride	3 (0.7)	1 (0.2)	4 (0.5)
other therapeutic products	2 (0.5)	3 (0.7)	5 (0.6)
paclitaxel	22 (5.4)	31 (7.5)	53 (6.5)
pegylated liposomal doxorubicin	1 (0.2)	2 (0.5)	3 (0.4)
pegylated liposomal doxorubicin hydrochloride	6 (1.5)	4 (1.0)	10 (1.2)
topotecan	4 (1.0)	1 (0.2)	5 (0.6)
Any hormonal agents	25 (6.1)	36 (8.8)	61 (7.4)
anastrozole	2 (0.5)	2 (0.5)	4 (0.5)
endocrine therapy	1 (0.2)	0 (0.0)	1 (0.1)
fulvestrant	2 (0.5)	1 (0.2)	3 (0.4)
letrozole	15 (3.7)	19 (4.6)	34 (4.2)
megestrol	6 (1.5)	8 (1.9)	14 (1.7)
megestrol acetate	2 (0.5)	5 (1.2)	7 (0.9)
tamoxifen	7 (1.7)	12 (2.9)	19 (2.3)
Any procedures, other non-therapeutic products or agents	3 (0.7)	10 (2.4)	13 (1.6)

	Pembrolizumab + CT (n=408)	Placebo + CT (n=411)	Total (n=819)
all other non-therapeutic products	1 (0.2)	5 (1.2)	6 (0.7)
apixaban	1 (0.2)	0 (0.0)	1 (0.1)
denosumab	0 (0.0)	2 (0.5)	2 (0.2)
doxycycline	0 (0.0)	1 (0.2)	1 (0.1)
fosaprepitant meglumine	0 (0.0)	1 (0.2)	1 (0.1)
heparin sodium	0 (0.0)	1 (0.2)	1 (0.1)
zoledronic acid monohydrate	1 (0.2)	0 (0.0)	1 (0.1)
Any radiotherapy	28 (6.9)	33 (8.0)	61 (7.4)
radiotherapy	28 (6.9)	33 (8.0)	61 (7.4)
Any other investigational or approved agents	20 (4.9)	34 (8.3)	54 (6.6)
abemaciclib	1 (0.2)	1 (0.2)	2 (0.2)
afatinib	1 (0.2)	0 (0.0)	1 (0.1)
alpelisib	0 (0.0)	1 (0.2)	1 (0.1)
antibody drug conjugates (adc)	0 (0.0)	1 (0.2)	1 (0.1)
antineoplastic agents	0 (0.0)	1 (0.2)	1 (0.1)
capivasertib	2 (0.5)	4 (1.0)	6 (0.7)
combinations of antineoplastic agents	0 (0.0)	1 (0.2)	1 (0.1)
etigilimab	0 (0.0)	2 (0.5)	2 (0.2)
everolimus	7 (1.7)	9 (2.2)	16 (2.0)
margetuximab	0 (0.0)	1 (0.2)	1 (0.1)
methotrexate	0 (0.0)	1 (0.2)	1 (0.1)
olaparib	5 (1.2)	9 (2.2)	14 (1.7)
onapristone	1 (0.2)	1 (0.2)	2 (0.2)
other antineoplastic agents	0 (0.0)	1 (0.2)	1 (0.1)
prexasertib	0 (0.0)	1 (0.2)	1 (0.1)
rebastinib	0 (0.0)	1 (0.2)	1 (0.1)
sacituzumab govitecan	1 (0.2)	0 (0.0)	1 (0.1)
selinexor	0 (0.0)	1 (0.2)	1 (0.1)
tebotelimab	0 (0.0)	1 (0.2)	1 (0.1)
trastuzumab	4 (1.0)	2 (0.5)	6 (0.7)
trastuzumab deruxtecan nxki	1 (0.2)	0 (0.0)	1 (0.1)
vibostolimab	0 (0.0)	2 (0.5)	2 (0.2)

Key: CT, chemotherapy; ITT, intention to treat

Notes: Every participant is counted a single time for each applicable specific anti-cancer treatment. A participant with multiple anti-cancer treatments within a therapy category is counted a single time for that category. Figures in this submission may not sum to figures in publications related to the same dataset as these figures relate to all patients, while other analyses may restrict the population to only those that had discontinued/completed study treatment.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (All-comer Disposition, Demographics and Concomitant Medications).[68]

B.2.7. Subgroup analysis

Subgroup analyses were conducted in accordance with the study's preplanned subgroups, as described in Table 5, to assess the consistency of the treatment effects.

Figure 12 presents the forest plot for PFS by prespecified subgroups. [redacted]Figure 13 presents the forest plot for OS by prespecified subgroups. The benefit of pembrolizumab + CT was generally consistent across key demographic subgroups. Similarly to PFS, results appeared to be heterogeneous according to ECOG PS (0/1 versus 2), most likely due to the small number of patients in this subgroup.

ORR was also generally consistent across key demographic subgroups. Further information on subgroup analyses is presented in Appendix E.

Figure 12: Forest Plot of PFS by subgroups factors for all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

[redacted]**Key:** dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, mismatch repair proficient.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy)[67]

Figure 13: Forest plot for OS by subgroup factors in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

[redacted]**Key:** dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, mismatch repair proficient.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLFs (all-comer efficacy)[67]

B.2.8. Meta-analysis

No other relevant studies supporting the use of pembrolizumab + CT, have been identified for inclusion in a meta-analysis. Therefore, a meta-analysis is not required.

B.2.9. Indirect and mixed treatment comparisons

As per the SLR report (presented in Appendix D), paclitaxel + carboplatin is the only relevant comparator for pembrolizumab + carboplatin + paclitaxel, and the KEYNOTE-868 (NRG-GY018) trial is the only direct comparison between pembrolizumab + carboplatin + paclitaxel versus carboplatin + paclitaxel. Consequently, a network meta-analysis (NMA) is not required.

B.2.10. Adverse reactions

The safety analyses presented in this section are from the KEYNOTE-868 (NRG-GY018) trial, specifically the All Participants as Treated population which includes 779 patients who received at least one dose of the study drug (391 patients receiving pembrolizumab + CT, 388 patients receiving placebo + CT). The safety data presented are for the all-comer population from the Efficacy and Safety Update (August 2023 data cut). The data for the individual dMMR/pMMR cohorts are presented in Appendix E.

Table 19 summarises the AEs for both treatment arms in all-comer patients. Almost all patients experienced AEs and the frequency was generally well balanced between treatment arms (388 patients [99.2%] in the pembrolizumab + CT group and 387 [99.7%] in the placebo + CT group). Most patients experienced AEs related to the drug (379 patients [96.9%] in the pembrolizumab + CT group, and 373 [96.1%] in the placebo + CT group). In the pembrolizumab + CT group, three patients (0.8%) died as a result of drug-related AEs, and in the placebo + CT group two patients (0.5%) died as a result of drug-related AEs.

The types and incidences of AEs and serious AEs were generally consistent with the established individual safety profiles of pembrolizumab monotherapy and the CT regimen.[66] No new safety concerns were identified.

Table 19: Summary of AEs in all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
AEs	388 (99.2)	387 (99.7)
Drug-related[a] AEs	379 (96.9)	373 (96.1)
Grade 3-5 AEs	257 (65.7)	191 (49.2)
Drug related Grade 3-5 AEs	195 (49.9)	132 (34.0)
SAEs	155 (39.6)	82 (21.1)
Drug related SAEs	98 (25.1)	49 (12.6)
AEs leading to death	10 (2.6)	4 (1.0)
Drug-related AEs leading to death	3 (0.8)	2 (0.5)

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy; SAEs, serious adverse events

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

B.2.10.1. Treatment exposure

The median duration on therapy was longer in the pembrolizumab + CT group compared with the placebo + CT group. Table 20 presents a summary of exposure-adjusted AEs. After

adjusting for exposure to study intervention, event rates in each AE category were [redacted] in the pembrolizumab + CT group and the placebo + CT group.

Table 20: Summary of exposure-adjusted AEs in all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

	Event Count and Rate (Events/100 person-months)[a]	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Total exposure in person-months	[redacted]	[redacted]
Total events (rate)		
AEs	[redacted]	[redacted]
Drug-related[a] AEs	[redacted]	[redacted]
Grade 3-5 AEs	[redacted]	[redacted]
Drug related Grade 3-5 AEs	[redacted]	[redacted]
SAEs	[redacted]	[redacted]
Drug related SAEs	[redacted]	[redacted]
AEs leading to death	[redacted]	[redacted]
Drug-related AEs leading to death	[redacted]	[redacted]

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy; SAEs, serious adverse events

Notes: [a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure. [b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cut-off date.

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety).[70]

B.2.10.2. Any grade adverse events

Table 21 presents the most frequently reported AEs (≥ 10%) for both the pembrolizumab + CT and placebo + CT treatment groups. The frequency and types of AEs are generally well balanced between treatment groups. The AEs most frequently reported in both treatment arms are fatigue (275 patients [70.3%] in the pembrolizumab + CT group, 248 patients [63.9%] in the placebo + CT group), anaemia (234 patients [59.8%] in the pembrolizumab + CT group, 220 patients [56.7%] in the placebo + CT group), and alopecia (215 patients [55.0%] in the pembrolizumab + CT group, 223 patients [57.5%] in the placebo + CT group).

Table 21: Any grade AEs occurring in ≥ 10% of all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
One or more adverse events	388 (99.2)	387 (99.7)
Fatigue	275 (70.3)	248 (63.9)
Anaemia	234 (59.8)	220 (56.7)
Alopecia	215 (55.0)	223 (57.5)
Nausea	200 (51.2)	178 (45.9)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Constipation	184 (47.1)	162 (41.8)
Diarrhoea	165 (42.2)	138 (35.6)
Peripheral sensory neuropathy	146 (37.3)	158 (40.7)
White blood cell count decreased	137 (35.0)	134 (34.5)
Neuropathy peripheral	135 (34.5)	116 (29.9)
Platelet count decreased	131 (33.5)	102 (26.3)
Arthralgia	128 (32.7)	140 (36.1)
Neutrophil count decreased	111 (28.4)	114 (29.4)
Dyspnoea	97 (24.8)	72 (18.6)
Lymphocyte count decreased	94 (24.0)	75 (19.3)
Hyperglycaemia	93 (23.8)	71 (18.3)
Decreased appetite	88 (22.5)	89 (22.9)
Vomiting	83 (21.2)	50 (12.9)
Hypomagnesaemia	82 (21.0)	67 (17.3)
Myalgia	79 (20.2)	70 (18.0)
Blood creatinine increased	76 (19.4)	36 (9.3)
Headache	73 (18.7)	48 (12.4)
Dizziness	72 (18.4)	62 (16.0)
Pruritus	72 (18.4)	46 (11.9)
Alanine aminotransferase increased	72 (18.4)	39 (10.1)
Cough	69 (17.6)	55 (14.2)
Abdominal pain	68 (17.4)	55 (14.2)
Pain in extremity	64 (16.4)	48 (12.4)
Rash	63 (16.1)	36 (9.3)
Hypokalaemia	62 (15.9)	76 (19.6)
Hypertension	62 (15.9)	62 (16.0)
Aspartate aminotransferase increased	61 (15.6)	27 (7.0)
Infusion related reaction	60 (15.3)	56 (14.4)
Blood alkaline phosphatase increased	60 (15.3)	47 (12.1)
Urinary tract infection	60 (15.3)	45 (11.6)
Hyponatraemia	58 (14.8)	36 (9.3)
Hypoalbuminaemia	56 (14.3)	38 (9.3)
Rash maculo-papular	56 (14.3)	23 (5.9)
Oedema peripheral	54 (13.8)	44 (11.3)
Hypothyroidism	54 (13.8)	15 (3.9)
Insomnia	53 (13.6)	44 (11.3)
Back pain	52 (13.3)	49 (12.6)
Vision blurred	44 (11.5)	28 (7.2)
Fall	44 (11.3)	26 (6.7)
Stomatitis	42 (10.7)	21 (5.4)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Dysgeusia	41 (10.5)	43 (11.1)
Weight decreased	41 (10.5)	34 (8.8)
Anxiety	41 (10.5)	31 (8.0)
COVID-19	41 (10.5)	28 (7.2)
Paraesthesia	40 (10.2)	38 (9.8)
Muscular weakness	40 (10.2)	23 (5.9)

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy;

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

B.2.10.3. Grade 3–5 adverse events

Table 22 presents the most frequently reported Grade 3–5 AEs (≥ 2%) for both the pembrolizumab + CT and placebo + CT treatment groups. The frequency and types of Grade 3–5 AEs are generally well balanced between treatment groups. The Grade 3–5 AEs most frequently reported in both treatment arms are anaemia (66 patients [16.9%] in the pembrolizumab + CT group, 45 patients [11.6%] in the placebo + CT group), decreased neutrophil count (55 patients [14.1%] in the pembrolizumab + CT group, 56 patients [14.4%] in the placebo + CT group), and decreased white blood cell count (36 patients [9.2%] in the pembrolizumab + CT group, 30 patients [7.7%] in the placebo + CT group).

Table 22: Grade 3–5 AEs occurring in ≥ 2% of all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Anaemia	66 (16.9)	45 (11.6)
Neutrophil count decreased	55 (14.1)	56 (14.4)
White blood cell count decreased	36 (9.2)	30 (7.7)
Lymphocyte count decreased	27 (6.9)	19 (4.9)
Hypertension	22 (5.6)	20 (5.2)
Platelet count decreased	19 (4.9)	9 (2.3)
Neutropenia	18 (4.6)	10 (2.6)
Syncope	16 (4.1)	16 (4.1)
Urinary tract infection	15 (3.8)	9 (2.3)
Hypokalaemia	14 (3.6)	14 (3.6)
Febrile neutropenia	13 (3.3)	5 (1.3)
Hyperglycaemia	13 (3.3)	2 (0.5)
Pulmonary embolism	12 (3.1)	10 (2.6)
Acute kidney injury	12 (3.1)	4 (1.0)
Dyspnoea	11 (2.8)	1 (0.3)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Diarrhoea	10 (2.6)	5 (1.3)
Hyponatraemia	9 (2.3)	2 (0.5)
Aspartate aminotransferase increased	8 (2.0)	1 (0.3)
Sepsis	8 (2.0)	5 (1.3)
Fatigue	6 (1.5)	10 (2.6)

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

Table 23 presents the most frequently reported drug-related Grade 3–5 AEs (≥ 2%) for both the pembrolizumab + CT and placebo + CT treatment groups. Similarly, the frequency and types of drug-related Grade 3–5 AEs are generally well balanced between treatment groups. The most frequently reported drug-related Grade 3–5 AEs in both treatment arms are anaemia (60 patients [15.3%] in the pembrolizumab + CT group, 34 patients [8.8%] in the placebo + CT group), decreased neutrophil count (45 patients [11.5%] in the pembrolizumab + CT group, 45 patients [11.6%] in the placebo + CT group), and decreased white blood cell count (29 patients [7.4%] in the pembrolizumab + CT group, 25 patients [6.4%] in the placebo + CT group).

Table 23: Drug-related Grade 3–5 AEs occurring in ≥ 2% of all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Anaemia	60 (15.3)	34 (8.8)
Neutrophil count decreased	45 (11.5)	45 (11.6)
White blood cell count decreased	29 (7.4)	25 (6.4)
Lymphocyte count decreased	18 (4.6)	15 (3.9)
Platelet count decreased	17 (4.3)	8 (2.1)
Neutropenia	14 (3.6)	8 (2.1)
Hyperglycaemia	9 (2.3)	0 (0.0)
Urinary tract infection	8 (2.0)	1 (0.3)
Acute kidney injury	8 (2.0)	2 (0.5)
Hypokalaemia	5 (1.3)	11 (2.8)

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy;

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

B.2.10.4. Adverse events of special interest

AEs of special interest are defined based on a compiled list of preferred AE terms potentially linked to immune response or reactions to infusions, causally associated with pembrolizumab. The AEs of special interest terms were identified by the Sponsor using the Medical Directory for Regulatory Activities, known as MedDRA, Version 26.1 preferred terms, and were based on ongoing monitoring of the pembrolizumab safety profile during the programme development.

Table 24 presents a summary of AEs of special interest for all-comer patients. The frequency of AEs of special interest are generally balanced between treatment arms.

Table 24: Summary of AEs of special interest for all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
AEs	[redacted]	[redacted]
Drug-related[a] AEs	[redacted]	[redacted]
Grade 3-5 AEs	[redacted]	[redacted]
Drug related Grade 3-5 AEs	[redacted]	[redacted]
SAEs	[redacted]	[redacted]
Drug related SAEs	[redacted]	[redacted]
AEs leading to death	[redacted]	[redacted]
Drug-related AEs leading to death	[redacted]	[redacted]

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy; SAE, serious adverse event

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

Table 25 presents the AEs of special interest reported for all-comer patients. The most frequently reported were [redacted] The types and rates of the AEs of special interest in the pembrolizumab + CT group were generally consistent with those seen with pembrolizumab monotherapy, with the exception of infusion reactions. Infusion reactions were similar in both the pembrolizumab + CT group and placebo + CT group, and are associated with the CT administered, and were primarily low grade. No new indication-specific AEs of special interest were identified when pembrolizumab was administered concurrently with CT. AEs of special interest in the pembrolizumab + CT group were manageable with the use of corticosteroids and/or pausing or stopping treatment.

Table 25: AEs of special interest in all-comer patients (APaT population; Efficacy and Safety Update; August 2023 data cut)

Event, n (%)	All-comer Population (n = 779)	
	Pembrolizumab + CT (n = 391)	Placebo + CT (n = 388)
Infusion related reaction	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]
Vasculitis	[redacted]	[redacted]
Immune-mediated enterocolitis	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]
Iritis	[redacted]	[redacted]
Encephalitis	[redacted]	[redacted]
Guillain-Barre syndrome	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]
Rhabdomyolysis	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Pulmonary sarcoidosis	[redacted]	[redacted]
Erythema multiforme	[redacted]	[redacted]

Key: AE, adverse event; APaT, All Participants as Treated; CT, chemotherapy;

Source: KEYNOTE-868 (NRG-GY018) Efficacy and Safety Update TLF (all-comer safety)[70]

B.2.11. Ongoing studies

The KEYNOTE-868 (NRG-GY018) trial is currently ongoing with final analysis estimated to take place in [redacted] for both the pMMR and dMMR populations.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings of the clinical evidence base

As explained in Section B.1.3.5, patients with advanced or recurrent EC have a high symptom burden, poor HRQoL and poor prognosis, with an average 5-year survival of less than 20%.[20] Outcomes for women with EC have not improved over the past 40 years. Although there have been recent innovations, particularly in the 2L setting, advancements have been limited for a long time. The SoC for the 1L treatment of advanced/recurrent patients with EC remains as CT, which underscores the need for new effective treatments.[18,19] This is particularly relevant for the pMMR population; as discussed in B.1.3.5, these tumours are associated with less a favourable prognosis than dMMR tumours, and there are fewer treatment options available for patients with pMMR tumours.

ECs are a prime candidate for treatment with ICIs, which can enhance the antitumour immune response, especially when utilised in combination with CT.[56-61] There is a clear unmet need for a new treatment option for patients with advanced or recurrent EC in the 1L setting, and the addition of pembrolizumab + CT to this pathway offers a promising new treatment option.

The KEYNOTE-868 (NRG-GY018) trial provides pivotal evidence demonstrating the efficacy of pembrolizumab + CT followed by pembrolizumab for the treatment of patients with advanced or recurrent EC, irrespective of dMMR/pMMR status. In the trial, the addition of pembrolizumab to SoC CT, followed by pembrolizumab maintenance, resulted in [redacted] risk of disease progression or death than placebo + CT [redacted], and prolonged PFS by [redacted]. This benefit of pembrolizumab + CT was consistently reflected in the results of the subgroup analyses, irrespective of MMR status. Treatment with pembrolizumab + CT also provided a clinically meaningful improvement in OS and DOR, and a greater ORR versus placebo + CT, as outlined in Section B.2.6.

Previous trials of monotherapy drugs which target PD-1/PD-L1 in patients with recurrent or advanced pMMR EC resulted in only modest improvement compared to CT alone.[71-74] This underscores the importance of the results from the KEYNOTE-868 (NRG-GY018) trial for patients with advanced/recurrent EC, across both MMR subgroups. The success of the

KEYNOTE-868 (NRG-GY018) trial highlights the potential for combining immunotherapies with traditional treatments like CT to more effectively prolong survival, irrespective of MMR status.

The safety profile of pembrolizumab + CT as 1L therapy is generally consistent with established safety profiles of pembrolizumab monotherapy and CT (paclitaxel + carboplatin). Importantly, the addition of pembrolizumab did not appear to increase the occurrence of AEs typically associated with combination CT, and no new safety signals emerged. In addition, the frequency of immune-mediated AEs was consistent with what has been observed in previous trials of pembrolizumab monotherapy in patients with EC. AEs can be effectively managed with standard medical care or treatment interruption, discontinuation, or dose modification.

Furthermore, the addition of pembrolizumab [redacted] on patients' HRQoL for the pMMR population assessed. [redacted] in overall HRQoL, physical function, and fatigue were observed between the pembrolizumab + CT and placebo + CT treatment groups.

Overall, the combination of pembrolizumab and CT not only enhances therapeutic outcomes, compared with CT alone, but also maintains a manageable safety profile and the HRQoL of the patient, making it a valuable treatment option for patients with advanced or recurrent EC.

B.2.12.2. Strengths and limitations of the clinical evidence base

The population outlined in KEYNOTE-868 (NRG-GY018) aligns with the relevant population for the decision problem presented in the submission: adults with primary advanced or recurrent EC, in line with the anticipated marketing authorisation.

The KEYNOTE-868 (NRG-GY018) trial is a high-quality, randomised, Phase III trial in EC that adhered to a pre-specified protocol to minimise any potential bias. The trial was designed as a global clinical trial to investigate the efficacy and safety of pembrolizumab + CT across four country populations: the US, Canada, Japan and South Korea. A broad range of patients were enrolled onto the trial in terms of histology, prior therapies, stage at diagnosis, disease status, MMR status and ECOG PS. This included patients that are ECOG PS 2, who are not typically included in these trials. The study population was racially diverse and representative; with 14.2% of all-comer patients identifying as Black. This proportion aligns with the higher incidence of histologic and molecular subtypes linked to poorer prognosis observed among Black women compared with women of other races.[6]

Potential limitations exist when assessing the generalisability of KEYNOTE-868 (NRG-GY018) to EC patients in the UK, since no patients were enrolled in the trial from the UK or EU. However, the patient population of KEYNOTE-868 (NRG-GY018) has similar characteristics to the patients identified in a recent real world study in England (n = 902).[75] Patients in the real world study had a median age of 66.6 years, similar to patients of the KEYNOTE-868 (NRG-GY018) who had a median age of 66.1 years. In both the real-world study and the KEYNOTE-868 (NRG-GY018) trial, most patients were White (85.9% and 74.1%, respectively.[75] UK clinical experts also confirmed that the KEYNOTE-868 (NRG-GY018) trial population is broadly similar to the patients seen in real-world clinical practice.[3]

The primary and secondary efficacy outcomes of the KEYNOTE-868 (NRG-GY018) trial are well established trial endpoints which are most relevant to patients with EC, carers and healthcare professionals in UK clinical practice. HRQoL endpoints also allow further assessment of the impact of advanced or recurrent EC. Although the evidence for HRQoL [redacted] for pembrolizumab + CT, it demonstrates that the addition of pembrolizumab [redacted] HRQoL. Progressive disease is associated with deterioration in HRQoL. As outlined in Section B.2.6, pembrolizumab + CT has demonstrated significantly better PFS in both dMMR and pMMR cohorts at interim analysis, supported by longer term follow-up in the all-comers population. Additionally, pembrolizumab + CT improved OS, and a greater number of patients achieved a response (particularly complete response), with a longer duration of response. Therefore, it is expected that, in the longer term, patients treated with pembrolizumab + CT may experience a better HRQoL than patients treated with the comparator. Long-term OS extrapolations are presented in Section B.3.3.4.

The KEYNOTE-868 (NRG-GY018) trial was designed to evaluate pMMR and dMMR patient populations independently, allocating statistical power to each cohort separately. Given that these two populations are distinct in their biology and response to immunotherapies, it was anticipated that the statistical assumptions would also differ. KN-868 is the only study to date to independently evaluate the pMMR patient population.

A wide range of subsequent treatments were received by patients following study treatment discontinuation. UK clinical experts indicated that there are some differences to the options available in UK compared to that used in the trial. The impact of this is uncertain, however the subsequent treatments were adjusted and validated to align with UK clinical practice (refer to Section B.3.5.2 for further information).

Pooling of the KEYNOTE-868 (NRG-GY018) trial data was necessary to assess the all-comer population relevant to the decision problem and this resulted in an increased sample

size for an EC cohort. Pembrolizumab + CT demonstrated efficacy for all advanced or recurrent EC patients at the 1L setting, irrespective of MMR status (refer to Appendix E for results of separate pMMR/dMMR cohorts).

B.3. Cost effectiveness

Summary of key cost effectiveness information

Objective:

- To examine the cost-effectiveness of pembrolizumab + CT versus CT alone for patients with primary advanced or recurrent endometrial cancer

Model structure:

- A de novo three-state partitioned survival model (PFS, PD, and death) was developed
- An SLR of published cost-effectiveness analyses in this indication was conducted, but no studies were directly applicable to the decision problem. A review of past NICE technology appraisals in similar gynaecological conditions was also conducted and influenced the design of the model used in this submission

Model inputs:

Patient population inputs:

- The modelled patient population is patients with primary advanced or recurrent EC

Clinical efficacy inputs:

- Clinical data (PFS, OS, and TTD) used in this economic analysis were based on the results from the KEYNOTE-868 (NRG-GY018) trial (data cut-off August 2023)
- Extrapolations of PFS and OS were conducted in accordance with NICE TSD 14 to obtain long-term estimates to support the model. Direct KM data were used for TTD due to its availability up to the end of the treatment period
- Treatment stopping rules included in the model base case are in line with the administration of treatments in KEYNOTE-868 (NRG-GY018)

Utility inputs:

- In the absence of utility data collected from KEYNOTE-868 (NRG-GY018), health-state utility values were informed by EQ-5D-3L data collected in another trial of pembrolizumab for advanced or recurrent EC (KEYNOTE-158) from patients who had received one prior line of therapy, to align as closely as possible to the current decision problem

Costs and resource use inputs:

- Costs and healthcare resource use captured in the analysis included treatment acquisition and administration costs, monitoring costs, AE costs, subsequent treatment costs, and end-of-life costs
- Inputs on healthcare resource utilisation were obtained from a UK clinician ad-board
- Grade 3+ AEs that occurred in ≥5% of patients in either arm were included in the model

Base case results and sensitivity analyses:

- In the deterministic base case, pembrolizumab + CT was associated with [redacted] incremental costs and 1.33 incremental QALYs compared to CT, which corresponds to an ICER of [redacted] per QALY gained.
- The probabilistic results are closely aligned with the deterministic results, and show that at a WTP threshold of £30,000 and £20,000, the probability of pembrolizumab + CT being cost-effective is [redacted] and [redacted] respectively.
- In a one-way sensitivity analysis parameters relating to second line immunotherapy in the CT arm, and utility values had the greatest effect on the ICER, although varying them around their standard error didn't not affect the cost-effectiveness conclusion at £30,000

Scenario analyses:

- Extensive scenario analyses were conducted to address underlying uncertainty
- The most influential scenarios include 10 year time horizon, choosing the standard log-normal CT OS curve, or two-piece log-normal pembrolizumab + CT OS curve

Cost effectiveness conclusions:

- This analysis is the first within the UK to assess the cost-effectiveness of pembrolizumab + CT as a 1L treatment for advanced/recurrent EC, irrespective of MMR status
- Results of this cost-effectiveness analysis show that pembrolizumab + CT is a cost-effective treatment for primary advanced or recurrent EC in the UK
- The results of the extensive sensitivity and scenario analyses yielded results consistent with that of the base case ICER value, suggesting that the base case analysis is plausible, robust and transparent.

B.3.1. Published cost-effectiveness studies

An initial SLR was conducted on 29 May 2019, to identify published cost-effectiveness studies that met the inclusion criteria relating to adult patients with advanced / recurrent EC irrespective of line of therapy. The searches were updated three times: on 6 January 2021, 8 November 2021 and 16 March 2024. Full details of the review are provided in Appendix G.

A total of 28 reports, which examined 26 unique studies, were found to meet the inclusion criteria.

Of the 26 studies that were included in the SLR, no studies were from the perspective of the UK healthcare system. Seven studies focused specifically on 1L therapy, with only one of these studies evaluating the use of pembrolizumab + CT in primary advanced / recurrent EC, but in a dMMR subpopulation.[76] This study employed a 3-state Markov model over a 3-year time horizon, but took a US payer perspective and therefore may not be informative for decision making in the UK. [76]

In addition to studies identified via the SLR, four NICE appraisals for relevant treatments in advanced / recurrent EC were identified at the time of this submission (TA779[52], TA904[50], TA914[51], and TA963[53]). The features of these HTAs are summarised later in Table 27 and informed the development of the current analysis.

B.3.2. Economic analysis

B.3.2.1. Patient population

The modelled patient population for primary advanced / recurrent EC reflects the final NICE scope and the anticipated marketing authorisation for pembrolizumab + CT for first-line treatment of primary advanced / recurrent EC in adults.

This decision problem is reflected by the all-comer population of KEYNOTE-868 (NRG-GY018), which includes patients irrespective of MMR status. Unless stated otherwise, the all-comer dataset is used throughout the cost-effectiveness analysis.

Baseline patient characteristics

Baseline patient characteristics for the all-comer population used in the model were sourced from KEYNOTE-868 (NRG-GY018). Weight and body surface area (BSA) were used to calculate drug dosing, where applicable. Population inputs are summarised in Table 26.

Table 26: Summary of population inputs

Variable	Mean	N	SD	SE	Source
Age (years)	65.40	819	[redacted]	[redacted]	KEYNOTE-868 (NRG-GY018)
Female (%)	100		NA	NA	
Weight (kg)	[redacted]		[redacted]	[redacted]	
BSA (m^2)	[redacted]		[redacted]	[redacted]	
pMMR (%)	71.6		NA	NA	

Key: BSA, body surface area; N, number of trial participants; SD, standard deviation; SE, standard error

Discussions with UK clinicians indicated that the trial population was broadly similar to the patients seen in real-world clinical practice in the UK (Section B.2.12). [3] In addition, the relative split between patients with dMMR/pMMR disease in KEYNOTE-868 (NRG-GY018) was deemed representative of that in the real world.

B.3.2.2. Model structure

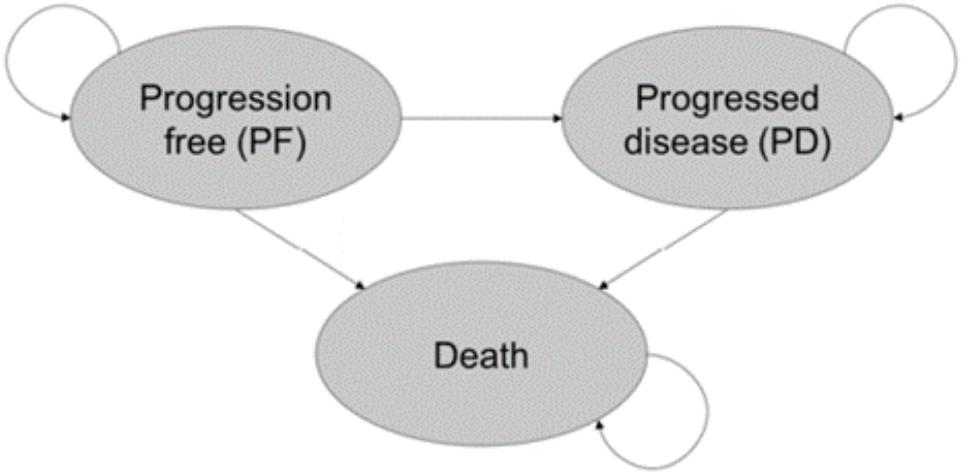
The economic model developed to assess the cost-effectiveness of pembrolizumab + CT in 1L EC follows a standard 3-state partitioned survival modelling approach. Consistent with best practice guidance on developing cost-effectiveness models, including NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 13[77], 14[78], 19[79], and 21[80], the partitioned survival modelling framework was selected after review of the literature and considering each of the following factors:

- Partitioned survival models are widely used in oncology modelling. Previous NICE appraisals in advanced / recurrent EC (TA779[52], TA904[50], TA914[51], and TA963[53]) have also utilised partitioned survival modelling to capture treatment benefits in terms of both delaying time to disease progression, delaying time to next treatment and improving survival, as has been observed in KEYNOTE-868 (NRG-GY018).
- A partitioned survival model will allow efficacy endpoints (PFS, OS, and TTD to be modelled directly from the outcomes observed in the KEYNOTE-868 (NRG-GY018) trial. These endpoints and survival functions can be used to inform state membership.
- Partitioned survival models allow for considerable flexibility in the incorporation of long-term extrapolations of efficacy outcomes, and for performing scenario analysis to address uncertainty.

Figure 14 illustrates the health states and possible transitions in each model treatment arm. All patients enter the model in the 'progression-free' (PF) state and receive treatment with pembrolizumab + CT, or CT only. Each cycle, patients may remain progression-free, may

progress, or may die. Patients who have progressed may remain alive within the progressed-disease (PD) state and receive subsequent treatment, or die, with death being the absorbing state. The health states in the model are mutually exclusive and fully exhaustive, and patients can only occupy one of the states at any given point in time.

Figure 14: Economic model structure



In accordance with NICE DSU TSD 19[79], the de novo partitioned survival model uses modelled PFS, OS, and TTD curves from KEYNOTE-868 (NRG-GY018) to estimate health state occupancy over time using the area under the curve (AUC) approach. The proportion of patients in the PF state is estimated directly from the AUC of the extrapolated PFS curve over time, the proportion in the Death state is estimated directly as 1−OS curve over time, while the proportion of patients in the PD state is estimated as the difference between the extrapolated PFS and OS curves. The modelled PFS and OS curves are described in Section B.3.3.3 and Section B.3.3.4 respectively. TTD curves were used directly to estimate the proportion of patients receiving treatment such that all treatment-associated costs and impact can be assigned accordingly to reflect actual use observed in the trial (Section B.3.3.5).

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 capped by age-matched general population mortality, sourced from the latest available Office for National Statistics Life Tables, such that modelled mortality risk did not fall below that of general population mortality at any time point[81]

- 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.

General model settings

The model uses a 1-week cycle length. The length was considered appropriate to reflect the dosing and administration frequency for both arms, allowing precise calculation of drug acquisition and administration costs over time. Half-cycle correction was not applied due to the short cycle length. The economic analysis is undertaken using the perspective of NHS and personal social services (PSS), with a discounting of 3.5% applied for costs and effects as per NICE reference case.[54] A lifetime time horizon of 35 years was chosen to reflect a horizon that is sufficiently long to reflect all differences in costs or outcomes between pembrolizumab + CT and CT only.[54]

Four previous NICE appraisals within advanced/recurrent EC were identified and informed development of the model. Only one of these, TA963, is in the 1L setting, although it considered the dMMR population only.[53] The selected features of the current economic analysis, the justifications, as well as comparison against the model settings of past appraisals, are described in Table 27.

Table 27: Features of the economic analysis and comparison to previous NICE appraisals in advanced/recurrent EC

Factor	Previous evaluations				Current evaluation	
	TA779[52]	TA904[50]	TA914[51]	TA963[53]	Chosen values	Justification
Time horizon	Lifetime (40 year)	Lifetime (40 years)	Lifetime	Lifetime	35 years (Lifetime)	Sufficiently long enough to capture all the relevant costs and outcomes, based on a mean age of 65 years in KEYNOTE-868 (NRG-GY018). All patients have died by the end of the horizon in both arms
Population	Previously treated advanced or recurrent EC with high microsatellite instability or mismatch repair deficiency	Previously treated advanced or recurrent EC	Previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency	Advanced or recurrent EC with high microsatellite instability or mismatch repair deficiency	Primary advanced or recurrent EC	In accordance with final NICE scope

Factor	Previous evaluations				Current evaluation	
	TA779[52]	TA904[50]	TA914[51]	TA963[53]	Chosen values	Justification
Population in line with marketing authorisation	Yes	Yes	Yes	Yes	Yes	N/A
Intervention	Dostarlimab	Pembrolizumab + lenvatinib	Pembrolizumab	Dostarlimab + CT	Pembrolizumab + CT	In accordance with final NICE scope, intervention in KEYNOTE-868 (NRG-GY018)
Comparator	Basket of chemotherapy, including carboplatin + paclitaxel, paclitaxel monotherapy, carboplatin + pegylated liposomal doxorubicin, carboplatin monotherapy, and hormone therapy	Paclitaxel or doxorubicin	Paclitaxel or doxorubicin	Chemotherapy consisting of paclitaxel and carboplatin	Chemotherapy consisting of paclitaxel and carboplatin	In accordance with final NICE scope, comparator in KEYNOTE-868 (NRG-GY018), and reflective of current standard of care in the UK (Section B.1.3.4)
Type of economic analysis and model structure	CUA, 3-state partitioned survival model	CUA, 3-state partitioned survival model	CUA, 3-state partitioned survival model	CUA, 3-state partitioned survival model	CUA, 3-state partitioned survival model	Flexible model structure that allows direct utilisation of trial data. High amount of precedence in previous appraisals
Severity modifier / End of life criteria	End of life criteria was deemed met by ERG	End of life criteria was deemed met by ERG	Yes, 1.2X modifier was applied	No, does not qualify	No, does not qualify	QALY shortfall not met for CT alone

Factor	Previous evaluations				Current evaluation	
	TA779[52]	TA904[50]	TA914[51]	TA963[53]	Chosen values	Justification
Treatment waning effect?	Included	Not included	Included	Not included	Not included	There is currently no evidence suggestive of a treatment waning effect. This has been further supported by a recent NICE appraisal (GID-TA11197).[82] The impact of treatment waning is assessed in a scenario analysis.
Source of utilities	RWE – GARNET study	KEYNOTE-775	KEYNOTE-158	RUBY-1	Analysis of KEYNOTE-158 - open-label trial of pembrolizumab in participants with dMMR / MSI-H cancers across different tumour types. Data considered specifically from the subgroup of patients with EC who have failed at least one line of therapy.	EQ-5D was not collected in KEYNOTE-868 (NRG-GY018). EQ-5D-3L was available from the EC sub-population of KEYNOTE-158 who had only one prior line of therapy, which aligned most closely with the population in the decision problem.
Source of costs	eMIT, BNF, NHS Reference cost	eMIT, BNF, NHS Reference cost	eMIT, BNF, NHS Reference cost	eMIT, BNF, NHS Reference cost	eMIT, BNF, NHS Reference cost	Reflective of costs incurred by NHS PSS

Key: BNF, British national formulary; CDF, Cancer Drugs Fund; CT, Chemotherapies; CUA, cost-utility analysis; EC, endometrial cancer; eMIT, electronic market information tool; NHS, National health service; TA, technical appraisal.

B.3.2.3. Intervention technology and comparators

Pembrolizumab + CT arm

The intervention, pembrolizumab + CT, is implemented within the model as per its anticipated MHRA marketing authorisation. In KEYNOTE-868 (NRG-GY018), pembrolizumab + CT were administered in the combination phase for a maximum of 6 cycles as follows:

- Pembrolizumab: 200 mg intravenous (IV) every three weeks (Q3W)
- CT
    - Paclitaxel: 175 mg/m^2 IV Q3W
    - Carboplatin IV Q3W, to reach an AUC of 5

Thereafter, patients receive IV pembrolizumab in the maintenance phase at 400mg once every 6 weeks (Q6W) until progression or for a duration of up to 14 cycles.

A maximum of 20 cycles of treatment with pembrolizumab is permitted (approximately 2 years of treatment; see Table 28). This is reflected within the economic model (further details on duration of treatment provided in Section B.3.3.5). Carboplatin dose is reported to reach an AUC of 5. However, 750 mg is used within the model, which represents the maximum dose of carboplatin a patient can take during a cycle.[83]

Table 28: Dosing schedule for pembrolizumab + CT applied within the model

Drug	Dose	Route	Frequency
Combination phase			
Pembrolizumab	200 mg	IV	Once every 3 weeks for a maximum of 6 cycles
Paclitaxel	175 mg/m^2	IV	Once every 3 weeks for a maximum of 6 cycles
Carboplatin	750mg	IV	Once every 3 weeks for a maximum of 6 cycles
Maintenance phase			
Pembrolizumab	400 mg	IV	Once every 6 weeks for a maximum of 14 cycles

Key: AUC, area under the curve; IV, intravenous; mg, milligram; m, meter

Comparator arm

The relevant comparator is chemotherapy (CT) alone, consisting of a combination of paclitaxel and carboplatin, as confirmed by UK clinical experts.[3] The administration schedule for CT alone in current clinical practice is the same as the placebo + CT arm in KEYNOTE-

868 (NRG-GY018) (Table 29). Similarly to the intervention arm, carboplatin is dosed at 750 mg in the model.

Table 29: Dosing schedule for CT applied within the model

Drug	Dose	Route	Frequency
Paclitaxel	175 mg/m^2	IV	Once every 3 weeks for a maximum of 6 cycles
Carboplatin	750mg	IV	Once every 3 weeks for a maximum of 6 cycles

Key: AUC, Area under the curve; IV, intravenous; mg, milligram; m, meter

B.3.3. Clinical parameters and variables

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

The primary source of clinical data for the economic model is KEYNOTE-868 (NRG-GY018) because it provides direct evidence for pembrolizumab + CT versus placebo + CT in the population of interest. The key endpoints of interest used to inform the model are PFS, OS and TTD, described in this section. HRQoL and AEs are also considered as outlined in Section B.3.4.

B.3.3.2. Approach

Key efficacy outcomes (OS and PFS) for pembrolizumab + CT and CT alone were modelled using patient-level data (PLD) for the all-comer population from KEYNOTE-868 (NRG-GY018) (data cut-off August 2023). The median duration of follow-up was [redacted] months in the pembrolizumab + CT arm and [redacted] months in the CT arm. Therefore, extrapolation of PLD beyond the trial period is required to assess the cost-effectiveness of pembrolizumab + CT over a lifetime, in line with the NICE reference case. In contrast, given that TTD data is available up to the end of the pembrolizumab treatment period, the observed KM data is used directly to inform time on treatment.

For each outcome (PFS and OS), following methodology outlined in NICE DSU TSD 14 and 21[78,80], seven parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalised gamma) were fitted to the observed data from KEYNOTE-868 (NRG-GY018). Additionally, when required, flexible models including two-piece models (KM data followed by parametric survival model fits from a pre-specified time point onwards) and spline models (1, 2, and 3 knots, using normal, odds, and hazard scales) were considered to best capture time-varying hazards, both observed and unobserved, that are commonly associated with treatment of cancer with immunotherapy.[84]

Consistent with recommendations in the NICE DSU TSDs 14 and 21[78,80], models were assessed systematically for each endpoint based on the following criteria:

- Assessment of proportional hazards
- Visual fit to the observed KM data within the trial period for KEYNOTE-868 (NRG-GY018)
- Assessment of goodness-of-fit statistics per the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values
- Assessment of the underlying hazard functions
- Clinical validity and plausibility of the extrapolated outcomes (Section B.3.14.2)

The most appropriate and clinically plausible models for PFS and OS were used to inform the model base case, with alternative models tested in scenario analyses. These selections are summarised in Table 41. Further details on the approach to modelling PFS, OS, and TTD are provided in Sections B.3.3.3, B.3.3.4, and B.3.3.5.

B.3.3.3. Progression-free survival

PFS is the primary endpoint of the KEYNOTE-868 (NRG-GY018) trial. As described in Section B.2.6.1, median PFS was [redacted] in the pembrolizumab + CT arm and [redacted] in the CT arm[redacted]B.2.6.1[redacted]

The appropriateness of the proportional hazards assumption was assessed using Schoenfeld residuals, time-dependent hazard ratio and log-cumulative hazard plots in Figure 15, Figure 16 and Figure 17 respectively. Separately-fitted models were eventually used for each arm in accordance with NICE TSD 14, which notes it is generally unnecessary to use a proportional hazards modelling approach when patient-level data are available for both the intervention and the comparator[78]:

- Visual inspection of the KM curve, time-dependent HR plot, and log-cumulative hazard plots suggest that the proportional hazards assumption does not hold as the plots cross in the first few months (Figure 15, Figure 16, and Figure 17 respectively). However, assessment of the time-dependent HR plot suggests that after the initial crossing of the curves, the HR remains fairly constant for the remainder of the trial period (Figure 16)
- The addition of pembrolizumab to CT improves the hazard profile and progression trajectory for patients, compared with what is anticipated with CT alone (Figure 17).

This is consistent with observations from clinical trials assessing pembrolizumab in other indications:[85-87]

- The mechanism of action of pembrolizumab differs from chemotherapy as it harnesses the body's immune system against cancer cells, as opposed to exerting direct cytotoxic effect.[88] It is therefore expected to produce a sustained treatment effect beyond what has been observed with CT alone
- It is evident from the PFS results in KEYNOTE-868 (NRG-GY018) that patients receiving CT alone progress faster compared with patients treated with pembrolizumab + CT (Section B.2.6.1)

Figure 15: Kaplan–Meier curve and Schoenfeld residual PFS – pembrolizumab + CT versus CT (all-comers)
Key: CT, paclitaxel + carboplatin; ID, identification; PFS, progression-free survival.

Figure 16: Time-dependent hazard ratio in PFS - pembrolizumab + CT versus CT (all-comers)
Key: CI, confidence interval; CT, paclitaxel + carboplatin; HR, hazard ratio; PFS, progression-free survival

Figure 17: Cumulative hazard plot – PFS – pembrolizumab + CT versus CT (all-comers)
Key: CT, paclitaxel + carboplatin; PFS, progression-free survival

Standard parametric models – CT and pembrolizumab + CT

The standard parametric models along with the observed PFS KM data from KEYNOTE-868 (NRG-GY018) are shown in Figure 18 and Figure 19 for CT and pembrolizumab + CT respectively. Table 30 summarises goodness-of-fit for the parametric models to the observed data as assessed by the AIC and BIC statistics. The following conclusions were drawn:

- All standard parametric curves provided poor visual fit to the observed KMs and severely underestimated PFS from week 120 onwards for both arms (Figure 18 and Figure 19); this is clear for both CT and pembrolizumab + CT arms
- No standard parametric model adequately reflected the shape of the hazard profile in the CT arm (Figure 20), particularly around week 38
- No standard parametric models captured the hazard profile observed in the pembrolizumab + CT arm (Figure 21). Based on these assessments standard parametric models were deemed to be inappropriate to estimate long-term outcomes in

both treatment arms. Flexible survival models were explored further for PFS to provide a more accurate fit to the data.

Figure 18: Parametric fitting and extrapolation of long-term PFS – CT (all-comers)

[redacted]**Key:** CT, paclitaxel + carboplatin; PFS-INVW1, progression-free survival using protocol censoring rule by ITT

Figure 19: Parametric fitting and extrapolation of long-term PFS – pembrolizumab + CT (all-comers)

[redacted]**Key:** CT, paclitaxel + carboplatin; PFS-INVW1, progression-free survival using protocol censoring rule by ITT.

Table 30: Summary of parametric fitting performances of PFS for pembrolizumab + CT and CT (all-comers)

Treatment	Pembrolizumab + CT			CT		
Extrapolation	AIC	BIC	Average	AIC	BIC	Average
Exponential	2297	2301	2299	2699	2703	2701
Weibull	2296	2304	2300	2676	2684	2680
Log-normal	2272	2280	2276	2626	2634	2630
Log-logistic	2273	2281	2277	2625	2633	2629
Gompertz	2295	2303	2299	2701	2709	2705
Gamma	2293	2301	2297	2660	2668	2664
Generalised Gamma	2274	2286	2280	2625	2637	2631

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; PFS, progression-free survival.

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Figure 20: PFS hazard function assuming smooth spline or various parametric distributions used for long-term extrapolation - CT (all-comers)

[redacted]**Key:** CT, paclitaxel + carboplatin; PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Figure 21: PFS hazard function assuming smooth spline or various parametric distributions used for long-term extrapolation - pembrolizumab + CT (all-comers)

[redacted]**Key:** CT, paclitaxel + carboplatin; PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Flexible survival models – CT and pembrolizumab + CT

Since the standard parametric models for PFS do not reasonably fit the data for either arm, a range of flexible models were explored, consistent with guidance provided in NICE DSU TSD 21.[80] These included spline models and two-piece survival models (KM data followed by parametric extrapolations). Overall, both the spline and two-piece models provided better fit to the observed data compared to the standard parametric models, more closely captured

the observed hazard profiles (Figure 24Figure 24, Figure 25, Figure 28, Figure 29 and Figure 30), and generally provided more plausible long-term extrapolations. This is the case for both arms, CT and pembrolizumab + CT. The corresponding AIC and BIC statistics are provided in Table 31, Table 32, and Table 33. Further details are provided below.

Two-piece models

Initially, two-piece models were explored. An overlay of the two-piece models with the observed KM data is shown in Figure 22 for CT and Figure 23 for pembrolizumab + CT. Visual inspection of the hazard of progression or death for both arms shows a change in hazards at around [redacted] (Figure 24Figure 24 and Figure 25).

Supplementary Chow tests were also conducted to confirm the presence of break points, where two inflection points at approximately weeks [redacted] were detected, as shown in Appendix N. The earlier cut-off of [redacted] was selected for the two-piece models, as it reflected the inflection point observed in the hazards plots while retaining as much statistical power as possible for the analysis.

Figure 22: Two-piece fitting and extrapolation of long-term PFS - CT (all-comers)
[redacted]**Key:** CT, paclitaxel + carboplatin; MMR, mismatch repair; PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Figure 23: Two-piece fitting and extrapolation of long-term PFS – pembrolizumab + CT (all-comers)
[redacted]**Key:** CT, paclitaxel + carboplatin; MMR, mismatch repair; PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Figure 24: Two-piece PFS hazard function - CT (all-comers)
[redacted]**Key:** CT, paclitaxel + carboplatin; MMR, PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Figure 25: Two-piece PFS hazard function - pembrolizumab + CT (all-comers)
[redacted]**Key:** CT, paclitaxel + carboplatin; MMR, PFS-INVW1, progression-free survival using protocol censoring rule by ITT MMR

Table 31: Summary of parametric fitting performances of two-piece extrapolation of PFS for pembrolizumab + CT and CT (all-comers)

Treatment	Pembrolizumab + CT			CT		
Extrapolation	AIC	BIC	Average	AIC	BIC	Average
Exponential	871	875	873	770	774	772
Weibull	861	868	864	767	774	770
Log-normal	859	866	862	765	772	769
Log-logistic	858	865	861	762	769	766

Gompertz	854	861	857	761	767	764
Gamma	862	869	866	769	775	772
Generalised Gamma	860	871	865	766	776	771

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; PFS, Progression-free survival

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Spline models

As an alternative to two-piece models, analyses were conducted for 1, 2, and 3 knot spline models, using normal, odds, and hazard scales. Knots were placed uniformly along the distribution of uncensored log event times. These models were assessed based on the same criteria outlined above in Section B.3.3. Overlays of the spline models with the observed KM data are shown in Figure 26 and Figure 27. The use of splines improved the AIC and BIC in both arms compared with the standard models (Table 32 and Table 33), also providing suitable fit to both observed KM and hazard for CT (Figure 28). However for pembrolizumab + CT, the spline models either had relatively poor fit to the observed hazards and visual fit to the KM data (1-knot splines) or were deemed clinically implausible due to predicting a high proportion of long-term progression-free survivors relative to estimates provided by UK clinical experts (2-knot and 3-knot splines; Table 35). In addition, the pembrolizumab + CT spline models did not provide any improvement in the visual fit compared to two-piece models described above.

Hazard plots for pembrolizumab + CT can be found in Appendix N.

Figure 26: Spline extrapolation of PFS – CT (all-comers)

[redacted]Key: CT, paclitaxel + carboplatin; k, knot; KM, Kaplan-Meier; PFS, progression-free survival

Table 32: Summary of parametric fitting performances of spline models of PFS for CT (all-comers)

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	2612	2603	2606	2624	2620	2626	2618	2612	2616
Odds	2613	2604	2606	2625	2620	2626	2619	2612	2616
Normal	2624	2603	2606	2636	2619	2626	2630	2611	2616

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; k, knot

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Figure 27: Spline extrapolation of PFS – pembrolizumab + CT (all-comers)

[redacted]

Table 33: Summary of parametric fitting performances of spline models of PFS for pembrolizumab + CT (all-comers)

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	2268	2243	2246	2280	2259	2266	2274	2251	2256
Odds	2267	2245	2247	2279	2261	2267	2273	2253	2257
Normal	2274	2247	2247	2286	2263	2267	2280	2255	2257

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; k, knot

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Figure 28: 1-knot PFS hazard function - CT (all-comers)

Figure 29: 2-knot PFS hazard function - CT (all-comers)

Figure 30: 3-knot PFS hazard function - CT (all-comers)
Key: CT, paclitaxel + carboplatin; k, knot; PFS, progression-free survival

Validation and selection of base case model – CT and pembrolizumab + CT

CT

Both the two-piece and spline models provided suitable extrapolations for the CT arm based on statistical and visual fit, and clinical plausibility. A summary of the assessment of curves for use in the base case and scenario analyses is provided below:

- **Statistical fit and visual fit to the observed KM:**
    - Two-piece: The two-piece Gompertz, log-logistic and log-normal curves had the lowest AIC / BIC values among all distributions. The AIC / BIC values were within 5 points of each other, indicating that all three curves have relatively good statistical fit without any meaningful differences between them.[89] While the Gompertz curve had the best statistical fit, the predicted plateau in PFS after 3 years was deemed clinically implausible in the CT arm (Figure 22).[3] Among the remaining curves with plausible long-term estimates, the log-logistic curve had the best statistical fit.
    - Splines: The 2-knot normal had the lowest BIC, with 1-knot hazard and the remaining 2-knot splines being within 5 points. All other 2-knot and 3-knot curves were within 5 of the lowest AIC and BIC average. All these curves' AIC and BIC were lower than that of the best performing standard parametric curve. While the 2-knot and 3-knot models matched the hazard profile well this led to an plateau from 5 years at 15% that was deemed clinically implausible (Figure 26).[3] The remaining spline curve with the best statistical fit was the 1-knot hazard.
- **Clinical plausibility:**
    - Landmark survival estimates for each curve option were compared against the expected PFS estimated by UK clinical experts (Table 34 and Section B.3.14.2). To align with the decision problem for this appraisal, clinical experts were presented with curves from the all-comer population, as well as the pMMR and dMMR subgroups, and thereafter provided their opinions on which curves best represented expected outcomes for the patient population.[3] Due to the sheer number of curves to validate (a total of more than 14 options), a pragmatic decision was required regarding the number and type of curves that could be visually presented on a graph. This decision was primarily guided by the assessment of statistical and visual fit described above. When

discussing the all-comer population, the experts confirmed that progression and survival outcomes would be better in the dMMR subgroup compared with the pMMR group of patients.

- Clinical experts consulted for this appraisal suggested that up to 5% of patients treated with CT could remain progression-free in the 1L EC setting in the longer term (5 years).
- At the 10-year timepoint most patients will have progressed, but between 2-3% of patients might still remain progression-free. This suggests that there are a very small number of patients who respond well to treatment, and experience sustained long-term benefit, under current standard of care. This represents a minimum baseline expectation in long-term PFS outcomes in 1L EC. The two-piece exponential, gamma and Weibull curves, and 1-knot normal spline curve, for the CT arm were therefore deemed inappropriate as they estimate 0-1% PFS at 10 years, while the two-piece Gompertz, and all 2-knot and 3-knot curves predictions were too high (Table 34).
- Previous advisors for NICE TA963 corroborate the view above, although estimates were provided specifically for the dMMR population. It was predicted that up to 7% of dMMR patients could remain progression-free after 10 years of treatment with CT. As discussed in B.1.3.5, it is generally accepted (and confirmed by clinical experts) that patients with dMMR EC are expected to have better outcomes than those with pMMR status; [3] therefore, survival expectations in the dMMR subgroup may be reflective of an upper bound estimate for the decision problem relevant to an all-comer population. This supports the views described above with regards to plausible curves.
- While some of both the two-piece and spline models provide long-term extrapolation that are aligned with clinical expert opinion, splines had greater concordance at 10 years.
- Of the remaining the remaining 2 splines, 1-knot hazard and 1-knot odds, the 1-knot hazard both had better AIC/BIC and visual fit to hazards.

- Based on the above assessment, the **1-knot hazard spline was selected as the base case for the CT arm** as it reflected the best balance between long-term clinical plausibility, visual, and statistical fit

- Scenario analyses were conducted using the two-piece log-logistic distribution as it presented a good balance between long-term clinical plausibility, visual, and statistical fit using the two-piece methodology. The impact on the results is relatively small (Section B.3.11.3)

Table 34: Estimates from clinical experts and two-piece and spline extrapolations of proportion of progression-free patients at landmark time points (CT)

Estimates	Years			
	2	5	10	20
Clinical expert – weighted calculation of estimates for all-comers[3]	11%	3-5%	2-3%	-
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	23%	9%	7%	6%
Two-piece models (KEYNOTE-868 [NRG-GY018]) – all-comers				
*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]
*Gamma**	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline models (KEYNOTE-868 [NRG-GY018]) – all-comers				
1-knot, hazards	[redacted]	[redacted]	[redacted]	[redacted]
1-knot, odds	[redacted]	[redacted]	[redacted]	[redacted]
*1-knot, normal**	[redacted]	[redacted]	[redacted]	[redacted]
*2-knot, hazards**	[redacted]	[redacted]	[redacted]	[redacted]
*2-knot, odds**	[redacted]	[redacted]	[redacted]	[redacted]
*2-knot, normal**	[redacted]	[redacted]	[redacted]	[redacted]
*3-knot, hazards**	[redacted]	[redacted]	[redacted]	[redacted]
*3-knot, odds**	[redacted]	[redacted]	[redacted]	[redacted]
*3-knot, normal**	[redacted]	[redacted]	[redacted]	[redacted]

Key: 1L, first-line; CT, paclitaxel + carboplatin; dMMR, mismatch repair deficient; EC, endometrial cancer

Note: Clinical experts provided estimates aligned to the clinical trial design of KEYNOTE-868 (NRG-GY018), for the pMMR and dMMR cohort individually.[3] This approach also supported comparability of estimates against those available for the dMMR subgroup from NICE TA963. These were then calculated for the all-comer population which is relevant to the decision for this appraisal, based on weights of 27.2% dMMR and 71.8% pMMR.

*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.
Model in **bold** selected for base case.

Pembrolizumab + CT

The same considerations and process were undertaken for the pembrolizumab + CT arm.

As described in Section B.3.3.3 the standard parametric curves had a poor fit to the trial

data, so spline and two-piece models were therefore assessed further. A summary of the assessment of curves for use in the base case and scenario analyses is provided below:

- **Statistical fit and visual fit to the observed KM:**
    - Two-piece: The three best fitting curves were the Gompertz, log-logistic, and log-normal distributions. All three curves had AIC / BIC values within 5 points of each other, indicating that there is no meaningful difference between them.[89]
        - While the Gompertz hazard function was the closest to that of the observed, the plateau at around 40% from year 3 onwards was deemed clinically implausible (Figure 23).
        - Based on visual and statistical fit alone, the log-normal curve was preferred over the log-logistic curve. The log-normal curve had the best visual fit to the tail of the observed KM curve for pembrolizumab + CT, while all other curves visually deviated from the observed data from week 120 onwards. The deviation of the other curves away from the KM continued over time, meaning that the longer-term fits are especially poor (Figure 23).
    - Splines: The spline models provided an improvement in AIC/BIC compared to the standard parametric fits (Table 33 vs Table 30). The 2-knot hazard had the lowest AIC/BIC with both remaining 2-knot curves being within 5 AIC/BIC and all 3-knots being within 5 AIC. All 2 and 3-knot splines fit to the observed hazards well, but as with the Gompertz, the plateaus of all of these curves were deemed too high, especially at 20 years. The remaining 1-knot splines did not provide an improvement to the visual fit of the KM data compared to the standard models, again underestimating the PFS benefit seen in the tail of the KM (Figure 27).
- **Clinical validation:** Clinical experts were not asked to hypothesise on the potential outcomes associated with pembrolizumab + CT at specific landmarks, although general validation was sought through discussion of the expected use of pembrolizumab in the 1L EC setting, as well as the benefit of IO in the current dMMR population where dostarlimab + CT has been evaluated for use.[3] Additionally, advisors for the previous appraisal of the anti-PD-1 dostarlimab + CT in the subgroup of patients with dMMR disease (NICE TA963) provided some landmark estimates for

the dostarlimab + CT arm. Some comparisons have been made in this section to understand the plausibility of survival models for pembrolizumab in the all-comer population.

- As previously outlined, clinical experts confirmed that PFS in the all-comer population would lie between the expected outcomes in the dMMR and pMMR subgroups individually. This has been demonstrated in the observed period of the KEYNOTE-868 (NRG-GY018) trial (Section B.2.6), with the experts indicating that this would continue to be the case beyond the observed period.
    - Furthermore, patients treated with IOs should experience better survival outcomes than those treated only with CT. Under current standard of care with CT, as per expert landmarks, up to 5% of patients could remain progression-free in the 1L EC setting in the longer term (5 years) and between 2-3% of patients might still remain progression-free at 10 years. All of the two-piece and spline extrapolations for pembrolizumab + CT maintained these minimum criteria, with the possible exception of the two-piece exponential curve which predicted 2% PFS in the pembrolizumab + CT arm at 10 years and 0% survivors at 20 years (Table 35)
    - The trajectory of PFS beyond approximately 7-10 years varied between the curves. The clinical experts consulted for this appraisal specifically referred to the notion of long-term response for some patients in 1L EC; this was noted above in the discussion of patients treated with CT and would continue to be the case for IO in the all-comer population. The comments are similar to suggestions from advisors involved in a previous anti-PD-1 appraisal (NICE TA963), who estimated that PFS specifically in the dMMR cohort may be around 30% at 20 years, implying that long-term survivorship would extend far beyond 20 years (Table 35)
        - As described in the final draft guidance of NICE TA963, most relapses in dMMR/MSI-H tumour types occur in the first 2 years, and in this subgroup of patients, from as early as years 2 to 3 there is already a clear plateauing in PFS [53]
        - Notably, long-term benefit of treatment with IO is not isolated to the group of patients with dMMR status; good long-term survivorship may also be seen in patients in the pMMR subgroup, with the clinical

experts expecting a plateau in PFS for the pMMR subgroup from approximately 5 years.[3]

        - While the long-term projections of the 2 and 3-knot splines predict a long and durable response, they may be too close to the advisors estimates for the dMMR population in TA963 to be clinically plausible for an all comers population (comprising 28% dMMR patients), and would therefore likely present an overly optimistic scenario for pembrolizumab + CT. In contrast all 1-knot splines likely underestimated PFS. For these reasons two-piece models were the preferred choice.

    - It is clear that PFS in the pembrolizumab + CT arm should be non-zero between the 10- and 20-year timepoints. Based on this, the two-piece exponential, gamma and Weibull curves are clinically implausible.

        - This persistence in treatment effect is in line with trials of pembrolizumab in other malignant cancers where plateaus in PFS were observed in the long-term (see Section B.3.3.5 for further discussion on long-term treatment effect associated with IO and evidence to support long-term effect with pembrolizumab in particular).[87 90]

- Therefore, the **two-piece log-normal curve was selected as the base case for pembrolizumab + CT** as it had good visual and statistical fit, and had alignment with long-term estimates
- For scenario analyses, the two-piece log-logistic was tested to demonstrate the impact on results if a more conservative plausible extrapolation was selected. The resulting change to the overall ICER is minimal (Section B.3.11.3) suggesting that any impact of potential uncertainty associated with the selection of PFS curves is small.

In summary, long-term PFS outcomes are expected to be higher in the pembrolizumab + CT arm than CT alone. A plateau in PFS for the pembrolizumab + CT arm is expected to start at approximately 5 years after initiating treatment, and this trajectory would reasonably extend beyond 10 and 20 years in the model. It is important to note that with the introduction of IO in 1L EC, a good proportion of patients should survive beyond 20 years. As described in the

final draft guidance of NICE TA963, most relapses in dMMR/MSI-H tumour types occur in the first 2 years, and from years 2 to 3 there is a clear plateauing in PFS and OS.

Table 35: Estimates from clinical experts and two-piece and spline extrapolations of proportion of progression-free patients at landmark time points (pembrolizumab + CT)

Estimates	Years			
	2	5	10	20
NICE TA963 company and EAG advisors' mean for 1L dMMR EC patients receiving dostarlimab + CT	60%	42%	33%	27%
Two-piece models (KEYNOTE-868 [NRG-GY018])				
*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]
*Gamma**	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline models (KEYNOTE-868 [NRG-GY018])				
1-knot, hazards**	[redacted]	[redacted]	[redacted]	[redacted]
1-knot, odds**	[redacted]	[redacted]	[redacted]	[redacted]
1-knot, normal**	[redacted]	[redacted]	[redacted]	[redacted]
2-knot, hazards	[redacted]	[redacted]	[redacted]	[redacted]
2-knot, odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot, normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot, hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot, odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot, normal	[redacted]	[redacted]	[redacted]	[redacted]

Key: 1L, first-line; CT, paclitaxel + carboplatin; dMMR, mismatch repair deficient; EC, endometrial cancer

Note: *Models in *grey italics* excluded due to likelihood of clinical implausibility based on clinical experts' estimates. **Models did not show a good visual fit to KM data and provided no visual improvement over standard models.

Selected PFS curves

The selected base case curves for PFS for both arms are presented in Figure 31.

Figure 31: Predicted long-term progression-free survival models used in the model

[redacted] **Key:** CT, paclitaxel + carboplatin; KM, Kaplan–Meier; PFS, progression-free survival

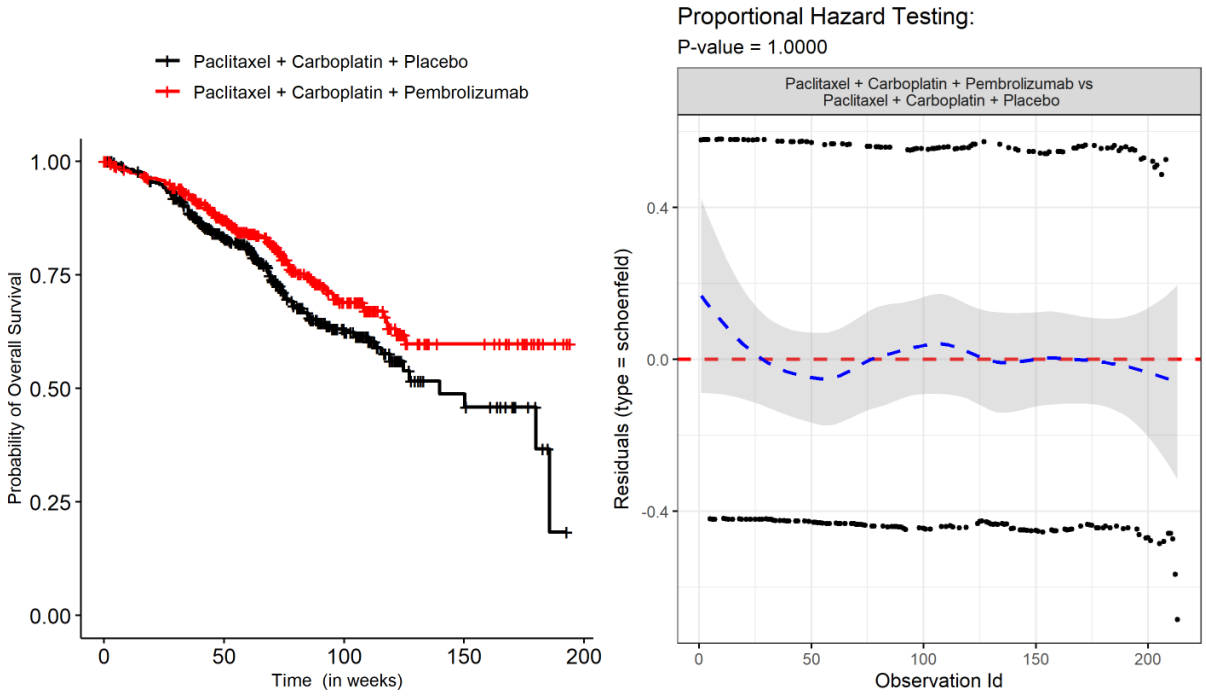
B.3.3.4. Overall survival

As described in Section B.2.6.2 median OS was not reached for pembrolizumab + CT. OS rates were higher in the pembrolizumab + CT group compared with the placebo + CT group

at 18 months (75.8% versus 69.2% for each treatment arm, respectively) and 42 months (59.8% versus 36.7%).

The Schoenfeld residual and time-dependent HR plots are shown in Figure 32 and Figure 33, respectively. Visual inspection of the KM curve and log-cumulative hazard plots (Figure 34) demonstrate that the cumulative hazards cross in the first few months of the trial and that the proportional hazards assumption does not hold. After the initial crossing of the cumulative hazards, the time-dependent HR remains fairly constant for the remainder of the trial period (Figure 33). Therefore, models were fitted independently to the respective arms.

Figure 32: Kaplan–Meier curve and Schoenfeld residual – pembrolizumab + CT versus CT (all-comers)

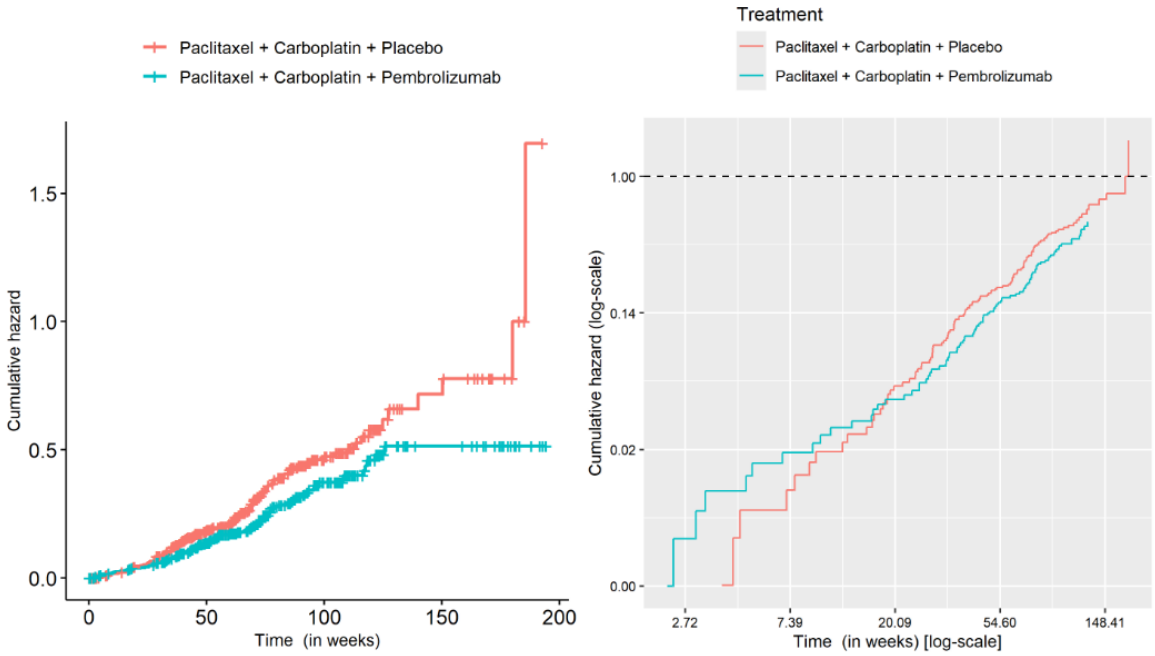


Key: CT, paclitaxel + carboplatin; MMR, mismatch repair; OS, overall survival

Figure 33: Time-dependent hazard ratio in OS - pembrolizumab + CT versus CT (All-comers)

Key: CI, confidence interval; CT, paclitaxel + carboplatin; HR, hazard ratio; OS, overall survival

Figure 34: Cumulative hazard - OS – pembrolizumab + CT versus CT (all-comers)



Key: CT, paclitaxel + carboplatin; OS, Overall survival

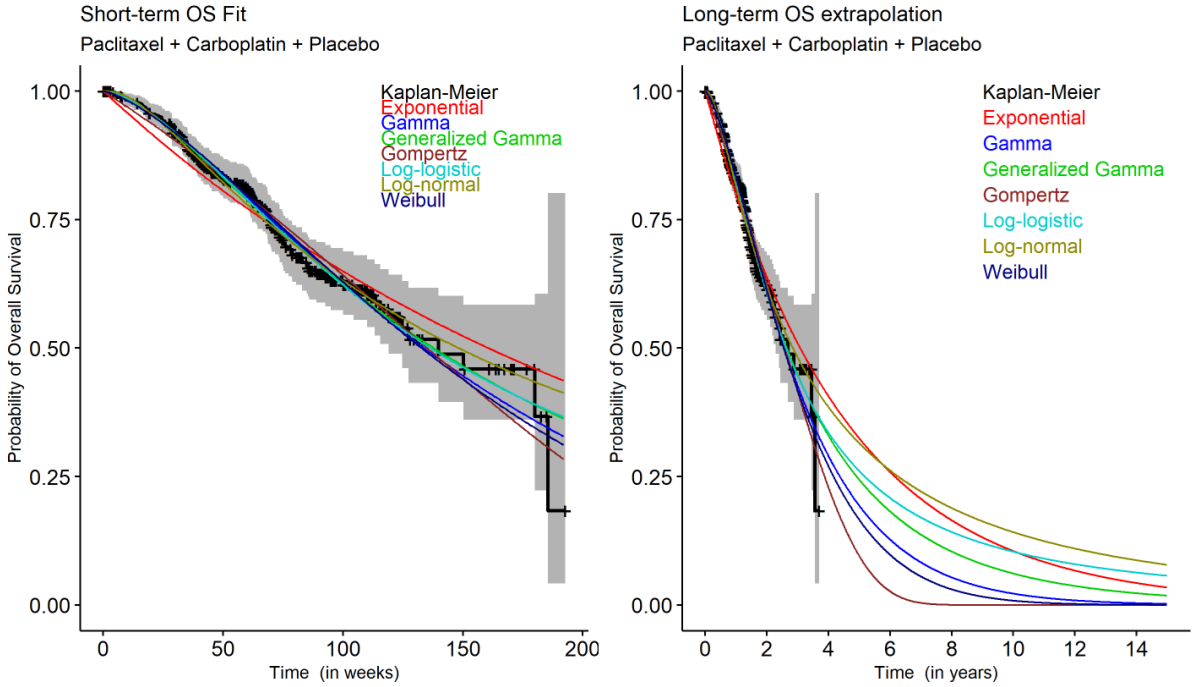
Standard parametric models – CT and pembrolizumab + CT

The standard parametric models and observed OS KM data from KEYNOTE-868 (NRG-GY018) are presented in Figure 35 and Figure 36 for the CT and pembrolizumab + CT arms respectively. Table 36 summarises goodness of fit for the parametric models to the observed data as assessed using AIC and BIC statistics. The assessment concluded that:

- Several of the standard parametric models provided relatively close resemblance to the KM data and hazard function observed in the trial for the CT arm (Figure 35 and Figure 37)
- In contrast, none of the standard parametric models provided a good visual fit to the KM data or were able to capture the hazards observed in the pembrolizumab + CT arm (Figure 36 and Figure 38)

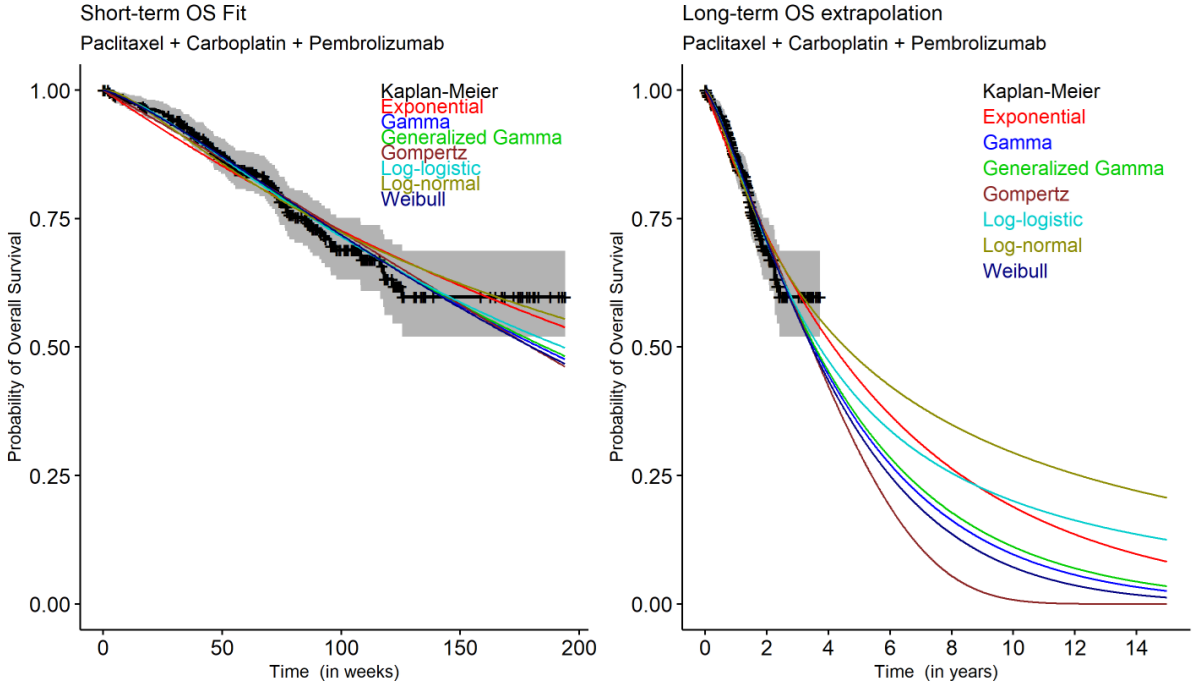
Based on these assessments, standard parametric models were deemed to offer a very reasonable fit to the observed data in the CT arm, but were inappropriate to estimate long-term outcomes in the pembrolizumab + CT arm.

Figure 35: Parametric fitting and extrapolation of long-term OS - CT (all-comers)



Key: CT, paclitaxel + carboplatin; OS, overall survival

Figure 36: Parametric fitting and extrapolation of long-term OS – pembrolizumab + CT (all-comers)



Key: CT, paclitaxel + carboplatin; OS, overall survival

Table 36: Summary of parametric fitting performances of OS for pembrolizumab + CT and CT (all-comers)

Treatment	Pembrolizumab + CT			CT		
Extrapolation	AIC	BIC	Average	AIC	BIC	Average
Exponential	1271	1275	1273	1536	1540	1538
Weibull	1267	1275	1271	1521	1529	1525
Log-normal	1271	1279	1275	1521	1529	1525
Log-logistic	1266	1274	1270	1519	1527	1523
Gompertz	1270	1278	1274	1529	1537	1533
Gamma	1266	1274	1270	1520	1528	1524
Generalised Gamma	1268	1280	1274	1521	1533	1527

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; OS, overall survival

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Figure 37: OS hazard function assuming smooth spline or various parametric distributions used for long-term extrapolation - CT (all-comers)

Key: CT, paclitaxel + carboplatin; OS, overall survival

Figure 38: OS hazard function assuming smooth spline or various parametric distributions used for long-term extrapolation - pembrolizumab + CT (all-comers)

Key: CT, paclitaxel + carboplatin; OS, overall survival

Flexible models – CT and pembrolizumab + CT

Spline models and two-piece models (KM plus parametric extrapolations) were explored, consistent with guidance provided in NICE DSU TSD 21.[80] Details are provided below.

Note that it was only necessary to explore flexible models for the pembrolizumab + CT arm, since the standard parametric curves fitted to the OS KM data did not provide reasonable fits for this treatment arm. For completeness, flexible models were also fitted to the CT arm but were not considered necessary to achieve good statistical and visual fit, or clinical plausibility; these are described briefly in the text, however for further details please refer to Appendix N. Overall, for the pembrolizumab + CT arm, both the two-piece and spline models provided a range of curves with better visual fit compared to the standard parametric models. Further details are provided below.

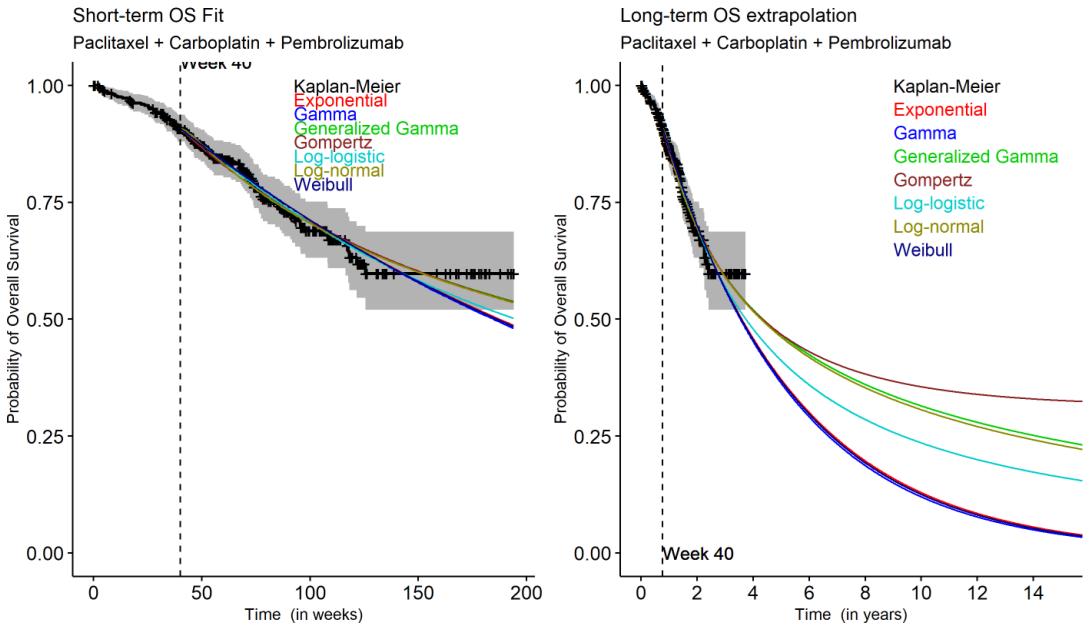
Two-piece models

An overlay of the two-piece models with the observed KM data is shown in Figure 39 for pembrolizumab + CT, and in Appendix N for CT. The corresponding hazard function for

pembrolizumab + CT is plotted against that of the observed hazards in Figure 40, and the fit statistics are provided in Table 37.

Visual inspection of the hazard of progression or death for the pembrolizumab + CT arms reflect an inflection point at around 40 weeks and a peak at 80 weeks.(Figure 38, and Appendix N). Supplementary Chow tests were conducted to confirm the presence of break points (Appendix N). As with PFS, an earlier break point of 40 weeks was chosen to preserve statistical power.

Figure 39: Two-piece fitting and extrapolation of long-term OS – pembrolizumab + CT (all-comers)



Key: CT, paclitaxel + carboplatin; OS, overall survival

Figure 40: Two-piece OS hazard function - pembrolizumab + CT (all-comers)
Key: CT, paclitaxel + carboplatin; OS, overall survival

Table 37: Summary of parametric fitting performances of two-piece extrapolation of OS for pembrolizumab + CT and CT (all-comers)

Treatment	Pembrolizumab + CT			CT		
Extrapolation	**AIC**	**BIC**	**Average**	**AIC**	**BIC**	**Average**
Exponential	757	761	759	839	843	841
Weibull	759	767	763	840	847	844
Log-normal	756	764	760	845	852	849
Log-logistic	758	765	761	840	847	844
Gompertz	758	766	762	840	848	844
Gamma	759	767	763	840	847	844
Generalised Gamma	758	770	764	842	853	847

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; OS, overall survival

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Spline models

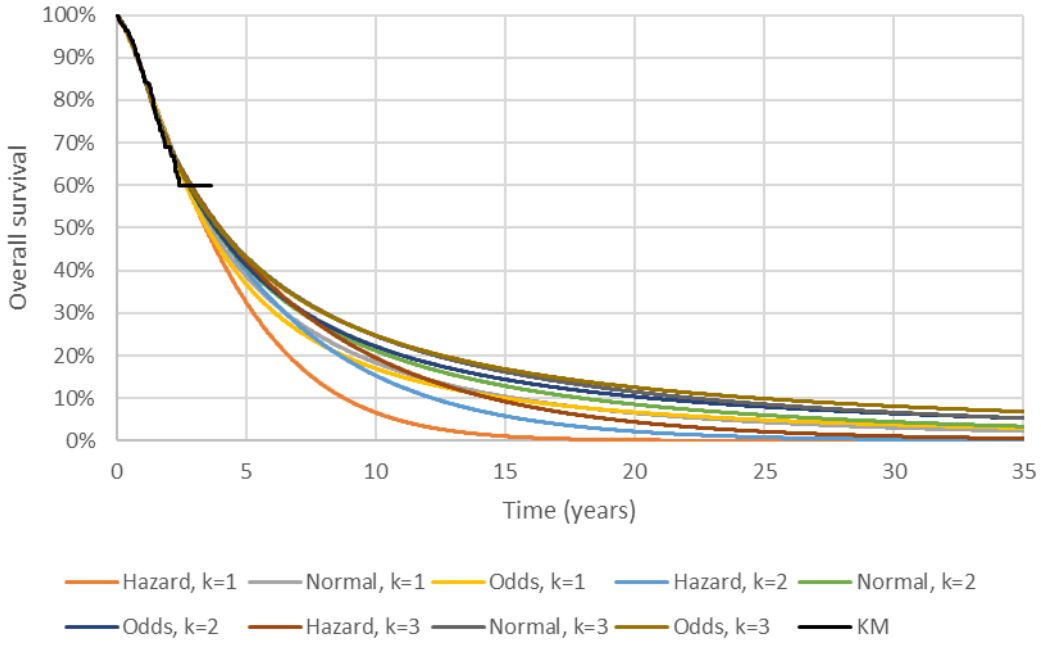
Flexible spline models were fitted to the observed OS data of each arm from KEYNOTE-868 (NRG-GY018). One- two- and three-knot spline models (k=1, 2, 3) were explored, with three alternative models for each (normal, proportional hazards, and proportional odds). Knots were placed uniformly along the distribution of uncensored log event times. Spline models were assessed based on the same criteria outlined in Section B.3.3.2, primarily for the pembrolizumab + CT arm, as the standard parametric curves were deemed sufficiently appropriate for the CT arm.

Based on an assessment of all spline models for the pembrolizumab + CT arm, these provided improved visual fit to the observed hazard compared with the standard parametric models and similar hazards past week 40 against the two-piece models (Figure 42, Figure 43 and Figure 44). This said, no model presented fully captured the scale in the reduction in hazard that was observed past 80 weeks in the trial.

The spline models also provided similar visual fit to the KM data compared to two-piece models (Figure 41). A comparison of long-term survival estimates is included in Table 39.

All spline model outputs for CT are presented in Appendix N

Figure 41: Spline extrapolation of OS – pembrolizumab + CT (all-comers)



Key: CT, paclitaxel + carboplatin; k, knot; KM, Kaplan-Meier; OS, overall survival

Table 38: Summary of parametric fitting performances of spline models of OS for pembrolizumab + CT (all-comers)

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	1269	1268	1270	1281	1284	1290	1275	1276	1280
Odds	1267	1268	1269	1279	1284	1289	1273	1276	1279
Normal	1266	1268	1269	1278	1283	1289	1272	1276	1279

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; k, knot

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 5 points from the best statistical fit.

Figure 42: 1-knot OS hazard function – pembrolizumab + CT (all-comers)

[redacted]**Figure 43: 2-knot OS hazard function – pembrolizumab + CT (all-comers)**

[redacted]**Figure 44: 3-knot OS hazard function – pembrolizumab + CT (all-comers)**
Key: CT, paclitaxel + carboplatin; k, knot; OS, overall survival

Validation and selection of base case model – CT and pembrolizumab + CT

CT

The standard parametric models were regarded to provide suitable extrapolations for the CT arm. The use of flexible models does not provide any notable improvement in visual fit against the observed data or hazards plots (Figure 37), statistical fit (AIC/BIC values for splines in the CT arm were equivalent or slightly higher than for the standard extrapolations (Appendix N), and they do not seem to offer more suitable long-term extrapolations; therefore, the additional complexity was not necessary.

The assessment of the standard parametric curves for use in the base case and scenario analyses is summarised below:

- **Statistical fit and visual fit to the observed KM:** The log-logistic curve had the best statistical fit, followed by the gamma, generalised gamma, log-normal, and Weibull curves. The log-logistic and gamma curve had the closest alignment to the observed hazards.
- **Clinical plausibility:** Landmark survival estimates for each curve option were compared against the expected OS proportions estimated by UK clinical experts[3] (Table 39)
    - Based on their estimates, long-term PFS treatment benefit is clearly translated into OS. While up to 5% of patients could remain progression-free in the 1L EC setting at 5 years after initiation of CT, OS could be up to 25%.
    - Clinical experts consulted for this appraisal suggested that at the 10-year timepoint almost 10% of patients could remain alive based on current standard of care. The advisors in NICE TA963 suggested that survivorship specifically in the dMMR cohort is also highly likely to extend beyond 20 years. By implication, long-term survival in the all-comer 1L EC population is above zero, and non-negligible.
    - While it was again confirmed that patients with dMMR EC in the CT arm would be expected to have better prognosis than patients with pMMR EC, the long-term benefit of CT treatment is not restricted to the dMMR subgroup. The advisor estimates reported for the dMMR/MSI-H population in NICE TA963 are directionally consistent with the estimates from clinical experts consulted for this appraisal which included the pMMR cohort (Table 39)

Based on the above, **the standard log-logistic curve was selected for CT in the modelled base case**. This curve had the best fit to the observed data, aligned the closest with the clinicians' long-term estimates at 5 years and 10 years, and reflected the possibility of survival at 20 years and beyond. As such, the standard log-logistic curve was deemed to be the most clinically plausible.

The following extrapolations were also explored in scenario analyses for OS in the CT arm:

- Standard log-normal model: Third best statistical fit, close alignment with observed hazards, and acceptable concordance with landmark estimates from UK experts. The model also estimates a more optimistic survival for the CT arm than the base case
- Standard generalised gamma model: Relatively acceptable visual fit and concordance with landmark estimates, but with a more pessimistic survival in the CT arm

Table 39: Estimates from clinical experts and standard and spline extrapolations of proportion of alive patients at landmark time points (CT)

Estimates	**Years**			
	2	5	10	20
Clinical Expert – weighted calculation of estimates for all-comers[3]	54-57%	21-25%	9%	-
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	58%	30%	17%	13%
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	64%	32%	11%	1%
*Weibull**	*61%*	*17%*	*1%*	*0%*
Log-normal	62%	32%	14%	5%
Log-logistic	**61%**	**26%**	**10%**	**4%**
*Gompertz**	*63%*	*10%*	*0%*	*0%*
*Gamma**	*61%*	*19%*	*2%*	*0%*
Generalised Gamma	61%	24%	6%	1%

Key: 1L, first-line; CT, paclitaxel + carboplatin; dMMR, mismatch repair deficient; EC, endometrial cancer

Note: Clinical experts provided estimates aligned to the clinical trial design of KEYNOTE-868 (NRG-GY018), for the pMMR and dMMR cohort individually.[3] These are then calculated for the all-comer population which is relevant to the decision for this appraisal, based on 27.2% dMMR and 71.8% pMMR

Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Pembrolizumab + CT

Standard parametric models did not provide a good statistical or visual fit to the observed data, therefore, following the same approach as described previously (Section B.3.3.3), flexible models were considered.

Based on a comparison of the two-piece and spline models, both provided curve options with similar and reasonable overall fit to both KM data and hazard profiles. A summary of the assessment of two-piece and spline models for the pembrolizumab + CT arm is provided below:

- **Statistical fit and visual fit to the observed KM**:
    - Two-piece: The AIC / BIC values for all curves were within 5 points of the best fitting curve (exponential), thereby indicating that these curves all have similar statistical fit to the observed data.
        - Within the set of two-piece models, the hazard function of the exponential, Weibull, and gamma distributions did not provide a good fit to the hazards observed in the trial, projecting a constant or near constant hazard over time (Figure 40). This is inconsistent with the mechanism of action of IO versus CT alone, evidence of a substantially reduced long-term risk of progression and death over time, and subsequent plateau in survival outcomes, previously observed in IOs (see Section B.3.3.5 for further discussion on long-term treatment effect for IOs and pembrolizumab specifically).
        - In terms of their height, shape and general trajectory the log-logistic, log-normal and generalised gamma curves produced similar hazard functions, but the log-normal distribution provided a better match to the overall shape of the hazards and is supported by a slightly better statistical fit according to the AIC/BIC values (Table 37)
        - There was good visual fit of the modelled curves to the observed KM for all curves. Of the best statistically fitting curves, the two-piece log-logistic and two-piece log-normal curves are both possible options.
        - In summary, the assessment of statistical and visual fit supports the use of the log-normal or log-logistic curve to model OS in the pembrolizumab + CT arm.
    - Splines: The AIC values for all curves were within 5 points of the best fitting curve (1-knot normal), thereby indicating that these curves all have similar statistical fit to the observed data (Table 38).

- Across the follow up period of the KM data, all splines provided sufficient visual fit, in line with some of the best fitting two-piece curves (Figure 41).
- While the 1-knot splines resulted in the lowest AIC/BIC, none provided a suitable fit to the observed hazard profile as they were unable to capture the turning point or the extent of the downward trend in hazard after 80 weeks (Figure 42).
- The 2 and 3-knot odds and normal curves all provided suitable fit to the observed hazards, in line with the shapes of the best fitting two-piece curves past the cut-point (40 weeks), although all the 2 and 3-knot hazard splines showed flat or increasing hazard towards 200 weeks, which is not seen the in observed smoothed hazards (Figure 43 and Figure 44).

- **Clinical validation:** As with PFS, general validation was sought through discussion of the expected use of pembrolizumab in the 1L EC setting, as well as the benefit of IO in the current dMMR population where the anti-PD-1 dostarlimab + CT has been evaluated for use.[3] Long-term benefit clearly translates from PFS into OS, as noted in the final draft guidance of NICE TA963 which confirms that a clear plateauing applies to OS in the dMMR population from as early as 2 to 3 years.
  - With the consensus that clinical experts would expect outcomes to be much better for patients treated with IOs than with CT alone, 1-knot and 2-knot hazard splines were rejected as they cross the CT OS curve and are therefore considered clinically implausible extrapolations.
  - A lower bound of pembrolizumab + CT OS landmarks was constructed using the weighted average of the PD-1 inhibitor + CT OS landmarks taken from TA963 for the dMMR population and the CT OS landmarks for the pMMR population from the advisory board. This would represent an OS landmark for all comers in which pembrolizumab provides no benefit over CT in the pMMR subpopulation. This represents a highly conservative scenario, given that clinical experts expect the addition of pembrolizumab to improve overall survival versus CT regardless of MMR status. Supporting evidence of this assumption is given in Appendix N.

        - Of the two-piece models the exponential, Weibull, and gamma curves all fall below this weighted landmark at 10 years. Similarly, all 1-knot and hazard curves provide long term predictions below this lower bound at 10 and/or 20 years. If one of these curves were to be selected for decision-making, this would imply that there is no to minimal incremental benefit associated with pembrolizumab + CT in long-term OS in pMMR, contradicting the incremental benefits already observed in KEYNOTE-868 (NRG-GY018) at the current duration of follow up as well as commentary around long-term benefit of treatment with IOs more generally (Table 40, Section B.3.3.5 and NICE TA963).
        - Additionally, given that the advisors in NICE TA963 had expected OS in the dMMR cohort to extend beyond 20 years, the long-term survival estimates of the exponential, Weibull, and gamma curves seem implausible when considering this cohort within the all-comer population.
        - Conversely, the Gompertz curve resulted in estimates that were too optimistic, with a difference of just 4% in OS estimates between 10 and 20 years, and just 1% between 20 and 30 years.
    - The remaining clinically plausible curve options are therefore log-normal, log-logistic and generalised gamma for the two-piece models and 2 and 3-knot odds and normal for the splines. All 6 curves provided similar and plausible long-term estimates.
- Further assessment was required to distinguish between the suitability of the six remaining clinically plausible curves. This was driven by an assessment of the clinical plausibility of the implied OS HRs over time, as produced by the selected curves for pembrolizumab + CT and CT alone, compared to the smoothed HR observed in the trial. These implied HRs over time were calculated using the standard log-logistic OS curve for CT (as presented in Figure 45).
    - The comparison of implied HRs over time suggests that the splines provided the best fit to the observed HR ‘bell’ shape between 20 to 90 weeks (Figure 45).

- From 90 weeks, both 2-knot splines and the two-piece log-logistic begin to deviate from the observed HR, representing a potentially unrealistic conservative scenario which may underestimate the true HR.
- While the two-piece log-normal provides the best fit to the HR plot in the tail, the implied long-term hazard (and resulting HR) may be overly optimistic. With little difference in fit and long-term extrapolations between 3-knot odds and 3-knot norm, the 3-knot odds provides a marginally better fit to the beginning of the observed HR between 5 and 50 weeks

Based on the above criteria on visual and statistical fit, clinical plausibility, and representation of the observed HR, the **3-knot odds spline curve was selected as the base case for the pembrolizumab + CT arm**.

The following scenarios were explored to understand the potential impact on the results:

- Two-piece log-normal: Best statistical fit (AIC) among two-piece models, similar visual fit to both the KM data and hazard (past 40 weeks) compared with 3-knot odds. Good visual fit to the tail of the observed HR over time
- Two-piece log-logistic model: Third best statistical fit among two-piece models with relatively close fit to observed KM and provided a more pessimistic estimate of long-term survival in the pembrolizumab + CT arm.
- 2-knot odds spline model: Good statistical fit (within 5 points of the best fitting spline) and the lowest AIC/BIC of the final four splines considered. It provides a more pessimistic estimate of long-term survival in the pembrolizumab + CT arm.

Table 40: Estimates from clinical experts and two-piece and spline extrapolations of proportion of alive patients at landmark time points (pembrolizumab + CT)

Estimates	**Years**			
	2	**5**	**10**	**20**
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving PD-1 Inhibitor + CT	82%	59%	46%	38%
Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from clinical experts)*	59%	27%	16%	10%***
Two-piece models (KEYNOTE-868 [NRG-GY018])				
*Exponential***	*70%*	*37%*	*13%*	*2%*
*Weibull***	*70%*	*37%*	*13%*	*1%*
Log-normal	70%	46%	31%	18%
Log-logistic	70%	41%	24%	12%

Estimates	Years			
	2	5	10	20
*Gompertz**	*70%*	*47%*	*36%*	*32%*
*Gamma**	*70%*	*36%*	*12%*	*1%*
Generalised Gamma	70%	47%	31%	19%
Spline models (KEYNOTE-868 [NRG-GY018])				
*1-knot, hazards**	*71%*	*33%*	*7%*	*0%*
*1-knot, odds**	*70%*	*37%*	*17%*	*7%*
*1-knot, normal**	*70%*	*39%*	*18%*	*6%*
*2-knot, hazards**	*70%*	*40%*	*15%*	*2%*
2-knot, odds	70%	41%	22%	10%
2-knot, normal	70%	41%	21%	9%
*3-knot, hazards**	*70%*	*42%*	*19%*	*4%*
3-knot, odds	**69%**	**43%**	**25%**	**13%**
3-knot, normal	70%	43%	25%	11%

Key: 1L, first-line; CT, paclitaxel + carboplatin; dMMR, mismatch repair deficient; EC, endometrial cancer; IO, Immunotherapy

Note: *Weighted average calculated using a dMMR proportion of 27.2%, as reported in the KEYNOTE-868 (NRG-GY018) trial **Models excluded due to clinical implausibility based on clinical experts' estimates, and poor fit to observed hazards ***Clinical experts did not provide estimates for 20 years, so for this figure, pMMR survival was assumed to be 0%. Excluded models indicated in *grey italics*. Model in **bold** selected for base case.

Figure 45: Comparison of implied OS HRs (pembrolizumab + CT using two-piece log-normal and two-piece log-logistic curves; versus CT using standard log-logistic curve)

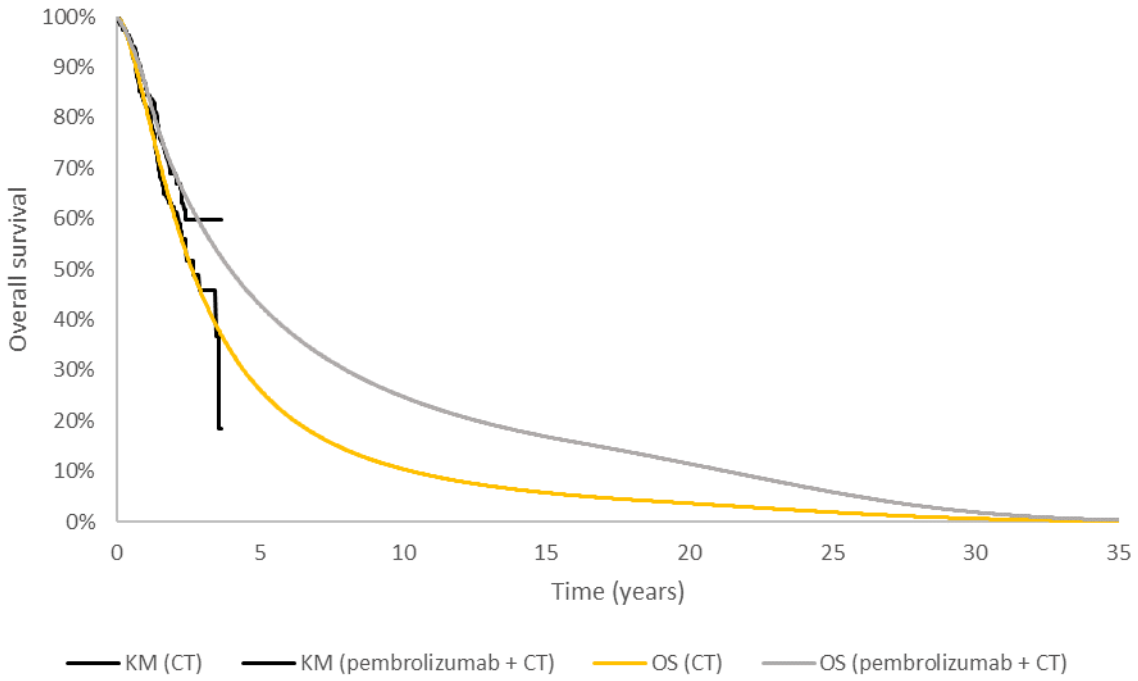
Key: 2P, two-piece model; CT, paclitaxel + carboplatin; K, knot

Note: Due to the use of the piecewise approach, the observed KM data are used up to week 40, therefore the implied HR with the two curve options for pembrolizumab + CT start at week 40.

Selected OS curves

The selected base case curves for OS for both arms are presented in Figure 46.

Figure 46: Predicted long-term overall survival models used in the model



Key: CT, paclitaxel + carboplatin; KM, Kaplan–Meier; OS, overall survival

B.3.3.5. Time to treatment discontinuation

TTD is defined as the time from the date of the first dose until the date of the last dose of the protocol regimen for any treatment components for participants who discontinued study treatment for any reason, and is used directly to estimate the proportion of patients who are on or off treatment in each model cycle. TTD is censored at the date of the last known treatment dose prior to the database cutoff date should a patient still be on treatment. TTD is expressed in months, and the KM curve is shown in Figure 47.

Patients in the pembrolizumab + CT arm were on treatment for longer than those in the placebo + CT arm, with a median time to discontinuation of [redacted] for the respective arms. The KM curves were largely similar up to 3 months and diverged thereafter. After month 3, there is a steep decline in the proportion of patients who were still on the assigned treatment in the CT arm. This was likely due to a protocol-specified unblinding procedure that allowed for a patient or their physician to request to be unblinded once in the pembrolizumab/placebo maintenance phase (i.e. after completion of CT). This was included in the protocol due to the potential harm related to risk of exposure to COVID, especially for those not receiving pembrolizumab. Those found to be on pembrolizumab were encouraged to remain on treatment. This meant that a large proportion of patients in the CT arm discontinued study

treatment (i.e. placebo) after completion of the CT component, thereby resulting in the stark difference in TTD observed between the two arms.

Given that the KM curve is available up to the end of the pembrolizumab treatment period, the KM estimates from the trial are used directly to inform the duration of treatment in the model.

Figure 47: Kaplan–Meier curve of TTD (all-comer)
[redacted]**Key:** TTD, time to treatment discontinuation

Treatment stopping rules
Treatment stopping rules included in the model base case are in line with the administration of treatments in KEYNOTE-868 (NRG-GY018) (Section B.3.2.3). In brief, pembrolizumab treatment is administered for a maximum of 24 months, and therefore all patients in the pembrolizumab + CT arm were assumed to discontinue pembrolizumab treatment from month 24 onwards. CT is administered for a maximum of 6 cycles, and therefore all patients in the CT were assumed to discontinue CT from week 15 onwards.

Treatment waning
The key justifications for allowing the modelled treatment effect of pembrolizumab + CT versus CT alone to be sustained over time are as follows:

- The mechanism of action of pembrolizumab supports a sustained treatment effect. Studies in the metastatic setting have identified high ORR in patients receiving chemotherapy having been exposed to immune checkpoint inhibitors compared with patients who only received prior chemotherapy. ORR was 75.2% for pembrolizumab + CT in KEYNOTE-868 (NRG-GY018). There are different hypotheses supporting this phenomenon, including increased pool of activated T cells or increased tumour sensitivity to subsequent therapies induced by exposure to anti-PD1.[91]
- Observed trial data supports a sustained treatment effect. Based on the trial data for pembrolizumab + CT and placebo + CT, there is no clear evidence to indicate a treatment waning effect as the KM curves for PFS and, in particular, OS separated and remained separated throughout the evaluation period in favour of pembrolizumab (Figure 17 and Figure 34). Also, the HR over the trial period for both PFS and OS suggests that the long-term benefits of pembrolizumab + CT are stable after approximately 100 weeks of treatment with a slight trend favouring pembrolizumab thereafter (Figure 16 and Figure 33)

- Despite the extensive precedent in the application of treatment waning hypothetically, there remains no concrete and substantial evidence of treatment waning effect for IOs, which include pembrolizumab.[82]
- Long-term data from historic pembrolizumab trials in other indications support a sustained treatment effect. Longer term data from other KEYNOTE clinical trials have shown a continued treatment effect post-discontinuation of pembrolizumab treatment. Some indicative studies include:
    - KEYNOTE-006 represents the longest follow-up (median 7 years) from a phase 3 trial of anti-PD-1/L1 therapy for advanced melanoma available to date. The long-term outcomes observed in KEYNOTE-006 with patients treated up to 2 years is generally consistent with those observed in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule.[92-94]
    - In KEYNOTE-024 (a trial of pembrolizumab monotherapy in PD-L1 ≥50% NSCLC), there was no narrowing of the PFS treatment benefit of pembrolizumab monotherapy versus chemotherapy through 5 years of follow-up (HR at 11.2 months was equal to the HR at 5 years, with a sustained separation of the curves), despite a high degree of crossover to pembrolizumab among those who progressed on chemotherapy.[86,87,95]

For these reasons, no treatment effect waning is assumed in the base case analysis.

For completeness, a scenario analysis is presented for the comparison with chemotherapy in which a gradual treatment waning effect in OS 7 years from the start of pembrolizumab treatment (i.e. 5 years following discontinuation of pembrolizumab) is applied to 24.8% of patients who did not attain ORR in the pembrolizumab + CT arm. The cycle-specific hazard for pembrolizumab gradually becomes equal to that in the CT alone arm over the subsequent 2 years. This time point has been chosen to reflect the follow up of KEYNOTE-006 which, even after 7 years, did not show evidence of waning.

B.3.3.6. Background mortality

General population mortality was sourced from national life tables for England and Wales[81]. General population mortality was applied using the baseline age (65.4 years old) observed in KEYNOTE-868 (NRG-GY018), such that at any time point, the hazard of PFS and/or OS cannot fall below that of general population mortality risk.

B.3.3.7. Summary of base case modelling approach

A comprehensive assessment of appropriate survival models for OS and PFS was conducted (Section B.3.3.3 and Section B.3.3.3 respectively). This process considered the visual and statistical fit of the extrapolated curves to the observed data, the clinical plausibility of long-term extrapolations and the clinical plausibility of the hazard functions. Directly observed TTD data was used with no further extrapolations given its completeness. The most appropriate and clinically plausible models for OS and PFS were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses.

Table 41: Summary of OS, PFS, and TTD models selected for economic analysis

Analysis	Arm	OS model	Justification	PFS model	Justification	TTD	Justification
Base case	Pembrolizumab + CT	3-knot odds	Good statistical and visual fit, landmark estimates in line with UK clinical experts', implied HR accurately reflects the HR over time in KEYNOTE-868 (NRG-GY018)	Two-piece log-normal	Good statistical and visual fit, clinical plausible with landmark estimates in line with UK clinical experts'	Observed KM	KM data complete up till end of pembrolizumab treatment period; further extrapolations not necessary
	CT	Standard log-logistic	Best statistical fit among standard extrapolations with good visual fit. Landmark estimates in line with UK clinical expert's	1-knot hazard	Good statistical and visual fit, clinical plausible with landmark estimates in line with UK clinical experts'	Observed KM	KM data complete; further extrapolations not necessary
For the scenario analyses, please refer to Table 65							

Key: CT; paclitaxel + carboplatin; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

B.3.4. Measurement and valuation of health effects

The model incorporates the important impact of EC on HRQoL based on disease progression status and impact of AEs due to treatment. A health-state utility approach is used in the base case, assigning a health state utility value to capture patient's HRQoL based on their progression status. It is expected that patients who are progression-free will experience higher HRQoL than those who have progressed. The absorbing death state assumes utility is zero. Additionally, decrements to HRQoL due to AEs and natural decline of age-related HRQoL were considered in line with the NICE reference case.

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

HRQoL and patient-reported outcomes (PRO) data were collected in the KEYNOTE-868 (NRG-GY018) trial as described in section B.2.6.4. EQ-5D data were not collected and therefore NICE's preferred instrument to measure HRQoL are not available directly from KEYNOTE-868 (NRG-GY018). To support this cost-effectiveness analysis for this appraisal, alternative utility analyses were considered:

- Using data available to MSD from two other trials of pembrolizumab in gynaecological cancers: KEYNOTE-158 (pembrolizumab for previously-treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency [dMMR EC subgroup considered for the purposes of this analysis]) and KEYNOTE-826 (pembrolizumab + CT [± bevacizumab] for first-line treatment of persistent, recurrent or metastatic cervical cancer). A summary of the trials and utility analyses are provided below. Note that unpublished utility values from KEYNOTE-775 (pembrolizumab in combination with lenvatinib for previously-treated advanced EC) could not be used by MSD for the purpose of this appraisal due to contractual obligations with a third party.
- Exploring mapping algorithms to estimate trial-based utility values based on the HRQoL measures from KEYNOTE-868 (NRG-GY018), which could then be used within the model (see Appendix P).
- Identification of evidence for utility values in advanced or recurrent EC based on published literature (see Section B.3.4.3).

<u>KEYNOTE-158</u>

KEYNOTE-158 was an open-label trial of pembrolizumab in participants with dMMR / MSI-H cancers across different tumour types, including EC, and who have failed at least one line of

therapy. EQ-5D-3L data were collected in the trial.[96] This clinical trial is an informative data source for use in this appraisal because it included a subgroup of patients with EC who were treated with pembrolizumab, which aligns reasonably well with the inclusion criteria for KEYNOTE-868 (NRG-GY018). There are two key differences between the trial populations:

- KEYNOTE-158 was conducted in patients in a later-line setting (2L+) for EC compared with KEYNOTE-868 (NRG-GY018). In the application of health state utility values it is implied that having progressive disease is the key driver of the reduction in HRQoL, therefore the utilities in KEYNOTE-158 may slightly underestimate the expected utilities for patients in KEYNOTE-868 (NRG-GY018).
- The KEYNOTE-158 trial is specific to the dMMR cohort, a subgroup of all-comers which is relevant to this appraisal and representative of 223 patients in the KEYNOTE-868 (NRG-GY018) trial. There are no utility values from the KEYNOTE-158 trial that directly represent the pMMR cohort.

To support this appraisal, an analysis was performed on the EQ-5D-3L data in the EC sub-population of KEYNOTE-158 who had only one prior line of therapy, to ensure the utilities were as representative as possible of the relevant population. An EQ-5D assessment was regarded to have the 'progression-free' status if it was assessed prior to the date of the first documented disease progression per RECIST 1.1, or if it was assessed no later than the censoring date of PFS. The EQ-5D assessment was considered to have the progression status if it was assessed at or after the date of the first documented disease progression per RECIST 1.1. A total of [redacted] patients were included in this analysis from the latest data cut in January 2022. Due to the small sample size, only descriptive analyses were reported as regression analyses may yield spurious results. EQ-5D-3L scores were analysed using the UK value set. The utility estimates based on progression status are shown in Table 42. It is worthy to note that the utility values from KEYNOTE-158 may underestimate that of the 1L population in this appraisal; clinical experts opined that there would be a decrease in HRQoL as patients progress from 1L to 2L.[3]

KEYNOTE-826

KEYNOTE-826 is a large double-blind, randomised controlled trial examining the use of pembrolizumab + CT [± bevacizumab] versus CT [± bevacizumab] in patients for untreated persistent, recurrent or metastatic cervical cancer.[97] EQ-5D-5L data were collected in the trial. Although it did not enrol patients with EC, the clinical trial is an informative data source for consideration because it assessed HRQoL in people with a gynaecological cancer in a 1L treatment setting, similar to the population in KEYNOTE-868 (NRG-GY018). It may therefore

provide an alternative set of utilities which more closely align with the prior treatment status of patients with primary advanced or recurrent EC in the current appraisal.

Based on the data cut of October 2022, a total of 545 patients were included in the analysis. A crosswalk of the collected EQ-5D-5L data to EQ-5D-3L was conducted using the mapping function from Hernandez Alava[98], in accordance with the latest NICE guidance.[54] The mean utility value for the progression-free and progressed states is [redacted] and [redacted] respectively.

A series of mixed linear effects regression models with random intercept were also used to estimate utility values based on disease progression status, and to account for within-subject correlation. The analyses were conducted [redacted] Variables used within the models include mapped EQ-5D-3L value, progression status, presence of grade 3+ AEs, and treatment group assignment. Fit statistics were used to select the final model, where the model with the lowest AIC was chosen as it represented the most conservative approach. The resulting health state utility values are presented in Table 42.

Table 42: EQ-5D-3L values from KEYNOTE-158 and KEYNOTE-826 based on progression status

Progression status	KEYNOTE-158 (N=[redacted]) Mean (SE)	KEYNOTE-826 (N=545) Mean (SE)
Progression-free	[redacted]	[redacted]
Progressed	[redacted]	[redacted]

Key: SE, standard error

Time-to-death utilities

Apart from progression-based utility values, utility values by time-to-death from KEYNOTE-826 were included as a scenario analysis. The time-to-death approach highlights the declining quality of life patients may experience as they move closer to death. This approach also removes the dependence on progression status but is still able to be driven by the underlying disease trajectory.

The mean time-to-death utilities value were available from KEYNOTE-826 and are presented in Table 43. Time-to-death is calculated as the time between the EQ-5D observation and time of death, recorded in the following categories: <30, 30-89, 90-179, 180-259, and ≥360 days.

Note that it was not possible to conduct a scenario analysis using time-to-death utilities from KEYNOTE-158 as the small number of patients in the EC subgroup who had one prior line of therapy precluded a robust regression analysis.

Table 43: Time-to-death utilities from KEYNOTE-826

Time to death	KEYNOTE-826 (N=545) Mean (SE)
≥360 days	[redacted]
180-359 days	[redacted]
90-179 days	[redacted]
30-89 days	[redacted]
<30 days	[redacted]

Key: SE, standard error

B.3.4.2. Mapping

In accordance with NICE's guidance[54], utility values used to inform health effects in the economic analysis should be derived using the EQ-5D-3L questionnaire as the preferred approach where possible. In situations where EQ-5D was not collected in the pivotal trial, such as in the case of the KEYNOTE-868 (NRG-GY018) trial, it may be appropriate to map other HRQoL measures that were collected in the trial to EQ-5D.[98]

A targeted literature review (TLR) was conducted to identify (a) any available mapping algorithms between the different questionnaires administered in KEYNOTE-868 (NRG-GY018) and the EQ-5D, and (b) evidence to support instrument performance and validity. However, the TLR yielded no suitable mapping algorithms for any of the instruments used in KEYNOTE-868 (NRG-GY018) (Appendix P).

Since it is not possible to estimate utility values from the KEYNOTE-868 (NRG-GY018) trial, utility values identified in the SLR were also considered for use in the cost-effectiveness model as alternatives to the utility analyses presented in Section B.3.4.1.

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

An SLR was conducted to identify evidence for utility and HRQoL in advanced or recurrent EC. Searches were run in June 2019, and updated in January 2021, November 2021, July 2022 and most recently in March 2024. Full details of the review are provided in Appendix H. In total, 11 unique studies across 12 publications were identified as appropriate to provide evidence for utility and HRQoL in advanced / recurrent EC.

Among the 11 included studies, eight included utility values that were specific to patients with EC (three were economic studies in EC that used utilities collected from patients with other tumour types). Of these, two studies were not considered further as they had either used values from other studies within this list (Feng et al., using values reported by Thurgar et al., 2021) or had values that were redacted (TA779). The remaining six studies are

reported in Table 44. None of these studies reported HRQoL of patients with primary (first-line) advanced / recurrent EC, and no trials reported HRQoL of advanced/recurrent EC in the UK (i.e. based on a UK value set).

Table 44: HRQoL studies identified from SLR

Study name	Type of study	Country	Population utility values were elicited from	HRQoL instrument	Utility values
2L					
Thurgar 2021[99]	Cost-utility analysis	US	Patients with previously treated unresectable or metastatic endometrial cancer and dMMR from KEYNOTE-158	EQ-5D-3L, US value set	PFS: 0.817 PD: 0.779
O'Malley 2022[100]	Cost-utility analysis	International	Patients with previously treated unresectable or metastatic endometrial cancer and dMMR from KEYNOTE-158	EQ-5D-3L (value set not specified)	<u>Overall cohort</u> Baseline: 0.72 Change from baseline at week 9: + 0.04 <u>Complete response / Partial response</u> Baseline: 0.73 Change from baseline at week 9: +0.08 <u>Stable disease</u> Baseline: 0.79 Change from baseline at week 9: 0.00 <u>Progressive disease</u> Baseline: 0.63 Change from baseline at week 9: -0.03

Study name	Type of study	Country	Population utility values were elicited from	HRQoL instrument	Utility values
PBAC_Pembrolizumab 2022[101]	Cost-utility analysis	Australia	Patients with advanced, recurrent, or metastatic endometrial cancer that have progressed following prior treatment (from KEYNOTE-775)	EQ-5D-5L (Australian value set)	PFS: 0.736 PD: 0.700
Ralph 2024[102]	Cost-utility analysis	Sweden	Patients with previously treated advanced endometrial cancer (from KEYNOTE-775)	EQ-5D-5L, Swedish value set	Utility, time to death (overall population: 360d: 0.869 270–359d: 0.861 180–269d: 0.830 90–179d: 0.822 30–89d: 0.772 <30d: 0.675 Utility, health state (overall population) Progression free: 0.851 Progressive disease: 0.817
Adjuvant					
Lachance 2007[103]	Cost-utility analysis	US	Patients receiving adjuvant treatment for stage I endometroid carcinoma	Physician survey	Selected values No adjuvant complication, recurrence: 1 No complication but with vaginal recurrence: 0.69

Study name	Type of study	Country	Population utility values were elicited from	HRQoL instrument	Utility values
					No complication but with pelvic recurrence: 0.38 No complication but with distant recurrence: 0.24
Unspecified					
Hildebrandt 2014[104]	Cross-sectional study	Germany	Patients with endometrial carcinoma	EQ-5D-3L, Germany value set	Primary disease: 0.999 Advanced disease: 0.887

Key: 1L, first-line; 2L, second-line; dMMR, deficient DNA mismatch repair; EC, endometrial cancer; HRQoL, health-related quality of life; PD, progressed disease; PFS, progression-free survival; TTO, time trade off; UK, United Kingdom; US, United States.

Notably, two of the six studies are based on KEYNOTE-158 (Thurgar 2021[99] and O'Malley 2022[100]), and two of the studies are based on KEYNOTE-775 which looks at pembrolizumab in combination with lenvatinib in the 2L (PBAC 2022[101] and Ralph 2024[102]). The latest analysis presented in Section B.3.4.1 provides the most recent and most applicable values to the UK setting from KEYNOTE-158 when considering the decision problem in this appraisal.

The other two studies reported utility values elicited via research conducted in the US and Germany.[103,104] Health state valuations were performed by US physicians and the German general public, respectively, and therefore may not represent UK population preferences. As such, the resulting utility values from these studies may be less relevant to the UK setting and are not in line with the NICE reference case. The study characteristics were also considered less appropriate, and the reported health states are also slightly different than as defined in the model structure for this appraisal. Lachance et al. reported utility values that were not elicited directly from patients and focused on disease recurrence by anatomical location,[103] while Hildebrandt et al. estimated HRQoL of patients with advanced endometrial carcinoma based on primary or advanced diseased in a very small sample size (n=11).[104]

A supplementary review of utility values in previous NICE appraisals in other gynaecological cancers was also conducted. Health-state utility values were used for all non-endometrial cancers with a PFS utility value of 0.750 – 0.830, and a PD utility value of 0.680 – 0.770. Among the four appraisals for endometrial cancers, two (TA904[50] and TA914[51]) included TTD utility values, while the remaining two used health-stated utility values, but values were redacted. Full results of this review can be found in Appendix H.

B.3.4.4. Adverse events

The impact of AEs on HRQoL is incorporated into the model using incidences of treatment-related AEs reported from KEYNOTE-868 (NRG-GY018). Adverse events (Grade 3+) that occurred in at least 5% of patients in either arm of KEYNOTE-868 (NRG-GY018) were included in the model, in accordance with other oncology appraisals.[50,51] The frequencies of Grade 3+ AEs that occurred in at least 5% of patients in either arm, are presented in Table 45. The duration of AEs presented in Table 46 were derived from the patient-level data from KEYNOTE-868 (NRG-GY018); the average number of AE events per subject was also considered to accurately capture the impact of AEs. A disutility value for each AE was sourced from the literature (Table 46).

For each AE, a QALY decrement was calculated as the product of the incidence rate, disutility associated with the AE, and the duration of AE. The total QALY decrement due to

AEs was then applied as a one-off decrement in the first cycle, assuming that AEs occur immediately after treatment and would only require acute care.[51,53,105]

Table 45: Grade 3+ AE occurring in ≥5% of patients

Event	Incidence		Source
	Pembrolizumab + CT	CT	
Neutrophil count decreased	14.1%	14.4%	KEYNOTE-868 (NRG-GY018)
White blood cell count decreased	9.2%	7.7%	KEYNOTE-868 (NRG-GY018)
Lymphocyte count decreased	6.9%	4.9%	KEYNOTE-868 (NRG-GY018)
Hypertension	5.6%	5.2%	KEYNOTE-868 (NRG-GY018)
Anaemia	16.9%	11.6%	KEYNOTE-868 (NRG-GY018)

Key: AE, adverse event; CT, paclitaxel + carboplatin

Table 46: Adverse event disutility and duration

Event	Number of AE events per subject*	Duration (days)*	Disutility	Source (disutility)
Neutrophil count decreased	[redacted]	[redacted]	0.00	Assumed to have no utility impact, as per NICE TA963
White blood cell count decreased	[redacted]	[redacted]	0.00	Assumed to have no utility impact, as per NICE TA963
Lymphocyte count decreased	[redacted]	[redacted]	0.00	Assumed to have no utility impact, as per NICE TA963
Hypertension	[redacted]	[redacted]	-0.02	NICE TA963
Anaemia	[redacted]	[redacted]	-0.119	NICE TA963

Key: AE, adverse event

*Number of AE events per subject and duration of AEs were obtained from KEYNOTE-868 (NRG-GY018)

B.3.4.5. Age-related utility decrement

Utility values used in the model are adjusted to account for the natural decline in quality of life associated with age. This was carried out by estimating the utility values of the general population at each age and creating a utility multiplier.

Age-related utility decrements are calculated based on the age of the cohort in each model cycle based on the algorithm published by Hernandez Alava.[98]

B.3.4.6. Health-related quality-of-life data used in the cost-effectiveness analysis

Since EQ-5D data were not collected in KEYNOTE-868 (NRG-GY018) and no mapping algorithms are available to support a mapping study of the HRQoL data available from the trial, it is necessary to identify and use relevant health state utility values from alternative data sources for the cost-effectiveness analysis in this appraisal.

A range of options for estimating health state utility values were considered, including an analysis of the EQ-5D data collected in KEYNOTE-158 and KEYNOTE-826, an SLR of published literature in EC, and previous NICE appraisals in other gynaecological cancers. None of the published literature in EC identified by the SLR used UK value sets, and almost all of the published studies were already based on KEYNOTE-158. Therefore, the analysis presented in Section B.3.4.1 is consistent with the majority of the published literature in EC while having the advantage of being conducted on the most recently available data from KEYNOTE-158 and based on the UK value set.

Using a data source that is specific to patients with EC is preferable to assuming the relevance of alternative gynaecological cancers. One of the potential advantages of using data from studies in alternative gynaecological cancers could be that those clinical trials were generally much larger than KEYNOTE-158; however, while the sample sizes vary across the clinical trials from each appraisal, the relevance of using data collected from patients with EC is deemed to outweigh any potential benefit of a larger sample size. Therefore, in the base case analysis, utility values were sourced from the EC subgroup of KEYNOTE-158 who had received one prior line of therapy.

In order to explore the uncertainty around utilities, extensive scenario analyses were undertaken using alternative utility values identified via other sources. This included progression-based and time-to-death utilities from KEYNOTE-826, and the progression-based utility values from KEYNOTE-775 using both the published Australian and Swedish EQ-5D-5L value set.

Table 47: Summary of utility values for base case cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Progression-free	[redacted]	[redacted]	Section B.3.4.1	Estimated directly from KEYNOTE-158

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Progressed	[redacted]	[redacted]	Section B.3.4.1	EQ-5D data, in line with the NICE reference case.[54]
Neutrophil count decreased	0.00 (0.00)	0.00	Section B.3.4.4	Used in previous NICE appraisal TA963. [53]
White blood cell count decreased	0.00 (0.00)	0.00	Section B.3.4.4	
Lymphocyte count decreased	0.00 (0.00)	0.00	Section B.3.4.4	
Hypertension	-0.020 (0.004)	(-0.028, -0.012)	Section B.3.4.4	
Anaemia	-0.119 (0.024)	(-0.166, -0.072)	Section B.3.4.4	

Key: CI, confidence interval; SE, standard error

Table 48: Summary of utility values for scenario analyses

Source	State	Utility value: mean (SE)	Justification
KEYNOTE-826, time-to-death	360+ days	[redacted]	KEYNOTE-826 is conducted in a gynaecological cancer in a 1L treatment setting, similar to the population in KEYNOTE-868 (NRG-GY018)
	180-359 days	[redacted]	
	90-179 days	[redacted]	
	30-89 days	[redacted]	
	<30 days	[redacted]	
KEYNOTE-826, progression-based	Progression-free	[redacted]	
	Progressed	[redacted]	
PBAC_Pembrolizumab 2022[101]	Progression-free	0.736	Utility values derived from KEYNOTE-775, which is based on patients with 2L EC
	Progressed	0.700	
Ralph 2024[102]	Progression-free	0.851	Utility values derived from KEYNOTE-775, which is based on patients with 2L EC
	Progressed	0.817	

Key: 1L, first-line; 2L, second-line; EC, endometrial cancer; SE, standard error

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

An SLR was conducted to identify relevant studies reporting cost and resource use data in adult patients with advanced or recurrent EC. Full details of the review are provided in Appendix I.

The initial SLR search was caried out in May 2019 and was followed by two updates in 2021, as well as the most recent update in March 2024. The final evidence base included 24 unique studies from 28 publications, with only 3 of those studies focusing on a UK setting. Data were highly limited, and the studies were not deemed informative for the analysis due to (a) the lack of granularity to the type of resource use, and (b) inconsistent patient populations. A summary of findings is provided below:

- Guest et al., 2006 estimated the mean total cost and resource use of palliative care of 14 advanced uterine cancer patients in the UK.[106] Although the disease setting is relevant it is not solely based on EC; the estimates are highly likely to be outdated, potentially no longer reflecting current real-world practice; and it is based on a very small sample size
- One prospective cohort study (Pennington et al., 2016) conducted in England for patients with endometrial cancer estimated the average cost of treatment of Stage IV disease 5-years after diagnosis, but did not report elements of resource use[107]
- A cost–consequence analysis (Dixon et al., 2018) based on a randomised controlled trial conducted in England estimated the mean healthcare cost associated with routine follow-up, but in Stage 1 endometrial cancer patients, which differs from the patient population considered in this appraisal[108]

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

- Intervention, comparators' and subsequent therapy costs and resource use
    - Drug acquisition costs
    - Subsequent therapy drug acquisition cost
    - Drug administration costs
- Health state resource use costs (e.g., ongoing monitoring and follow-up)
    - Disease management costs

- End-of-life care costs/terminal care costs

- Adverse reaction unit costs and resource use

Where necessary, costs were inflated to the 2023/4 cost year using inflation indices annual percentage increase for adult services published by PSSRU.[109]

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

Drug acquisition and administration costs for pembrolizumab + CT and CT alone are calculated for patients who were on treatment in each arm of the model. These costs were calculated per component, based on the TTD observed in KEYNOTE-868 (NRG-GY018) (detailed in Section B.3.3.5), the planned dosing and administration regimen (detailed in Section B.3.2.3, and Table 49), acquisition cost (Table 51), and missed doses for each treatment.

The dosing schedules are implemented for each treatment as outlined in Table 49. Pembrolizumab + CT is implemented in the economic model according to the anticipated EMA and MHRA marketing authorisation and the KEYNOTE-868 (NRG-GY018) trial protocol.[67] Carboplatin and paclitaxel are included as per their licenced dose. Paclitaxel is dosed according to weight or body surface area using the average mean baseline characteristics obtained from KEYNOTE-868 (NYG-G018), as detailed in Section B.3.2.1.

Table 49: Dosing schedules used in the analysis

Drug	Dosing per administration	Dosing frequency
Combination phase		
Pembrolizumab	200 mg	Q3W
Carboplatin	750mg	Q3W
Paclitaxel	175 mg/m^2	Q3W
Maintenance phase		
Pembrolizumab	400 mg	Q6W

Key: mg, milligram, m^2 ,square meter; Q3W, every 3 weeks; Q6W, every 6 weeks

The list price for pembrolizumab is sourced from the British National Formulary (BNF) database. [110] Carboplatin and paclitaxel are available in generic formulation with unit costs relevant to the NHS England setting sourced from the electronic market information tool (eMIT) (Table 50).[111] A commercial access agreement (CAA) is in place for pembrolizumab which makes it available to the NHS at a confidential discount (see Appendix K for details).

Table 50: List price unit costs for each treatment included in the model

Treatment	Mg per unit	Units per pack	Cost per pack (£)	Source
Pembrolizumab	100	1	2,630	BNF accessed 26/06/2024[110]
Carboplatin	150	1	20.22	eMIT[111]
	450	1	48.09	eMIT[111]
Paclitaxel	30	1	3.88	eMIT[111]
	300	1	24.43	eMIT[111]

Key: BNF, British National Formulary; eMIT, electronic market information tool; mg, milligram

Drug acquisition costs are applied as the cost per acquisition to the time on treatment curve for each intervention. Relative dose intensity (RDI) from the trial was used in the model to calculate the drug acquisition costs, to account for dose interruptions and reductions over the treatment period that would be expected in clinical practice. The total costs per cycle of each treatment are summarised in Table 51, along with the RDI. No vial sharing is assumed in the model.

Table 51: Drug acquisition costs per treatment per model cycle

Treatment arm	Phase	Drug	Total cost per cycle (£)	RDI
Pembrolizumab + CT	Combination	Pembrolizumab (up to 6 cycles)	5,056	94.1%
		Carboplatin		98.1%
		Paclitaxel		98.0%
	Maintenance	Pembrolizumab (cycles 7-20)	9,899	94.1%
CT	Combination	Carboplatin	106	98.6%
		Paclitaxel		98.2%

Key: CT, paclitaxel + carboplatin; RDI, relative dose intensity.

Drug administration costs are accrued for the duration of treatment in each treatment arm (Section B.3.3.5) and applied in line with the planned administration schedule. The study treatments included in the model are administered intravenously in an outpatient setting. The unit costs of treatment administration are sourced from NHS reference costs 2022-2023 (Table 52).[112]

Table 52: Drug administration unit costs

Administration type	Cost per administration (£)	Drug	Source
Oral*	0	-	Assumption

Administration type	Cost per administration (£)	Drug	Source
Complex chemotherapy, including prolonged infusional treatment at first attendance	277.00	Pembrolizumab + CT, CT	NHS Reference costs 2022/23 (SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance, outpatient)[112]
Simple chemotherapy	217.00	Pembrolizumab maintenance	NHS Reference costs 2022/23 (SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance, outpatient)[112]

Key: CT, paclitaxel + carboplatin; NHS, National Health Service

Note: *Oral therapies are included in subsequent treatment

The drug administration costs per model cycle are found in Table 53. In the case where a patient needs to receive a treatment infusion more than once a day, it is assumed that costs are assigned only once for those treatments. The complex chemotherapy administration cost is used for combination therapies (pembrolizumab + CT and CT), and the simple chemotherapy administration cost is used for maintenance monotherapy with pembrolizumab. This is in line with the approach advised by the Cancer Drugs Fund lead in a recent pembrolizumab submission (TA983).[113] As this assumption applies to both arms in the economic model, it is expected to have minimal impact on the results.

Table 53: Drug administration costs per treatment per model cycle

Treatment arm	Phase	Drug	Total cost per cycle (£)
Pembrolizumab + CT	Combination	Pembrolizumab (up to 6 cycles)	277.00
		Carboplatin	
		Paclitaxel	
	Maintenance	Pembrolizumab (cycles 7-20)	217.00
CT	Combination	Carboplatin	277.00
		Paclitaxel	

Key: CT, paclitaxel + carboplatin; RDI, relative dose intensity.

The SmPC[114] for paclitaxel mandates patients must be given corticosteroids, antihistamines and H2-receptor antagonists prior to paclitaxel administration, in order to prevent severe hypersensitivity reactions. However, as paclitaxel use is similar in both arms of the model, pre-medication costs were not included as the impact is expected to be negligible.

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

Costs associated with disease management, monitoring and patient follow-up are included in the economic model, in line with the NICE reference case. Separate resource use was assumed for the PFS and PD states as resource utilisation may differ between the two health states. In addition, resource use also differs depending on the status of treatment in the PFS, according to UK clinical experts.[3] Costs were applied to each resource, summed across all resources, and accrued according to time spent in each health state, where:

- Weekly PFS (on treatment) disease management costs are applied to the proportion of patients at that point on the TTD curve.
- Weekly PFS (off treatment) disease management costs are applied to the proportion of patients between the PFS and TTD curve
- Weekly PD disease management costs are applied to the proportion of patients between the OS and PFS curves

All relevant unit costs were sourced from either PSSRU or NHS reference cost 2022/23, in line with the NICE reference case. [54,109,112]

Resource use items and frequency of use were obtained via a combination of clinical expert opinion via an advisory board for resource use for both PFS and PD, and by conducting hand searches of other health technology appraisals in related disease areas including uterine, cervical and ovarian cancers for resource use in the PD state.

Table 54: Resource use and costs associated with model health states

Health state	Resource	Frequency per week	Source	Cost (£)	Source
PFS (On treatment): pembrolizumab + CT	CT scan	0.08	Advisory board	160.83	NHS Reference Costs 2022/23 - RD22Z: Computerised Tomography Scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	0.17	Advisory board	179.00	NHS Reference Costs 2022/23 - Gynaecological Oncology service - service code 503
	Blood test	0.17	Advisory board	5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PFS (Off treatment): pembrolizumab + CT	CT scan	0.08	Advisory board	160.83	NHS Reference Costs 2022/23 - RD22Z: Computerised Tomography Scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	0.06	Advisory board	179.00	NHS Reference Costs 2022/23 - Gynaecological Oncology service - service code 503
	Blood test	0.17	Advisory board	5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PFS (On treatment): CT	CT scan	0.09	Advisory board	160.83	NHS Reference Costs 2022/23 - RD22Z: Computerised Tomography Scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	0.29	Advisory board	179.00	NHS Reference Costs 2022/23 - Gynaecological Oncology service - service code 503
	Blood test	0.29	Advisory board	5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PFS (Off treatment): CT	CT scan	0.08	Advisory board	160.83	NHS Reference Costs 2022/23 - RD22Z: Computerised Tomography Scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	0.06	Advisory board	179.00	NHS Reference Costs 2022/23 - Gynaecological Oncology service - service code 503

Health state	Resource	Frequency per week	Source	Cost (£)	Source
	Blood test	0.00	Advisory board	5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PD	CT scan	0.04	Advisory board	160.83	NHS Reference Costs 2022/23 - RD22Z: Computerised Tomography Scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	0.11	Advisory board	179.00	NHS Reference Costs 2022/23 - Gynaecological Oncology service - service code 503
	Blood test	0.11	Advisory board	5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)

Key: CT, paclitaxel + carboplatin; CT scan, computerised tomography scan; NHS, National Health Service; PFS, progression-free survival; PD, progressed disease

Subsequent therapy

Following progression on any of the modelled treatments, patients may receive further rounds of therapy. These costs are considered in the economic model as a calculated one-off cost, applied at the point of entry to the PD state. The total average cost per patient of subsequent treatment is based on the proportion of patients receiving subsequent therapies, average time on treatment, the distribution of each subsequent treatment, and drug acquisition and administration costs.

Evidence for the proportion of patients assumed to receive further rounds of therapy was available from KEYNOTE-868 (NRG-GY018). This was adjusted and validated by UK clinicians to account for clinical practice in England and Wales (Table 55). [3] Following this discussion, the distribution of patents receiving subsequent treatments in the all-comer population was updated where necessary. The resulting treatments were then re-weighted accordingly to ensure that the total distribution of subsequent treatments sum up to 100% within each arm of the model.

Key points which have been incorporated into the distribution of subsequent therapies used in the cost-effectiveness model are summarised below:

- Comments specific to the all-comer population[3]
    - Re-treatment with pembrolizumab is generally not permitted.
    - Radiotherapy use will be higher than that reported in KEYNOTE-868 (NRG-GY018); approximately twice as what was reported in the trial.
- Comments specific to the pMMR cohort (incorporated through weighting) [3]
    - UK clinical experts stated that after 1L CT, of those that receive active treatment 40% of patients would receive pembrolizumab with lenvatinib
    - In addition, 15% of patients would receive paclitaxel monotherapy
- Comments specific to the dMMR cohort[3]
    - UK clinical experts stated that after 1L CT, of those that receive active treatment, around 75% receive IO monotherapy.

The duration of subsequent therapy was also derived from KEYNOTE-868 (NRG-GY018). Inputs relating to the cost of drug acquisition for subsequent therapy are listed in Table 56, and are sourced from the BNF, eMIT and the respective SmPCs.[110,111,114] Note that list prices

are used for all therapies; confidential discounts, which may be in place for some agents, are unknown to MSD.

Table 55: Distribution of subsequent therapies in base case analysis

Subsequent treatment	Initial treatment					
	Pembrolizumab + CT			CT		
	%	Mean Duration (SE)		%	Mean Duration (SE)	
Carboplatin	1.65%	[redacted]	[redacted]	1.84%	[redacted]	[redacted]
Carboplatin + paclitaxel	14.31%	[redacted]	[redacted]	11.34%	[redacted]	[redacted]
Doxorubicin	13.69%	[redacted]	[redacted]	1.22%	[redacted]	[redacted]
Letrozole	7.31%	[redacted]	[redacted]	4.60%	[redacted]	[redacted]
Megestrol	0.00%	[redacted]	[redacted]	1.84%	[redacted]	[redacted]
Paclitaxel	8.27%	[redacted]	[redacted]	8.98%	[redacted]	[redacted]
Pembrolizumab	0.00%	[redacted]	[redacted]	16.76%	[redacted]	[redacted]
Pembrolizumab + lenvatinib	0.00%	[redacted]	[redacted]	23.95%	[redacted]	[redacted]
Radiotherapy	23.06%	[redacted]	[redacted]	11.68%	[redacted]	[redacted]
No treatment	31.72%	[redacted]	[redacted]	17.78%	[redacted]	[redacted]

Key: CT, paclitaxel + carboplatin; SE, standard error.

Note: Subsequent treatment distribution based on KEYNOTE-868 (NRG-GY018), adjusted to reflect the clinical expert opinion[3]

Table 56: Subsequent therapy - drug formulation, dose, and total drug acquisition cost per week

Subsequent treatment	Drug	Dosing regimen	Cost per vial/pack	Vial/ tablet strength	Vials/tablets per admin	Total cost per week	Source
Carboplatin	Carboplatin	750mg IV Q3W	£20.22	150	2	£26.72	eMIT (December 2023)
			£48.09	450	1		
Carboplatin + paclitaxel	Carboplatin	750mg IV Q3W	£20.22	150	2	£35.99	eMIT (December 2023)
			£48.09	450	1		
	Paclitaxel	175mg/m2 IV Q3W	£24.43	300	1		
			£3.88	30	2		
Doxorubicin	Doxorubicin	60mg/m2 IV Q3W	£3.91	10	2	£9.49	eMIT (December 2023)
			£12.15	50	2		
Letrozole	Letrozole	17.5mg PO every week	£0.03	2.5	7	£0.22	eMIT (December 2023)
Megestrol	Megestrol	1,120mg PO every week	£0.65	160	7	£4.55	BNF online (accessed 26/06/2024)
Paclitaxel	Paclitaxel	80mg/m^2 IV Q1W	£9.13	100	1	£12.72	eMIT (December 2023)
			£3.88	30	2		
Pembrolizumab monotherapy	Pembrolizumab	200mg IV Q3W	£2,630	100	2	£1,753.33	BNF online (accessed 26/06/2024)
		400mg IV Q6W (maintenance dose)			4	£1,753.33	

Subsequent treatment	Drug	Dosing regimen	Cost per vial/pack	Vial/ tablet strength	Vials/tablets per admin	Total cost per week	Source
Pembrolizumab + lenvatinib	Pembrolizumab	200mg IV Q3W	£2,630	100	2	£2,423.93	BNF online (accessed 26/06/2024)
	Lenvatinib	140mg PO every week	£47.90	10	14		
	Pembrolizumab (maintenance)	400mg IV Q6W	£2,630	100	2	£2,423.93	BNF online (accessed 26/06/2024)
	Lenvatinib (maintenance)	140mg PO every week	£47.90	10	14		

Key: BNF, British National Formulary; eMIT, electronic market information tool; IV, intravenous; mg, milligrams; PO, per os; QxW, every x weeks.

Note: The drug costs provided in this table are list prices, and pembrolizumab and lenvatinib are expected to have a confidential discount

B.3.5.3. Adverse reaction unit costs and resource use

As outlined in Section B.3.4.4, the costs associated with Grade 3+ AEs occurring in more than 5% of patients in either arm are included in the economic model. The unit costs associated with managing these AEs are based on the most relevant cost databases for the UK setting (NHS reference costs 2022/2023).[112] A summary is presented in Table 57. Costs of adverse event management are applied as a one-off in the first model cycle and are the product of rate of AE per subject, number of AE episodes per subject, and the cost of each AE episode.

Table 57: Adverse event costs applied in the model

Event	Cost per episode (£)	Description	Source
Neutrophil count decreased	0.00	Assumed no cost (as with TA904)	TA904[50]
White blood cell count decreased	0.00	Assumed no cost (as with TA904)	TA904[50]
Anaemia	565.40	Weighted 2022/3 NHS Reference Cost (SA03G, SA03H, SA04G, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J, SA08G, SA08H, SA08J) National Schedule of NHS Costs - Year 2022-23	NHS Reference costs 2022/23[112]
Lymphocyte count decreased	0.00	Assumed no cost	N/A
Hypertension	735.07	2022/23 National Cost Collection. EB04Z (NES): Hypertension	NHS Reference costs 2022/23[112]

Key: N/A, not appropriate; NES, non-elective stay; NHS, National Health Service

B.3.5.4. Miscellaneous unit costs and resource use

Cost of testing

MMR testing is routinely done for all patients diagnosed with endometrial cancer to identify tumours with dMMR, as per NICE diagnostic guidance DG42.[48] Therefore, testing costs were not included within the base case economic analysis as no additional testing is required.

End-of-life cost

The model included a one-off "end-of-life (EOL)" cost at the end of a patient's life upon entry into the "Death" state, to reflect the costs of terminal care. The cost was calculated based on the average cost from Georghiou et al., which estimates the hospital and non-hospital costs

for people in the last 90 days of life relating to GP contacts, community nursing, local authority-funded social care, institutional hospice care and hospitals.[115] The cost was inflated to 2023 values using the PSSRU 2023, resulting in a cost of £7,287.99 per patient upon death.

B.3.6. Severity

Patients with advanced / recurrent EC experience worsening of both their expected length of life and quality of life compared with the general population. The QALY shortfall calculator developed by Schneider et al. 2021 was used to validate absolute and proportional QALY shortfall estimates using HRQoL norms from the Health Survey for England (HSE) 2017-2018 EQ-5D-5L mapped to EQ-5D-3L using the Hernández-Alava algorithm.[54,81,116]

The base case settings were used to inform the total expected QALYs of patients with the disease treated with CT. This was then compared with the total expected QALYs in patients without advanced/recurrent EC to evaluate the QALY shortfall and the applicability of a QALY severity modifier. Within the NICE framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within given cut-off ranges.

A summary of the QALY shortfall analysis is presented in Table 58. The expected discounted QALYs for people living with primary advanced or recurrent endometrial cancer on current standard treatment (i.e. CT) are also detailed in Table 59, based on the model results described in Section B.3.10 below. This resulted in an absolute QALY shortfall of [redacted] and a proportional shortfall of [redacted]% versus the general populations. As the absolute QALY shortfalls are all below 12 and the proportional QALY shortfalls are all less than 85%, therefore no multiplier for disease severity is considered appropriate for any of the comparisons.

Table 58: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
% Female	100%	Section B.3.2.1
Starting age	65.40	

Key: QALY, quality-adjusted life year

Table 59: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
10.99	[redacted]	[redacted]	[redacted]	x1

Key: QALY, quality-adjusted life year

B.3.7. Uncertainty

The approach presented in this submission has fully considered the currently available evidence. Nevertheless, there is still some residual uncertainty, which has been thoroughly explored where possible through discussion with clinical experts (Section B.3.14.2), implementing scenarios, testing key structural assumptions, and the evaluation of joint parameter uncertainty (see Section B.3.10 to B.3.12). The key areas of uncertainty in this economic analysis are described below:

- There was a high proportion of patients who were unblinded in the CT arm and received IO therapy before disease progression (Section B.2.6). The receipt of IO therapy by these patients may therefore bias any comparative results of pembrolizumab + CT versus placebo + CT in favour of the CT arm. The results used in the analysis (in the base case, and any other scenarios) may therefore be ultimately regarded as conservative.
- Validating the long-term extrapolations based on relatively immature clinical trial data for IO therapies is a common challenge in oncology indications where the only existing option under standard of care is chemotherapy. The assessment of an appropriate PFS and OS extrapolation is further complicated by the need to consider non-standard hazard functions, which have been observed with pembrolizumab across a number of indications as well as other IO therapies. As discussed in Section B.3.3, an extensive assessment and validation of different extrapolations has been undertaken following general guidance from NICE. While the choice of PFS curve selections has a minor impact on the results, the OS data for pembrolizumab + CT are relatively immature and there is uncertainty associated with long-term survival outcomes.
- As discussed in Section B.3.4, EQ-5D data were not collected in KEYNOTE-868 (NRG-GY018) and therefore NICE's preferred instrument to measure HRQoL was not available directly from the clinical trial. The approach in this submission considered a range of alternative data sources which included data available to the Company from the KEYNOTE-158 and KEYNOTE-826 trials which assessed pembrolizumab, as well as utility values from the published literature in EC and previous NICE appraisals in other gynaecological cancers. Out of all considered utilities, KEYNOTE-158 was considered to best reflect the base case population, as it provided EC-specific UK utilities.

- The use of different utility sources did not lead to significant changes to overall model results.
- In addition, patients in KEYNOTE-158 are in a later stage of EC, as all patients had received one prior line of therapy. The utility values from KEYNOTE-158 may therefore underestimate the true 1L EC utilities, as confirmed by clinical experts.[3] However, the impact of this has been explored via scenario analyses using alternative utilities from a range of sources, which showed this had a minimal impact on the cost-effectiveness estimates.

- There was a wide range of subsequent treatments received by patients in KEYNOTE-868 (NRG-GY018) following study treatment discontinuation. Discussions with UK clinical experts indicated that there are some differences in the options available in the UK compared to that used in the clinical trial. The impact of receiving a different mix of treatment has been considered in the costing approach in this submission, but there remains some uncertainty in any impact on efficacy.

B.3.8. Managed access proposal

The Company regards the improvement in PFS and OS observed in KEYNOTE-868 (NRG-GY018), and the results of the economic analysis, as justification for pembrolizumab + CT for patients with primary advanced or recurrent endometrial cancer to enter into routine commissioning. However, MSD prioritises access for patients and will therefore consider all available access routes.

B.3.9. Summary of base case analysis inputs and assumptions

B.3.9.1. Summary of base case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 60.

Table 60: Summary of variables applied in the economic model

Variable	Value	SE	Within PSA varied by	Reference to section in submission
Settings				
Time horizon	35	-	Not varied	B.3.2.2
Age (years)	65.40	[redacted]	Lognormal	B.3.2.1
BSA (m2)	[redacted]	[redacted]	Lognormal	
Weight (kg)	[redacted]	[redacted]	Lognormal	

Variable	Value	SE	Within PSA varied by	Reference to section in submission
Discount rate costs and outcomes	3.5%	-	Not varied	
Clinical outcomes				
PFS (pembrolizumab + CT)	Two-piece log-normal	-	-	B.3.3.3
PFS (CT)	1-knot hazard	-	-	
OS (pembrolizumab + CT)	3-knot odds	-	-	B.3.3.4
OS (CT)	Log-logistic	-	-	
TTD (pembrolizumab + CT)	Observed KM	-	-	B.3.3.5
TTD (CT)	Original	-	-	
Cost inputs				
Pembrolizumab (up to 6 cycles)	£5,260.00	-	Not varied	B.3.5.1
Pembrolizumab (cycles 7-20)	£10,520.00	-	Not varied	
Carboplatin	£80.15	-	Not varied	
Paclitaxel	£27.82	-	Not varied	
Pembrolizumab + CT admin cost	£277.00	NR	Gamma	
Pembrolizumab + CT maintenance admin cost	£217.00	NR	Gamma	
CT admin cost	£277.00	NR	Gamma	
Resource use cost				
CT scan	£160.83	NR	Gamma	B.3.5.2
Blood test	£5.00	NR	Gamma	
Outpatient physician visit	£179.00	NR	Gamma	
Resource use frequency				
CT scan, progression-free, on-treatment	0.09	NR	Lognormal	B.3.5.2
Blood test, progression-free, on-treatment	0.29	NR	Lognormal	
Outpatient physician visit,	0.29	NR	Lognormal	

Variable	Value	SE	Within PSA varied by	Reference to section in submission
progression-free, on-treatment				
CT scan, progression-free, off-treatment	0.08	NR	Lognormal	
Blood test, progression-free, off-treatment	0.00	NR	Lognormal	
Outpatient physician visit, progression-free, off-treatment	0.06	NR	Lognormal	
CT scan, progressed,	0.04	NR	Lognormal	
Blood test, progressed,	0.11	NR	Lognormal	
Outpatient physician visit, progressed,	0.11	NR	Lognormal	
AE cost				
Neutrophil count decreased	£0.00	NR	Gamma	B.3.5.3
White blood cell count decreased	£0.00	NR	Gamma	
Lymphocyte count decreased	£0.00	NR	Gamma	
Hypertension	£735.07	NR	Gamma	
Anaemia	£565.40	NR	Gamma	
AE probability				
Neutrophil count decreased, pembrolizumab + CT	14.1%	NR	Beta	B.3.4.4
White blood cell count decreased, pembrolizumab + CT	9.2%	NR	Beta	
Lymphocyte count decreased, pembrolizumab + CT	6.9%	NR	Beta	
Hypertension, pembrolizumab + CT	5.6%	NR	Beta	

Variable	Value	SE	Within PSA varied by	Reference to section in submission
Anaemia, pembrolizumab + CT	16.9%	NR	Beta	
Neutrophil count decreased, CT	14.4%	NR	Beta	
White blood cell count decreased, CT	7.7%	NR	Beta	
Lymphocyte count decreased, CT	4.9%	NR	Beta	
Hypertension, CT	5.2%	NR	Beta	
Anaemia, CT	11.6%	NR	Beta	
Utility inputs				
PFS	[redacted]	[redacted]	Beta	B.3.4.6
PD	[redacted]	[redacted]	Beta	

Key: AE, adverse event; BSA, body surface area; CT, paclitaxel + carboplatin; CT scan, computerised tomography scan; kg, kilogram; m, meter; NR, not reported; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; SE, standard error; TTD, time to treatment discontinuation

Note: SE of 20% was assumed where no SE was reported (NR)

B.3.9.2. Assumptions

Key assumptions of the economic analysis are summarised in Table 61. 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.

Table 61: Summary of assumptions of the economic analysis

Category	Assumption	Justification
Population and comparators	Adult patients with primary advanced or recurrent endometrial cancer.	Aligned with the decision problem for this appraisal.
	CT is an appropriate comparator for pembrolizumab in combination with chemotherapy.	Aligned with decision problem for this appraisal and confirmed by UK clinical experts
Model structure and settings	Baseline characteristics in line with all-comer populations from KEYNOTE-868 (NRG-GY018) and are reflective of the UK population	Confirmed by UK clinical experts
	The economic model health states capture the elements of the disease and care pathway that are important	The partitioned survival model structure is an established model framework to assess cost-effectiveness of oncology

Category	Assumption	Justification
	for patient health outcomes and NHS England costs.	treatments and used in previous NICE submissions in endometrial cancer. The health states are consistent with the natural disease progression in patients with advanced/recurrent endometrial cancer
	UK NHS and PSS	In line with NICE reference case
	Lifetime horizon	A 35-year time horizon was chosen based on the mean starting age in KEYNOTE-868 (NRG-GY018) assuming no patients survive beyond a mean age of 100 years. At this time point within the model, ~100% of patients are dead.
Clinical effectiveness	Treatment efficacy data sourced from KEYNOTE-868 (NRG-GY018) trial for treatments.	In line with the NICE reference case
	Based on the different mechanism of action for pembrolizumab + CT and CT, different survival trajectories and hazard profiles are expected; this is best reflected by independently fitted models for OS and PFS selected in the base case (and tested in scenarios).	In line with guidance from NICE DSU TSD 14[78]
	Treatment waning	There is currently no evidence suggestive of a treatment waning effect for IO therapies. This has been further supported in a recent NICE appraisal (GID-TA11197)[82]
Cost and resource use inputs	The duration of treatment for pembrolizumab + CT and CT are based on the KEYNOTE-868 (NRG-GY018) TTD KM data	The in-trial data adequately reflects the expected time on treatment for patients
	Patients receiving pembrolizumab + CT stop treatment with pembrolizumab at 24 months, which is applied to pembrolizumab acquisition and administration costs.	In line with current dosing recommendations
	Wastage of doses	In line with expected clinical practice
	Disease management costs are assumed to be dependent on treatment status and are treatment specific. Resource use estimates are aligned with previous submissions and were validated by UK clinical experts	Based on UK clinical expert opinion

Category	Assumption	Justification
	based on treatment phase, health state and treatment.	
	Treatment discontinuation for pembrolizumab + CT and CT aligned with KEYNOTE-868 (NRG-GY018) trial discontinuation criteria and treatment SmPCs.	NRG-GY018 trial and SmPC discontinuation criteria reflect clinical practice as validated by UK clinicians
	After discontinuation from treatment, all patients will go on to receive some form of licenced and reimbursed subsequent systemic treatment	In line with current clinical practice in UK
	Societal costs are excluded	In line with the NICE reference case
	End-of-life costs applied as a one-off cost in the year at which patients die.	Patients will accrue end-of-life care costs before they die and therefore, they are applied within the year of death.
Quality of life inputs	Progression-based utilities from KEYNOTE-158	KEYNOTE-158 was identified as the most appropriate source as it is closely aligned with the population of interest in this decision problem
	Grade ≥ 3 AEs from KEYNOTE-868 (NRG-GY018) ITT population for the subgroup of interest, in addition AE of special interest have been included. Cost incurred assumed occur in the first cycle of the model time horizon.	AEs were likely to occur rapidly after treatment and only require acute care.

Key: AE, adverse event; CT, paclitaxel + carboplatin; DSU, decision support unit; ITT, intention to treat; KM, Kaplan–Meier; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSS, personal social services; SmPC, Summary of Product Characteristics; TSD, technical support document; TTD, time to treatment discontinuation

B.3.10. Base case results

B.3.10.1. Base case incremental cost-effectiveness analysis results

Table 62 shows the cost-effectiveness results for pembrolizumab + CT versus CT using the list prices of all treatments. The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an additional [redacted] LYs and 1.33 QALYs gained per patient lifetime. Treatment with pembrolizumab + CT is associated with incremental costs of [redacted], resulting in an ICER of [redacted] per QALY gained. The ICER is lower than the willingness-to-pay threshold of £20,000-£30,000. This, paired with the improvement in health benefits for patients who would otherwise have limited access to suitable treatment

options, supports the addition of pembrolizumab + CT to the advanced/recurrent EC treatment pathway. The net health benefit (NHB) is displayed in Table 63 and is [redacted] and [redacted] for a WTP threshold of £20,000 and £30,000 respectively. This implies that overall population health would be increased as a result of introducing pembrolizumab + CT.

Table 62: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-
CT	[redacted]	3.79	[redacted]	[redacted]	[redacted]	1.33	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 63: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Pembrolizumab + CT	[redacted]	[redacted]	-	-	-	-
CT	[redacted]	[redacted]	[redacted]	1.33	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted on key model inputs, and involves sampling a value from each of the inputs uncertainty distribution over a large number of iterations. The gamma distribution was used for costs and resource use estimates as it is a non-negative distribution. The beta distribution was used for utilities and probabilities as it provides values between 0 and 1. Full details on the distributions used for key inputs can be found in Section B.3.9.

The results of the PSA based on 1,000 iterations are presented in Table 64. Pembrolizumab + CT was associated with [redacted] incremental costs and 1.43 incremental QALYs, which corresponds to an ICER of £[redacted] per QALY gained, which is less than the willingness-to-pay threshold of £20,000. Furthermore, the mean outcomes of the analysis are consistent with the base case results presented in Section B.3.10 (£[redacted] compared with £[redacted] per QALY gained), which signifies that the analysis is reliable despite uncertainties within parameter distributions.

Figure 48 shows the cost-effectiveness acceptability curve that demonstrates the probability that pembrolizumab + CT will be cost-effective against CT at a number of willingness-to-pay thresholds. At a willingness to pay of £30,000 the probability that pembrolizumab + CT is cost-effective is [redacted]%. Figure 49 presents the cost-effectiveness plane for pembrolizumab + CT which plots the mean incremental costs and QALYs of the PSA. The majority of the points lie with the north-east quadrant of the plane, indicating that pembrolizumab + CT is more costly and more effective than the comparator.

Table 64: Mean probabilistic base case results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-
CT	[redacted]	3.79	[redacted]	[redacted]	[redacted]	1.43	[redacted]

Key: ICER, incremental cost effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Figure 48: Cost effectiveness acceptability curve, pembrolizumab + CT versus CT

[redacted]

Figure 49: Cost-effectiveness plane: pembrolizumab + CT versus CT

[redacted]

B.3.11.2. One-way sensitivity analysis

One-way sensitivity analysis was conducted by varying key model parameters with its upper and lower limit, or by +/- 20% of its standard error when the limits are not available. The resultant ICERs were tabulated and ranked according to their highest deviation from the base case ICER. Figure 50 shows the 10 parameters which have the greatest influence on the ICER for pembrolizumab + CT versus CT. Parameters relating to second line immunotherapy in the CT arm, and utility values had the greatest effect on the ICER, although varying them around their standard error didn't not affect the cost-effectiveness conclusion at £30,000.

Figure 50: Tornado diagram showing OWSA results – pembrolizumab + CT versus CT

[redacted]Abbreviations: 2L, 2nd line; pd, progressed disease; sd, standard deviation

B.3.11.3. Scenario analysis

To further explore uncertainty within the model, an extensive list of scenarios was tested. These scenarios were listed throughout Section B.3, and the results are summarised within Table 65. The most impactful scenarios are 10 year time horizon, choosing the standard log-normal CT OS curve, or two-piece log-normal pembrolizumab + CT OS curve.

Table 65: Results for scenario analyses explored in the cost-effectiveness analysis

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
-	**Base case**				[redacted]	-
1	Time horizon	35	10	Estimating impact if a shorter time-horizon is selected	[redacted]	[redacted]
2		35	20		[redacted]	[redacted]
3	Discount rate (costs and utilities)	3.5%	1.5%	As per NICE guidance	[redacted]	[redacted]
4	Impact of AE (cost and disutilities)	Include	Exclude	Remove potential double counting of impact of AEs	[redacted]	[redacted]
5	Utility values	KN-158	KN-826 TTD	Explore a wide range of utility sources given that trial-based EQ-5D was not available from KEYNOTE-868 (NRG-GY018)	[redacted]	[redacted]
6		KN-158	KN-826 progression-based		[redacted]	[redacted]
7		KN-158	KN-775 (Swedish value set)		[redacted]	[redacted]
8		KN-158	KN-775 (Australian value set)		[redacted]	[redacted]
9	Subsequent treatment	Re-weighted trial-based treatment mix based on UK clinician inputs	Per KEYNOTE-868 (NRG-GY018)	Understand the impact of using different subsequent treatment composition in the UK, including IO	[redacted]	[redacted]
10	Subsequent treatment (CT): dostarlimab	Dostarlimab: 0.00%	Dostarlimab takes pembrolizumab monotherapy share: = 20.71%	Estimate impact of a scenario where dostarlimab becomes standard of care for 2L	[redacted]	[redacted]
11	Healthcare resource utilisation	UK clinician inputs	Healthcare resource use reported in TA963	Estimate impact of a different healthcare resource utilisation pattern	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
12	OS extrapolation	Pembrolizumab + CT: 3-knot odds CT: standard log-logistic	Pembrolizumab + CT: 3-knot odds CT: **standard generalised gamma**	CT: standard generalised gamma model as it had acceptable visual fit and concordance with landmark estimates, but with a more pessimistic survival in the CT arm	[redacted]	[redacted]
13			Pembrolizumab + CT: 3-knot odds CT: **standard log-normal**	CT: standard log-normal model as it had third best statistical fit, close alignment with observed hazards, and acceptable concordance with landmark estimates from UK experts but with a more optimistic long-term survival in the CT arm	[redacted]	[redacted]
14			Pembrolizumab + CT: two-piece **log-normal** CT: standard log-logistic	Pembrolizumab + CT: two-piece log-normal. Best statistical fit (AIC) among two-piece models, good visual fit to both the KM data and hazard (past 40 weeks). Good visual fit to the tail of the observed HR over time	[redacted]	[redacted]
15			Pembrolizumab + CT: **two-piece log-logistic** CT: standard log-logistic	Pembrolizumab + CT: two-piece log-logistic model, as it had the third best statistical fit among two-piece models with relatively close fit to observed KM, and provided a more pessimistic estimate of long-term survival in the pembrolizumab + CT arm	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
16			Pembrolizumab + CT: **2-knot (odds)** CT: standard log-logistic	Pembrolizumab + CT: 2-knot odds spline, as it had good statistical fit, captured the turning point in the hazard profile, and provided a more pessimistic estimate of long-term survival	[redacted]	[redacted]
17	PFS extrapolation	Pembrolizumab + CT: two-piece log-normal CT: 1-knot (hazard)	Pembrolizumab + CT: **two-piece log-logistic** CT: **two-piece log-normal**	Pembrolizumab + CT: Reasonable statistical and visual hazards fit, represents a conservative survival estimate compared to base case CT: Reasonable statistical fit, represents a more optimistic estimate for the CT arm	[redacted]	[redacted]
18	Treatment waning	No waning	Applied to 24.8% of pembrolizumab + CT of patients. Assumed start at 7 years (post treatment initiation) for 2 years before effect of CT is assumed	In accordance with previous IO therapies, waning is applied to patients who did not have an ORR. It is applied from 7 years based on the long-term follow-up reported in KEYNOTE-006 where no evidence of treatment effect waning is observed.	[redacted]	[redacted]
19	TTD extrapolation	Pembrolizumab + CT: Observed KM CT: Observed KM	Pembrolizumab + CT: Standard generalised gamma CT: Standard Weibull	Exploring a scenario where TTD is based on best-fitting extrapolations	[redacted]	[redacted]

Key: 2L, second-line; AE, adverse event; CT, paclitaxel + carboplatin; IO, immunotherapy; ICER, incremental cost effectiveness ratio; ITT, intention to treat; KM, Kaplan–Meier; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; TTD, time to treatment discontinuation

B.3.12. Subgroup analysis

To supplement the base case analyses in the all-comer population, an exploratory scenario was conducted within the pMMR and dMMR subgroups. These exploratory scenarios have been conducted based on data in the individual cohorts from KEYNOTE-868 (NRG-GY018), aligned to the design of the clinical trial. The analysis undertaken in the exploratory scenarios generally follow the same approach used and described in Document B for the all-comer population. More details of the subgroup analysis, including population-specific inputs and the curve extrapolation and selection process can be found in Appendix O. Full results from the subgroup analyses are presented in Appendix O.3.

B.3.12.1. dMMR subgroup

The results for the dMMR subgroup are driven by the substantial improvement in survival in both the progression-free and progressed health states with pembrolizumab + CT compared with CT alone. This supports the degree of cost-effectiveness in the all-comer population.

The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an additional [redacted] LYs and 2.14 QALYs. Treatment with pembrolizumab + CT is associated with incremental costs of [redacted], resulting in an ICER of [redacted] per QALY gained. The ICER is substantially lower than the willingness-to-pay threshold of £30,000/QALY.

B.3.12.2. pMMR subgroup

The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an additional [redacted] LYs and 1.18 QALYs. Treatment with pembrolizumab + CT is associated with incremental costs of [redacted], resulting in an ICER of [redacted] per QALY gained.

The results in the pMMR subgroup demonstrate that these patients would still experience a substantial incremental benefit from treatment with pembrolizumab, both in terms of the longevity and quality of life. This supports the degree of cost-effectiveness in the all-comer population.

B.3.13. Benefits not captured in the QALY calculation

As well as the significant health benefits explored within this submission, pembrolizumab + CT may also provide benefits to patients and caregivers which are not captured within the QALY calculation. Research indicates that endometrial cancer and its associated treatments can significantly affect the HRQoL of both caregivers and families of patients. Furthermore, as this analysis specifically examines the impact of EC, there may be additional concerns for individuals and families when the patient is of child-bearing age and wishes to have children in the near future.

B.3.14. Validation

B.3.14.1. Quality control

The economic model was extensively quality checked by an independent health economist who was not involved in the model's construction. The model was reviewed for coding errors, inconsistencies and the plausibility of inputs. The model was tested using a checklist of known modelling errors, which was developed based on publicly available checklists such as Drummond and Philips as a guide.[117,118] This also includes all checks listed in the published technical verification (TECH-VER) checklist.[119]

B.3.14.2. Clinical and economic validation

An advisory board was conducted with six clinical oncologists across the UK to validate key assumptions in the submission and explore potential areas of clinical uncertainty. [3] The advisory board was structured as brief presentations of clinical data and group discussion, conducted on 18 July 2024 over a total duration of 4 hours. The experts provided consent that anonymised responses would be used as part of this submission.

An outline of key points discussed and validated during the advisory board is provided below:

- General discussion regarding the treatment pathway in the UK, where experts agreed that treatment for primary EC includes chemotherapy, surgery, and radiotherapy; and discussion of the level of unmet need for patients with EC in the UK. This has been incorporated into Section B.1 and B.2.12 accordingly
- Review and confirmation regarding generalisability of the KEYNOTE-868 (NRG-GY018) trial population to the 1L EC patient population in the UK, which has been considered throughout this submission.

- Discussion and validation of long-term PFS and OS estimates, including landmark estimates and consideration of suitable survival extrapolations for patients treated with current standard of care in 1L EC. These discussions were highly detailed and informative for understanding the survival trajectories for patients in the CT arm. This informed the selection of PFS and OS curves for use in the cost-effectiveness model relevant for the decision problem (Section B.3.3.3 and B.3.3.4, respectively), as well as exploratory scenarios for the dMMR and pMMR subgroups (Appendix O)
- Discussion and confirmation of healthcare resource use based on treatment and progression status which were used directly in the cost-effectiveness model (Section B.3.5.2)

B.3.15. Interpretation and conclusions of economic evidence

This analysis is the first within the UK to assess the cost-effectiveness of pembrolizumab + CT followed by pembrolizumab maintenance as a 1L treatment for advanced/recurrent EC in the all-comer population. The economic evaluation uses data from the KEYNOTE-868 (NRG-GY018) trial, a Phase III trial comparing the efficacy and safety of pembrolizumab + CT versus placebo + CT in adults with advanced or recurrent EC. The trial offers both a direct comparison of both treatments of interest, and data for the population of interest. As per the final scope, a de novo cost-effectiveness model was developed to compare pembrolizumab + CT versus CT.

As well as patient level data from KEYNOTE-868 (NRG-GY018), information was collected from an economic SLR and a review of previous HTAs within advanced/recurrent EC. Inputs used within the model were also validated by clinical experts to confirm that they accurately reflected what was used within UK clinical practice. Curve selection for clinical endpoints was conducted in line with NICE DSU TSD guidelines[79], meaning that the base case analysis used the best-fitting survival extrapolations with other suitable models being explored within scenario analyses.

In the base case the incremental costs and QALYs of pembrolizumab + CT versus CT were estimated to be £[redacted] and 1.33 QALYs respectively, resulting in an ICER of £[redacted] per QALY gained. The probabilistic ICER was £[redacted], which is similar to that reported within the base case. OWSA and scenario analysis was also conducted within the analysis to explore uncertainty within the model. The results of these analyses yielded results consistent with that of the base case ICER value, suggesting that the base case analysis is plausible, robust and transparent.

The results of the economic evaluation presented here demonstrate that pembrolizumab + CT is a highly cost-effective treatment option for patients with advanced/ recurrent EC, representing a potential new treatment option for patients who currently have limited treatment choices and face a poor prognosis.

B.4. References

1. Morrison J, Balega J, Buckley L, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. European journal of obstetrics, gynecology, and reproductive biology 2022;270:50-89. (In eng). DOI: 10.1016/j.ejogrb.2021.11.423.

2. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev 2010;2010(12):Cd007926. (In eng). DOI: 10.1002/14651858.CD007926.pub2.

3. MSD. Key Summary, Plan of Action and Meeting Summary for the UK Endometrial Cancer Advisory Board 2024. 2024.

4. European Medicines Agency. Keytruda SmPC. 01 January (https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf).

5. Merck. Keytruda (pembrolizumab) Plus Chemotherapy Significantly Improved Progression-Free Survival Compared to Chemotherapy Alone as First-Line Therapy for Advanced or Recurrent Endometrial Carcinoma, Regardless of Mismatch Repair Status. 27 March 2023 (https://www.merck.com/news/keytruda-pembrolizumab-plus-chemotherapy-significantly-improved-progression-free-survival-compared-to-chemotherapy-alone-as-first-line-therapy-for-advanced-or-recurrent-endometrial-carcinoma/#:~:text=About%20endometrial%20carcinoma&text=In%20the%20U.S.%2C%20it%20is,15th%20most%20common%20cancer%20overall.).

6. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. The New England journal of medicine 2023;388(23):2159-2170. (In eng). DOI: 10.1056/NEJMoa2302312.

7. Cancer Research UK. What is womb cancer? 08 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/about).

8. Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet 2021;155 Suppl 1(Suppl 1):45-60. (In eng). DOI: 10.1002/ijgo.13866.

9. Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology 2022;33(9):860-877. (In eng). DOI: 10.1016/j.annonc.2022.05.009.

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

11. Leon-Castillo A. Update in the molecular classification of endometrial carcinoma. Int J Gynecol Cancer 2023;33(3):333-342. (In eng). DOI: 10.1136/ijgc-2022-003772.

12. Cancer Research UK. Symptoms of womb cancer. 09 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/symptoms).

13. National Disease Registration Service. Case-mix adjusted percentage cancers diagnosed at Stages 1 and 2 by CCG in England, 2019 data tables. (https://files.digital.nhs.uk/6A/DBCFFF/CMA%202013-2019%20Data.ods).

14. Cancer Research UK. Uterine cancer mortality statistics. 31 May 2022 (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/mortality#heading-Zero).

15. Huijgens AN, Mertens HJ. Factors predicting recurrent endometrial cancer. Facts Views Vis Obgyn 2013;5(3):179-86. (In eng) (https://www.ncbi.nlm.nih.gov/pubmed/24753943).

16. 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. Int J Gynecol Cancer 2018;28(3):614-622. (In eng). DOI: 10.1097/IGC.0000000000001204.

17. Gao H, Xiao M, Bai H, Zhang Z. Sexual Function and Quality of Life Among Patients With Endometrial Cancer After Surgery. Int J Gynecol Cancer 2017;27(3):608-612. (In eng). DOI: 10.1097/IGC.0000000000000905.

18. McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: Not your grandmother's cancer. Cancer 2016;122(18):2787-98. (In eng). DOI: 10.1002/cncr.30094.

19. Wan YL, Beverley-Stevenson R, Carlisle D, et al. Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions. Gynecologic oncology 2016;143(2):287-293. (In eng). DOI: 10.1016/j.ygyno.2016.08.333.

20. Cao SY, Fan Y, Zhang YF, Ruan JY, Mu Y, Li JK. Recurrence and survival of patients with stage III endometrial cancer after radical surgery followed by adjuvant chemo- or chemoradiotherapy: a systematic review and meta-analysis. BMC cancer 2023;23(1):31. (In eng). DOI: 10.1186/s12885-022-10482-x.

21. Office for National Statistics. Cancer survival in England - adults diagnosed. (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed).

22. Fountzilas E, Kotoula V, Pentheroudakis G, et al. Prognostic implications of mismatch repair deficiency in patients with nonmetastatic colorectal and endometrial cancer. ESMO Open 2019;4(2):e000474. (In eng). DOI: 10.1136/esmoopen-2018-000474.

23. Cancer Research UK. Uterine cancer incidence. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero).

24. Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. Br J Cancer 2022;126(12):1765-1773. DOI: 10.1038/s41416-022-01718-5.

25. Cleveland Clinic. Uterine Cancer (Endometrial Cancer). 21 March 2023 (https://my.clevelandclinic.org/health/diseases/16409-uterine-cancer).

26. American Cancer Society. Endometrial Cancer Risk Factors. 27 March 2019 (https://www.cancer.org/cancer/types/endometrial-cancer/causes-risks-prevention/risk-factors.html).

27. Cancer Research UK. Types and grades of womb cancer. 19 Mar 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/stages-types-grades/types-grades).

28. Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162(2):383-394. DOI: 10.1002/ijgo.14923.

29. Hong R, Liu W, DeLair D, Razavian N, Fenyo D. Predicting endometrial cancer subtypes and molecular features from histopathology images using multi-resolution deep learning models. Cell reports Medicine 2021;2(9):100400. (In eng). DOI: 10.1016/j.xcrm.2021.100400.

30. Bogani G, Ray-Coquard I, Concin N, et al. Endometrial carcinosarcoma. Int J Gynecol Cancer 2023;33(2):147-174. DOI: 10.1136/ijgc-2022-004073.

31. Cancer Research UK. Stages of womb cancer. 09 April 2023 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/stages-types-grades/stages).

32. ONCOLOGY N. NRG-GY018 protocol - A PHASE III RANDOMIZED, PLACEBO-CONTROLLED STUDY OF PEMBROLIZUMAB (MK-3475, NSC #776864) IN ADDITION TO PACLITAXEL AND CARBOPLATIN FOR MEASURABLE STAGE III OR IVA, STAGE IVB OR RECURRENT ENDOMETRIAL CANCER. 2022.

33. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther 2018;35(4):577-589. (In eng). DOI: 10.1007/s12325-018-0683-3.

34. 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. (In eng). DOI: 10.1016/j.ygyno.2006.02.011.

35. Siegenthaler F, Lindemann K, Epstein E, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecologic oncology 2022;165(2):230-238. DOI: 10.1016/j.ygyno.2022.02.024.

36. NHS digital. Cancer Registrations Statistics, England 2021- First release, counts only. (https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only#).

37. Office for National Statisitics. Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018. 12 August 2019 (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018).

38. Cancer Research UK. Survival for womb cancer. 19 Mar 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/survival).

39. NHS. Symptoms - womb (uterus) cancer. 21 October 2021 (https://www.nhs.uk/conditions/womb-cancer/symptoms/).

40. American Cancer Society. Signs and Symptoms of Endometrial Cancer. 27 March 2019 (https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/signs-and-symptoms.html).

41. Gil-Ibanez B, Davies-Oliveira J, Lopez G, Diaz-Feijoo B, Tejerizo-Garcia A, Sehouli J. Impact of gynecological cancers on health-related quality of life: historical context, measurement instruments, and current knowledge. Int J Gynecol Cancer 2023;33(11):1800-1806. DOI: 10.1136/ijgc-2023-004804.

42. Zandbergen N, de Rooij BH, Vos MC, et al. Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis. Acta Oncol 2019;58(5):790-800. DOI: 10.1080/0284186X.2018.1560498.

43. Peaches Trust. Stories. (https://peachestrust.org/stories/).

44. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014;23(2):121-30. (In eng). DOI: 10.1002/pon.3409.

45. Jonsdottir B, Wikman A, Sundstrom Poromaa I, Stalberg K. Advanced gynecological cancer: Quality of life one year after diagnosis. PloS one 2023;18(6):e0287562. (In eng). DOI: 10.1371/journal.pone.0287562.

46. National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral. 02 October (https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer).

47. Cancer Research UK. Tests for womb cancer. 27 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/getting-diagnosed/tests-womb-cancer).

48. National Institute for Health and Care Excellence (NICE). Testing strategies for Lynch syndrome in people with endometrial cancer. (https://www.nice.org.uk/guidance/dg42).

49. National Institute for Health and Care Excellence (NICE). Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer. (https://www.nice.org.uk/guidance/ipg356).

50. National Institute for Health and Care Excellence (NICE). Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. (https://www.nice.org.uk/guidance/TA904).

51. National Institute for Health and Care Excellence (NICE). Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer

with high microsatellite instability or mismatch repair deficiency. (https://www.nice.org.uk/guidance/ta914).

52. 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 2021. 16 March 2022 (https://www.nice.org.uk/guidance/ta779).

53. National Institute for Health and Care Excellence (NICE). Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. (https://www.nice.org.uk/guidance/ta963).

54. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. 31 October 2023 (https://www.nice.org.uk/process/pmg36).

55. ClinicalTrials.gov. Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer. 16 May 2024 (https://classic.clinicaltrials.gov/ct2/show/NCT03914612).

56. Senovilla L, Vitale I, Martins I, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science (New York, NY) 2012;337(6102):1678-84. (In eng). DOI: 10.1126/science.1224922.

57. Sevko A, Michels T, Vrohlings M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. J Immunol 2013;190(5):2464-71. (In eng). DOI: 10.4049/jimmunol.1202781.

58. Liechtenstein T, Perez-Janices N, Gato M, et al. A highly efficient tumor-infiltrating MDSC differentiation system for discovery of anti-neoplastic targets, which circumvents the need for tumor establishment in mice. Oncotarget 2014;5(17):7843-57. (In eng). DOI: 10.18632/oncotarget.2279.

59. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20(11):2831-7. (In eng). DOI: 10.1158/1078-0432.CCR-13-3141.

60. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. Cellular immunology 2010;263(1):79-87. (In eng). DOI: 10.1016/j.cellimm.2010.03.001.

61. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer cell 2015;28(6):690-714. (In eng). DOI: 10.1016/j.ccell.2015.10.012.

62. Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer 2018;118(8):1130-1141. (In eng). DOI: 10.1038/s41416-018-0029-6.

63. Donkers H, Bekkers R, Massuger L, Galaal K. Systematic review on socioeconomic deprivation and survival in endometrial cancer. Cancer Causes Control 2019;30(9):1013-1022. (In eng). DOI: 10.1007/s10552-019-01202-1.

64. Njoku K, Barr CE, Hotchkies L, Quille N, Wan YL, Crosbie EJ. Impact of socio-economic deprivation on endometrial cancer survival in the North West of England: a prospective database analysis. Bjog 2021;128(7):1215-1224. (In eng). DOI: 10.1111/1471-0528.16618.

65. Illah O, Adeeko D, Olaitan A, Gentry-Maharaj A. Racioethnic Disparities in Endometrial Cancer Outcomes. Diagnostics (Basel) 2024;14(4) (In eng). DOI: 10.3390/diagnostics14040417.

66. MSD. A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer. 2023.

67. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Efficacy (All-comer Participants Population). 2024.

68. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Disposition, Demographics and Concomitant Medications (All-comer Participants Population). 2024.

69. MSD. MK-3475 Supplemental Statistical Analysis Plan (sSAP). 2023.

70. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Analysis of Adverse Events (All-comer Participants Population). 2024.

71. Antill Y, Kok P, Robledo K, et al,. Activity of durvalumab in advanced endometrial cancer (AEC) according to mismatch repair (MMR) status: the phase II PHAEDRA trial (ANZGOG1601). J Clin Oncol 2019;37(15):Suppl, 5501.

72. Konstantinopoulos PA, Luo W, Liu JF, et al. Phase II Study of Avelumab in Patients With Mismatch Repair Deficient and Mismatch Repair Proficient Recurrent/Persistent Endometrial Cancer. J Clin Oncol 2019;37(30):2786-2794. (In eng). DOI: 10.1200/jco.19.01021.

73. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. J Immunother Cancer 2022;10(1) (In eng). DOI: 10.1136/jitc-2021-003777.

74. Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1-Positive Endometrial Cancer: Results From the KEYNOTE-028 Study. J Clin Oncol 2017;35(22):2535-2541. (In eng). DOI: 10.1200/jco.2017.72.5952.

75. Alvaro Ingles Russo Garces. Demographics and Survival Outcomes in Patients with Advanced or Recurrent Endometrial Cancer in the English Real-World Setting. (https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/0214cb59-a124-

470f-af22-724a2e9bcb91/0214cb59-a124-470f-af22-724a2e9bcb91_viewable_rendition__v.pdf?REF--ALL-004799).

76. Kim J, Lim J, Lee SW, et al. Immune checkpoint inhibitors with chemotherapy for primary advanced mismatch repair-deficient endometrial cancer: A cost-effectiveness analysis. Gynecologic oncology 2023;179:106-114. DOI: 10.1016/j.ygyno.2023.11.004.

77. NICE DSU. NICE DSU TSD 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. March 2013 (https://www.sheffield.ac.uk/nice-dsu/tsds/full-list).

78. NICE DSU. NICE DSU TSD 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. March 2013 (https://www.sheffield.ac.uk/nice-dsu/tsds/full-list).

79. NICE DSU. NICE DSU TSD 19: Partitioned survival analysis for decision modelling in health care: a critical review. (https://www.sheffield.ac.uk/nice-dsu/tsds/full-list).

80. NICE DSU. NICE DSU TSD 21: Flexible Methods for Survival Analysis. (https://www.sheffield.ac.uk/nice-dsu/tsds/full-list).

81. Office of National Statistics. National life tables: England and Wales. (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables).

82. National Institute for Health and Care Excellence (NICE). Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]. 30 July 2024 (https://www.nice.org.uk/guidance/indevelopment/gid-ta11197/documents).

83. NHS. Chemotherapy protocol - gynaecological cancer. (https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Uterine-cancer/Endometrial-Carboplatin-Cisplatin-Paclitaxel-RT-21day.pdf).

84. Palmer S, Borget I, Friede T, et al. A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies. Value in Health 2023;26(2):185-192. DOI: https://doi.org/10.1016/j.jval.2022.07.009.

85. Herbst RS, Garon EB, Kim D-W, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1–Positive Advanced NSCLC. Journal of Thoracic Oncology 2021;16(10):1718-1732. DOI: 10.1016/j.jtho.2021.05.001.

86. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol 2019;37(7):537-546. (In eng). DOI: 10.1200/jco.18.00149.

87. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol 2021;39(21):2339-2349. (In eng). DOI: 10.1200/jco.21.00174.

88. Kumar AR, Devan AR, Nair B, Vinod BS, Nath LR. Harnessing the immune system against cancer: current immunotherapy approaches and therapeutic targets. Mol Biol Rep 2021;48(12):8075-8095. (In eng). DOI: 10.1007/s11033-021-06752-9.

89. Bungey G, Brown L, De Boisvilliers S, et al. The Use of Akaike Information Criterion and Bayesian Information Criterion Rules of Thumb in Nice Oncology Appraisals: A Targeted Review. ISPOR Europe 2021. Copenhagen: Denmark; 2021.

90. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol 2023;41(11):1992-1998. (In eng). DOI: 10.1200/jco.22.01989.

91. Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19(2):462-8. (In eng). DOI: 10.1158/1078-0432.Ccr-12-2625.

92. Robert C, Carlino MS, McNeil C, et al. Seven-Year Follow-Up of the Phase III KEYNOTE-006 Study: Pembrolizumab Versus Ipilimumab in Advanced Melanoma. J Clin Oncol 2023;41(24):3998-4003. (In eng). DOI: 10.1200/jco.22.01599.

93. Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Annals of oncology : official journal of the European Society for Medical Oncology 2019;30(4):582-588. (In eng). DOI: 10.1093/annonc/mdz011.

94. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. The New England journal of medicine 2015;372(21):2018-28. (In eng). DOI: 10.1056/NEJMoa1501824.

95. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 2016;375(19):1823-1833. (In eng). DOI: 10.1056/NEJMoa1606774.

96. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38(1):1-10. (In eng). DOI: 10.1200/jco.19.02105.

97. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. The New England journal of medicine 2021;385(20):1856-1867. DOI: 10.1056/NEJMoa2112435.

98. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics 2023;41(2):199-207. (In eng). DOI: 10.1007/s40273-022-01218-7.

99. Thurgar E, Gouldson M, Matthijsse S, et al. Cost-effectiveness of pembrolizumab compared with chemotherapy in the US for women with previously treated deficient mismatch repair or high microsatellite instability unresectable or metastatic

endometrial cancer. J Med Econ 2021;24(1):675-688. DOI: 10.1080/13696998.2021.1917140.

100. O'Malley DM, Bariani GM, Cassier PA, et al. Health-related quality of life with pembrolizumab monotherapy in patients with previously treated advanced microsatellite instability high/mismatch repair deficient endometrial cancer in the KEYNOTE-158 study. Gynecologic oncology 2022;166(2):245-253. DOI: 10.1016/j.ygyno.2022.06.005.

101. Pharmaceutical Benefits Advisory Committee. Pembrolizumab (Endometrial cancer): Solution concentrate for I.V. infusion 100 mg in 4 mL. 1 July 2022 (https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-03/pembrolizumab-endometrial-cancer-solution-concentrate-for-iv-infusion).

102. Ralph L, Young K, Upadhyay N, et al. Cost effectiveness of pembrolizumab plus lenvatinib compared with chemotherapy for treating previously treated advanced endometrial cancer in Sweden. J Med Econ 2024;27(1):483-491. DOI: 10.1080/13696998.2024.2329022.

103. Lachance JA, Stukenborg GJ, Schneider BF, Rice LW, Jazaeri AA. A cost-effective analysis of adjuvant therapies for the treatment of stage I endometrial adenocarcinoma. Gynecologic oncology 2008;108(1):77-83. DOI: 10.1016/j.ygyno.2007.08.072.

104. Hildebrandt T, Thiel FC, Fasching PA, et al. Health utilities in gynecological oncology and mastology in Germany. Anticancer Res 2014;34(2):829-35. (In eng) (https://www.ncbi.nlm.nih.gov/pubmed/24511019).

105. 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. (https://www.nice.org.uk/guidance/TA962).

106. 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. Eur J Cancer Care (Engl) 2006;15(1):65-73. DOI: 10.1111/j.1365-2354.2005.00623.x.

107. 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):e0165539. DOI: 10.1371/journal.pone.0165539.

108. Dixon P, Beaver K, Williamson S, Sutton C, Martin-Hirsch P, Hollingworth W. 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):415-427. (In eng). DOI: 10.1007/s40258-018-0378-6.

109. Jones KCaW, Helen and Birch, Sarah and Castelli, Adriana and Chalkley, Martin and Dargan, Alan and Forder, Julien E. and Gao, Minyue and Hinde, Seb and Markham, Sarah and Premji, Shainur and Findlay, D. and Teo, H. Unit Costs of Health and Social Care 2023 Manual. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York), 2024.

110. British National Formulary. Pembrolizumab [Specialist drug]. (https://bnf.nice.org.uk/drugs/pembrolizumab-specialist-drug/).

111. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 5 April 2024 (https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit).

112. NHS. 2022/23 National Cost Collection Data. (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/).

113. National Institute for Health and Care Excellence (NICE). Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma. 12 June 2024 (https://www.nice.org.uk/guidance/ta983).

114. Fresenius Kabi. Summary of Product Characteristics: Paclitaxel. (https://www.fresenius-kabi.com/my/documents/SPC_PACLITAXEL_KABI_6_mgml_Filaxis.pdf).

115. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 26 September 2014 (https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life).

116. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. 12 January 2022 (https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d).

117. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8(36):iii-iv, ix-xi, 1-158. (In eng). DOI: 10.3310/hta8360.

118. Drummond MF, Schulpher MJ, Torrance G. Methods for the economic evaluation of health care programme. Oxford: Oxford University Press, 2005.

119. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics 2019;37(11):1391-1408. (In eng). DOI: 10.1007/s40273-019-00844-y.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381]

Summary of Information for Patients (SIP)

September 2024

File name	Version	Contains confidential information	Date
ID6381_Pembro_1l_EC_SIP_v1.0	1.0	No	4th September 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Pembrolizumab (KEYTRUDA®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Pembrolizumab, in combination with chemotherapy (followed by pembrolizumab maintenance), is intended to be used as the first treatment option for adults with advanced or recurrent endometrial cancer. “Advanced” means that the cancer has spread beyond its original site to other parts of the body, and that it is in a later stage (Stage III or IVA; see 2a for more information on staging). “Recurrent” means that the cancer has returned.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The application for marketing authorisation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) is currently ongoing. Please refer to Section B.1.2. of the company submission for the anticipated dates for approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Stakeholder	Financial transaction	Have met with MSD	Relationship
Cancer52	Yes (2023)	Yes	MSD paid a fee of £10,000 for corporate membership of Cancer52 between 12 December 2022 and 31 December 2023. MSD is in ongoing conversations to renew this membership for 2024/25.
Eve Appeal	No	Yes	MSD has met with Eve Appeal several times to discuss shared priorities. MSD is in active dialogue with Eve Appeal regarding financial support for activity around HPV elimination in 2024.
Macmillan Cancer Support	No	Yes	MSD has met with Macmillan several times to discuss shared priorities.
Maggie's Centres	No	Yes	MSD has met with Maggie's once in 2024 to discuss shared priorities. MSD sponsored the UK charity for TNBC to host a roundtable on TNBC. The roundtable was hosted at a Maggie's Centre in Nottingham.
Peaches Womb Cancer Trust	No	Yes	MSD has met with Peaches several times in 2023 and 2024 to discuss shared priorities. Peaches applied for an MSD grant in 2024, but was unsuccessful due to the highly competitive nature of the programme.
Tenovus Cancer Care	Yes (2023)	Yes	MSD is a corporate member of Wales Cancer Industry Forum, of which Tenovus is a leading partner. MSD provided sponsorship for, and attended, a policy roundtable hosted by Tenovus in April 2023. The total sponsorship in 2023 came to £6,300.
Key: HPV, human papillomavirus; TNBC, triple-negative breast cancer.			

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Endometrial cancer (EC) is a cancer of the inner lining of the uterus (womb) called the endometrium.[1] It is the fourth most common female cancer in the UK, with approximately 9,700* new diagnoses each year.[1] The number of new diagnoses of EC is increasing; projections calculated by the Cancer Intelligence Team at Cancer Research UK suggest that by 2038–2040 there will be approximately 11,800* new diagnoses of EC annually in the UK.[2]

Risk factors for EC include obesity, hormonal changes, age and family history.[3] Hormonal changes that increase the risk of EC may be a result of a higher than average number of menstrual cycles over the course of a person's life, use of medication such as oestrogen therapy or tamoxifen, and the presence of ovarian tumours or polycystic ovary syndrome.[3]

EC is classified into different types. It is also graded and staged to determine how advanced it is and how it should be treated. These categorisation systems are as follows:

- **Types:** includes endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, mixed carcinoma, undifferentiated carcinoma, carcinosarcoma, and others. Endometrioid adenocarcinoma and serous carcinoma are the most common[4]
- **Grades:** Low grade (Grades 1 and 2) and high grade (Grade 3). High-grade tumours grow faster and are more likely to spread[5]
- **Staging[4]:**
  - Stage I: Cancer is in the uterus and ovary
  - Stage II: Cancer has invaded the cervix
  - Stage III: Cancer has spread locally or regionally
  - Stage IV: Cancer has spread to distant sites, such as the bladder or intestines

EC is a disease with four different molecular subtypes as defined by The Cancer Genome Atlas, each with different outcomes for patients: [5-8]

- *POLE*-ultramutated (*POLE*mut): This type of EC has favourable outcomes, meaning there is a higher chance of controlling the disease for these patients
- p53-abnormal (p53abn): This type of EC has poor outcomes. Patients with this type may not respond as well to treatment, and there is a lower chance of controlling the disease
- No specific molecular profile (NSMP): This is the most common type of EC. Patients with this type have intermediate outcomes, meaning their outlook is somewhere in the middle of *POLE*mut and p53abn
- Mismatch repair deficient (dMMR): This type is also associated with intermediate outcomes. Like NSMP, their outlook is somewhere in the middle

Most diagnoses of EC are diagnosed early, due to 'red flag' symptoms like abnormal vaginal bleeding.[9] Cases of EC that are diagnosed in advanced stages have poorer outcomes. However, for those patients diagnosed at the most advanced stage (Stage IV), only 15%* of patients will still be alive at 5 years after diagnosis.[10-12] In addition, approximately 18% of patients with EC experience recurrence, which is where the cancer comes back.[13] Recurrent disease is associated with poor prognosis; only 20% of patients with recurrent disease will still be alive at 5 years after diagnosis, compared with 89% of patients without recurrent disease.[14] Patients who are diagnosed with later-stage disease (Stage IIB–IV) have a higher risk of recurrence.[14]

EC comes with many symptoms. The most common symptom is abnormal vaginal bleeding, especially in post-menopausal women.[10] Other symptoms can include heavy bleeding between periods, unusual vaginal discharge, pelvic pain, blood in urine, and unintended weight loss.[15,16] Patients with EC often have a lower quality of life compared with the general population, experiencing higher levels of anxiety, depression, pain, fatigue, and difficulties with physical, social and emotional functioning.[17,18] Additionally, with advanced disease or disease recurrence, quality of life is reported to decrease further, with an increase in anxiety and depression.[19,20]

Notes: *Statistics shared are for uterine cancer. EC is the most common type of uterine cancer, accounting for approximately 95% of diagnoses. Therefore, these statistics are referred to as EC for simplicity.[2,21]

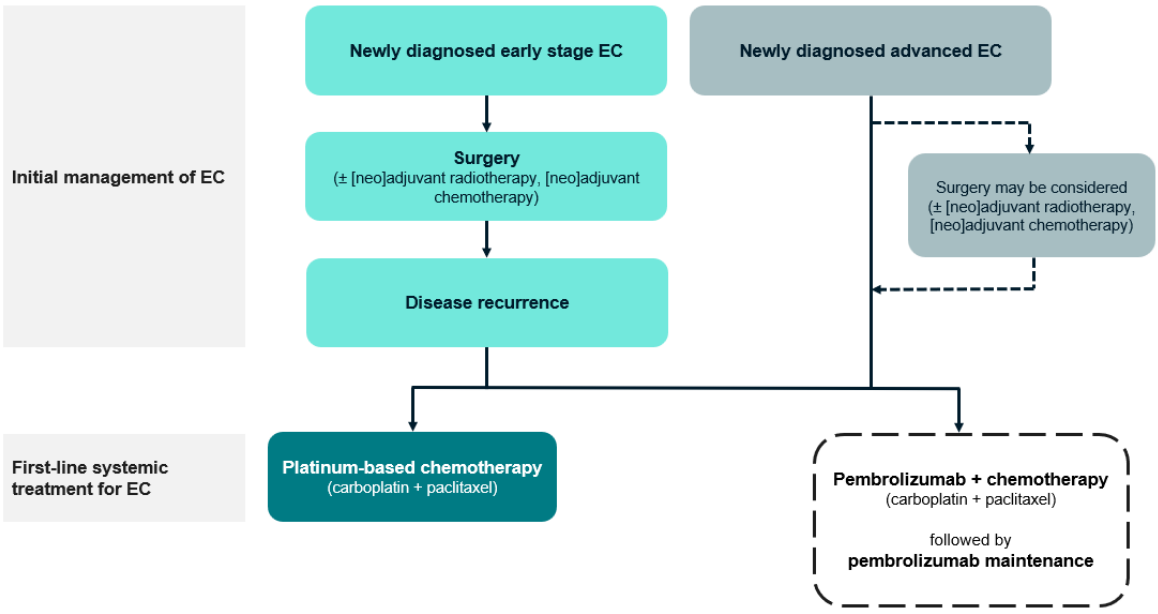
2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Currently, there is no screening programme for EC in the UK. If a patient has symptoms, their GP should refer them for further tests using the suspected cancer referral pathway.[22] Following referral, women should undergo a full abdominal and pelvic examination, which involves checking the cervix with a speculum, a transvaginal ultrasound to measure the thickness of the endometrium, and additional imaging tests such as X-rays, computed tomography (CT) scans and magnetic resonance imaging (MRI) scans.[5,23,24] These tests help to determine the location, size and possible spread of the tumour. A biopsy will be performed to determine the type, grade, and molecular characteristics of the cancer.[5,23,24]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
The goal of currently available treatments for patients with advanced (Stage III or IVA) or recurrent EC is to provide relief from symptoms, maintain quality of life, prevent disease progression, delay time to next treatment, and extend life. This differs from early-stage disease, where the intent is usually curative. The treatment of patients with advanced or recurrent EC depends on the patient's overall health, the extent of the cancer, the previous treatments they have received, their suitability for surgery, the molecular profile of their disease (such as hormone receptor status and mismatch repair deficiency), and their personal preferences.[5,24] Currently, there are limited treatment options for patients with advanced/recurrent EC in the UK. The latest guidelines for this type of cancer in the UK come from the British Gynaecological Cancer Society (BGCS), the European Society of Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) (ESGO/ESTRO/ESP).[5,7,24] Figure 1 presents the current treatment pathway with the proposed placement of pembrolizumab plus chemotherapy.

Figure 1: Treatment pathway of primary advanced or recurrent EC with the proposed positioning of pembrolizumab plus chemotherapy



Key: EC, endometrial cancer.

Notes: Proposed treatment positioning is indicated by the dashed box.
Source: British Gynaecological Cancer Society guidelines.[24]

Patients who are newly diagnosed with early-stage EC usually receive surgery. Radiation therapy and chemotherapy are often offered alongside surgery. In patients where the disease recurs, the first treatment option is chemotherapy, specifically the combination of the drugs carboplatin and paclitaxel. This is recommended regardless of the specific subtype of EC.[24] For some patients, carboplatin plus paclitaxel is unsuitable, due to health status, the presence of other conditions or personal choice. These patients may be offered hormone therapy, carboplatin alone, or other chemotherapy options.[24]

Patients who are diagnosed with advanced EC may be considered for surgery as the initial management of EC; however, not all patients are suitable. Similar to patients who have disease recurrence following surgery for early-stage EC, the first treatment option for advanced EC is chemotherapy (carboplatin and paclitaxel).[24]

Pembrolizumab combined with chemotherapy, followed by maintenance pembrolizumab, is a new treatment option for adults with newly diagnosed advanced or recurrent EC. This would be used as a first treatment option.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

EC presents with a wide range of symptoms. The most common symptom is abnormal vaginal bleeding, particularly in women who have gone through menopause.[10] Other symptoms include heavy or ongoing bleeding between periods, abnormal vaginal discharge, pelvic pain, blood in urine, or unintended weight loss.[15,16] These symptoms can be very severe and have a significant impact on a patient's daily life. Abnormal bleeding and discharge can be distressing and inconvenient, while pelvic pain and other physical symptoms can limit mobility and make everyday activities difficult. Additionally, the emotional toll of dealing with these persistent symptoms can lead to increased anxiety and depression, further affecting the overall quality of life for patients with EC. Multiple case reports indicate that patients often struggle with the symptoms of EC and its treatments, which can significantly impact their mental health.[25]

Patients with EC are often shown to have a lower quality of life, with higher levels of anxiety, depression, pain, fatigue, and difficulties with both physical, social and emotional functioning.[17,18] One study found that 23% of patients with gynaecological cancers, like EC, suffered from depression. This rate is higher compared with other cancers, such as breast cancer (11%) and respiratory tract cancer (3%).[26] This is especially true for those with advanced EC, as they tend to have more health issues and a higher tumour stage, which often results in a poorer quality of life. With cancer recurrence, the quality of life of the patient usually decreases even further, with increased anxiety and depression.[19,20]

For the patients with advanced or recurrent EC who are eligible for surgery (see 2c), the procedure often involves removing the uterus and other affected tissues, which can damage sex organs and affect sexual function. A study found that 68.6% of patients experienced sexual problems after treatment. After surgery, patients may also have pain during sex, trouble moving around, and difficulty doing everyday activities. The impact of these physical limitations on patients' mental well-being can be substantial.[20,25]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

An important role of the immune system is the ability to be able to tell the difference between normal and abnormal cells. The level of activity of immune cells, such as T cells, is crucial to maintaining a balanced immune response.[27,28]

Normally, a protein called programmed death-ligand 1 (PD-L1), which naturally occurs on cells, plays an important role in maintaining this balanced immune response.[27,28] PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This way, the body ensures that normal cells are protected from excessive damage. However, PD-L1 is produced in larger amounts on cancerous cells than normal cells. As a result, when binding to PD-1 on immune T cells, this interaction tricks the immune system into protecting the tumour from being attacked by the body's immune system.[27,28]

PD-1 inhibitors, such as pembrolizumab, act to block the interaction between PD-1 and PD-L1 – and, by doing so, boost the immune response. This helps the person's own immune cells to detect and attack the cancer cells.[27,28]

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link:
https://www.medicines.org.uk/emc/product/2498

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pembrolizumab is intended to be used in combination with chemotherapy (specifically carboplatin and paclitaxel). New research shows that, in addition to killing cancer cells and stopping cell growth, chemotherapy might also help activate the immune response to target the cancer cells.[29-34] As explained in 3a, pembrolizumab is a PD-1 inhibitor, which means it blocks the interaction between PD-1 and PD-L1 and boosts the immune system's ability to attack the cancer. Therefore, pembrolizumab can be used together with chemotherapy to help the immune system fight the cancer more effectively and for longer.

Chemotherapy with paclitaxel and carboplatin is the standard first-line treatment that patients with advanced/recurrent EC currently receive in the UK.[24] It is therefore readily available in the UK. The most common side effects of chemotherapy include infection and fever (due to chemotherapy reducing a patient's white blood cell count, the cells that help fight infection), flu-like symptoms, nausea, tiredness, and hair loss.[35]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

For adults, the recommended dose of pembrolizumab is 200 mg given with chemotherapy, specifically the combination of the drugs carboplatin and paclitaxel, every 3 weeks for six treatment cycles. This is followed by 400 mg of pembrolizumab given alone every 6 weeks for 14 treatment cycles as maintenance therapy. Pembrolizumab is administered as an infusion into the vein (intravenous infusion) over 30 minutes.[36] When administering pembrolizumab with intravenous chemotherapy, pembrolizumab should be administered first.[36]

The medicine can only be obtained with a prescription, and treatment must be started and supervised by a doctor experienced in the treatment of cancer. Patients should be treated with pembrolizumab for a maximum of 20 cycles, as long as a) it is working (i.e. as long as the cancer does not progress) and b) the side effects are tolerable.[36]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

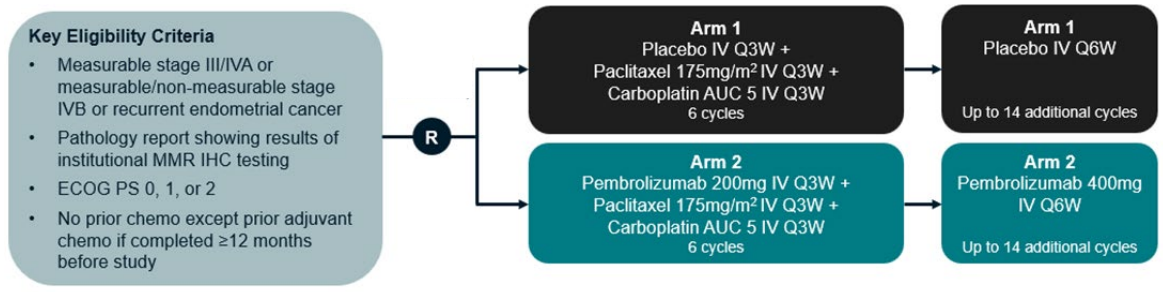
The pivotal evidence used to support the use of pembrolizumab in combination with chemotherapy for the treatment of patients with advanced/recurrent EC is the KEYNOTE-868 (NRG-GY018) trial: an ongoing Phase III, global, double-blind trial in which patients are randomised to receive either pembrolizumab plus chemotherapy or placebo plus chemotherapy.[37] The trial is being conducted at 217 sites in four countries (the US, Canada, Japan and South Korea).

Figure 2 presents the design of the KEYNOTE-868 (NRG-GY018) trial. To be included in the trial, patients must meet all the following criteria:

- Have advanced (measurable Stage III or IVA), Stage IVB (with or without measurable disease), or recurrent (with or without measurable disease) EC
- Have test results for mismatch repair status in their cancer cells
- Not have had chemotherapy previously, except for chemotherapy given after surgery (known as 'adjuvant chemotherapy'), which must have been completed 12 months or more before randomisation
- Meet certain health status criteria

Following randomisation, 816 patients were included in the trial.[37] The patients were divided into two cohorts based on their type of disease: patients with dMMR disease, which means their cells have trouble fixing DNA mistakes, and patients with mismatch repair-proficient (pMMR) disease, which means their cells can fix DNA mistakes normally. In each cohort, patients were randomly assigned to receive either pembrolizumab plus chemotherapy or placebo plus chemotherapy.[37]

Figure 2: KEYNOTE-868 (NRG-GY018) trial design



Key: AUC, area under the curve; CSR, clinical study report; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; pMMR, mismatch repair proficient; PS, performance status; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomisation.
Source: Eskander et al. 2023.[37]

Further information/publications for KEYNOTE-868 (NRG-GY018) can be found below:
clinicaltrials.gov (NCT03914612) – https://classic.clinicaltrials.gov/ct2/show/NCT03914612
Publication (Eskander et al. 2023) – https://pubmed.ncbi.nlm.nih.gov/36972022/

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Evidence from the KEYNOTE-868 (NRG-GY018) trial

The KEYNOTE-868 (NRG-GY018) trial demonstrated that pembrolizumab plus chemotherapy has improved efficacy compared with placebo plus chemotherapy, regardless of mismatch repair status.[37]

As discussed in 3d, the KEYNOTE-868 (NRG-GY018) trial was designed to assess the treatments in two separate groups (i.e. in dMMR patients and pMMR patients). In the interim analysis (data-cut December 2022), efficacy was examined and reported separately as the dMMR and pMMR cohorts. Additional analyses using data from a later data-cut (August 2023) were conducted to analyse the overall population of patients.

Primary endpoint – Progression-free survival
The following data presented is from the interim analysis (December 2022 data-cut).[37] Progression-free survival data from the later data-cut (August 2023) are confidential; please refer to Document B.

Progression-free survival is the length of time during which patients stay alive and their disease does not progress. A statistically significant improvement in progression-free survival was observed with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in both the pMMR and dMMR cohorts.[37]

In the pMMR population (median follow-up: 7.9 months), the median progression-free survival was 13.1 months with pembrolizumab plus chemotherapy and 8.7 months with placebo plus chemotherapy. The results for these patients also demonstrated a 46% relative reduction in the risk of disease progression or death, when patients received treatment with pembrolizumab plus chemotherapy in comparison with those who received placebo plus chemotherapy.

In the dMMR cohort (median follow-up: 12 months), the risk of disease progression or death was 70% lower with pembrolizumab than with placebo.[37] The median PFS was not reached with pembrolizumab plus chemotherapy (meaning researchers could not calculate a median progression-free survival because more than half of the patients in the study were still living or their disease had not progressed), and was 7.6 months with placebo plus chemotherapy.[37]

These results demonstrate that adding pembrolizumab to standard of care chemotherapy improves efficacy, irrespective of mismatch repair status. The findings are further supported by data from the August 2023 data-cut for the overall population, as presented in Document B.

Secondary endpoints
The following data presented is based on the full population from the August 2023 data cut.[38]

Overall survival
Overall survival is the length of time patients remain alive after starting treatment. Overall survival was improved with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy, with a 26% reduction in the risk of death.[38] However, it should be noted that the overall survival data is still preliminary as data is still being collected.[38]

Objective response rate
Objective response rate is the proportion of patients whose cancer has either disappeared (showing no signs of cancer in the body) or shrunk after treatment. Pembrolizumab plus chemotherapy provides a statistically significant improvement in the objective response rate.[38] This means that more patients experienced their tumours completely or partially shrinking compared with placebo plus chemotherapy. The percentage of patients with an objective response was 75.2% with pembrolizumab plus chemotherapy, compared with 62.6% with placebo plus chemotherapy.[38]

Duration of response
Duration of response is the length of time that a tumour responds to treatment without growing or spreading. The median duration of response was longer with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy (12.1 months compared to 6.2 months).[38]

Data limitations
The KEYNOTE-868 (NRG-GY018) trial is a global trial. Although the trial did not include patients from the UK or Europe, the findings can still be considered generalisable to patients in England because the patient population shows similarities to the characteristics of patients identified in a recent real-world study in England.[39] Additionally, UK clinical experts felt that the trial population of KEYNOTE-868 (NRG-GY018) was broadly similar to the patients seen in real-world clinical practice.[40]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The KEYNOTE-868 (NRG-GY018) trial evaluated the quality of life in the pMMR cohort.[37] The trial measured quality of life, physical functioning, and fatigue using three different tools that patients filled out themselves:

1. The Trial Outcome Index of the Functional Assessment of Cancer Therapy–Endometrial (FACT-En-TOI)
2. The Patient-Reported Outcomes Measurement Information System (PROMIS)–Fatigue

3. The PROMIS–Physical Function

These assessments were carried out at scheduled times and were still in progress at the time the Eskander paper was published.[37]

The trial found that adding pembrolizumab to chemotherapy did not make a meaningful difference in the overall quality of life, physical function, or fatigue compared with chemotherapy alone. Further unpublished evidence can be found in Document B.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

KEYNOTE-868 (NRG-GY018) evaluated the safety of pembrolizumab plus chemotherapy separately in the pMMR and dMMR cohorts during the interim analysis (data-cut December 2022).[37] Additional safety data from the later data-cut (August 2023), which looked at the overall population of patients, is presented in Document B.

The safety profile of pembrolizumab plus chemotherapy demonstrated by the KEYNOTE-868 (NRG-GY018) trial was generally consistent with the established individual safety profiles of pembrolizumab alone and chemotherapy alone.[37] Adding pembrolizumab to chemotherapy generally did not increase the frequency or severity of common side effects typically seen with chemotherapy, and no new safety concerns were found.[37]

The types and frequency of adverse events (side effects) were similar between the group taking pembrolizumab with chemotherapy and the group taking placebo with chemotherapy, in both the pMMR and dMMR cohorts.[37] The most common adverse events (reported in over 35% of patients) in both treatment groups were fatigue (feeling very tired); peripheral sensory neuropathy (a condition that affects the nerves in the hands and feet, leading to feelings of tingling, numbness, pain or weakness); anaemia (low red blood cell count, which can lead to symptoms like weakness, shortness of breath, dizziness, and a rapid heartbeat); nausea (feeling sick); and constipation (difficulty with bowel movements).[37]

When looking at more severe adverse events (Grade 3–5), the overall number of more severe adverse events was higher in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group in both the pMMR and dMMR cohorts.[37] The most common severe side effects (occurring in > 8% of patients) in both treatment groups were: anaemia and decreased neutrophil count (a type of white blood cell), which can increase risk of infections.[37] In the dMMR cohort (215 patients), there was one death recorded in the pembrolizumab plus chemotherapy group and two deaths recorded in the placebo plus chemotherapy group; however, these were considered unlikely to be related to the treatment. In the pMMR cohort (550 patients), there were six deaths recorded in the pembrolizumab plus chemotherapy group and two deaths recorded in the placebo plus chemotherapy group. Only one death in this cohort – in the pembrolizumab plus chemotherapy group – was deemed to be possibly related to pembrolizumab.[37]

The trial also monitored adverse events of special interest.[37] These were certain immune-related side effects that are known to be associated with pembrolizumab, such as hypothyroidism, hyperthyroidism, infusion reactions, skin reactions, pneumonitis, and colitis.[37] In both cohorts: these were consistent with what is usually seen when pembrolizumab is used on its own. Infusion reactions were balanced between the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group; and no new side effects of special interest specific to the combination of pembrolizumab and chemotherapy were identified.[37]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Pembrolizumab plus chemotherapy offers a first-line treatment option for patients with advanced or recurrent EC, regardless of their molecular subtype.

The results of the KEYNOTE-868 (NRG-GY018) trial demonstrate that adding pembrolizumab to chemotherapy[37]:

- Increases length of time during which patients stay alive and their disease does not progress compared with chemotherapy alone
- Provides an improved objective response rate compared with chemotherapy alone
- Increases the length of time that a tumour responds to treatment without growing or spreading compared with chemotherapy alone
- Has a similar effect on quality of life to chemotherapy alone, meaning the patient's quality of life is maintained, while providing meaningful extension of life
- Results in similar types and numbers of side effects as seen with chemotherapy alone

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients are at an increased risk of developing immune-related side effects, which occur when the immune system starts attacking healthy cells in the body.[36] These side effects can affect various organs and systems, leading to conditions such as inflammation of the lungs (pneumonitis), liver (hepatitis), or intestines (colitis); skin rashes; and thyroid problems.[36] These immune-related side effects can sometimes persist even after the patient has stopped taking pembrolizumab, necessitating long-term monitoring and management to address any ongoing health issues. This means patients may need to undergo regular check-ups, take medications to control inflammation, and be vigilant about any new or worsening symptoms. Most of these side effects, including severe reactions, got better after starting the right medical treatment or stopping pembrolizumab. Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects.[36]

Pembrolizumab, like any other medicine, does not work the same in every patient. Not all patients' cancer will respond to treatment, and it may not result in an extended life expectancy.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

MSD has developed a cost-effectiveness model to assess the value and economic considerations of using pembrolizumab plus chemotherapy compared with chemotherapy alone. Currently, chemotherapy (consisting of paclitaxel + carboplatin) is regarded as the first-line therapy in patients with advanced/recurrent EC. The model accounts for resources, costs, survival, and quality of life of patients receiving either pembrolizumab plus chemotherapy, or chemotherapy alone.

The model simulates a patient's progression through a set of distinct health states over the entire lifetime of the patient. These health states are relevant to patients with EC, and each health state is associated with a certain amount of costs and a certain quality of life.

The following health states were used in this cost-effectiveness model:

- Progression-free: a patient's disease is stable or responding to treatment and not actively progressing. Costs in this health state are associated with treatment received, treatment administration costs, management of disease, and adverse events, with costs varying over time. Quality of life is higher compared with patients with progressed disease and is also affected by treatment-related adverse events
- Progressed disease: a patient's disease is assumed to have progressed. Costs in this health state are associated with treatment received, treatment administration costs, and management of disease. Quality of life is lower compared with patients with progression-free disease and is also affected by treatment-related adverse events
- Death: This state includes costs associated with provision of care towards the end of life

The model uses the clinical data available for pembrolizumab plus chemotherapy and chemotherapy alone to estimate how fast a patient progresses through these different health states. More specifically, it uses the data on progression-free survival from the KEYNOTE-868 (NRG-GY018) trial to estimate how long patients spend in the progression-free state, and the overall survival data to estimate how fast patients progress to death. The time spent in each health state is then adjusted for the quality of life of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient as a result of the treatment

received. This is then compared with the total costs associated with that treatment (consisting of treatment costs, subsequent treatment costs, adverse event costs, and general costs associated with management of EC such as routine visits and testing). This comparison allows for an assessment of whether the costs associated with using pembrolizumab plus chemotherapy are justifiable based on the additional QALYs patients gain.

Clinical benefits included in the model

The model predicted that treatment with pembrolizumab plus chemotherapy would lead to more clinical benefit (i.e. more QALYs) gained than treatment with chemotherapy alone (please note that the exact QALY results are confidential). This benefit was mainly driven by the progression-free survival and overall survival benefit that pembrolizumab plus chemotherapy has over chemotherapy alone. This resulted in a longer time spent in the progression-free health state (compared with chemotherapy alone), which was associated with a better overall quality of life, and a longer survival overall.

Costs included in the model

Pembrolizumab is subject to confidential price agreements with the NHS, so full cost information cannot be presented. However, broadly, treatment with pembrolizumab plus chemotherapy was associated with higher costs than treatment with chemotherapy alone. This was mostly driven by higher treatment costs of pembrolizumab, and as patients live for longer, more disease management costs are accrued. However, patients receiving chemotherapy were expected to incur higher subsequent treatment costs.

Model results

Overall, the model determined that treatment with pembrolizumab plus chemotherapy was associated with sufficient additional benefit to patients (QALYs) to justify any additional costs compared with chemotherapy alone. Therefore, in addition to offering a meaningful clinical benefit to patients, pembrolizumab plus chemotherapy is also considered a cost-effective treatment option for patients in EC. Pembrolizumab plus chemotherapy remained cost-effective across a range of sensitivity analyses, which tested the model's assumptions and confirmed the robustness of the results.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Pembrolizumab represents a step change in the management of patients with advanced/recurrent EC and should be considered innovative in its potential to make a significant and substantial impact on health-related benefits. If approved, pembrolizumab in combination with chemotherapy (followed by pembrolizumab maintenance) will be the first targeted treatment that can be used to treat patients in the first line with advanced/recurrent EC regardless of molecular subtype.

3k) Equalities

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 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
EC only affects women, and unlike many other cancers, survival for people with EC has not improved in the past 40 years.[41,42] Better access to effective treatments is needed to ensure that women with EC have the same chances of getting good care as those with other cancers. In England, women in the most deprived areas have about a 17% higher rate of EC compared with those in the least deprived areas. About 640 diagnoses of EC each year are linked to deprivation.[2] Differences in socio-economic status affect exposure to risk factors like obesity, which is a major risk factor for EC.[43] It is important to make sure that people in the most deprived areas have access to effective treatments for diseases that disproportionately affect them. EC rates are higher among Black women compared with White women in England.[44] It is one of the top 10 most common cancers for women in Asian, Black, and mixed/multiple ethnic groups, but only the 14th most common for White women.[44] In addition, Black Caribbean and Black African women are more likely to be diagnosed at a late stage compared with women from other ethnic groups.[44]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Patient groups and charities: • Peaches Womb Cancer Trust: https://peachestrust.org/ • Eve Appeal: https://eveappeal.org.uk/gynaecological-cancers/womb-cancer/ • Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/womb-cancer Further information on NICE and the role of patients: • Public involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in HTA: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/

4b) Glossary of terms

Advanced cancer: Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumour, slow the growth of cancer cells, or relieve symptoms.[45]

Adverse event: An unexpected medical event that arises during treatment with a drug or other therapy. Adverse events can be classified as mild, moderate or severe.[45]

Biopsy: The removal of cells or tissues for examination by a pathologist.[45]

Diagnosis: The process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests (such as blood tests, imaging tests, and biopsies) may be used to help make a diagnosis.[45]

Disease progression: Cancer that continues to grow or spread.[45]

Clinical staging: A method used to find out the stage of cancer (amount or spread of cancer in the body) using tests that are done before surgery. These include physical exams, imaging tests, laboratory tests (such as blood tests), and biopsies.[45]

Clinical guidelines: Guidelines developed to help healthcare professionals and patients make decisions about screening, prevention, or treatment of a specific health condition.[45]

Clinical trial: A type of research that studies new tests and treatments and evaluates their effects on human health outcomes.[45]

Eligibility criteria: In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.[45]

Endometrial cancer (EC): Cancer that forms in the tissue lining the uterus (the small, hollow, pear-shaped organ in a woman's pelvis in which a foetus develops). Most endometrial cancers are adenocarcinomas (cancers that begin in cells that make and release mucus and other fluids).[45]

First-line therapy: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it does not cure the disease or it causes severe side effects, other treatments may be added or used instead. Also called induction therapy, primary therapy, and primary treatment.[45]

Immunotherapy: A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way.[45]

Intravenous (IV): Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein.[45]

Maintenance therapy: Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.[45]

Molecular subtype: In cancer, a term used to describe the smaller groups that a type of cancer can be divided into, based on whether certain genetic changes or other biomarkers are present. For example, breast cancer can be broken down into several molecular subtypes based on whether the cancer cells have estrogen receptor (ER), progesterone receptor (PR), or HER2 on their surface. Knowing the molecular subtype of a cancer may help plan treatment, find out how well treatment is working, or make a prognosis.[45]

Objective response rate: The percentage of people in a study or treatment group who have a partial response or complete response to the treatment within a certain period of time. A partial response is a decrease in the size of a tumour or in the amount of cancer in the body, and a complete response is the disappearance of all signs of cancer in the body. In a clinical trial, measuring the objective response rate is one way to see how well a new treatment works.[45]

Overall survival: The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works.[45]

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.[45]

Progression-free survival: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.[45]

QALY: A measure of health outcomes pertaining to disease burden and is used to assess the value of medical interventions. As health can be defined as the length of life and the quality of life, the QALY combines the two factors into a single figure.[46]

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[47]

Symptom: Something that a person feels or experiences that may indicate that they have a disease or condition.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Cancer Research UK. What is womb cancer? 08 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/about).
2. Cancer Research UK. Uterine cancer incidence. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero).

3. American Cancer Society. Endometrial Cancer Risk Factors. 27 March 2019 (https://www.cancer.org/cancer/types/endometrial-cancer/causes-risks-prevention/risk-factors.html).
4. Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162(2):383-394. DOI: 10.1002/ijgo.14923.
5. Oaknin A, Bosse TJ, Creutzberg CL, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology 2022;33(9):860-877. (In eng). DOI: 10.1016/j.annonc.2022.05.009.
6. Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet 2021;155 Suppl 1(Suppl 1):45-60. (In eng). DOI: 10.1002/ijgo.13866.
7. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31(1):12-39. (In eng). DOI: 10.1136/ijgc-2020-002230.
8. Leon-Castillo A. Update in the molecular classification of endometrial carcinoma. Int J Gynecol Cancer 2023;33(3):333-342. (In eng). DOI: 10.1136/ijgc-2022-003772.
9. Funston G, O'Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Recognizing Gynecological Cancer in Primary Care: Risk Factors, Red Flags, and Referrals. Adv Ther 2018;35(4):577-589. (In eng). DOI: 10.1007/s12325-018-0683-3.
10. Cancer Research UK. Symptoms of womb cancer. 09 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/symptoms).
11. National Disease Registration Service. Case-mix adjusted percentage cancers diagnosed at Stages 1 and 2 by CCG in England, 2019 data tables. (https://files.digital.nhs.uk/6A/DBCFFF/CMA%202013-2019%20Data.ods).
12. Cancer Research UK. Uterine cancer mortality statistics. 31 May 2022 (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/mortality#heading-Zero).
13. Siegenthaler F, Lindemann K, Epstein E, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecologic oncology 2022;165(2):230-238. DOI: 10.1016/j.ygyno.2022.02.024.
14. Huijgens AN, Mertens HJ. Factors predicting recurrent endometrial cancer. Facts Views Vis Obgyn 2013;5(3):179-86. (In eng) (https://www.ncbi.nlm.nih.gov/pubmed/24753943).
15. NHS. Symptoms - womb (uterus) cancer. 21 October 2021 (https://www.nhs.uk/conditions/womb-cancer/symptoms/).
16. American Cancer Society. Signs and Symptoms of Endometrial Cancer. 27 March 2019 (https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/signs-and-symptoms.html).
17. Gil-Ibanez B, Davies-Oliveira J, Lopez G, Diaz-Feijoo B, Tejerizo-Garcia A, Sehouli J. Impact of gynecological cancers on health-related quality of life: historical context, measurement instruments, and current knowledge. Int J Gynecol Cancer 2023;33(11):1800-1806. DOI: 10.1136/ijgc-2023-004804.
18. Zandbergen N, de Rooij BH, Vos MC, et al. Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis. Acta Oncol 2019;58(5):790-800. DOI: 10.1080/0284186X.2018.1560498.
19. 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. Int J Gynecol Cancer 2018;28(3):614-622. (In eng). DOI: 10.1097/IGC.0000000000001204.
20. Gao H, Xiao M, Bai H, Zhang Z. Sexual Function and Quality of Life Among Patients With Endometrial Cancer After Surgery. Int J Gynecol Cancer 2017;27(3):608-612. (In eng). DOI: 10.1097/IGC.0000000000000905.

21. Cleveland Clinic. Uterine Cancer (Endometrial Cancer). 21 March 2023 (https://my.clevelandclinic.org/health/diseases/16409-uterine-cancer).
22. National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral. 02 October (https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer).
23. Cancer Research UK. Tests for womb cancer. 27 Feb 2024 (https://www.cancerresearchuk.org/about-cancer/womb-cancer/getting-diagnosed/tests-womb-cancer).
24. Morrison J, Balega J, Buckley L, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. European journal of obstetrics, gynecology, and reproductive biology 2022;270:50-89. (In eng). DOI: 10.1016/j.ejogrb.2021.11.423.
25. Peaches Trust. Stories. (https://peachestrust.org/stories/).
26. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014;23(2):121-30. (In eng). DOI: 10.1002/pon.3409.
27. Luke JJ, Ott PA. PD-1 pathway inhibitors: the next generation of immunotherapy for advanced melanoma. Oncotarget 2015;6(6):3479-92. (In eng). DOI: 10.18632/oncotarget.2980.
28. LaFleur MW, Muroyama Y, Drake CG, Sharpe AH. Inhibitors of the PD-1 Pathway in Tumor Therapy. J Immunol 2018;200(2):375-383. (In eng). DOI: 10.4049/jimmunol.1701044.
29. Senovilla L, Vitale I, Martins I, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science (New York, NY) 2012;337(6102):1678-84. (In eng). DOI: 10.1126/science.1224922.
30. Sevko A, Michels T, Vrohlings M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. J Immunol 2013;190(5):2464-71. (In eng). DOI: 10.4049/jimmunol.1202781.
31. Liechtenstein T, Perez-Janices N, Gato M, et al. A highly efficient tumor-infiltrating MDSC differentiation system for discovery of anti-neoplastic targets, which circumvents the need for tumor establishment in mice. Oncotarget 2014;5(17):7843-57. (In eng). DOI: 10.18632/oncotarget.2279.
32. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20(11):2831-7. (In eng). DOI: 10.1158/1078-0432.CCR-13-3141.
33. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. Cellular immunology 2010;263(1):79-87. (In eng). DOI: 10.1016/j.cellimm.2010.03.001.
34. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer cell 2015;28(6):690-714. (In eng). DOI: 10.1016/j.ccell.2015.10.012.
35. Cancer Research UK. About side effects of chemotherapy. 12 Dec 2023 (https://www.cancerresearchuk.org/about-cancer/treatment/chemotherapy/side-effects/about).
36. European Medicines Agency. Keytruda SmPC. 01 January (https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf).
37. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. The New England journal of medicine 2023;388(23):2159-2170. (In eng). DOI: 10.1056/NEJMoa2302312.

38. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Efficacy (All-comer Participants Population). 2024.
39. Alvaro Ingles Russo Garces. Demographics and Survival Outcomes in Patients with Advanced or Recurrent Endometrial Cancer in the English Real-World Setting. (https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/0214cb59-a124-470f-af22-724a2e9bcb91/0214cb59-a124-470f-af22-724a2e9bcb91_viewable_rendition__v.pdf?REF--ALL-004799).
40. MSD. Key Summary, Plan of Action and Meeting Summary for the UK Endometrial Cancer Advisory Board 2024. 2024.
41. McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: Not your grandmother's cancer. Cancer 2016;122(18):2787-98. (In eng). DOI: 10.1002/cncr.30094.
42. Wan YL, Beverley-Stevenson R, Carlisle D, et al. Working together to shape the endometrial cancer research agenda: The top ten unanswered research questions. Gynecologic oncology 2016;143(2):287-293. (In eng). DOI: 10.1016/j.ygyno.2016.08.333.
43. Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer 2018;118(8):1130-1141. (In eng). DOI: 10.1038/s41416-018-0029-6.
44. Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. Br J Cancer 2022;126(12):1765-1773. DOI: 10.1038/s41416-022-01718-5.
45. National Cancer Institute (NCI). NCI Dictionary of Cancer Terms. (https://www.cancer.gov/publications/dictionaries/cancer-terms).
46. Health analytics. What Is A Quality Adjusted Life Year (QALY)? (https://healthanalytics.com/expertise/what-is-a-quality-adjusted-life-year-qaly/).
47. World Health Organization (WHO). WHOQOL User Manual. (https://www.who.int/tools/whoqol).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer ID6381

Clarification questions

September 2024

File name	Version	Contains confidential information	Date
PEMBRO clarification questions[CON]_MSD_responseV1.0	V1	No	08 October 2024

Section A: Clarification on effectiveness data

Literature searching (clinical effectiveness)

A1. *Please can the company provide the reference list of excluded studies and reasons for exclusion at the secondary (Level 2) screening stage for the clinical effectiveness review (page 21 CS Appendix D.1.3.1).*

The reference list of excluded studies is embedded below:

List of excluded studies.xlsx

A2. *Please provide the search details for the conference proceedings and the United States (US) National Institutes of Health Clinical Trial Registry, including the date(s) the searches were carried, platform used and search terms (CS Appendix D.1.1).*

The United States (US) National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) was searched to identify completed clinical trials with results that have not yet been published. The search terms used are presented in Table 1.

Further searches of the most recent two years of the following conference abstracts as of the SLR initiation were also conducted:

- American Society of Clinical Oncology (ASCO), 2022-2023
- European Society for Medical Oncology (ESMO), 2022-2023
- Society of Gynecologic Oncology (SGO), 2023-2024
- European Society of Gynecological Oncology (ESGO), 2023-2024

The most recent two years of the ASCO and ESMO conferences prior to the SLR initiation were the 2022 and 2023 editions, while ESGO and SGO were available for 2023 and 2024. In addition to the hand-searches of all the conference abstracts, ASCO and ESMO were also searched using the Northern Lights database which allowed for a reproducible search. However, Northern Lights searches were not conducted for ESGO and SGO because these conferences were not indexed in the database. Search terms used to search the conferences are provided in Table 2 to Table 4.

Table 1. United States National Institutes of Health Clinical Trial Registry search

Source	Search terms	Search date	Hits
Clinicaltrials.gov [classic]	Endometrial cancer + clinical trials + all studies (with or without results) + not yet recruiting or recruiting or active not recruiting or enrolling by invitation or completed + no age restriction + Phase 1, 2, 3 and 4	1 November 2023	497
Clinicaltrials.gov	Endometrial cancer + phase: 1, 2, 3, 4 + interventional studies + last update posted from 11/01/2023 to 04/04/2024	4 April 2024	85

Table 2: Northern Lights ASCO search

Northern light life sciences conference abstracts <2010 - 2023 Week 44>		
Search date: 19 November 2023		
1	exp endometrium carcinoma/	3113
2	((endometrium or endometrial) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	6312
3	((endometrium or endometrial) adj3 (metastasis or metastatic*)).ti,ab.	225
4	or/1-3	7530
5	(advance$ or metasta$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or recurrent or migration$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or incurable or "not curable").mp.	357351
6	American Society of Clinical Oncology annual meeting.cf.	66711
7	4 and 5 and 6	260
8	limit 7 to yr=2022 - current	67

Table 3: Northern Lights ESMO search

Northern light life sciences conference abstracts <2010 - 2023 Week 44>		
Search date: 19 November 2023		
1	exp endometrium carcinoma/	3113
2	((endometrium or endometrial) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	6312
3	((endometrium or endometrial) adj3 (metastasis or metastatic*)).ti,ab.	225
4	or/1-3	7530
5	(advance$ or metasta$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or recurrent or migration$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or incurable or "not curable").mp.	357351
6	European Society for Medical Oncology.cf.	22763
7	4 and 5 and 6	84
8	limit 7 to yr=2022 - current	19

Table 4: Conference hand-search

Conference	Source	Terms	Included abstracts
ASCO 2022	https://ascopubs.org/jco/meeting	Endometrial	0
ASCO 2023	https://ascopubs.org/jco/meeting	Endometrial	0
ESMO 2022	https://oncologypro.esmo.org	Endometrial cancer and abstracts and eposter	0
ESMO 2023	https://oncologypro.esmo.org	Endometrial cancer and abstracts and eposter	1
SGO 2023	https://www.sciencedirect.com/journal/gynecologic-oncology/vol/176/suppl/S1	Endometrial	1
SGO 2024	https://clin.larvol.com/conference/abstract/SGO%202024	Endometrial cancer	1
ESGO 2023	https://ijgc.bmj.com/content/33/Suppl_3	Endometrial	0
ESGO 2024	https://ijgc.bmj.com/content/34/Suppl_1	Endometrial	0

Note: 2022/2023 conference abstracts hand-search were initially conducted on 20th November 2023 and repeated on 22nd April 2024 for all conference abstracts.
Abbreviations: ASCO, American Society of Clinical Oncology; ESGO, European Society of Gynecological Oncology; ESMO, European Society for Medical Oncology; SGO, Society of Gynecologic Oncology.

A3. *Please could you provide details of inclusion and exclusion criteria related to the clinical effectiveness systematic literature review, relating to country of study and publication type?*

The PICOTS table for the clinical effectiveness SLR inclusion/exclusion criteria, including country of study and publication type, is provided in Table 5.

Table 5: PICOTS inclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	• Stage III, Stage IV, or recurrent endometrial cancer • May have received prior radio-sensitizing chemotherapy in the neoadjuvant or adjuvant setting. • May have received prior radiation without concurrent chemotherapy. • May have received prior hormonal therapy for treatment of endometrial carcinoma. • May have received 1 prior line of systemic adjuvant and/or	No population of interest reported

	neoadjuvant platinum-based chemotherapy. • Patients have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better.	
Interventions	Pembrolizumab with carboplatin + paclitaxel	No intervention of interest reported
Comparators	Carboplatin + paclitaxel	No comparator of interest reported
Outcomes	The following outcomes will be considered for inclusion: • Overall survival • Progression-free survival • Duration of response • Objective response rate • Complete response • Partial response • Disease control rate • Drug related adverse events (AEs) ≥10% • Grade 3-5 AEs (all, drug related) • Discontinuation due to AE • Serious AEs • Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	No outcome of interest reported
Time	Unrestricted	Not applicable
Study design	Randomized controlled trials, non-randomized clinical trials, and single-arm clinical trials.	Prospective and retrospective cohort studies, case-control studies, cross-sectional studies, case reports, and case series.
Country of study	Unrestricted	Not applicable
Publication type	Journal articles Congress abstracts and proceedings	Publication type not on the inclusion list

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ , European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

Clinical effectiveness clarification

A4. *Please provide summary details of the real-world study [75](Alvaro Ingles Russo Garces) on the findings and their consistency with the trial results?*

The real-world (RW) study by Alvaro Ingles Russo Garces and colleagues investigated demographics, first-line (1L) treatment patterns and survival outcomes in patients diagnosed with advanced/recurrent endometrial cancer (EC) in England between January 1, 2013 and December 31, 2019, with follow-up until August 23, 2021.[1] This descriptive, non-interventional, retrospective study used routine population-level data available through NHS England's National Cancer Registration and Analysis Service (NCRAS), which aggregates patient data from several sources to create the Cancer Analysis System (CAS). The study identified and evaluated two cohorts: the immune checkpoint inhibitors (ICI)-eligible 1L cohort (patients who received 1L therapy and were eligible for ICIs) and a sub-population within this group, the ICI-eligible 1L carboplatin-paclitaxel cohort (patients who solely received carboplatin-paclitaxel at 1L).[1]

The study identified 13,954 patients with advanced/recurrent EC, with 2,376 included in the ICI-eligible 1L cohort, and 902 patients in the ICI-eligible 1L carboplatin-paclitaxel cohort.[1] The patients identified in the ICI-eligible 1L carboplatin-paclitaxel cohort had similar characteristics to the patient population of KEYNOTE-868 (NRG-GY018) trial. For instance, the median age was 66.6 years in the RW study compared to 66.1 years in KEYNOTE-868 (NRG-GY018). Additionally, most patients were White in both studies (85.9% in the RW study and 74.1% in KEYNOTE-868 [NRG-GY018]).[1,2]

Almost all patients in the ICI-eligible 1L cohort received at least one systemic anti-cancer regimen (98.7%), with the majority receiving carboplatin-paclitaxel (n = 1,824; 77.8%). This aligns with BGCS guideline recommendations and is consistent with the treatment regimen used in the KEYNOTE-868 (NRG-GY018) trial, which also employed a carboplatin-paclitaxel combination.[3,4]

The RW study found that ICI-eligible patients who received only carboplatin-paclitaxel had poorer long-term clinical outcomes compared to patients in the overall ICI-eligible cohort, who may have received other treatments alongside chemotherapy.[1] Specifically, the median overall survival (OS) was 17.2 months (95% CI: 15.5, 19.0) for the ICI-eligible 1L carboplatin-paclitaxel cohort, and 27.2 months (95% CI: 24.7, 30.2) for the ICI-eligible 1L cohort.[1] Although the median OS in the placebo + CT arm of the KEYNOTE-868 (NRG-GY018) trial (32.2 months) was higher than that observed in both of the RW cohorts, trial

populations often perform better than real-world populations. This difference may be attributed to better overall health and closer monitoring for adverse events (AEs) in trial participants, as confirmed by UK clinicians. In addition, clinicians indicated that although data collection procedures in UK registries has generally improved over the past decade, historical UK registry data for EC should be interpreted with caution as older data may not be reliable.[5] In the KEYNOTE-868 (NRG-GY018) trial, over a median follow-up of 16.3 months, the median OS was not reached for the pembrolizumab + CT arm (see Section B.2.6.2 of Document B). At 18 and 42 months, the OS rates were higher in the pembrolizumab + CT group compared with the placebo + CT group (75.8% versus 69.2% and 59.8% versus 36.7%, respectively), showcasing its efficacy as a superior treatment option over standard chemotherapy alone.[6]

Both the RW study and the KEYNOTE-868 (NRG-GY018) trial underscore the necessity for new effective treatment strategies in advanced/recurrent EC. The consistency in patient demographics, treatment patterns, and the demonstration of improved outcomes with ICI treatments in the KEYNOTE-868 (NRG-GY018) trial highlight the potential for pembrolizumab to address the unmet needs identified in the RW setting.

A5. *Please provide further insights into the treatment discontinuation rates due to adverse events (AEs) in both arms? Specifically, how did these discontinuations impact the effectiveness analyses (e.g., in terms of modified intention-to-treat vs. per-protocol analysis)?*

As per our clarification call on 26th September, no additional analysis regarding adverse events has been, or is planned to be, conducted. Safety analyses were conducted in the 'All participants as treated' (APaT) analysis set, which included all randomised patients who received at least one dose of study treatment, as specified in the trial protocol. Efficacy analyses were conducted using the intention to treat (ITT) analysis set which included all randomised patients; therefore any patients who discontinued due to adverse events were included in the efficacy analyses.

A6. *Many patients in the placebo + CT arm received subsequent therapies, including pembrolizumab, after disease progression. Could you clarify the extent to which these subsequent treatments may have impacted the trial's effectiveness results, particularly the OS and PFS outcomes?*

Estimates of effectiveness for placebo + CT from the KEYNOTE-868 (NRG-GY-018) trial, including long-term extrapolations, were judged to have good clinical plausibility (see Section B.3.3.4 of Document B for further details). In addition, for placebo + CT the most common subsequent treatment was pembrolizumab: 165/248 (66.5%) of all patients in the placebo + CT arm who had subsequent therapy, received pembrolizumab as a later-line therapy (see Table 18 of Document B). As per the BGCS guidelines, patients requiring second-line (2L) systemic therapy should be offered PD-1/PD-L1 inhibitors if the cancer is mismatch repair deficient (dMMR).[4] Currently, pembrolizumab is the only anti-PD-1 inhibitor recommended by NICE for baseline commissioning for this indication in the UK (TA914).[7] In addition, as per TA904 NICE have also recommended pembrolizumab in combination with lenvatinib as a 2L treatment for patients with advanced or recurrent EC, regardless of MMR status.[8] In KEYNOTE-868 (NRG-GY018), 98/411 (23.8%) patients in the placebo + CT arm received subsequent treatment with lenvatinib, which was generally in combination with pembrolizumab (see Table 18 of Document B). Accordingly, clinical experts confirmed that pembrolizumab alone (for dMMR disease) or in combination with lenvatinib is usually considered the standard of care for 2L therapy in the UK for patients who are fit enough and not contraindicated.[5] Therefore, the subsequent treatments received in the placebo + CT arm of the trial are considered generalisable to UK clinical practice. Consequently, the trial effectiveness results for the placebo arm can be considered the reference case for efficacy in UK clinical practice.

A7. *The submission notes differences in efficacy between the dMMR and pMMR populations. Could you provide further subgroup analyses for other baseline characteristics (e.g., age, stage of cancer, ECOG status, prior treatments). Please provide detailed breakdowns, including hazard ratios and confidence intervals for each group.*

As per our clarification call on 26th September, forest plots including all pre-specified subgroup analyses have been provided in Document B (Figures 12 and 13).

A8. *Can you provide any additional follow-up data on long-term survival for patients in the treatment arm? How long were patients followed for survival outcomes, and were there any significant findings beyond the study's primary analysis window?*

The August 2023 data cut presented in the submission is the most recent data cut from the trial. The next planned data cut for this trial is Final Analysis, with outputs due in [redacted].

Please note that in our original submission we had stated expected final analysis was due in [redacted], but this has since been revised to [redacted].

A9. *Are there any ongoing studies or planned extensions that may provide additional data on the long-term effectiveness of pembrolizumab in this population? If so, when can we expect preliminary results?*

MSD is not conducting any other trials assessing pembrolizumab + carboplatin + paclitaxel in this patient population.

A10. *HRQoL outcomes were measured in the pMMR cohort. Could you clarify why HRQoL data were not collected or reported for the dMMR cohort, and how this impacts the overall assessment of pembrolizumab + CT in the all-comer population?*

KEYNOTE-868 (NRG-GY018) is a study of two cohorts; the proficient mismatch repair (pMMR), and deficient mismatch repair (dMMR) populations. As per the trial protocol, the HRQoL/PRO hypotheses in the study were to assess whether the patient-reported HRQoL, physical function, and fatigue are different when adding pembrolizumab to chemotherapy (carboplatin + paclitaxel) during the initial treatment phase and when continuing pembrolizumab monotherapy in the maintenance period. Due to the lack of sufficient statistical power in the dMMR group resulting from the smaller sample size, the analyses for HRQoL/PRO were prespecified to be conducted only in the pMMR cohort.

HRQoL/PROs collected in the trial were not used to estimate utility values used within the company submission. Within scenario analysis, utilities from similar populations that include both dMMR and pMMR patients were explored and the cost-effectiveness conclusion were unchanged. Therefore the impact of not collecting in dMMR is likely to have minimal effect on the cost effectiveness results presented in the company submission.

A11. *In addition to FACT-En-TOI and PROMIS-Fatigue/Physical Function, were there any exploratory HRQoL measures included in the study? If so, could you provide data on these outcomes?*

Exploratory HRQoL endpoints investigated whether the addition of pembrolizumab to chemotherapy is associated with self-reported neurotoxicity, as measured by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) subscale, and the extent to which patients differ on their self-reported bother from side

effects of cancer therapy.[9] As with the other HRQoL analyses, these exploratory analyses were conducted in the pMMR population only.[9]

FACT/GOG-Ntx subscale scores were [redacted] between the treatment groups during the evaluation period.[9] Table 6 presents the analysis of change from baseline to Week 18 in FACT GOG-NTX, and Figure 1 presents the mean change from baseline over time. At Week 18, FACT/GOG-Ntx subscale scores [redacted] in the pembrolizumab + CT group and the placebo + CT group (LS mean change: [redacted]).[9]

Table 6: Analysis of change from baseline to Week 18 in FACT GOG-NTX (PRO pMMR population; December 2022 data-cut)

Treatment	Baseline	Week 18			Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
Pembrolizumab + CT	254	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + CT	244	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Mean[a] (95% CI)**	**p-Value[a]**
Pembrolizumab + CT vs. Placebo + CT					[redacted]	[redacted]

Key: CI, confidence interval; CT, chemotherapy; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity; LS, least squares; pMMR, mismatch repair proficient; PRO, patient reported outcomes; SD, standard deviation.
Notes: a. Repeated measures model based on the missing at random (MAR) assumption. Model covariates will include the patients' randomly assigned study treatment, age at enrollment onto the study, pre-treatment QOL/PRO score, assessment time and treatment-by-time interaction.
For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[9]

Figure 1: Mean change from baseline and 95% CI for the FACT GOG-NTX over time by treatment group (PRO pMMR population; December 2022 data-cut)

[redacted]

Key: CI, confidence interval; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; pMMR, mismatch repair proficient; PRO, patient reported outcomes
Source: KEYNOTE-868 (NRG-GY018) CSR 2023.[9]

Changes from baseline in bother from side effects of cancer therapy were measured using the single-item GP5, "I am bothered by side effects of treatment," rated on a 5-point Likert scale.[9] Baseline FACT-GP5 scores in the pMMR population were [redacted] for both treatment groups. Mean FACT-GP5 scores [redacted] in both treatment groups at Week 6 and [redacted] through Week 54.[9]

A12. *Nine patients from the pMMR group were enrolled after the IA data cut-off (December 2022) and were not included in the interim analysis results. How did you account for these patients?*

As these nine patients were enrolled after the December 2022 data cut, they are not included in that interim analysis but they are included in the August 2023 data cut (Efficacy and Safety Update) that forms the basis of the company submission.

A13. *Many patients ([redacted]%) listed 'other' reasons for discontinuation, with the majority being attributed to unblinding ([redacted] patients total). Please provide reasons for the discontinuation of the unaccounted patients.*

The specific reasons for discontinuation (entered by investigators as free text) for participants listed in the category 'other' reasons for discontinuation, but not attributed to unblinding ([redacted] participants in total), can be found in Table 7 for pembrolizumab + CT and Table 8 for placebo + CT.

Note that out of [redacted] participants in the placebo + CT group who discontinued treatment with reason being attributed to unblinding, [redacted] participants were counted in another category for reason of treatment discontinuation in the disposition table (Table 9 in Document B) other than the 'Other' category, and one participant was unblinded prior to C1D1 (cycle1, day1) of chemotherapy treatment.

Table 7: Listing of Participant Disposition Due to Other Reasons excluding Unblinding for pembrolizumab + CT

ID	Treatment Group	End of Treatment	Pembrolizumab + CT	
		Status Paclitaxel	Status Carboplatin	Discontinuation Reason
1	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
2	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
3	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]

4	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
5	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
6	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
7	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
8	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
9	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
10	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]
11	Paclitaxel + Carboplatin + Pembrolizumab	[redacted]	[redacted]	[redacted]

Pembrolizumab discontinuation related to unblinding are excluded. Other discontinuation reasons such as alternative therapy without clear link to unblinding are included.
Participants who died prior to 16DEC2022 are excluded.
Database Cutoff Date: 18AUG2023

Table 8: Listing of Participant Disposition Due to Other Reasons excluding Unblinding for placebo + CT

ID	Treatment Group	End of Treatment		Pembrolizumab + CT
		Status Paclitaxel	Status Carboplatin	Discontinuation Reason
1	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
2	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
3	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
4	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
5	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
6	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]

7	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
8	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
9	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
10	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
11	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
12	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
13	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
14	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
15	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
16	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
17	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
18	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
19	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
20	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
21	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
22	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
23	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
24	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
25	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
26	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
27	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
28	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]

29	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
30	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
31	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
32	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
33	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
34	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
35	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
36	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
37	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
38	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
39	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
40	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
41	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
42	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
43	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
44	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
45	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
46	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
47	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
48	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
49	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]
50	Paclitaxel + Carboplatin + Placebo	[redacted]	[redacted]	[redacted]

Placebo discontinuation related to unblinding are excluded. Other discontinuation reasons such as alternative therapy without clear link to unblinding are included.

Participants who died prior to 16DEC2022 are excluded.
Database Cutoff Date: 18AUG2023

Section B: Clarification on cost-effectiveness data

Literature searching (cost-effectiveness)

B1. *Please provide a list of references and PDFs for the relevant SLRs and HTAs identified during the SLR that were hand-searched to identify any additional, relevant studies for inclusion in the cost-effectiveness studies SLR (CS Appendix G.2 and G.3), Health-related quality of life (HRQoL) / utility SLR (CS Appendix H.2) and the SLR cost and healthcare resources use in adult patients with advanced/ recurrent EC (CS Appendix I.2).*

There were no SLRs/HTAs identified during the SLR that were hand-searched to identify any additional, relevant studies for inclusion in the reviews.

B2. *Please provide a complete reference list and list of reasons for the excluded studies at the secondary (Level 2) screening stage of the SLR of cost-effectiveness studies (CS Appendix G), SLR of Health-related quality of life studies (CS Appendix H) and SLR of cost and healthcare resource identification, measurement and valuation studies (CS Appendix I).*

MSD_EC_Economic_
SLR_List%20of%20ex

Cost-effectiveness clarification

Utility values

B3. PRIORITY QUESTION: The EAG notes that the utility values were obtained from KEYNOTE-158. Please can the company provide the baseline characteristics of KEYNOTE 158 population of endometrial cancer patients with dMMR/MSI-H in a table in comparison with the decision problem population?

The baseline characteristics of the KEYNOTE-158 cohort who were used to derive utility values for this appraisal are provided in Table 9. The population in KEYNOTE-158 does represent a slightly younger population with lower average weight. It is also a population with further progressed disease. Due to the lack of direct EQ-5D data in KEYNOTE-868 (NRG-

GY018), extensive scenario analysis was run using alternative credible utility values to explore the uncertainty in this parameter. Importantly, these scenario analyses did not change the cost effectiveness conclusion of the company submission.

Table 9: Baseline characteristics of people with endometrial cancer that had received 1 prior line of therapy in KEYNOTE-158

Variable	Mean	Number	SE
Age (years)	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]		-
Weight (kg)	[redacted]		[redacted]
BSA (m^2)	[redacted]		[redacted]
pMMR (%)	0%		-

B4. *Please can the company clarify if separate utility values were considered for people in a progression-free health state (on treatment) and those in a progression-free health state (off treatment)?*

The approach undertaken in this economic model assumes that health-state utility values are driven by progression status. Health utility values in the model did not separately consider PFS (on-treatment) from PFS (off-treatment). This is because off-treatment health utilities were only collected for 8 patients in KEYNOTE-158, leading to concerns about the representativeness of this small sample size. In addition, as pembrolizumab + CT includes multiple treatment components of differing durations, any analysis of utility by treatment status should include both patients who have fully and partially discontinued their treatment, and there were insufficient data to explore this.

In addition, we do not expect that including on- and off-treatment utilities will have a meaningful impact on the model results. The AE profiles of the pembrolizumab + CT group and the placebo + CT group in KEYNOTE-868 (NRG-GY018) were comparable, indicating that most AEs are driven by the CT portion of the combination treatment. Consequently, we also expect that any on-/off-treatment disutility will be driven by CT use, and that treatment with pembrolizumab will not have a meaningful impact on patient utility. The assumption of equal utility benefit whether on or off treatment was also used and accepted in TA963, a recent appraisal in the first-line endometrial cancer population.[10] This supports the use of a single progression-free utility value that does not depend on any further adjustments based on treatments received in this health state.

B5. PRIORITY QUESTION: CS Document B, page 136, states that 'adverse events that occurred in at least 5% of patients were included in the model'. In table 46, page 137, states that hypertension and anaemia were associated with a disutility in the model. However, in the 'Adverse event disutility' worksheet, several additional adverse event disutilities are listed (e.g., pneumonitis, diarrhoea and hypokalaemia).

a. Please confirm whether these additional disutilities for these adverse events were included in the base-case analysis.

The model only considers adverse events that occurred in at least 5% of patients in either treatment arm and includes the functionality to explore additional AEs (e.g., pneumonitis, diarrhoea and hypokalaemia). However, these were not used in this submission since the incidence of these AEs in the KEYNOTE-868 (NRG-GY018) trial did not meet the 5% cut-off. Therefore, the proportion of patients who experienced these adverse events in the model was set to zero and did not affect the results.

b. Pneumonitis was varied in the probabilistic sensitivity analysis (PSA); however, it is not clear if this parameter was used in the base-case.

The proportion of patients experiencing pneumonitis in the model, as well as the standard error, is set to 0%, as shown in the 'References' sheet (row 264-266). Therefore, this parameter is not used in the base case nor varied in the PSA.

Treatment

B6. PRIORITY QUESTION: CS Document B, page 147, states that 'following progression on any of the modelled treatments, patients may receive further rounds of therapy.'

a. Please can the company clarify if this means that people could receive further rounds of the primary treatment and/or subsequent treatment?

If patients progress, they will not receive further rounds of the primary treatment (i.e. pembrolizumab) and may instead go on to receive subsequent therapies. Therefore, 'further rounds of therapy' refers to subsequent treatments only.

b. Please can the company elaborate on 're-treatment with pembrolizumab is generally not permitted?'

In UK clinical practice, re-treatment with checkpoint inhibitor therapy is only permitted in specific circumstances (i.e. following adjuvant/neoadjuvant immunotherapy, providing there is a mandatory interval of at least 6 months between the last date of administration of any prior adjuvant/neoadjuvant/maintenance immunotherapy and the date of first relapse). This re-treatment criteria does not apply to the advanced/recurrent setting which is the subject of this appraisal; therefore re-treatment with pembrolizumab would not be permitted for the population within the scope of this appraisal. The blueteq form criteria for the three main checkpoint inhibitor regimens in the second line setting for this population (PEMB23, PEMB25, DOS1_v1.0) all prohibit their use if prior antibody treatment which targets PD-1 has been used.[11] It is therefore assumed that patients who were treated with pembrolizumab before progression would only receive subsequent treatment regimens without pembrolizumab after progression, to ensure the modelled treatment use is in line with UK clinical practice. This assumption and the resulting subsequent treatment distributions in the model were also confirmed and validated with UK clinical experts.[5] For further details on how the subsequent treatment distributions in the model were generated, please see B7.

B7. PRIORITY QUESTION: The company stated that evidence about the proportion of participants assumed to receive subsequent therapy was available from KEYNOTE-868 (NRG-GY018), which was adjusted and validated by UK clinicians. Please can the company provide further details about the adjustment that was undertaken.

The following initial adjustments were applied:

- Subsequent treatments that are not approved within this setting in the UK were removed from the analysis.
- Lenvatinib was always assumed to be taken in combination with pembrolizumab.
- For the pembrolizumab + CT arm, use of subsequent immunotherapy (either pembrolizumab, pembrolizumab + lenvatinib, or dostarlimab) was set to 0% to reflect the treatment criteria in their respective blueteqs.[11]
- The remaining subsequent treatments were proportionally reweighted such that the proportion of patients that received no subsequent treatment post progression in

each arm remained equal (taken directly from trial) and the remaining treatments summed up to 100%.

These lists, split by MMR status, were presented to the clinicians at the advisory board to validate if any treatments were missing, if remaining treatments were not used in clinical practice, and whether the proportions presented for the placebo + CT arm represented the clinicians' experience of current clinical practice. The split by MMR was necessary to address the fact that second line treatment options differ between the pMMR and dMMR populations. Most notably dostarlimab and pembrolizumab monotherapies are only available to dMMR patients (although note that dostarlimab is currently only available via the CDF).

For the pMMR subgroup the clinicians said:[5]

- Of those that receive active treatment, 40% of patients would receive pembrolizumab with lenvatinib
- In addition, 15% of patients would receive paclitaxel monotherapy
- The remaining treatments were proportionally reweighted to fill the remaining 45%.

For the dMMR subgroup the clinicians said:[5]

- Of those that receive active treatment, around 75% receive IO monotherapy. (In the base case it was assumed 100% of IO monotherapy was pembrolizumab monotherapy, as dostarlimab monotherapy is still currently reimbursed via the CDF and therefore outside of the NICE reference case; use of dostarlimab monotherapy was explored in sensitivity analysis). Of those that received subsequent treatment in the CT arm of the dMMR cohort of the trial, 83% received IO.

This feedback was used to reweight the subsequent treatment proportions again ensuring no active treatment was fixed and the reweighting applied only to those that received active treatment.

B8. *In CS Document B, page 142, the company stated that no vial sharing is assumed in the model. Please can the company confirm if pack sharing was used for oral drugs?*

The model only included 'No vial sharing' for IV drugs, to account for the different available vial sizes. All oral drugs included in the model had a fixed dose, corresponding to the available mg per pill, which meant these drugs can be costed on a per pill basis. We

therefore do assume pack sharing for oral drugs, as is common practice in NICE submissions.

However, it should be noted that the only oral drugs in the model are 2L treatments. In addition, the majority of the 2L oral treatment costs in the model are driven by lenvatinib, which is only used in the CT arm. Therefore, adding 'no pack sharing' to the model would primarily increase the 2L lenvatinib use and costs for CT, resulting in a lower ICER.

B9. PRIORITY QUESTION: Table 5, CS Document B, page 148, presents the proportion of people receiving subsequent therapies following primary treatment for both pembrolizumab + CT and CT.

a. 31.72% and 17.78% of people who received pembrolizumab + CT and CT, respectively received 'no treatment'. Please can the company clarify if 'no treatment' refers to best supportive care?

This question refers to Table 55 in Document B. The term 'no treatment' refers to patients who are not receiving any anti-cancer therapy, as defined within the Clinical Study Report (CSR). All patients in KEYNOTE-868 (NRG-GY018) received supportive care, when appropriate.

Patients who received 'no treatment' in the model incur similar healthcare resource utilization and end-of-life costs compared to those who received subsequent therapy. As stated in Section B.3.5.2 of the CS Document B, healthcare resource utilization incurred in the progressed disease state was similar for all patients regardless of treatment assignment and receipt of subsequent therapy. End-of-life cost derived from Georghiou et al. which represented costs of terminal care, was applied to all patients regardless of treatment assignment.

While there may be some costs associated with supportive care, we do not expect this to differ materially between those who received subsequent treatment and those who did not. Therefore, no additional costs are assigned to patients who received 'no treatment'.

b. Additionally, what assumptions are made with regards to decrement associated with adverse events for people who received subsequent treatments?

The model applies a one-off decrement associated with adverse events (AEs) at the start of the first model cycle, following a standard and accepted approach in technology appraisals. Adverse events specific to the individual subsequent treatment options were not captured in KEYNOTE-868 (NRG-GY018), and hence were not included in the model explicitly. However, AEs were captured for the full duration of the trial, including the period in which patients receive subsequent treatment. The current approach should therefore already account for some of the adverse event impact of subsequent treatments, so modelling an additional AE decrement for subsequent treatments will likely lead to double counting.

In addition, patients receiving placebo + CT in KEYNOTE 868 (NRG-GY018) were more likely to receive subsequent immunotherapy ± lenvatinib (Table 18, CS Document B). Therefore, if the current approach underestimates the impact of subsequent treatment AEs, this should mostly affect people who received subsequent treatment in the CT arm. The current approach is therefore likely to present a conservative estimate of the cost-effectiveness of pembrolizumab + CT versus CT only.

Resource use and costs

B10. PRIORITY QUESTION: The company claimed to have uprated terminal care costs that were obtained from Geoghiou and Bardsley 2014, but to our knowledge, these costs do not reflect 2023 prices. Please can the company confirm whether the £7,2787.89 is based on the 2013/14 prices?

The value reported by Georghiou and Bardsley 2014 is £6,015.00, based on 2014 prices. This cost was subsequently inflated to 2023 prices using the inflation indices provided in Table 12.1.1 (page 98) of the PSSRU 2023 report and used within the company submission.[12]

On further inspection of the Geoghiou and Bardsley report, the £6,015 figure is an average across all patients. Within the same table (Table 9, page 23), a cancer-specific figure of £7,278 is provided. Given the patient population of interest, this is likely to be the more appropriate value. Inflated to 2023 prices (£8,829.07) and implementing into the base case analysis results in a small decrease in the ICER, from [redacted]. This is driven by the interplay of increased upfront OS in the pembrolizumab + CT arm alongside yearly discounting of costs.

Electronic model

B11. *Please can the company clarify how the 'Run Vial Optimization' button in the 'Drug Acquisition Costs' worksheet is being used in the model?*

The "Run Vial Optimization" button's functionality was removed during iterations of the model's adaptation. The model assumes no vial sharing. That is, when drug dosing is dependent on body surface area (BSA) or weight, the cost of a whole vial is used in the calculation of the drug acquisition cost, as opposed to working out the cost of the fraction of the vial that was needed.

Within the model only paclitaxel and doxorubicin are reliant on BSA. If full vial sharing (0% wastage) were to be assumed, this would bring down the cost of these drugs in the model. Given paclitaxel use as part of the study treatment regimen is broadly equal across study arms, and that subsequent paclitaxel and doxorubicin use is higher in the pembrolizumab + CT arm, it would be reasonable to expect that the ICER in such a scenario would further favour pembrolizumab.

B12. *The company stated that the model begins with a hypothetical cohort of people aged 65.40 years, and that the time horizon is lifetime (35 years). However, on inspection of the trace and formulae (=SUMIF($A$15:$A$2156,"<="&default_time_horizon_years,AK$15:AK$2156)*cycle_length_yrs) the model goes up to the age of 106 years. Please can the company confirm that there are no costs incurred or benefits accrued beyond the stated lifetime horizon of 35 years.*

In the base case scenario, the model begins with a cohort of individuals aged 65.4 years and uses a lifetime horizon of 35 years, hence the model captures costs and benefits up to the age of 100.40 years.

The provided formula ensures that no values beyond the specified time horizon (default_time_horizon_years) are included in the summation. While the model is capable of extending calculations up to 106 years, this flexibility is intended to accommodate potential variations in the cohort age and/or time horizon.

B13. PRIORITY QUESTION: The company undertook several scenario analyses, with one being about the use of subsequent treatments as observed

in the trial, returning values of incremental costs [redacted], incremental LYs ([redacted]) and incremental QALYs ([redacted]), which equates to an ICER of [redacted] per QALY.

a. Please can the company clarify if only the costs associated with these subsequent therapies were considered in this scenario analysis.

We can confirm that only drug acquisition and administration costs associated with these subsequent therapies were considered for this scenario.

b. Please can the company clarify what assumption(s) are being made about the benefit of subsequent treatments.

No specific assumptions regarding subsequent treatments were made. Any benefit derived from subsequent therapies in either arm have been modelled using the outcome data observed in the trial.

As discussed in response to A6, subsequent treatment use in the placebo + CT arm is largely reflective of the UK landscape. Input from the advisory board highlighted that the proportion of CT arm patients that receive IO as part of subsequent treatment is lower in the model than observed in the trial (50% vs 71% respectively). Given the known benefit of IOs in this population, the cost of the CT arm may be underestimated with the OS benefit potentially overestimated. Additionally, a small proportion of patients switched to receive IO prior to progression (see response to C7) which may result in some additional benefit in this arm. In the pembrolizumab + CT arm, a small proportion of all patients (15%) had retreatment with pembrolizumab ± lenvatinib which is not permitted in UK practice. However, there is currently no evidence to indicate an efficacy benefit associated with retreatment using the same (or an alternative) IO after progression, and it is likely that the capacity of patients to benefit from retreatment would be reduced compared those receiving IO treatment in the first-line setting. Therefore, any benefit associated with retreatment is likely to be very small, and the net result across the two arms is expected to be negligible.

B14. PRIORITY QUESTION: Please can the company provide a model that allows for updates to be undertaken, especially when undertaking the probabilistic sensitivity analysis.

As per our clarification meeting on 26th September and email correspondence on 7th October, this question has been addressed. To confirm, this issue related to the PSA macro

and how new parameters were randomly sampled; details clarifying the functionality of the PSA macro are provided here:

- Line 123 within the PSA macro starts the random number generation that is inputted into 'PSA Setup' column I [Hidden sheet], in turn creating new parameters for PSA iterations in column H.
- Line 128-132 saves the new parameter iteration in an array called "inputlist".
- Line 135-137 is used to change the named variables to the random PSA iterations. These changes can be seen in the 'References' sheet, which then cascade through the model producing the PSA iterations.

B15. PRIORITY QUESTION: The EAG noted that in the electronic model, there are two worksheets (DSA Results and OWSA) with tornado diagrams. With regards to the tornado diagram presented in the 'DSA Results' worksheet, it states that the base-case ICER is [redacted] but in Table 62, CS document B, page 162, the base-case ICER is [redacted]. Please can the company provide further details about the ICER of [redacted].

The model that was submitted to NICE is derived from a core "global" model that is adapted to specific country/regional needs. For the NICE submission the DSA functionality and sheets were not used, instead adding in, and using, bespoke OWSA and scenario analysis functionality to ensure the sensitivity analysis in the model aligned with NICE's requirements. The DSA functionality should have been deleted from the model but was unintentionally left in following the adaptation.

As such it is unknown exactly what this 'DSA Results' ICER relates to. This said, given that this scenario derives from the "global" model, it will have included the **list price** of pembrolizumab as opposed to the price reflecting the current commercial arrangement, as presented in the company submission.

***B16.** In the absence of confidence intervals, it appears to the EAG that the company assumed ±20% in the one-way sensitivity analysis, but in the probabilistic sensitivity analysis (PSA) ±10%. Please can the company provide rationale for using a narrower range in the PSA?*

After further review, it appears that the OWSA description in Document B was inaccurate. Both the PSA and OWSA used an assumed standard error of 10% for inputs where no uncertainty information was available. This is driven by the 'assumed_se' parameter in the References sheet of the model. This assumed standard error is used by both the PSA and OWSA, ensuring that both analyses use the same uncertainty inputs. This assumed standard error was incorrectly described as 20% in Document B, but the electronic model and presented OWSA and PSA results in Document B both rely on an assumed standard error of 10%.

Section C: Statistical methods

C1. PRIORITY QUESTION: Please provide clear Kaplan-Meier plots, separately for the Pembro + CT group and the CT only group, for both PFS and OS outcomes. Therefore, four plots. In these plots, please ensure that:

- ***These plots are as clear and large as reasonably possible***
- ***The lines of the KM plots are solid (i.e. not dashed) and coloured black***
- ***There are either no lines for censored observations, or that these lines are in a different colour***
- ***The number at risk table has numbers at as many timepoints (at least every 3 months)***

Detailed Kaplan-Meier plots, along with the underlying data, are provided within the model in the sheet <KM Data> and n at risks figures can also be found within Document B (Figures 5 and 6)

C2. *Please provide the individualised KM data for each outcome (therefore, two tables), in the following format:*

ID	*Group*	*Outcome*	*Time (months/weeks/etc)*	*PFS status 1=yes, 0=no*	*Censored?*
1	*Pembro + CT*	*PFS*	*12*	*0*	*Yes*
2	*CT only*	*PFS*	*6*	*1*	*No*

3	*CT only*	*PFS*	*7*	*1*	*No*
4	*Pembro + CT*	*PFS*	*18*	*0*	*Yes*
5	*CT only*	*PFS*	*32*	*1*	*No*
6	*Pembro + CT*	*PFS*	*29*	*1*	*No*
7	*CT only*	*PFS*	*21*	*0*	*Yes*
And so on…					

As per the response to C2, detailed Kaplan-Meier plots, along with the underlying data, are provided within the model in the sheet <KM Data>.

C3. *In the two-piece survival modelling, were any other cut-off points considered? And were any other methods to choose cut-off points considered?*

For each data set, two statisticians assessed the KM curves, hazard profile, number of events and number at risk to determine the most appropriate cut-off points. Chow test statistics were also conducted to support the choice of cut-off points. Both statisticians considered the cut-off points presented in the submission to be the most appropriate given the observed data across all treatment arms/outcomes. Number of events and number at risk were considered to ensure that past the cut-off point extrapolations were being made based on a sufficient sample size.

Please see the response to C4 for details on other cut-off points that were considered.

C4. *Were different cut-off points considered for the pembro+CT and CT only groups, instead of 38 weeks for both groups?*

The following process was used to arrive at the presented cut-off points:

PFS-PEM+CT: 1st peak at 38 weeks, 2nd peak at 49 weeks based on the Chow test plots indicating the potential presence of a natural cut point.

PFS- CT: 1st peak at 37/38 weeks, 2nd peak at 50 weeks based on the Chow test plots indicating the potential presence of a natural cut point.

Following a review of the KM curves, number of events, number at risk, and hazard plots, the 38 week cut point was selected for both arms due to a clear change in direction of the hazards for both arms at this timepoint, which was also supported by the Chow test plots. The later potential cut points may have also led to over fitting in the tail, with long term PFS being driven by a small sample size. There was no clear rationale to select different time points for the two arms.

OS-PEM+CT: 1st peak at 40 weeks, 2nd at 70 weeks based on the Chow test plots indicating the potential presence of a natural cut point.

Following inspection of the KM curves, number of events, and number at risk, 40 weeks was chosen as the cut point. The 40-week mark coincided with an inflection point in the hazard plots, which was also supported by the Chow test plots. While there was a peak in hazards close to 70 weeks, as with PFS this would have led to long term survival outcomes being driven by a small number of patients and events.

OS-CT: No real peaks were observed in the hazard plots or indicated in the chow test, indicating that there is not a clear turning point in the hazard profile for this arm, although a plateau forming at 40-50 weeks was observed. As discussed in B.3.3.4 of Document B, the standard parametric models provided a good fit to the observed data for the CT arm therefore two-piece models were not required. However, they were conducted for completeness and the 40 week cut point was selected for consistency between the two treatment arms.

C5. *Were any covariates adjusted for in any of the survival analysis modelling? If not, why?*

No covariates were adjusted for in the survival analysis modelling. Given that the trial was an RCT, any known or unknown confounders were likely to be balanced between arms. Clinicians at the advisory board also confirmed that the trial population was broadly similar to the UK setting.{MSD, 2024 #162} ECOG score was raised as a potential difference (higher ECOG 1 vs 0 in UK clinical practice), but subgroup analysis in both PFS and OS found that this was not a significant effect modifier.

C6. *Please confirm the software used for the survival analysis modelling, and packages used within the software.*

Survival analysis modelling was conducted using R, and the 'flexsurv' package was used for fitting both parametric and spline curves.

C7. *The final paragraph of Section B.2.6.1 notes how patients were unblinded and able to switch from their assigned treatment. Was treatment-switching analysis considered? Please explain why, if it was considered, those analyses were not presented. How does accounting for treatment switching influence the base-case ICER?*

As stated in the submission [redacted] patients in the CT arm received some form of subsequent treatment prior to progression, of which [redacted] patients received pembrolizumab ± lenvatinib. In the pembrolizumab + CT arm, [redacted] patients were recorded as receiving any subsequent therapy prior to progression; of these, [redacted] continued pembrolizumab, to which lenvatinib appears to have been added for [redacted] patients. The other subsequent therapies received pre-progression were chemotherapy agents, hormonal agents, radiotherapy, or regimens not considered to be anti-cancer therapies (Table 10). It may be reasonable to assume that some patients with a recorded subsequent therapy pre-progression received an additional benefit to both PFS and OS that may not be seen in UK clinical practice where treatment switching pre-progression is not common practice. Given more people in the CT arm switched pre-progression, it would be reasonable to assume that the incremental QALYs in the model are slightly underestimated.

Whilst methods to adjust for treatment switching are available, all such methods have limitations and would introduce additional uncertainty to the dataset. Therefore, given the small number of patients who switched to an active subsequent treatment before progression, and in particular the small number of patients who switched to IO therapy with pembrolizumab ± lenvatinib, it was considered unnecessary to introduce further complexity or uncertainty by adjusting the data to account for this switching.

Table 10. Participants with Subsequent Systemic Oncologic Therapy Received Prior to Progression in All-comers Participants

	Paclitaxel + Carboplatin + Pembrolizumab (N=408)	Paclitaxel + Carboplatin + Placebo (N=411)	Total (N=819)
Started Study Treatment	[redacted]	[redacted]	[redacted]
Discontinued Study Treatment	[redacted]	[redacted]	[redacted]
Received Any Subsequent Systemic Anti-cancer Therapy	[redacted]	[redacted]	[redacted]

Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	[redacted]	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]
Any Anti-angiogenic	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]
bevacizumab awwb	[redacted]	[redacted]	[redacted]
lenvatinib	[redacted]	[redacted]	[redacted]
lenvatinib mesilate	[redacted]	[redacted]	[redacted]
Any Chemotherapy	[redacted]	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]	[redacted]
cyclophosphamide	[redacted]	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]	[redacted]
doxorubicin	[redacted]	[redacted]	[redacted]
liposomal doxorubicin	[redacted]	[redacted]	[redacted]
liposomal doxorubicin hydrochloride	[redacted]	[redacted]	[redacted]
other therapeutic products	[redacted]	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]	[redacted]
Any Hormonal agents	[redacted]	[redacted]	[redacted]
fulvestrant	[redacted]	[redacted]	[redacted]
letrozole	[redacted]	[redacted]	[redacted]
megestrol	[redacted]	[redacted]	[redacted]
megestrol acetate	[redacted]	[redacted]	[redacted]
tamoxifen	[redacted]	[redacted]	[redacted]
Any Procedures, Other Non-Therapeutic Products or Agents	[redacted]	[redacted]	[redacted]
all other non-therapeutic products	[redacted]	[redacted]	[redacted]
apixaban	[redacted]	[redacted]	[redacted]
fosaprepitant meglumine	[redacted]	[redacted]	[redacted]
zoledronic acid monohydrate	[redacted]	[redacted]	[redacted]
Any Radiotherapy	[redacted]	[redacted]	[redacted]
radiotherapy	[redacted]	[redacted]	[redacted]
Any Other Investigational or Approved Agents	[redacted]	[redacted]	[redacted]

An analysis was conducted as part of the study statistical analysis plan looking at an alternative exploratory censoring rule for PFS that censored patients at the last visit prior to

starting a new anti-cancer therapy (Table 12). When comparing the primary protocol censoring rule with the pre-progression censoring rule the PFS HR goes [redacted] (Table 11).

While there is potential for this analysis to improve the ICER (in favour of pembrolizumab + CT) a decision was taken not to explore this further in the submission. The rationale for this decision was based on wanting to minimise uncertainty, which would have inevitably been introduced by the additional censoring of 106 patients.

Table 11: Analysis of PFS based on investigator assessment per RECIST 1.1 (exploratory censoring rule) in all-comer population (ITT population; Efficacy and Safety Update; August 2023 data cut)

	All-comer population (n = 819)	
	Pembrolizumab + CT (n = 408)	**Placebo + CT (n = 411)**
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)[a]	[redacted]	[redacted]
PFS HR (95% CI)[b]	[redacted]	
Nominal p-value[c]	[redacted]	
PFS rate at month 6, % (95% CI)	[redacted]	[redacted]
PFS rate at month 12, % (95% CI)	[redacted]	[redacted]
PFS rate at month 18, % (95% CI)	[redacted]	[redacted]
PFS rate at month 24, % (95% CI)	[redacted]	[redacted]
PFS rate at month 30, % (95% CI)	[redacted]	[redacted]
PFS rate at month 36, % (95% CI)	[redacted]	[redacted]

Key: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, Intention-to-Treat; PFS, progression-free survival.
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status and prior chemotherapy.
[c] One-sided p-value based on log-rank test stratified by MMR status and prior chemotherapy.
NR = Not reached.

Table 12: Progression-free survival censoring rules

Situation	**Protocol based PFS (base case)**	**Exploratory pre-progression switching censoring analysis**
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Progressed at date of documented PD or death	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessments and new anticancer therapy, if any
No PD and no death; new anticancer treatment is not initiated	Censored at last contact date	Censored at last disease assessment

No PD and no death; new anticancer treatment is initiated	Censored at last contact date	Censored at last disease assessment before new anticancer treatment

Abbreviations: PD, progressed disease; PFS, progression-free survival.

Section D: Textual clarification and additional points

D1. *In Table 47, CS Document B, pages 138-139, the company presents the summary of the utility values and adverse event decrements along with their standard errors and 95%CIs. Please can the company clarify why the lower and upper bounds for stable disease and progressed disease do not match the upper and lower bounds in the OWSA Data or the OWSA worksheets.*

The CIs and standard errors provided in Table 47 were calculated via bootstrapping (under the assumption of the central limit theorem), this method makes no assumption about the distribution of the utility values. This standard error was then used within the model to produce confidence intervals and random draws for the OWSA/PSA under the assumption that utility values follow a beta distribution.

The differences in 95% CIs are small (all equal to 2 decimal places). Outside of OWSA and PSA other utility values were explored in scenario analysis. These scenarios did not have any significant impact on the ICER.

D2. *Please can the company clarify if the number of adverse events per participant and the duration (days) of the adverse events are commercial in confidence? In the Table 46, CS Document B, page 137, these numbers are commercial in confidence but not in the 'Adverse event disutility' worksheet.*

These figures **should** be marked as commercial in confidence in the model. MSD apologise for any confusion.

D3. *For clarity, please can the company provide explanation for the use of* ***xxx*** *violet/purple highlight used within the Reference worksheet?*

The shading within the reference worksheet is used to indicate cells where the reported standard error was not available and was therefore calculated. In these instances, the reported mean is instead adjusted by multiplying it with the 'assumed_se' parameter, which

is set to 10% in the base case scenario. This approach is used to maintain consistency in the model's calculations where standard errors are not provided.

References

1. Alvaro Ingles Russo Garces. Demographics and Survival Outcomes in Patients with Advanced or Recurrent Endometrial Cancer in the English Real-World Setting. (https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/0214cb59-a124-470f-af22-724a2e9bcb91/0214cb59-a124-470f-af22-724a2e9bcb91_viewable_rendition__v.pdf?REF--ALL-004799).
2. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Disposition, Demographics and Concomitant Medications (All-comer Participants Population). 2024.
3. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. The New England journal of medicine 2023;388(23):2159-2170. (In eng). DOI: 10.1056/NEJMoa2302312.
4. Morrison J, Balega J, Buckley L, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. European journal of obstetrics, gynecology, and reproductive biology 2022;270:50-89. (In eng). DOI: 10.1016/j.ejogrb.2021.11.423.
5. MSD. Key Summary, Plan of Action and Meeting Summary for the UK Endometrial Cancer Advisory Board 2024. 2024.
6. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Efficacy (All-comer Participants Population). 2024.
7. National Institute for Health and Care Excellence (NICE). Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. (https://www.nice.org.uk/guidance/ta914).
8. National Institute for Health and Care Excellence (NICE). Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. (https://www.nice.org.uk/guidance/TA904).
9. MSD. A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer. 2023.
10. National Institute for Health and Care Excellence (NICE). Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. (https://www.nice.org.uk/guidance/ta963).
11. NHS England. Cancer Drugs Fund list, v1.326. (https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/).
12. Jones KC, Weatherly H, Birch S, et al. Unit Costs of Health and Social Care 2023 Manual. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York), 2024.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

Patient Organisation Submission

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	Volunteer Policy Lead
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. Peaches Womb Cancer Trust also hosts 'Peaches Patient Voices', a patient and public involvement group for people affected by womb cancer. We work with, and advocate for, people affected by womb cancer – diagnosed at all stages – and their loved ones.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No

If so, please state the name of the company, amount, and purpose of funding.	
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?	Peaches Womb Cancer Trust has contributed the views, insights, and expertise of our Peaches Patient Voices network, and used our evidence to highlight the difficult situation many patients face when diagnosed with primary advanced or recurrent endometrial cancer. As an organisation, we have presented our evidence on the impact of advanced and recurrent endometrial cancer, and available treatments, on our Patient Voices community. Peaches Womb Cancer Trust has valued the opportunity to use evidence obtained from members of Peaches Patient Voices to demonstrate the potential positive outcome for many people facing a primary advanced or recurrent endometrial cancer diagnosis.The following submission includes evidence obtained from extensive patient engagement, including: • focus groups and questionnaires that informed our previous submissions (ID3811 and ID3968) and involved women with lived experience of advanced or recurrent endometrial cancer • the focus groups included women with stage 3 and 4 endometrial cancer and, in the focus group that informed ID3968, two carers of women with stage 4 endometrial cancer who had undergone primary treatment with surgery and/or chemotherapy and radiotherapy • a previously used statement from a patient expert with lived experience of being on pembrolizumab (Hannah) – along with an updated statement from the same patient to reflect her experiences after completing pembrolizumab, in line with a 2-year stopping rule Note that some quotes or experiences may reflect patients' experience of a PD-1 inhibitor immunotherapy, which is not the technology under appraisal. The rationale for including these is that side effects are likely to be similar.

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 vaginal bleeding, pain and discomfort, watery vaginal discharge, urinary urgency/ incontinence, reduced appetite, nausea, fatigue, and abdominal swelling. These symptoms impacted their quality of life, due to the practical implications of bleeding and urge incontinence, and some women found it challenging to leave the house to socialise and work. Many women experienced diagnosis-induced feelings of terror and fear at having to face one's own mortality, and many of those diagnosed with stage 3 cancer 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. Many felt like a different person following their diagnosis and treatment, in part due to feeling physically different, but mostly due to the psychological impact. Many felt that their relationships with family and friends altered following their diagnosis, and that people treated them differently. There was also ongoing worry and anxiety about how their diagnosis would impact family members and children, and how they would cope. One woman described how her teenage son's anxiety had become significantly worse following her diagnosis resulting in him needing additional mental health support. Other patients reported: *"I panicked about dying. Nobody definitively told me I wouldn't. I cried about not seeing my children get married; maybe never holding my grandchildren."*

	"I worry about dying if the treatment stops working. We try to make the most of my good days, but always worry what is round the corner. Will I see my youngest grandchild start school? How far ahead can we make plans? Can I think about skiing next year or will I be dead by Christmas?" *"I am taking [an anti-depressant], something I never thought I would do. I was a successful [professional] for 19 years and coped well with everything that was thrown at me, I had [treatment for] breast cancer [several years ago] but sailed through it, this has been so much harder."* *"I am constantly anxious and hypervigilant for any signs of recurrence. I have symptoms that could be recurrence and have my 3-monthly check up in 2 weeks. So, even though I finished treatment [last year], cancer is still part of my daily life."* *"Current treatments do not negate the possibility of recurrence, so the fear of recurrence is real and present. I have asked, but no one will make assurances or predictions for me. They generalise and make hopeful comments, whilst acknowledging they have no crystal ball. They know, and I know, that everyone did their best for me, but that sometimes the best still fails."* Women with stage 4 cancer report difficulty managing symptoms caused by the disease. One of the women with stage 4 disease had ascites at the time of diagnosis. This caused significant pain and a reduction in her mobility, as well as impacting her ability to perform activities of daily living, leaving her increasingly reliant on friends and family for help. The ascites required recurrent drains resulting in frequent trips to the hospital with associated costs and impact on quality of life. Following her diagnosis, she also required bilateral nephrostomies due to ureteric obstruction, which impacted her physically, reducing her mobility. Another woman had ongoing bowel problems, including pain and constipation at the time of diagnosis due to a recurrence resulting in a tumour in her upper rectum.

	People caring for those with advanced or recurrent endometrial cancer face significant challenges. Many described the emotional challenges of being a carer, the constant feeling of helplessness, and the psychological impact on them. Caring for someone at home who is end of life causes significant challenges, both physically and psychologically. Many will require care around the clock, resulting in carers having to take time off work, impacting financially, but also resulting in fatigue, burnout, guilt, frustration and grief. *"The carer takes over the huge burden of looking after the patient, the family, continuing work and providing emotional as well as physical support to the patient. They might be taking the patient to the hospital appointments, encounter long waiting times, arrange for GP appointments, etc. All these commitments for a carer are on top of all the other family commitments the carer has to take on."* *"[It's] terrible to watch your loved one failing and relying on you for support. My health and wellbeing [were] impacted trying to be strong and keep things together. The emotional support of loved ones is seriously lacking as they have to be strong, but it is deeply emotional and resulted in me suffering from panic attacks and prescribed antidepressants."* *"You feel guilt that you cannot fix it or do it for them."* One carer described the pain of anticipatory grief from caring for someone who is at the end of their life: *"You are constantly wondering when they will stop replying to your messages, or when the ticks on WhatsApp will stop turning blue."*

	Following the death of someone from advanced or recurrent endometrial cancer, there is a long-term impact of grief, including uncertainty about how you acted; whether you could have done more; whether you could have spent more time with them; or whether you should have done something differently.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**1. Women were dissatisfied and frustrated by current treatments for advanced and recurrent endometrial cancer, which include surgery, chemotherapy and radiotherapy** Women found chemotherapy challenging 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, mouth pain, hair loss, change in bladder and bowel habit and neutropenia. Many had to take additional medication to try and reduce the side effects, but found they also experienced other side effects from the additional medications. Several women mentioned the effect of chemotherapy on the immune system and felt it left them vulnerable. This significantly impacted their quality of life, with many unable to work face-to-face or requiring time off, and others unable to go out, spend time with family and friends, or engage in activities like swimming due to the risk of infection. "*The current treatments are brutal; you lose a week of your life every three weeks. A week where it is impossible to be 'normal'. The steroids alter your appearance, you lose your hair and eyebrows and eyelashes, and you lose your identity!"* *"The two years since I was diagnosed have been really hard. Hard for family, and for me. They have already lived through my breast cancer diagnosis, and I think they knew that this time I wasn't as hopeful. The surgery was harder, the recovery longer. I couldn't do any of my normal activities for months. The radiotherapy was longer (every day, a 70-mile trip for five weeks), with more intensive side effects, (which are still affecting me). The chemotherapy had a greater impact on me. The side effects were worse and for longer. Psychologically it is harder. The success rate is lower, and we all knew this. The treatments are less well managed and less effective."* *"I never felt despair when I had breast cancer, I was always assured that there [were] many different treatment options. So very different from endometrial cancer. I was told that this time chemo might not be effective as I have had it before and my recurrence occurred quickly. I lost all hope. I really thought I was going to die in months."* – Patient who received immunotherapy (not pembrolizumab) following an advanced endometrial cancer diagnosis. She previously had breast cancer.

	2. Many patients reported long term, often debilitating, side effects as a result of treatment which prevents them from living a fulfilling life Long term side effects of current first-line treatments for advanced or recurrent endometrial cancer included pain, bowel and bladder issues, lymphoedema and fatigue, which have left women anxious: *"I experienced fatigue like never before. At times I would be doing ok and then it would feel as if something had been 'switched off' – no run down, gradual descent, just instantaneous."* 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. For others, limited mobility and pain means they are unable to leave the house. This also takes a significant toll on their mental health. Chemotherapy-induced peripheral neuropathy can cause pain in hands and feet. One patient reported: *"I still have neuropathy in my feet, sharp enough to make me yelp in surprise sometimes, painful enough to be annoying, but not life changing."* **3. Many patients have been left unable to work, due to after-effects of treatment, 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 treatment-related symptoms at work and access to a private toilet. Patients reported: *"I was left virtually incontinent of both bladder and bowel […] and although I have had physio for this, there has not been a huge amount of improvement. It is affecting my ability to return to a job I love."*

	"I couldn't work for about 18 months so I ran out of sick pay, and I'm currently on a phased return to work, so reduced pay, as I can only manage about 18 hours a week at the moment." *"It has had a huge impact on my work, family and social life. I have lost a lot of confidence due to the effects I still struggle with and rarely go out on an evening. At the weekend I can't manage to do something sociable during the day and then go out on an evening too."* *"I had to stop work for 11 months because of my treatment. I was told unequivocally by my oncologist at the start that I wouldn't be returning to [work] that year. At the time, this seemed incredible to me, but the roller-coaster of all the treatment cycles (fatigue/ nausea/ low neutrophil counts/ frequent hospital visits which were a two hour round trip) meant that it would have been impossible for me to continue going to work."* **4. Endometrial cancer treatment has substantial impact on finances** Patients reported significant impacts on their finances both through the time it takes to receive treatment and the long-term side effects. This included: • cost of travel to treatment and parking at hospital • long term sick leave with implications to pay • cost of living at home (e.g. heating) • cost of complementary therapies to support wellbeing or manage side effects **5. Some women are unable to live fully independently due to physical symptoms and limited mobility** Due to the impacts of treatment, 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. 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.

	"I don't have the energy to do normal daily tasks which means that […] my husband took on more work/chores [and] my 76-year-old mother had to come over to do washing for me." We spoke to a carer who cared for her friend who sadly passed away from endometrial cancer in her mid to late thirties. She told us of the additional challenges of undergoing treatment when one is pre-menopausal with no children. Her friend struggled with menopausal symptoms following surgical treatment, including hot flushes, fatigue and difficulty sleeping. The psychological impact of treatment for endometrial cancer on fertility is huge, and delays in diagnosis leading to advanced stage disease may mean that fertility options are not available, leaving women angry, frustrated and distressed. **6. Treatments including hysterectomy and radiotherapy also significantly impacted on sexual intimacy** These impacts are due to multiple factors, including vaginal discomfort, bleeding and the vulnerability and trauma that comes with repeated intimate examinations. *"I was very traumatised by the diagnosis process regarding intimate examinations, which included painful examinations in an emergency situation and other multiple different examinations. This meant brachytherapy was particularly difficult for me, and my oncologist kindly performed the procedures, rather than the nursing team, because I trusted her. This has also greatly impacted my sexual function – both due to the trauma of invasive and difficult examinations and the long-term side effects of a shortened vagina from surgery, narrowing caused by vaginal stenosis (narrowing) caused by scar tissue, and menopause."*

8. Is there an unmet need for patients with this condition?	**There is a significant unmet need for patients with all molecular subtypes of primary advanced or recurrent endometrial cancer to have earlier access to effective treatment options. While the approval of immunotherapies has been a breakthrough for those previously treated with platinum-based chemotherapies, patients with primary advanced or recurrent cancer have clearly articulated a need for treatments beyond 'bog standard chemotherapy'.** **Part of this unmet is need is for earlier intervention with immunotherapy to prevent recurrence from happening in the first place. Earlier access to pembrolizumab could prevent women with stage 3 disease from later being diagnosed with incurable stage 4 disease by stopping recurrence and progression of their cancer.** Existing PD-1 inhibitor immunotherapy treatment options are primarily offered to patients who have previously received treatment. **However, patients diagnosed with primary advanced endometrial cancer only have access to limited treatment options that are not very effective.** This results in increased likelihood and worry about recurrence, along with associated physical and mental impacts (such as the need for additional surgery or other treatment and the psychological burden). Although people diagnosed with primary stage 4 or recurrent endometrial cancer may be able to access immunotherapy as a second-line treatment, there is an unmet need to be able to access a more effective treatment earlier in the pathway, which offers hope of a better outcome. Access to immunotherapy at the point of first diagnosis offers hope of slowing or halting progression and being able to **live a longer and fuller life with manageable side effects**. **Having limited effective first-line treatment options for advanced and recurrent endometrial cancer leaves women feeling frustrated, disappointed, angry and abandoned.** Many expressed feelings of being left behind or not prioritised for effective treatment options. They felt that women affected by endometrial cancer had fewer effective treatment options compared with other cancers. Several patients referred to availability of multiple lines of treatment for breast cancer, and the wish to have access to multiple lines of treatment for endometrial cancer. One patient expressed that:

	"*The UK has some of the poorest cancer survival rates as compared to Europe. However, where improvements in cancer survival rates are seen [it] is in those cancer[s] where a combined treatment approach is clinically available on the NHS, involving traditional chemotherapy plus newer targeted type treatments. In many cancer[s], these are available in both first-line and second-line treatments. All patients regardless of their cancer [type] should have equal access to the potential survival benefits these newer cancer treatments may offer."* Another highlighted: *"The current approach is geared towards expecting a recurrence and then adding a more effective second-line treatment. It is paramount to offer endometrial cancer patients a first-line treatment which will further reduce the chance of the cancer recurring."* For those with recurrent cancer, there was anxiety around survival and treatment options given the lack of access to effective lines of treatment beyond 'bog-standard chemotherapy'. Patients said that: *"I have […] twice been subject to clinical investigation for suspected recurrent disease. Being aware that survival rates for advanced disease are considered poor and knowing that my only treatment option that would be offered to me in the NHS would be 'bog standard chemotherapy' as first line, filled me with dread and fear."* *"Recurrent cancer is just given top up chemotherapy and there are very little alternatives available. There are little or no options available especially specific to womb cancer."* Where some options may be already available through special licence or the Cancer Drugs Fund, this could lead to delays in accessing treatment. One carer, speaking about her deceased mother, said: *"[My mother's] cancer was aggressive and oestrogen sensitive. There is a lot of paperwork and red tape to get funding. Patients and their families don't have time to wait for approvals, it needs to be available and ready."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The main advantages of the technology that patients identified are: 1. **Patients with stage 3 endometrial cancer would get access to a first-line treatment that reduces the chance of recurrence.** *"[I want] the cancer to be gone and the risk of recurrence to be hugely, (ideally completely), eliminated"* 2. **For patients with stage 4 disease and recurrence, the treatment offers the chance of extended progression free survival with a better overall quality of life, time with family and friends, and hope of living a meaningful life.** *"I want a treatment that will stop the spread, reduce the size of, or get rid of the cancer. Preferably the latter. I want my life prolonged, the worry to stop, and to get back to normal."* 3. **Getting access to more effective treatments earlier in the pathway would improve both survival and quality of life by better symptom control and fewer debilitating symptoms in the longer term**. Pembrolizumab, used as a maintenance treatment, may keep patients in remission or with stable disease for longer, enabling them to maintain their independence longer and live life as fully as possible. 4. **Pembrolizumab as a maintenance treatment offers ongoing active treatment with manageable side effects.** Access to an effective maintenance treatment without difficult-to-manage side effects provides increased hope to patients. 5. **Pembrolizumab as a maintenance therapy for stage 4 or recurrent disease may enable patients to feel well enough to engage in activities meaningful to their lives, promoting mental wellbeing and allowing them to thrive**. Access to pembrolizumab could mean 'living with' cancer' and may help patients to remain well for longer.

6. **Patients may be able to stay well for longer which would improve the likelihood of bridging to future treatments.**

7. **Earlier access to more effective treatments may prevent the need for additional surgeries to manage tumour growth after initial treatment**. Recurrence following stage 3 or 4 cancer may require additional surgical intervention. For example, in the case of Hannah (whose story is shared below), her recurrence occurred in her rectum, requiring a Hartmann's procedure to create a colostomy. Earlier intervention with pembrolizumab and ongoing maintenance treatment may have prevented additional surgery.

8. **Access to immunotherapies provides hope for patients facing an advanced endometrial cancer diagnosis.** One patient with stage 4 disease highlighted that access to her immunotherapy (not pembrolizumab) gives:

   "HOPE…Optimism for a future. A treatment without the brutal side effects, a treatment that doesn't take over your life. A treatment that enables you to travel and plan for a future, giving me a belief that I might see my granddaughter start school. […] Hope is the most important, an option when other doors are closing."

Patient story:

Hannah* was diagnosed with stage 4, grade 3 endometrial cancer in November 2019, age 30, and underwent hysterectomy, platinum-based chemotherapy, radiotherapy and brachytherapy. She relapsed 6 months after finishing treatment for her primary cancer – with tumours in her bowel, scar tissue and one near her liver.

After undergoing surgery which removed 3 of 4 tumours, she started pembrolizumab as a monotherapy which shrunk the final tumour so that there is nothing visible on her scans. She has now finished treatment and has been in remission for over a year.

	Hannah has also been able to live a “healthier and more fulfilling life” despite an incurable cancer diagnosis and has been ‘living well with cancer’ for over 3 years both on and off pembrolizumab. Although there have been a couple of setbacks (mainly underactive thyroid due to the treatment) and fatigue, the benefits much outweigh these – and are much easier to manage than those she experienced on chemotherapy. Although Hannah only received pembrolizumab as a monotherapy, her experience demonstrates the potential benefit of pembrolizumab as a maintenance treatment following platinum-based chemotherapy with pembrolizumab. Hannah reported: *“I have found the treatment to be much kinder and more manageable than any others that I have had and I have experienced fewer side effects. With pembrolizumab, I feel much more relaxed and able to live a normal life and am able to go to the office, meet friends, occasionally go out dancing and attend social and family events. I am grateful every day that I am able to live my life fully and without many of the side effects of previous treatments. Sometimes, I even forget that I have stage 4 cancer!”* Hannah has since finished treatment and has been off treatment for over a year with no evidence of disease on scans. During this time, she has been able to have an active social and work life, travel to Greece and Costa Rica and attend festivals. *Pseudonym used

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Key disadvantages of the technology that patients identified include: **1. Fatigue** Some patients receiving either chemotherapy combined with an immunotherapy or immunotherapy as a monotherapy report fatigue. One patient describes how she has experienced worse fatigue than when her primary tumour was treated *"I have one complete day when I can do nothing, I get exhausted walking up stairs."* Patient on an immunotherapy with chemotherapy – not pembrolizumab) One patient, who received pembrolizumab as a monotherapy, reported: *"Whilst I was on treatment, I was able to life a nearly normal life, although I needed to rest more and avoid overdoing it. However, pembrolizumab had a cumulative impact on my energy levels and I have been living with fatigue for the past couple of years even after treatment. I have some periods of more intense fatigue where I struggle to do as much. However, without pembrolizumab, I would not be alive so it's worth it."* **2. Impact on biochemical markers** Pembrolizumab may have additional impact on biochemical markers. *"I'm taking magnesium supplements for low levels which hasn't happened before, and I know my haemoglobin levels are low."* (Patient on an immunotherapy with chemotherapy – not pembrolizumab)

	"*I have had some challenges with very low ferritin levels following immunotherapy. Although I am not sure if they are linked, I had to get an iron infusion to top them up and stop feeling so tired.*" (Patient on pembrolizumab as a monotherapy) **3. Immune-related adverse impacts** One patient reported that they were diagnosed with an underactive thyroid caused by pembrolizumab. Initially this led to feelings of profound fatigue. Following levothyroxine treatment, the patient does not have any ongoing side effects although treatment is lifelong. *"Due to the initial impact on my thyroid, I became incredibly fatigued (the worst of the entire treatment) and struggled to even get off the sofa and do basic things like cook or shower. It took a little while for my thyroid to completely stop functioning and I couldn't have treatment until then. This meant I had to live with debilitating fatigue for 4-6 weeks until I could start the treatment. It took another month or two to feel the benefit of the levothyroxine. This was one of the most difficult times on treatment."*

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.	Certain subgroups of endometrial cancer tumours have been shown to have a better response to the technology than others. In particular, that includes those tumours with mismatch repair deficiency.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

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.	1. There are limited effective treatment options for women with primary advanced endometrial cancer, leaving them feeling frustrated, hopeless and abandoned. 2. There is a significant unmet need for patients with all molecular subtypes of primary advanced or recurrent endometrial cancer to have earlier access to effective treatment options. 3. Patients with primary stage 3 disease are fearful of recurrence and want a treatment that prevents it or stops it progressing to an incurable state, sparing them from additional symptoms and treatments like potentially life-changing surgery. 4. Women want treatment options that will increase life expectancy and offer hope of a longer, meaningful life, with many willing to accept some increase in treatment-related side effects for improved long-term survival. 5. Women want equal opportunity to access innovative treatment options as those diagnosed with other cancer types.

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 select YES if you would like to receive information about other NICE topics - YES or NO

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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with endometrial cancer or caring for a patient with endometrial cancer. The text boxes will expand as you type.

In part 2 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).

NICE National Institute for Health and Care Excellence

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.

The deadline for your response is **5:00pm** on **Monday 16 December 2024.** 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, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with primary advanced or recurrent endometrial cancer

Table 1 About you, endometrial cancer, current treatments and equality

1. Your name	Grace Teeling
2. Are you (please tick all that apply)	☒ A patient with endometrial cancer? ☒ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with endometrial cancer? - TICKED ACCIDENTALLY AND UNABLE TO UNTICK ☒ 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 endometrial cancer? **If you are a carer (for someone with endometrial cancer) please share your experience of caring for them**	I was originally diagnosed with at least stage 3c (likely stage 4) 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 in 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. Following 2 years of successful treatment with pembrolizumab monotherapy, I have been in remission and off any treatment. I now have check up appointment every 3 months and monitoring scans every 9-12 months.
7a. What do you think of the current treatments and care available for primary advanced or recurrent endometrial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. I 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 side effects under question 8.

	The lack of 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 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. As someone with Lynch Syndrome, I was lucky enough to access pembrolizumab through special licence. Since I started pembrolizumab, it is great to see that more drugs have been approved – providing hope for many patients. However, it is scary to think if I didn't have Lynch syndrome then I still may not have access to effective treatment options. Although I consider myself very lucky to have received immunotherapy when I did, if I had had it earlier in my cancer journey, it may have prevented a recurrence in the first place. My diagnosis was stage 3c/4 and there may have been a missed opportunity for more effective treatment. I also needed to have Hartmann's procedure and how have a colostomy which is likely to be permanent. If I had had earlier treatment, it may have prevented the need for further surgery to prevent bowel obstruction. 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 a while. 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 was able to live life and thrive 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. One of my friends stopped responding to my messages a couple of years

	ago – I am too scared to find out whether or not she made it. By contrast, I am now in remission and moving on with my life.
8. If there are disadvantages for patients of current NHS treatments for primary advanced or recurrent endometrial cancer (for example, how they are 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) 4-7 days of debilitating fatigue every 3 week 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. With 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 have had to put significant time (years) and money into counselling to deal with the impacts of treatment. 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 each cycle. 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 choir or having an active social life. I also struggled with intense hot flushes for the first few days after treatment as well as myoclonic jerks which made it difficult to sleep (though this could've been due to anxiety around my immune system). I was also unable to work due to fatigue and brain fog; unable to be as active as I would like due to fatigue; and I 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 – and it took a year to even feel remotely back to my normal self. And I feel

	lucky to have escaped without long-term side effects such as pelvic radiation disease or peripheral neuropathy. Whilst the proposed technology includes chemotherapy initially, I think the above side effects would be more bearable with the increased likelihood of durable response and potentially living longer and/or the possibility of remission (as in my experience).
9a. If there are advantages of pembrolizumab 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 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**	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 was able to thrive whilst on active treatment. I found the treatment to be much kinder and more manageable than any others that I have had, (chemotherapy, radiotherapy and brachytherapy), and I experienced far fewer side effects. It has also meant there is currently no evidence of cancer on my most recent CT scan. Following treatment, I have been in remission for 18 months – this means not spending time in hospital and being able to instead get on with my life! 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. Whilst I was on treatment with pembrolizumab, I was 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 and live a fulfilling and happy life. In the time since beginning treatment, I have had two promotions (including one on active treatment). I have travelled to Prague, Greece, Costa Rica and I am about to leave for New Zealand and Australia for a month. I have also recently started training to be a yoga teacher so I can offer yoga retreats for people living with advanced cancer.

	I feel that I have been offered a second chance at life. I moved back to Bristol from Scotland 18 months ago and have been living a very full life with my family and friends. I have made my 5-year-old nephew's birthday party which I never thought I would make! 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 recently had a big birthday party with my friends to celebrate being '35 and still alive'. 9b. My priority for my life, as someone living with stage 4 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. The biggest advantage of pembrolizumab is that it offers patients time to live and thrive for longer. In my case, being in remission feels like a miracle. 9c. My experience of pembrolizumab is that it is much kinder and more tolerable than any previous treatments (chemotherapy, radiotherapy and brachytherapy) with fewer side effects and less of an impact on my quality of life. Although there is still chemotherapy as an option in this situation, access to pembrolizumab offers hope

	for the future which helps to deal with the side effects and get through the short term challenges.
10. If there are disadvantages of pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't think there are any disadvantages of pembrolizumab over existing treatments. Although I have outlined disadvantages here, they were much more tolerable than chemotherapy: 1. **Fatigue:** I have needed 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 still have fatigue which has, at times, been difficult to manage, even after treatment. This has slowly and steadily improved over the past year or so. I am managing much better now than on treatment and immediately after. 2. **Thyroid issues:** 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 lung inflammation (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. When I was on pembrolizumab, I was not on any other medication apart from levothyroxine – and I always sent my anti-emetics back to the pharmacy as I didn'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. All of these have 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 by keeping healthy and active. 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 my initial treatment (chemotherapy, radiotherapy and brachytherapy), I was also completely exhausted all the time. By contrast, I did get more tired on immunotherapy when compared to my peers – but this is something that can be managed to enable me to live my life to the full – to work, socialise, volunteer and exercise.
11. Are there any groups of patients who might benefit more from pembrolizumab 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. As someone with Lynch Syndrome, I am aware that I was lucky enough to be eligible to receive an immunotherapy-based treatment. Those with pMMR tumours still face having to wait for progression to receive treatment and face fewer treatment options. 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 have found that I am able to thrive on pembrolizumab in a way that I wasn't able to on existing standard treatments and live a relatively normal life for someone of my age.

	I feel I was let down by the healthcare system in failing to diagnose my cancer early enough that I was likely to have 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. 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.
12. Are there any potential equality issues that should be taken into account when considering primary advanced or recurrent endometrial cancer and pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage 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: 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 on my survival. Despite living with recurrent, advanced endometrial cancer, I am currently no evidence of disease. I have also been off treatment for 18 months.
- If I had earlier access to pembrolizumab, it may have prevented an additional surgery which has resulted in a colostomy which is likely to be permanent.
- 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. They also offer limited hope for the future.
- 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 live fully and well - rather than be faced with a lack of options which make us feel abandoned and hopeless. 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.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

Clinical expert statement

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 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.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5:00pm** on **Monday 09 December 2024.** 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, 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 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 primary advanced 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	Gemma Eminowicz
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant clinical oncologist
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 endometrial cancer? ☐ A specialist in the clinical evidence base for 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 primary advanced or recurrent endometrial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Main aim of treatment is to improve quality of life and control disease (ie tumour shrinkage with subsequent delay in progression of disease, thereby reducing disease burden and symptoms extending survival) Historically these patients are not cured. However, with the use of targeted treatments for isolated recurrence and oligometastatic disease as well as the introduction of immunotherapy in MMR deficient (MMRd) cases there are a proportion of these patients who may be more likely to be 'cured'.
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)	Clinically meaningful improvement in quality of life ie improvement in functional status meaning patients can do what they want to do. Length of extension of survival depends upon the duration of treatment duration and toxicity burden
10. In your view, is there an unmet need for patients and healthcare professionals in primary advanced or recurrent endometrial cancer?	Yes, these patients often have extensive symptoms and, depending upon their disease pattern, may be a significant burden on healthcare resources eg with bowel obstruction, fluid accumulation (pleural or ascitic). With the current access to dostarlimab for MMRd, I see that there is more of an unmet need now in the MMR proficient (MMRp) population which is a much more heterogenous group of patients and includes the very poor prognosis p53abnormal group.
11. How is primary advanced 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?	Overall the pathway of care is well defined within my practice (which is within England) but across the country I am aware that the pathway of care is not always well defined. In general guidance such as the ESMO/ESP/ESTRO guidance are followed but these are not very specific and other guidelines such as BGCS uterine cancer guidelines have not been updated particularly recently. If patients have disease that is amenable to surgical resection without any anticipated residual they may be operated on. This, however, is not consistent practice across the country and depends upon surgical expertise and experience. This surgery would then be followed by chemotherapy and possibly radiotherapy if disease was pelvic confined and/or nodal confined.

	If patients have single site of disease they may undergo surgery, radiotherapy or other focal therapy to try to remove or ablate the disease. The TCGA molecular classification should impact the treatment offered. However, even the testing for MMR, p53 and POLE which are all essential to be able to molecularly classify a patient is not consistently carried out across the country. P53abnormal disease is generally treated with chemotherapy (6 cycles of carboplatin and paclitaxel) and possibly radiotherapy depending upon disease pattern. MMRd disease is usually treated now with carboplatin paclitaxel and dostarlimab immunotherapy (aka RUBY trial- CDF) Hormone positive low grade disease (NSMP) may be managed with systemic hormonal therapy if the symptom burden is not significant. All other disease, ie multisite inoperable disease which is MMRp/NSMP, is generally treated with palliative chemotherapy – carboplatin and paclitaxel up to 6 cycles and perhaps radiotherapy depending upon disease pattern. This, however, is a very heterogenous group and response can be variable. Second line therapy may depend upon how long an interval it has been since the first line treatment as in a scenario of long interval (several years) then rechallenge with the same chemotherapy may be appropriate. Otherwise, second line therapy is Pembrolizumab and Lenvatinib up to 2 years if MMRp or single agent immunotherapy if MMRd and not already received immunotherapy. Third line therapy is generally trials (including ADCs) or weekly paclitaxel chemotherapy. If there was access to chemotherapy plus pembrolizumab for all patients irrespective of molecular classification then the pathway would change to carboplatin paclitaxel pembrolizumab for all patients first line and weekly taxol or trials second line.

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)	In the MMRd cohort there is already access to carboplatin paclitaxel and dostarlimab (RUBY regimen) in this setting. This treatment combination with pembrolizumab in my view does not have any clear advantages in regard to efficacy or safety but the duration of treatment is only 2 years compared to 3 years of RUBY regimen. In the MMRp population this would be new to the first line setting and would reduce the use of pembrolizumab and Lenvatinib in the second line setting. This treatment would only be delivered in specialist cancer centres. In general, as pembrolizumab is used second line and for many other tumour sites there should be no additional training or equipment etc. However, this would increase the burden on the chemotherapy treatment suites due to the longer duration of treatment first line. One could argue that this burden will be similar to the current second line therapy but there may be a higher proportion of patients who receive this as they may not be fit enough when they need second line therapy
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?	As stated above there is no efficacy advantage with this combination over the RUBY regimen in the MMRd population. I therefore do not expect any clinically meaningful benefits compared to the standard of care except for duration of therapy being shortened. Regarding the MMRp population, the published data supporting pembrolizumab in combination with chemotherapy in the first line setting (NRGGY018/KEYNOTE 868) shows median progression free survival was improved by 4 months. It is important to note that overall survival data and QoL data has not yet been published. During treatment there will probably be very similar quality of life to standard of care. During the 4 months where the patients would have progressed and have not we could assume there may be some improvement in quality of life due to the lack of progressive disease but if this is picked up early and treated this may not be a very significant difference. Of note, Pembrolizumab and Lenvatinib in the second line setting provides a progression free survival advantage of approximately 3 months in these patients with overall survival advantage of 5 months (KEYNOTE 775, Makker et al NEJM

	2022). We do not know what the overall survival advantage is using pembrolizumab upfront compared to second line. With the introduction of immunotherapy in the first line setting second line treatment options will be more limited and a significant proportion of patients may not be fit enough for trials.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This addition of immunotherapy to chemotherapy is far more effective in the MMRd population compared to MMRp with a flat survival curve beyond 12 months and it may possibly be leading to very prolonged disease control (?cure) for 30-40% of patients (looking at RUBY data). Within the MMRp population however, detail is less clear. It seems that possibly the p53abnormal population derive more benefit from the addition of immunotherapy upfront (but also parp-inhibitors from DUO-E trial) compared to NSMP and biologically this makes sense as a higher mutational burden leads to more response to immunotherapy but this is my interpretation of exploratory data and no concrete conclusions can be made.
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)	It is more burdensome to add immunotherapy first line to chemotherapy due to longer duration of treatment and need to monitor hormone bloods tests and increased burden on clinic appointments as well as chemotherapy suite. However, most clinicians should be getting experience with immunotherapy and should now be familiar with managing the toxicities etc and have referral pathways etc in place. Monitoring treatment response every 9-12 weeks with cross sectional imaging (usually CT CAP) would be standard if on maintenance therapy and this is probably not being currently done when only on surveillance. Some centres only monitor patients off treatment clinically and others may scan every 6-12 months but there is no set standard.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Toxicity and progression will be the reasons to stop therapy. Regular cross sectional imaging every 9-12 weeks will be done which is probably additional to current standard of care.

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	No, I think the QALY calculation will capture the relevant health related benefits.
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?	This treatment is a step change in endometrial cancer treatment and is revolutionary in the MMRd setting. However, in view of the heterogeneity of the MMRp population I am unsure if all patients will gain substantial benefit and it may be we need to be more selective in the population that this is delivered to.
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?	There is a significant risk of toxicity with this treatment but it does appear to all be manageable and as centres/clinicians are becoming more confident with management of immunotherapy toxicity this is not impacting quality of life for patients detrimentally.
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?	Yes, the clinical trials do reflect current UK clinical practice.

• Are there any adverse effects that were not apparent in clinical trials 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?	Minimal data in this setting on real world experience. In second line setting for the combination of pembrolizumab and Lenvatinib (so although a different line of therapy, the same patient population) real word data suggests a slightly older and slightly less fit population but similar response rates and toxicity profiles. I expect these differences to be similar with this treatment.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. 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 evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	In general the trials do not include as many ethnic minority patients as we see in clinical practice – this may mean that certain groups are underrepresented but also that in real world practice more aggressive histologys will be seen (black often have higher aggressive histology). There is also some data suggesting differential responses to immunotherapy in certain populations such as Asian but difficult to interpret impact of this on the data. Exclusion of patients with carcinosarcoma is also unfortunate as they often behave similarly to p53abnormal patients and may respond to this treatment. They were excluded due to poor prognosis. Carcinosarcoma appears to be more prevalent in certain ethnic minorities.

• 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. 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: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Locally advanced and recurrent endometrial cancer is a very heterogenous group of patientsClick or tap here to enter text.
The aim of treatment is generally to improve quality of life and survival where possible, but the introduction of immunotherapy for MMRd disease is potentially improving long term survival to the point of potential cure in a significant proportion of patients. Click or tap here to enter text.
The addition of prembrolizumab to first line chemotherapy does provide a progression free survival advantage but overall survival and quality of life data unpublished. Click or tap here to enter text.
In general, clinicians should be now familiar and comfortable managing patients on immunotherapy and their toxicities.Click or tap here to enter text.
Within the MMRp population there may be patients who benefit more from immunotherapy upfront compared to second line but the data on this is unclear currently regarding which biomarkers predict for this. Click or tap here to enter text.

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.

NICE National Institute for Health and Care Excellence

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

External Assessment Group's report for pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer ID6381

Produced by	*Warwick Evidence*
Authors	***Mandy Maredza**, Senior Research Fellow (Health Economics)[1]* ***Angela Mwape**, Research Fellow, Systematic Reviewer in Screening and Test Evaluation[1]* ***Mubarak Patel**, Research Fellow[1]* ***Aziza Osman**, Research Associate in Health Economics[1]* ***Christiana Anyebe**, Research Associate in Health Economics[1]* ***Naila Dracup**, Information Specialist[1]* ***Peter Auguste**, Assistant Professor in Health Economics & Decision Modelling[1]* ***Dr Sarah Kitson** Clinical Lecturer and Honorary Consultant Gynae-oncologist[2]* ***Dr Melanie Powell**, Consultant Clinical Oncologist[3]* ***Jo Parsons,** Assistant Professor of Health Science Research[1]* *[1]Warwick Evidence, Warwick Applied Health, Warwick Medical School, University of Warwick, Coventry, CV4 7AL* *[2]Division of Cancer Services, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PL* *[3]St Bartholomew's Hospital, London, EC1A 7BE*
Correspondence to	*Dr Jo Parsons* *Warwick Applied Health* *Warwick Medical School* *University of Warwick* *Coventry, CV4 7AL*
Date completed	*7th November 2024*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR169037.

Declared competing interests of the authors
The authors declare no competing interests.

Acknowledgements
We would like to thank Dr Daniel Todkill, Associate Clinical Professor; who quality assessed this report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Maredza M, Mwape A, Patel M, Osman A, Anyebe C, Dracup N, Auguste P, Kitson S, Powell M, Parsons J. Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381] EAG report: A Single Technology Appraisal. Warwick Evidence. 2024.

Contributions of authors
Mandy Maredza critiqued the cost-effectiveness evidence and undertook EAG modelling. Angela Mwape critiqued the clinical effectiveness evidence in the company submission. Mubarak Patel critiqued the statistical analysis. Aziza Osman critiqued the cost-effectiveness evidence. Christiana Anyebe critiqued the cost-effectiveness evidence. Naila Dracup critiqued the company's searches and conducted additional EAG searches. Peter Auguste critiqued the cost-effectiveness evidence and provided support to junior health economists. Sarah Kitson provided clinical expertise. Melanie Powell provided clinical expertise. Jo Parsons critiqued the clinical effectiveness evidence, coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Issues

Table of Figures

Table of abbreviations

1L	First-line
2L	Second-line
AE	Adverse event
AIC	Akaike information criterion
AS	Absolute QALY shortfall
BGCS	British Gynaecological Cancer Society
BIC	Bayesian information criterion
BSA	Body surface area
CCC	Clear cell carcinoma
CEM	Company economic model
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Carcinosarcoma
CT	Chemotherapy
dMMR	Mismatch repair deficient
DOR	Duration of response
EAG	External Assessment Group
EC	Endometrial cancer

ECOG	Eastern Cooperative Oncology Group
EEC	Endometrioid adenocarcinoma
EPAR	European Public Assessment Report
ESMO	European Society of Medical Oncology
FACT-En-TOI	Functional Assessment of Cancer Therapy–Endometrial
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group–Neurotoxicity
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	incremental cost-effectiveness ratios
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
Ios	Immunotherapies
IPD	Individual participant data
irAEs	immune-related AEs
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
MAE	Mean average error
MMR	Mismatch repair
MSI-H	High microsatellite instability
NES	Non-elective short stay
NHS	National Health Service
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PFS	Progression-free survival
PFS2	Progression-free survival on next-line therapy
pMMR	Mismatch repair proficient
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PS	Proportional QALY shortfall
PSSRU	Personal and social services research unit
QALY	Quality-adjusted life year
QoL	Quality of life
RECIST	RECIST – Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics

SoC	Standard of care
UC	Uterine cancer

Executive Summary

1 Executive summary

The CS provided evidence comparing pembrolizumab plus platinum-based chemotherapy (pembrolizumab + CT) then pembrolizumab maintenance, compared to placebo plus platinum-based chemotherapy (placebo + CT) then placebo maintenance for treating advanced or recurrent endometrial cancer. One study was identified for inclusion in the systematic literature review (SLR), KEYNOTE-868 (NRG-GY018), which is a phase III double-blind, placebo controlled, randomised trial of 819 patients (CS Document B, Table 6). Participants were recruited to KEYNOTE-868 (NRG-GY018) in two separate cohorts based on mismatch repair (MMR) status of participants, either mismatch repair proficient (pMMR) or mismatch repair deficient (dMMR).

Effectiveness analyses in the CS for the primary and secondary key endpoints for the pMMR and dMMR cohorts were based on pre-specified interim analysis (December 2022). The Efficacy and Safety Update provides an additional nine months follow-up data (August 2023) for the overall trial population (referred to as 'all-comer' patients), including all patients randomised before data cut-off dates (CS Document B, Section B.2.4.1). The KEYNOTE-868 (NRG-GY018) trial is ongoing, with final analysis expected to be completed in [redacted]

The EAG note the following areas:

- Due to the SLR including one trial only, no ITC was possible, and evidence on clinical effectiveness was based on the one study.
- The EAG note that KEYNOTE-868 (NRG-GY018) contained no UK patients and query the representativeness of the KEYNOTE-868 (NRG-GY018) trial baseline characteristics to patients in UK clinical practice.
- The EAG note the short follow-up data available in the KEYNOTE-868 (NRG-GY018) trial (median follow up was [redacted]) to inform economic modelling.
- The EAG note differences in intervention, comparator and sub-groups between the KEYNOTE-868 (NRG-GY018) trial and the NICE scope.

- The EAG has some concerns about the lack of Health-related quality of life (HRQoL) assessment in the dMMR cohort.
- The EAG note some concerns about the use of post-hoc analyses of the all-comer population, which might not be entirely representative of the original trial's intended population (i.e., separate cohorts for dMMR and pMMR patients).
- The EAG note the high numbers of discontinuation in the KEYNOTE-868 (NRG-GY018) trial

At the efficacy and safety update analysis (August 2023), analysis of the all-comer population showed a clinically meaningful [redacted] in the pembrolizumab + CT arm compared to the placebo + CT arm. Sub-group analysis showed [redacted] in pembrolizumab + CT arms in most outcomes, with dMMR cohorts often showing [redacted] pMMR cohort.

HRQoL outcomes were only assessed in the pMMR cohort, and there was a [redacted] overall in both pembrolizumab + CT and placebo + CT arms, in patient-reported outcomes (PRO) measures. There were [redacted] in PRO measures between treatment arms.

Overall, the type and frequency of AEs and drug-related AEs reported appear reasonable and were similar between treatment arms and cohorts. There were no unique AEs that were not also seen in the placebo + CT arm.

The cost-effectiveness model was developed in line with the NICE reference case and the EAG considered the model structure appropriate to address the decision problem. The EAG has concerns regarding some of the assumptions and key input parameters applied in the model. Noteworthy are:

- The baseline starting age, which does not seem to reflect the population seen in clinical practice within the NHS
- Overall survival (OS) extrapolations in the pembrolizumab+CT arm that appear to overestimate survival benefit of the intervention

- Health-related utility (EQ-5D) values applied in the model that were not derived from the pivotal (KEYNOTE-868 (NRG-GY018)) trial but a subgroup of endometrial cancer patients ([redacted]) who had received 1 prior line of therapy in KEYNOTE-158 study.
    - The EAG noted that KN-158 focussed on dMMR population only and question the assumption that the same utility values can be applied to the pMMR population.
    - KN-158 subgroup population were younger and fitter than KEYNOTE-868 (NRG-GY018) (confirmed through comparison of baseline characteristics shared by the company during clarification).

The EAG note the changes in ICER [redacted] when OS extrapolations assumptions and starting age in economic model are changed to reflect EAG's preferences as advised by EAG's clinical experts.

The other issues that had an impact on ICER are noted as: range of adverse events included in model, subsequent therapy treatment mix, resource use (notably, blood tests and outpatient visits) in pembrolizumab +CT arm.

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG'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. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID6381	Summary of issue	Report sections
Issue 1	Representativeness of the post-hoc analyses	2.3
Issue 2	Limitations of sub-groups examined	2.3
Issue 3	Short duration of follow-up of participants	3.2.1
Issue 4	Health-related quality of life (HRQoL) assessed in mismatch repair proficient (pMMR) cohort only	3.2.3.6
Issue 5	Uncertain degree of overall survival benefit in the pembrolizumab + CT arm	4.2.6.4.3
Issue 6	Starting age at baseline in the economic Model	3.2.1.3 and 4.2.3
Issue 7	Health state utilities applied in the model unlikely to be representative of all-comer population of KEYNOTE-868 (NRG-GY018) (relates to Key issue 5)	4.2.7.1
Issue 8	Resource use levels underestimated for pembrolizumab + CT arm in the model.	4.2.8.3
Issue 9	Adverse events selected for costing in the Model	4.2.8.4
Issue 10	Uncertainty around subsequent treatment mix for CT arm.	4.2.8.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

The company's selected OS extrapolations for pembrolizumab +CT predicts large (benefit) in terms of survival for the technology compared to the comparator.

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:

- Increasing overall survival and progression-free survival

Overall, the technology is modelled to affect costs by:

- Its higher unit price and it is taken in addition to the comparator treatment

The modelling assumptions that have the greatest effect on the ICER are:

- The magnitude of benefit of overall survival

1.3 The decision problem: summary of the EAG's key issues

The EAG's key issues related to the decision problem are listed in Table Issue 1 and Issue 2.

Issue 1: Representativeness of the post-hoc analyses

Report section	2.3
Description of issue and why the EAG has identified it as important	The post-hoc analyses of the all-comer population might not be entirely representative of the original trial's intended population (i.e., separate cohorts for dMMR and pMMR patients) and may have been conducted so that it is line with the population identified in the NICE scope.[1]. Post-hoc analyses, by their nature, are unplanned and conducted retrospectively. This introduces potential bias and risks overgeneralising the results of the all-comer population (the post hoc analysis). These concerns could reduce the certainty of the conclusions drawn when compared to the NICE scope, as the population in the post-hoc analyses may not fully reflect the characteristics of the populations initially intended for separate analysis.
What alternative approach has the EAG suggested?	Stratified analyses to maintain the all-comer analysis while preserving the separation between dMMR and pMMR patients, allowing for clearer insights into treatment effects. Subgroup analyses should further explore progression-free survival (PFS), as differences between dMMR and pMMR were seen in PFS but not overall survival. Additionally, propensity score matching could be used to adjust for imbalances between the two cohorts, ensuring more accurate comparisons when combining them.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is unknown.
What additional evidence or analyses might help to resolve this key issue?	Although further subgroup analyses, focusing separately on dMMR and pMMR patients were conducted in the CS, further sensitivity analyses exploring the impact of the post-hoc all-comer population approach could help assess the robustness of the pooled conclusions.

Issue 2: Limitations of sub-groups examined

Report section	2.3
Description of issue and why the EAG has identified it as important	The EAG note that the CS does not provide data on how pembrolizumab performs in local versus metastatic cases, or in patients with prior surgeries. The KEYNOTE-868 (NRG-GY018) trial[2] did not systematically collect data on the site of recurrence (local vs. metastatic) or on prior debulking surgery, limiting subgroup analyses which were outlined in the NICE scope.[1] Consequently, the treatment indications for pembrolizumab could be broadly defined, as patients who were enrolled may have been those unsuitable for other therapies.
What alternative approach has the EAG suggested?	The EAG does not have an alternative approach to suggest, given the lack of systematic data collection on these subgroups within the pivotal trial. However, future trials should aim to collect more detailed subgroup information to align with NICE's requirement for specific subgroup analyses, such as local versus metastatic cases or surgical history.
What is the expected effect on the cost-effectiveness estimates?	Without specific data on local vs metastatic subgroups, it is difficult to determine the precise impact on cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Analysis of these sub-groups would provide a thorough examination of the clinical effectiveness of the appraisal.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG's key issues related to the clinical effectiveness evidence are reported in Issue 3 to Issue 4.

Issue 3: Short duration of follow-up of participants

Report section	3.2.1.1
Description of issue and why the EAG has identified it as important	The clinical effectiveness evidence is based on one trial (KEYNOTE-868 (NRG-GY018)) with a short follow-up period. [2](CS Document B, Section B.2) The study duration (including combination and maintenance phases) equates to approximately 2.2 years of active treatment. The median follow-up at the August 2023 data cut was [redacted]. This meant that survival estimates for 2 years+ are based on models that are highly susceptible to error due to the need to extrapolate. Consequently, survival projections beyond this period, including progression-free and overall survival estimates extending out to 20 years, are based on assumptions that are susceptible to uncertainty. The relatively short follow-up period thus limits the robustness of long-term effectiveness conclusions, as these projections may not accurately reflect real-world survival in advanced/recurrent endometrial cancer.
What alternative approach has the EAG suggested?	The EAG do not have an alternative approach to suggest for this, however future studies should aim to provide longer follow-up periods.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of the cost-effectiveness estimates is unknown, as we are unable to predict what long-term follow-up data will show.
What additional evidence or analyses might help to resolve this key issue?	Longer follow-up of participants (beyond median [redacted]) would inform the impact of treatment and would strengthen the clinical effectiveness evidence. The company has previously confirmed in response to clarification questions that further data from the KEYNOTE-868 (NRG-GY018) trial will only be available following Final Analysis, which is currently planned for [redacted].

Issue 4: Health-related quality of life (HRQoL) assessed in mismatch repair proficient (pMMR) cohort only

Report section	3.2.3.6
Description of issue and why the EAG has identified it as important	HRQoL was assessed in the pMMR cohort only. The EAG sought clarification (Clarification question A10) on this issue. The company state that this was due to the lack of sufficient statistical power in the dMMR group resulting from the smaller sample size, meaning that the analyses for HRQoL/ patient-reported outcomes (PRO) were prespecified to be conducted only in the pMMR cohort. While the sample size of the dMMR cohort might be smaller than the [redacted] patients (Table 17 of CS Doc B) in the HRQoL analysis of the pMMR cohort, the reduced power indicates a higher risk of type II errors (failing to detect a true effect), which the EAG suggest could have informed the decision to focus HRQoL analyses on the pMMR group.
What alternative approach has the EAG suggested?	The EAG could not offer an alternative approach given the lack of data availability on PRO outcomes in dMMR cohort
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness is unknown
What additional evidence or analyses might help to resolve this key issue?	Given the final sample sizes (pMMR n=597, dMMR n=222), it may be reasonable to expect additional efforts to improve power and/or conduct exploratory analyses in the dMMR group would have provided valuable insights and completeness of data if included in the CS, even with caveats that finding are less conclusive.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG's key issues related to the cost effectiveness evidence are reported in Table Issue 5 to Table Issue 8.

Issue 5: Uncertain degree of overall survival benefit

Report section	4.2.6.4.3
Description of issue and why the EAG has identified it as important	The company models a long-term survival benefit for pembrolizumab +CT that appears inconsistent with what could be observed in clinical practice
What alternative approach has the EAG suggested?	The EAG's choice of the most plausible OS model in the pembrolizumab + CT arm is based on the plausible 20-year estimates as judged by the EAG's clinical experts, as well as statistical and visual fit. For pembrolizumab +CT, the EAG's preferred base case model is the two-piece log-logistic model with a 9.4-week data cut
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred OS assumptions to the company's base case increases the ICER by [redacted]. ICER =[redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up would assist with reducing the uncertainty about the future OS benefit.

Issue 6: Starting age at baseline in the economic model

Report section	3.2.1.2 and 4.2.3
Description of issue and why the EAG has identified it as important	The EAG consider that some of the baseline characteristics of the KEYNOTE-868 (NRG-GY018) trial are not representative of endometrial cancer (EC) patients in the UK. Most notably, EAG's clinical advisors noted that patients in KEYNOTE-868 (NRG-GY018) were much younger than patients seen in clinical practice in the UK. Similar issue was raised in a related technology appraisal (TA963)
What alternative approach has the EAG suggested?	Starting age at baseline is increased from 65.4 to 67.1 years to reflect EAG clinical experts' opinion, previous NICE appraisal committees' preference and relevant evidence from the literature (Table 7).
What is the expected effect on the cost-effectiveness estimates?	Increasing age of the population at baseline modestly increases the company's base case ICER (after clarifications) by [redacted]. ICER= [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional UK evidence would allow participants to be more representative of patients in UK clinical practice

Issue 7: Health state utilities applied in the model unlikely to be representative of all-comer population of KEYNOTE-868 (NRG-GY018) (relates to Key issue 5)

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	*Source of health state utilities*: EQ-5D data were not collected in KEYNOTE-868 (NRG-GY018). The subgroup of KEYNOTE-158 data used had very small sample size (n=[redacted]) and focused only on dMMR subgroup (i.e., not completely generalisable to the KEYNOTE-868 (NRG-GY018) trial). *Application of same utility values for both the pMMR and dMMR groups:* The EAG's clinical experts' opinion indicates that utilities will likely differ between pMMR and dMMR patients due to poorer response to treatment in pMMR group
What alternative approach has the EAG suggested?	The EAG considers that unpublished EQ-5D utility values (using the UK value set) from KEYNOTE-775 (pembrolizumab in combination with lenvatinib for previously treated advanced EC) is likely the most appropriate data source as EQ-5D data were collected in both the dMMR and pMMR populations. However, the data were not available as the company cites contractual obligations with a third party inhibiting its use. Alternative analyses were not possible due to this lack of data availability
What is the expected effect on the cost-effectiveness estimates?	The expected effect on the cost-effectiveness estimates is unknown
What additional evidence or analyses might help to resolve this key issue?	More detailed reporting of existing trials (e.g., KEYNOTE-775) may permit additional analyses using EQ-5D data derived from both subgroups.

Issue 8: Resource use levels for pembrolizumab + CT arm underestimated in the model

Report section	4.2.8.3
Description of issue and why the EAG has identified it as important	The EAG considers that the levels of resource used in the company's economic model are underestimated for the intervention arm. Clinical experts to the EAG stated that patients undergo series of blood test at the start of each chemotherapy cycle. Also, those on IOs will be tested for thyroid function, liver function and glucose levels.
What alternative approach has the EAG suggested?	The EAG's preferred approach was to source other resource use frequencies per week for patients receiving IO and chemotherapy combination from EAG's clinical experts and from previous HTAs. Two scenario analyses; 1) using values obtained from EAG's clinical experts and 2) using estimates from previous appraisals were performed.
What is the expected effect on the cost-effectiveness estimates?	The percentage change to the company's base case ICER is [redacted]. ICER= [redacted] for scenario 1 and [redacted] ICER= [redacted] for scenario 2.
What additional evidence or analyses might help to resolve this key issue?	Prospective studies or database reviews of resource utilisation by patients with advanced or recurrent EC undergoing IO + chemotherapy combination in the UK may offer invaluable insight into resource utilisation patterns observed in clinical practice in the NHS

1.6 Other key issues: summary of the EAG's view

The EAG's key issues related to the other evidence are reported in Table Issue 9 and Issue 10.

Issue 9: Adverse events selected for costing in the model

Report section	4.2.8.4
Description of issue and why the EAG has identified it as important	Adverse events (AE) costs are likely underestimated in the company cost-effectiveness results as hypertension and anaemia are the only AEs included in analysis (at the end of the follow-up period; median follow-up [redacted]). The EAG's clinical expert commented that AEs due to immunotherapy are the most expensive to treat but these were not captured in the analysis. The CS included AEs occurring in >5% of population.
What alternative approach has the EAG suggested?	The EAG proposes a scenario analysis whereby AEs occurring in ≥2% of the patients in all-comer population are included in analysis.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER minimally increases by [redacted], ICER= [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional evidence to incorporate all ≥2% AEs as observed in the trial.

Issue 10: Uncertainty around subsequent treatment mix for CT arm.

Report section	4.2.8.2
Description of issue and why the EAG has identified it as important	Subsequent treatment mix not reflective of UK clinical practice for patients who progressed after taking chemotherapy.
What alternative approach has the EAG suggested?	EAG explored one scenario analysis. The EAG's exploratory analysis was to assign all patients that receive pembrolizumab monotherapy as 2L treatment after chemotherapy to pembrolizumab + Lenvatinib. The EAG's clinical experts were uncertain about the subsequent treatment mix for patients with advanced EC but emphasised that pembrolizumab is not given as a monotherapy after chemotherapy.
What is the expected effect on the cost-effectiveness estimates?	The analysis as mentioned above led to a [redacted] to the company's base case ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional UK evidence on subsequent therapy mix for patients with advanced /recurrent EC who have progressed disease might help resolve the uncertainty.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumptions are outlined in Table 2, with further details in Section 6.4.

Table 2: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Section in EAG report	Incremental Costs	Incremental QALYs	ICER £/QALY (Individual impact on company base case ICER)
Company base-case		[redacted]	**1.33**	[redacted]
EAG 01: Starting age at baseline 67.1 years.	4.2.3	[redacted]	1.30	[redacted]
EAG 02: OS extrapolation for pembrolizumab +CT using a piecewise approach (log-logistic model with 9.4 week cut)	4.2.6.4.3	[redacted]	1.05	[redacted]

Preferred assumption	Section in EAG report	Incremental Costs	Incremental QALYs	ICER £/QALY (Individual impact on company base case ICER)
EAG03: OS extrapolation for placebo+CT. EAG maintains company's log-logistic model	4.2.6.4.3	[redacted]	1.33	[redacted]
EAG Base Case (Applied all changes cumulatively)	6.4	[redacted]	1.04	[redacted]

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The EAG has reviewed the company submission (CS) from Merck Sharp & Dohme (MSD) to NICE on the clinical effectiveness and cost-effectiveness of pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer (EC).

The company states that [redacted] (CS Document B, Section B.1.2).

2.2 Background

The company provides a description of pembrolizumab (pembrolizumab with platinum-based chemotherapy) and of the relevant health condition in sections 1.2 and 1.3 of the CS. The EAG provides a critique of the company overview of the disease, the technology, the positioning of pembrolizumab in the treatment pathway and additional input provided by the EAG clinical advisors.

2.2.1 Condition, epidemiology and symptoms

Endometrial cancer (EC) is one of the two primary types of cancer classified under the broader category of uterine cancer.[3] Uterine cancer (UC) refers to any cancer affecting the uterus (womb), which can be classified into two main types: endometrial cancer and uterine sarcoma.[3] Since EC accounts for 95% of all uterine cancer cases, the terms "EC" and "UC" are often used interchangeably to refer to EC.[4, 5] The CS focuses specifically on endometrial cancer and includes relevant references to support their description of the health condition (CS Document B, Section B.1.3.1).

In the UK, EC is now the fourth most common cancer in females, with approximately 9,800 new cases diagnosed each year,[6] (UC can develop in any individual with a uterus).[3] Since the early 1990s, the incidence rate has increased by nearly 58%.[6] The highest incidence rates are observed in females aged 75 to 79 (96.9 cases per

100,000 women) and rarely presents in younger women (age range 0 to 44), where the incidence rate remains below 7.5 cases per 100,000 women.[6]

We observe health inequalities in incidence of EC. Women in the most deprived areas have a 17% higher incidence rate compared to those in more affluent areas.[6] Incidence is also highest among Black women, lower in those of mixed or multiple ethnicities, and similar in the Asian ethnic group when compared to White ethnic groups.[6]. Besides ethnicity, the rise in incidence rates is also linked to lifestyle factors such as rising obesity rates, and associated conditions like high body mass index (BMI), diabetes, and sleep apnoea.[7] Each year, over 2,400 deaths in the UK are attributed to endometrial cancer, though the survival rate for 10 or more years is at approximately 72% because two thirds of patients present with early disease.[4]. The EAG verified all incidence data from Cancer Research UK and identified additional cited sources, all of which were secondary data.

Subtypes of EC

Endometrial carcinoma can be classified into histological subtypes, and a molecular classification also exists.[8, 9]

- Histologic subtypes include endometrioid adenocarcinoma (EEC), serous carcinoma (SC), clear cell carcinoma (CCC), mixed carcinoma (MC), undifferentiated carcinoma (UC), carcinosarcoma (CS), and rare types like mesonephric-like and gastrointestinal mucinous carcinomas.[10] Most cases are either endometrioid (70%-80%) or serous (10%), with serous types linked to lower survival rates due to higher metastasis and recurrence risks.[9] The histological classification of EC does not fully reflect the biological diversity of EC and has limited reproducibility.[11] Previous research has reported the strong prognostic value of the molecular EC subtypes and, more recently, its potential to inform treatment decisions.[11]
- These molecular subtypes can be distinguished into four groups namely, POLEmut, dMMR, NSMP, and p53abn.[10, 11] Each group presents specific biomarkers and clinical features, potentially guiding personalised treatment strategies and risk assessment discussed below:

- **POLEmut EC** (5–15% of cases) is defined by ultra mutation and typically presents with high-grade endometrioid histology, early-stage disease, younger patients, low BMI, and an excellent prognosis.
- **MMRd EC** (20–30%) is hypermutated due to microsatellite instability (MSI), linked with high BMI, more advanced stages, and an intermediate prognosis.
- **NSMP EC** (30–60%), the most common subtype, has a low tumour mutational burden, TP53 wild-type status, and tends to present as low-grade endometrioid cancer with an intermediate prognosis.
- **p53abn EC** (10–25%) is associated with high-grade tumours, TP53 mutations, low BMI, advanced stages, and poor prognosis.[11]

Risk factors and symptoms

Risk factors of EC increase with age, obesity, hormone therapy, tamoxifen use for breast cancer, diabetes, and Lynch syndrome.[7, 12] Protective factors include pregnancy, birth control pills, and physical activity.[7] Common presenting symptoms are abnormal vaginal bleeding, especially after menopause.[12-14]. The EAG clinical advisors also mentioned that *pain and weight loss are rare presenting symptoms which signify advanced disease. The CS states that EC patients have been shown to suffer from a decreased HRQoL with increased anxiety, depression, pain, fatigue, and impaired physical function and emotional functioning compared to the general population*.[15, 16] All HRQoL levels improve after treatment except for physical function which decreases and worsens among obese patients.[15]

The literature is consistent with these descriptions and therefore, the EAG agrees, and notes that findings were reported across all gynaecological cancers[16] and specifically for EC and ovarian cancer.[15] However, patients with progressive cancer who did not receive curative treatment were excluded from the HRQoL analysis in the study by Zanderberg.[15]

Recent findings from Gil-Ibanez et al.[16] state that EC patients suffer from decreased HRQoL, with increased levels of stress, anxiety, depression, sexual dysfunction, and sleep deprivation. However, impacts of sexual dysfunction on HRQoL is influenced by factors such as age, time since diagnosis, and whether the patient consulted a physician before engaging in sexual activity.[17]

Although the CS states that poor HRQoL levels are mainly associated with clinical characteristics including comorbidities, treatment and tumour stage, and lower socioeconomic status,[15] evidence suggests that lower social economic status was to a lesser extent among patients who received radiotherapy and had no comorbidities.[18]

2.2.2 Position of pembrolizumab + chemotherapy in the clinical pathway

In the UK, NICE recommends a suspected cancer pathway referral for women ≥ 55 years and a referral to be considered for those < 55 years with post-menopausal bleeding.[19] A GP may perform an ultrasound scan in women ≥ 55 years experiencing symptoms of unexplained vaginal discharge, have thrombocytosis or report haematuria, and high-blood glucose.[19] Other procedures include physical examination, pelvic examination and blood tests.[20] Following a GP referral, patients may receive endometrial biopsy, CT and/or MRI scans.[20] The CS states that currently no NICE guidelines exist for the management of EC; except for testing strategies for Lynch syndrome for people with EC and laparoscopic hysterectomy.[21] EAG clinical experts agreed but note that the British Gynaecological Cancer Society (BGCS) are used in the UK clinical practice.[22]

The treatment intent of EC depends on disease stage, based on the 2023 FIGO criteria,[10] which classify disease progression according to tumour location, invasion depth, and metastasis. Stage I is confined to the uterus and ovaries, with sub-stages showing different levels of myometrial invasion, histological types, and lymphovascular space invasion (LVSI). Stage II involves cervical stromal invasion, further divided based on the presence of LVSI or aggressive histological features. Stage III marks local or regional spread, including direct extension metastasis to structures like the serosa, ovaries, fallopian tubes, vagina, or lymph nodes. Stage IV indicates distant spread, involving organs like the bladder, bowel, liver, lungs, and brain.[10] Early or advanced stages are treated with surgery, radiotherapy and chemotherapy. Advanced or recurrent stages can be curative or palliative depending on sites of disease and previous treatment.[23] EAG clinical advisors stated that unless there is resectable/irradiated disease suitable for excision or curative radiotherapy, treatment of recurrent EC or stage 4B disease is typically not curable and is given with intent of palliation and/or disease control.

2.2.3 First line treatment

The CS summarises the UK treatment pathway in Figure 3. The anticipated positioning of pembrolizumab + CT, followed by pembrolizumab maintenance is shown at first-line therapy for those with advanced or recurrent EC. The company reports that their clinical advisors confirm that this treatment pathway aligns with that currently seen in UK clinical practice. The EAG clinical experts provided several corrections to the proposed treatment pathway for EC in the UK.

- For early-stage EC, they clarified that neoadjuvant radiotherapy (RT), or chemotherapy (CT) would not be given, and after surgery, patients may receive adjuvant RT with or without CT.
- In advanced EC, for locally advanced cases, surgery would be followed by adjuvant treatment, which could include RT and/or CT.
- For inoperable, locally advanced cases, neoadjuvant CT and/or RT may be considered.

Regarding first-line systemic treatment, the company cites the BGCS guidelines which suggest platinum-based chemotherapy (carboplatin + paclitaxel) irrespective of histology subtype as first line in the UK.[22] However, the EAG clinical advisor confirmed that *treatment depends on histologic subtypes, for pMMR patients, the standard first-line therapy is carboplatin and paclitaxel, while for deficient mismatch repair (dMMR) patients, the treatment involves carboplatin and paclitaxel combined with dostarlimab. While hormone therapy may only be selected for patients in whom carboplatin + paclitaxel is not suitable due to their ECOG performance status, comorbidities or patient preferences, the EAG clinical advisor also added that it is particularly considered for patients with estrogen receptor (ER) and/or progesterone receptor (PR)-positive tumours, where the potential benefits of chemotherapy are outweighed by its likely toxicity. This is especially relevant in cases with low disease burden and few or no symptoms, such as small, asymptomatic metastases, where hormone therapy may offer a safer alternative.*

The CS reports that for patients in the early-stage of EC who relapse more than 6 months after the last dose of platinum-based carboplatin + paclitaxel, retreatment with the same intervention may be considered after a 6 – 12-month disease-free interval

(company clinical advisor CS Section B 1.3.4, page 27). The EAG clinical advisors agree that this assumption is reasonable.

The treatment pathway for patients who progress after first-line treatment is discussed in CS section B.1.3.4. The current NICE guidance recommendation (TA904) is to receive pembrolizumab with lenvatinib or to be rechallenged with platinum-based CT.[24] The CS reports that in patients with dMMR tumours, pembrolizumab monotherapy is recommended and dostarlimab monotherapy is available via the cancers drug fund (CDF).

Overall, the EAG are mostly satisfied that the clinical pathway presented in the CS reflects current UK practice, but they have suggested important adjustments, particularly regarding neoadjuvant therapy and systemic treatment options.

2.2.4 Unmet need

The company suggest there is an unmet need. CS Section B.1.3.5 states that current standard of care (SOC) for those with advanced or recurrent EC remains chemotherapy (CT), and advancements in treatment options have been limited over the past decades.[25] The CS provides data on survival rates in women with advanced or recurrent EC to be much worse (average 5 – year survival less than 20%) in comparison to early-stage EC.[26] The CS emphasises the need for new therapeutic approaches, particularly for patients with pMMR tumors (approximately 70% of cases), for whom current treatments are inadequate.[27] Immune-oncology therapies, such as pembrolizumab combined with CT, show promise as effective first-line treatments. The EAG clinical advisors also agree and highlight that the paucity in data on the treatment landscape for EC reflects the limited treatment options available for women with EC.

Upon reviewing the citations provided by the CS 18 – 21, 35,53 that the evidence supports the claim of poor prognosis and limited treatment options for women with advanced or recurrent EC. However, the EAG notes that some of this data may be more generalized to uterine cancers,[28] and not specific to endometrial cancer. Additionally, the CS states that 18% of endometrial cancer patients experience recurrence, a figure obtained from the introduction of the cited paper. [29] However, the EAG note that the primary data presented in the same paper reports 17% of patients across all four molecular groups (POLEmut, MMRd, p53abn, and NSMP) experience

recurrence.[29] However, EAG clinical advisors also note that recurrence rates may well exceed 25%.

- The EAG clinical advisors agree that Black women are at higher risk of developing serous EC due to biological factors.

The CS makes their case that pembrolizumab + CT can address the current unmet need of people with advanced or recurrent EC with equitable access to effective EC treatments to help close the gap in survival rates for vulnerable populations.

2.3 Critique of company's definition of decision problem

The EAG comments on the company's decision problem can be seen in Table 3. There are some differences between the company decision problem and the final NICE scope,[1] but the EAG has no major concerns.

The evidence provided in the CS is largely aligned with the decision problem population. Key differences include

- Only patients with advanced (stage III or IV) or recurrent disease are included in the KEYNOTE-868 (NRG-GY018)
- Intervention in NICE scope states pembrolizumab in combination with platinum-based chemotherapy. The CS is limited to pembrolizumab in combination with "paclitaxel and carboplatin"
- Comparator in CS is limited to platinum-based chemotherapies specifically *paclitaxel and carboplatin*" (CS Doc B, section B.1.1. page 12) and does not include other treatments listed in the NICE final scope, such as cisplatin, doxorubicin and cyclophopamide. Additionally, other comparators not mentioned in the company's CS include hormone therapies like medroxyprogesterone, acetate and megestrol.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with primary advanced or recurrent endometrial cancer	As per NICE scope	N/A	The EAG agrees that the population is in line with the NICE scope. However, only patients with advanced (stage III or IV) or recurrent disease are included in the KEYNOTE-868 (NRG-GY018) trial.[29] To support the submission in line with population of the NICE scope, the company conducted post-hoc analyses of the all-comer population (CS section B.2.3.2, page 38). While this aligns with the anticipated licensed indication, conducting post-hoc analyses of the all-comer population in the KEYNOTE-868 (NRG-GY018) trial introduces potential bias and risks overgeneralising the results, potentially weakening the reliability of conclusions drawn for the broader NICE scope. This is because, the post-hoc analyses of the all-comer population might not be entirely representative of the original trial's intended population (i.e., separate cohorts for dMMR and pMMR patients). Nevertheless, the EAG maintains that the clinical evidence in the KEYNOTE-868 (NRG-GY018) trial is relevant to the decision problem.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Intervention	Pembrolizumab in combination with platinum-based chemotherapy followed by pembrolizumab maintenance treatment	As per NICE scope	N/A	The EAG agrees that the final scope is in line with the NICE scope in terms of the overall therapeutic approach (combination therapy followed by maintenance with pembrolizumab). However, the CS limits platinum-based chemotherapy to "*paclitaxel and carboplatin*" (CS Doc B, section B.1.1. page 12) followed by pembrolizumab maintenance treatment. Pembrolizumab, as monotherapy or in combination with other agents is currently indicated for various types of cancer including lung cancer, colorectal cancer, and endometrial cancer. Pembrolizumab with paclitaxel and carboplatin followed by pembrolizumab maintenance treatment is anticipated to be indicated for, [redacted] (CS document B, Section B.1.1., page 11)
Comparator(s)	Following treatment options, followed by routine surveillance: • Platinum-based chemotherapy (such as	Platinum-based chemotherapy specifically refers to carboplatin + paclitaxel to align with		Although the advice to the EAG from the clinical advisors indicates that standard first-line chemotherapy typically consists of carboplatin/paclitaxel, there is no established standard for second-line chemotherapy in this

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide) • Hormone therapy (such as medroxyprogesterone acetate and megestrol)Carboplatin +	the BGCS Endometrial Cancer Guidelines.[1] Hormone therapy is typically used when all other treatment options are exhausted, or if chemotherapy is not suitable for patients. In this setting, it has a palliative intent rather than clinical response, i.e. it would not be a comparator for pembrolizumab or any other active treatment, and there is no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival.[1 2]		setting and therefore, variation in clinical practice might be observed. The EAG clinical advisors also noted that weekly paclitaxel, Caelyx (doxorubicin), or topotecan can be used as second-line therapies and are considered appropriate comparators. The company did not include Hormone therapy as per NICE final scope.[1] Advice from the EAG clinical advisors also indicated that hormone therapy is not regarded as a relevant comparator, as it is generally reserved for patients for whom other treatment options are not suitable.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		Clinical advisors highlighted that while a small proportion of low-grade, low-volume, hormone-receptor positive patients may receive hormone therapy over chemotherapy, the evidence base is lacking, and they did not consider hormone therapy a comparator in this population [3]		
Outcomes	The outcome measures to be considered include: Progression-free survival Response rates Duration of response Overall survival Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Progression-free survival Response rates Duration of response Overall survival Adverse effects of treatment	N/A	The EAG agrees that the outcomes presented reflect those in the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		Health-related quality of life		
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and	As per NICE scope	N/A	The EAG agrees that the cost-effectiveness of pembrolizumab addressed in the CS has been evaluated in line with the NICE reference case and is appropriate for this appraisal.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Molecular subgroups, such as MMR status • Local versus metastatic recurrence • People who have had primary debulking surgery versus those who have not had surgery	MMR immunohistochemistry status	Information concerning site of recurrence was not systematically collected in the KEYNOTE-868 (NRG-GY018) trial. Forest plots available in the CSR make a distinction between subgroups based on whether patients had recurrent or primary	The EAG notes that the KEYNOTE-868 (NRG-GY018) trial did not systematically collect data on the site of recurrence (local vs. metastatic) or on prior debulking surgery, limiting subgroup analyses as outlined in the NICE scope. While molecular subgroups like MMR status can still be evaluated, the absence of site and surgical history data prevents a thorough understanding of pembrolizumab's effectiveness in these contexts. Clinical advice to the EAG emphasized that systemic treatment in the UK is typically reserved for multisite or extra-abdominal recurrence, and without this information, it is unclear how pembrolizumab performs in local versus metastatic cases or in patients with prior surgeries. Consequently, the treatment indications for pembrolizumab could be broadly defined (i.e., enrolled trial participants may have been those unsuitable for other therapies).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			advanced disease at the start of the trial, but not explicitly based on site of recurrence (local versus metastatic). Although the CSR for KEYNOTE-868 (NRG-GY018) does have indirect data points with regards to details about the site of recurrence, identification and prior therapies, which could potentially be used to assess some	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			of the site-relevant information for recurrent patients, more detailed data may have gaps and will likely be subject to limitations when attempting to interpret the data. Therefore, evidence does not allow for the consideration of the local versus metastatic recurrence subgroups. Information concerning	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			proportion of people who had primary debulking surgery versus those who have not had surgery was also not systematically collected in the KEYNOTE-868 (NRG-GY018) trial.	
Special considerations including issues related to equity or equality				The EAG note health inequalities in the UC population as described in CS section B.1.4.

Key: BGCS, British Gynaecological Cancer Society; CSR, clinical study report; MMR, mismatch repair; NHS, National Health Service.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify evidence for the efficacy and safety of interventions in the UK for first-line treatment of advanced or recurrent EC. The SLR was conducted in line with National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisals (CS Appendix D, Section D.1) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[30] and the Cochrane Handbook for Systematic Reviews.[31]

The EAG completed the modified ROBIS risk of bias assessment which can be found in Appendix 1.[32] Overall, the EAG considered the risk of bias of the company SLR to be unclear (low concern in 3 domains and unclear concern in 1 domain). The EAG considers that the company SLR is likely to have identified all studies relevant to the decision problem. Table 4 provides a summary of the EAG critique and references to the relevant section in the CS.

Table 4: Summary of the EAG's critique of the company SLR

Domain	Section(s) of CS assessed	EAG overall assessment
Study eligibility criteria	CS Document B, Section B.2.1 and CS Appendix D, Section D.1.2	Low concern
Identification and selection of studies	CS Document B, Section B.2.1, Appendix D, Section D.1.2 and responses to Clarification questions A2 and A3	Low concern
Data collection and study appraisal sections	CS Document B, Section B.2.5, CS Appendix D, Section D.1.2 and D.3	Low concern
Synthesis and findings	CS Document B, Section B.2.6	Unclear concern Incomplete information: The narrative synthesis did not discuss the RoB in the results.

The company note that carboplatin + paclitaxel (CT) are the only treatments recommended for this population in the UK, therefore this was the only comparator included in the SLR (CS, Appendix D, Section D.1.2). The EAG note the

comparators differ to those specified in the NICE scope (as described in Table 3 decision problem).

Consultation with our clinical experts suggests that hormone therapy is reserved for patients when no other treatment options are suitable, and that there is no evidence of survival benefit from hormone therapy. Therefore, the EAG agree with the companies' overall therapeutic approach taken.

The EAG also note that the intervention specified in the SLR is narrower than the NICE scope, including studies that look at pembrolizumab with carboplatin + paclitaxel only (CS Appendix D, Table 4), compared to the NICE scope that lists the intervention as *Pembrolizumab in combination with platinum-based chemotherapy followed by pembrolizumab maintenance treatment* (as described in Table 3 decision problem).

The methods of the SLR are detailed in CS Appendix D, and are critiqued in Section 3.1.1 of the EAG report.

3.1.1 Searches

Searches in a relevant set of bibliographic databases were undertaken on the 2nd April 2024. Suitable search terms including a variety of free-text and database-specific indexing terms for the condition/ population are used. No search terms for the intervention, comparator or outcome are included. Searching for the population only increases the sensitivity of the searches. The free-text search terms for Embase, Medline and the Cochrane Library are searched in title and abstract only (CS Appendix D.1.1 Tables 1, 2 and 3). The EAG note that searching in the keyword field would increase the sensitivity of the search. Unlike the searches conducted for cost-effectiveness, cost and healthcare resource identification, measurement and valuation and Health-related quality-of-life studies, the Medline, Embase and Cochrane Library searches for clinical effectiveness do not include the broader and related free-text and indexing terms such as 'womb' or 'uterus' cancer or search terms related to disease stage. The EAG suggest the omission of related free-text and indexing could reduce the sensitivity of the searches as endometrial cancer is a type of uterine/ womb cancer (CS Appendix G.1, H.1 and I.1).[12] The EAG would recommend the inclusion of a broad range of search terms relating to the intervention and comparator(s) (immune checkpoint inhibitors) in addition to a broad

range of terms for the population, rather than search terms for the disease stage to increase the specificity of the searches.

For the MEDLINE and Embase searches, a pragmatic RCT filter from a recognised source (Scottish Intercollegiate Guidelines Network) (SIGN) was applied.[33] The EAG note that this search filter is not validated nor the most sensitive, but it is a reasonable option for this CS. No language or date limits were applied (CS Appendix D.1.2).

Searches were carried out on the United States (US) National Institutes of Health Clinical Trial Registry/ ClinicalTrials.gov to capture unpublished trials. The search terms and numbers of results were provided in the clarification response (Clarification question A2). Four conference proceedings were searched manually and via Northern Lights for relevant conference abstracts published between 2022-2024 (Clarification question A2). The searches across the ASCO and ESMO conferences via Northern Lights included search terms for disease stage, which were not included in the main database searches which could limit the sensitivity of the searches (Clarification question A2).

The search results section reports that 103 results were identified from the conference abstract searches, which indicates a broad search was conducted (CS Appendix D.1.3). The EAG would recommend also searching the World Health Organization International Clinical Trials Registry Platform (ICTRP) clinical trials register to reduce the risk of publication bias. Bibliography checking is not reported to have been carried out for the clinical SLR. The EAG note that this is an important supplementary search approach, which can help retrieve additional relevant information.

3.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were pre-specified based on the Population, Interventions, Comparators, Outcomes, Study design and Time (PICOST) framework, and detailed in CS Appendix D, Table 4. Study country and publication type inclusion criteria were requested and provided by the company at clarification stage (Clarification question A3). The company confirmed that there were no restrictions on country of publication, and journal articles and congress abstracts and

proceedings were eligible for inclusion in the SLR. The EAG suggest the inclusion criteria for the review was appropriate.

As outlined in Table 3 (decision problem) comparators differ from the NICE scope, but the EAG have sought advice from clinical advisors on this and consider that this is appropriate (please see Section 2.3 for more information on this).

3.1.3 Study selection

Selection of studies in the CS was undertaken in two phases: (a) reviewing of abstracts and (b) full text screening. Both phases of screening were conducted by two reviewers independently, with any discrepancies resolved by a third reviewer. The company notes that outcome inclusion and exclusion criteria was only applied to full text screening stage.

The company report that of 380 full-texts screened, 379 were excluded. The EAG note that 241 of these exclusions were due to wrong population, which could have been reduced through a better constructed search (please refer to Section 3.1.1) (CS Appendix D, Section D.1.2). The EAG requested and reviewed a list of excluded studies (clarification question A1) and found that studies had been appropriately excluded.

Following screening, the company identified five records[2, 34-37] reporting one randomised controlled trial which were eligible for inclusion in the review. All included records report on the KEYNOTE-868 (NRG-GY018) trial which is the pivotal trial for the CS.[2] The reference of each study was not provided in the company submission and the EAG was not able to obtain the full text for two of the studies.[36, 37]

3.1.4 Critique of data extraction

The company stated that data was extracted by two reviewers independently, with any discrepancies resolved by a third reviewer. A summary of the data extracted was provided in the CS (study characteristics, interventions, patient characteristics and outcomes). The EAG note the lack of an extraction table and only brief information on what was extracted is presented in the CS (CS Appendix D, Section D.1.2).

3.1.5 Assessment of methodological quality

The company performed risk of bias assessment using the Cochrane collaboration's risk of bias tool version 2.[38] CS reports risk of bias assessments were conducted by two reviewers independently, with any discrepancies resolved by a third reviewer (CS Document B, Section B.2.5 and CS Appendix D, Section D.3).

The EAG independently assessed KEYNOTE-868 (NRG-GY018) and have rated the trial as low risk in all five of the domains, and an overall rating as low risk of bias. This is in line with the company rating across all domains. Comparison between the risk of bias rating of the Company and the EAG is provided in Table 5.

Table 5: Comparison of Company and EAG risk of bias assessment

Domain	Company rating	EAG rating
Bias arising from the randomization process	Low	Low
Bias due to deviations from intended interventions	Low	Low
Bias due to missing outcome data	Low	Low
Bias in measurement of the outcome	Low	Low
Bias in selection of the reported result	Low	Low
Overall risk of bias	Low	Low

3.1.6 Included studies in the SLR

As only one trial was included in the SLR (KEYNOTE-868 (NRG-GY018)), no ITC was conducted. This is critiqued in Section 3.3.

The EAG note that of the five studies identified as eligible in the SLR,[2, 34-37] evidence of the clinical effectiveness of pembrolizumab + CT is primarily based on one published study only; KEYNOTE-868 (NRG-GY018).[2]

EAG summary:

In summary, the SLR appears to be well conducted. Whist the reporting of the review methods is brief, the approach taken appears to be appropriate.

Only one trial was included in the CS, reported in one primary included study from the SLR and used to inform the cost-effectiveness analysis (See Section 4).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Clinical evidence for the safety and effectiveness of pembrolizumab presented in the CS was obtained by one trial, based on one published study included in the SLR; the KEYNOTE-868 (NRG-GY018) study.[2] A detailed summary of KEYNOTE-868 (NRG-GY018) was presented in CS Document B, Section B.2.3.1, including CS Table 5. The EAG critiques the KEYNOTE-868 (NRG-GY018) study methodology in Section 3.2.1.1.

3.2.1 KEYNOTE-868 (NRG-GY018)

KEYNOTE-868 (NRG-GY018) is a Phase III double-blind, placebo controlled, randomised trial,[2, 39] (CS Document B, Section B.2.3.1), investigating the safety and effectiveness of pembrolizumab + (CT) compared with placebo + CT in patients 18 years and over with advanced stage or recurrent endometrial cancer.

The EAG confirm that KEYNOTE-868 (NRG-GY018) and the description of the study in the CS Document B reflects the methodology detailed in the protocol,[39] and the company submitted protocol.[40]

3.2.1.1 KEYNOTE-868 (NRG-GY018) methodology

Participants were recruited to KEYNOTE-868 (NRG-GY018) in two cohorts; patients with dMMR disease and patients with pMMR disease. Enrolment to the study required examination of MMR status in a central laboratory[2](CS Document B, Section B.2.3.1). Pre-specified interim analysis was conducted on pMMR and dMMR cohorts at the December 2022 cut-off, and post hoc analysis was conducted on approximately 9 months additional follow-up data and analysed as all-comer population as the Efficacy and Safety Update in August 2023.

The CS focuses on results of analysis on the all-comer population, with subgroup analysis based on the two cohorts (pMMR and dMMR) provided in CS Appendix E, CS Document B, Section B.2.3.1. EAG critique is provided in Section 3.2.3.

The KEYNOTE-868 (NRG-GY018) study was conducted in 217 sites across four countries (US, Canada, Japan and South Korea) (CS Document B, Table 6). The EAG note that no UK sites were involved in the KEYNOTE-868 (NRG-GY018) study, and therefore there were no UK patients recruited to the study. The EAG consulted with clinical experts on this who felt that there were unlikely to be any significant differences in the management of endometrial cancer in these countries compared to the UK.

In KEYNOTE-868 (NRG-GY018) participants were randomised in a 1:1 ratio to two arms, to receive one of the following arms:

Arm 1: Placebo + CT combination phase followed by placebo monotherapy maintenance phase.

Combination phase: Patients in Arm 1 received placebo intravenously (IV) over 30 minutes on day 1, paclitaxel IV over 3 hours on day 1 and carboplatin IV over 30-60 minutes on day 1 of each cycle.

Maintenance phase: Patients received placebo IV over 30 minutes on day 1 of each cycle.

Arm 2: Pembrolizumab + CT combination phase followed by pembrolizumab monotherapy maintenance phase.

Combination phase: Patients received 200mg pembrolizumab IV over 30 minutes on day 1, paclitaxel IV over 3 hours on day 1 and carboplatin IV over 30-60 minutes on day 1 of each cycle.

Maintenance phase: Patients received 400mg pembrolizumab IV over 30 minutes on day 1 of each cycle.

For both combination phases, treatment was repeated every 3 weeks for 6 cycles in the absence of disease progression or unacceptable toxicity. For patients with stable disease, or partial response who still have measurable disease, patients may

continue up to a total of 10 cycles. Both maintenance phases were repeated every 6 weeks for up to 14 cycles in the absence of disease progression or unacceptable toxicity.

The overall study duration was a maximum of 30 weeks in the combination phase, followed by maximum of 84 weeks in the maintenance phase (equating to approximately 2.2 years) (CS Document B, Section B.2.3.1). At the August 2023 data cut (efficacy and safety update analysis), median follow-up was [redacted] (CS Document B, Section B.2) The EAG note the relatively short follow-up period. The EAG sought advice on this from clinical experts who suggest the study duration is appropriate for trials of advanced and recurrent EC but suggest a longer median follow-up would be preferable. Median follow-up of [redacted] *means that the survival estimates for 2 years+ are based on models that are highly susceptible to error due to the need to extrapolate.* Furthermore, since median OS was not reached in the pembrolizumab arm over the study period, estimating survival over two decades with a relatively limited dataset amplifies the uncertainty in those projections, particularly in the current setting of advanced/recurrent EC where longer-term survival data is scarce, as evidenced by the fact that no other relevant study was identified by either the company or EAG. Extrapolation over this period requires assumptions about disease progression and patient survival patterns that are unlikely to remain accurate without longer follow-up data to validate them. Extending follow-up to capture more mature OS data would significantly improve the reliability of the long-term survival estimates and reduce the inherent risks of long-term extrapolation.

The CS describe the flow of patients in the KEYNOTE-868 (NRG-GY018) study. Of 819 enrolled patients, 408 were randomly assigned to receive pembrolizumab + CT and 411 were randomly assigned to receive placebo + CT (CS Document B, Section B.2.4.3). Nine of these patients (from the pMMR cohort) were randomised after the interim analysis cut-off (December 2022) and so were not included in these interim results. During clarification (Clarification question A12) the company confirmed that these nine patients were included in the Efficacy and Safety Update analysis (August 2023).

At the efficacy and safety update analysis (August 2023) of the 819 enrolled patients, [redacted] patients in the pembrolizumab + CT arm and [redacted] patients in the placebo + CT arm are ongoing. However, [redacted] patients in the pembrolizumab + CT arm and [redacted] patients in the placebo + CT arm discontinued (CS Document B, Section B.2.4.3). The chi-squared test gives a p-value of 0.074 which, against a 5% significance level, suggests there is insufficient evidence to conclude that there is a difference in discontinuation rates between the two groups.

At the time of the August 2023 data cut, [redacted] patients in the pembrolizumab + CT arm and [redacted] patients in the placebo + CT arm received the study intervention. Of these, [redacted] in the pembrolizumab + CT arm and [redacted] in the placebo + CT arm completed the intervention (CS Document B, Section B.2.4.3). The [redacted] in both groups discontinued treatment, with [redacted] patients in the pembrolizumab arm and [redacted] in the control arm who are ongoing treatment as of submission. A total of [redacted] in pembrolizumab + CT arm and [redacted] in placebo + CT arm discontinued.

The EAG notes the high discontinuation rate in both arms, and the primary reason for discontinuation was reported as disease progression (pembrolizumab + CT n= [redacted], placebo + CT n= [redacted]). The EAG consulted with clinical experts on this point, who advised the EAG that a high rate of discontinuation due to disease progression and treatment side effects are often expected in trials of EC patients. Other reasons for discontinuation include adverse events (AEs) or complications (pembrolizumab + CT [redacted], placebo + CT [redacted]), patient withdrawal (pembrolizumab + CT [redacted], placebo + CT [redacted]) and death (pembrolizumab + CT [redacted], placebo + CT [redacted]). Full list of reasons for discontinuation can be found in CS Document B, Table 9).

EAG comment: The EAG notes some caution as the post-hoc analyses of the all-comer population might not be entirely representative of the KEYNOTE-868 (NRG-GY018) trial's intended population (i.e., separate cohorts for dMMR and pMMR patients). The population pooling may have been conducted so that it is line with the population identified in the NICE scope (see Table 3). Post-hoc analyses are not pre-

specified and are more susceptible to statistical biases, including "data dredging" or "p-hacking," where data are re-analysed in multiple ways until significant results are found. This could lead to overinterpretation of results that were not originally intended.

The EAG note that the pMMR and dMMR cohorts may appear to respond differently to the drug (subgroup analyses described in CS Appendix E) due to underlying biological differences in mismatch repair mechanisms. A post-hoc combination could therefore confound these distinct effects, making it difficult to attribute observed outcomes to either group specifically.

According to the EAG clinical experts, in clinical practice, dMMR and pMMR patients may be treated and managed differently. By combining the cohorts as in the CS, this could obscure insights necessary for informed treatment decisions in these distinct groups. The company also provided analyses for the dMMR and pMMR cohorts separately, in addition to the all-comer population, as per the trial design.

The EAG note the differences in comparators in the NICE scope to that in the KEYNOTE-868 (NRG-GY018) trial (Table 3: Summary of decision problem). The NICE scope includes Hormone therapy (such as medroxyprogesterone acetate and megestrol) as a comparator to pembrolizumab + CT, but the KEYNOTE-868 (NRG-GY018) trial compares only to placebo + CT. The EAG have consulted clinical experts and consider this an appropriate decision, based on the lack of evidence for the survival benefits in using hormone therapy.

3.2.1.2 Statistical analysis of KEYNOTE-868 (NRG-GY018)

Section B.2.2. of the CS presented information on the only relevant trial that was found by the company's SLR, KEYNOTE-868 (NRG-GY018). CS Table 3 describes the study characteristics in more detail.

Of the seven outcomes reported in the trial, only two were incorporated into the company's economic model. (See Section 4.2.6 for the critique of progression-free survival (PFS) and overall survival (OS).)

Though KEYNOTE-868 (NRG-GY018) was designed to assess the outcomes in two separate cohorts depending on MMR status (dMMR and pMMR), the results of the

all-comer population, comprising of both cohorts, were presented as the company felt this a more appropriate population to reflect the decision problem. The results of the all-comer population were conducted post-hoc and were an efficacy and safety update based on an August 2023 data cut, approximately nine months after the pre-specified interim analysis (see Section 3.2.1.1).

While the post-hoc results of the all-comer population feeds into the company's economic model, (on the company premise that this reflects the anticipated NHS population), it increases uncertainty in the results. The EAG note that if the two cohorts respond differently to treatment, modelling their outcomes as a single group, could lead to misleading cost-effectiveness estimates. For example, in Figure 12 of the CS document B which presents the subgroup analysis of PFS [redacted] In contrast, [redacted] The difference in hazard ratios and [redacted] After combining these two populations into the all-comer group, the resulting HR [redacted] Section B.2.4.2. of the CS describes the statistical methods used to analyse the data gathered from KEYNOTE-868 (NRG-GY018). The analysis is overall sound and employs the appropriate methodologies for time-to-event and response rate outcomes.

There are, however, points of concern noted by the EAG.

- The primary objective was to assess the efficacy (via PFS) of pembrolizumab + CT in two distinct groups, dMMR and pMMR. As mentioned above, combining the two groups can lead to potentially misleading conclusions in the cost-effectiveness modelling.

- Furthermore, combining these groups in the submission for cost-effectiveness purposes was not fully aligned with the trial's original hypothesis, which recognised the need for separate evaluation.
- Finally, the power at the interim analysis (50% for dMMR and 58% for pMMR) (CS Document B, Table 8) indicates that interim data might not have been fully powered to detect significant differences, particularly for dMMR patients. This could have implications for interpreting the results, especially if there is still considerable uncertainty at the interim data cut.

It should be noted that the company also provided analyses for the dMMR and pMMR cohorts separately, in addition to the all-comer population, as per the trial design.

3.2.1.3 Baseline characteristics of KEYNOTE-868 (NRG-GY018)

The company state that the KEYNOTE-868 (NRG-GY018) trial population is '*broadly similar'* to patients seen in real-world clinical practice (CS Document B, section B.2.3.3).

EAG comment: The EAG consulted our clinical experts to understand if the trial population was similar to the patients they see in UK clinical practice.

- Clinical experts felt that the trial population appears healthier than real-world clinical practice, with two thirds of participants in the KEYNOTE-868 (NRG-GY018) having a performance status of 0 (reflecting no restrictions on daily activities), often unseen from the perspective of our clinical advisors.
- Clinical experts felt that serous EC was overrepresented in the trial population (compared to UK clinical practice), but this may be attributed to trial eligibility, and the relatively high proportion of Black and African American participants who have a higher rate of serous endometrial cancers (CS Document B, Table 6).
- Clinical experts also suggest that in UK practice patients may likely be older, and there are likely to be fewer Hispanic and more Asian patients than the KEYNOTE- 868 (NRG-GY018) baseline characteristics.

The EAG note that socio-economic status of patients (such as deprivation) is not presented in the baseline demographics of the KEYNOTE-868 (NRG-GY018) trial, which would have been valuable given socioeconomic factors have been shown to disproportionately affect rates of EC (CS Document B, Section B.1.4 and Table 6). However, the EAG do note the relatively high proportion of Black and African American participants in the KEYNOTE-868 (NRG-GY018) trial. EAG clinical experts felt this was encouraging, given this group is traditionally under-represented in EC trials.

3.2.1.4 Summary of KEYNOTE-868 (NRG-GY018) methods:

The KEYNOTE-868 (NRG-GY018) appears to be well conducted, and methods are reported clearly in the CS. The EAG note the benefit of the relatively high proportion of Black and African American participants recruited to the trial and agree with the companies rating of low risk of bias of the SLR (see Section 3.1 for EAG critique of the SLR).

The EAG note the relatively short duration of the KEYNOTE-868 (NRG-GY018) study follow-up period, and potential differences in the baseline characteristics of the trial population in comparison to characteristics of patients in UK clinical practice, with trial population potentially being healthier and younger than patients that EAG clinical experts might expect to see in their patients in the UK.

3.2.2 Outcomes of KEYNOTE-868 (NRG-GY018)

The primary aim of KEYNOTE-868 (NRG-GY018) was to examine the safety and effectiveness of pembrolizumab + CT compared to placebo + CT for the treatment of advanced or recurrent endometrial cancer. The primary outcome was progression-free survival (PFS), assessed using the Response Evaluation Criteria in Solid Tumours (RECIST v1.1).[41]

Secondary outcomes of the KEYNOTE-868 (NRG-GY018) trial were OS, objective response rate (ORR), duration of response (DOR), concordance between institutional versus central MMR IHC testing results, Safety, health-related quality of

life (HRQoL) and time to treatment discontinuation (TTD) (CS, Document B, Table 5). The EAG note that the outcomes listed in the KEYNOTE-868 (NRG-GY018) trial are in line with the NICE scope.[1] (See Table 3 decision problem).

Most outcomes were assessed at six monthly timepoints from six to 36 months (PFS), six to 42 months (OS, PFS2) and six to 24 months and over (DOR). PROs were assessed at 0, 6, 18, 30 and 54 weeks to coincide with key points in the KEYNOTE-868 (NRG-GY018) trial (CS Document B, Table 16).

3.2.3 Description and critique of efficacy results for KEYNOTE-868 (NRG-GY018)

In the CS Document B, Section B.2.6, the company presented the clinical effectiveness results of pembrolizumab + CT from the KEYNOTE-868 (NRG-GY018) trial. Outcomes are reported for the all-comer population, at the August 2023 data-cut, and for dMMR and pMMR cohorts at the interim analysis at December 2022 (PFS and OS) and the August 2023 data-cut.

Effectiveness analyses were based on the intention-to-treat (ITT) population for the overall trial population (referred to as all-comer patients), including all patients randomised before data cut-off date. The safety analyses were based on all-participants-as-treated (APaT), including all randomised patients who received at least one dose of treatment (CS Document B, Section B.2.4.1). Patient reported outcomes (PRO) analyses were based on the full analysis set (FAS) of pMMR patients only. Sub-group analysis of dMMR and pMMR cohorts for outcomes are reported in CS Appendix E.

The majority of outcomes in the pMMR and dMMR cohorts were based on the Safety and Efficacy update analysis (August 2023 data cut), with PFS and OS also being available at the interim analysis (December 2022 data cut).PRO data was presented from the Interim analysis (December 2022). PRO data was not available from the Safety and Efficacy update analysis (August 2023 data cut).

3.2.3.1 Primary endpoint: Progression-free survival

PFS was defined as time from randomisation to the date of the first disease progression or death (whichever occurs first).

Analysis of the all-comer population is reported in the CS from the efficacy and safety update (August 2023) and supports the [redacted]During this additional analysis based on the all-comer populations, the median PFS in the pembrolizumab + CT arm was [redacted] and in the placebo + CT arms was [redacted] The hazard ratio for PFS was [redacted], representing a clinically meaningful [redacted] relative [redacted] in the risk of disease progression or death following treatment with pembrolizumab + CT when compared to placebo + CT. Rates of PFS were [redacted] in the pembrolizumab + CT arm at all timepoints (6, 12, 18, 24, 30 and 36 months) (CS Document B, Section B.2.6.1 and Table 10). These results reflect [redacted] PFS in the pembrolizumab + CT arm compared to placebo + CT arm.

The company note that as pre-specified end-points were met at the interim analysis, all patients were unblinded in [redacted]. The company note that the majority of patients in the placebo + CT condition who were progression-free discontinued treatment, in favour of a subsequent treatment. EAG clinical advisors confirmed this was appropriate.

The EAG note that this imbalance in discontinuation rate may bias the PFS (and OS) for the placebo + CT arm and may possibly lead to an overestimation of PFS (and OS) in placebo + CT arm (CS Document B, Section B.2.6.1).

3.2.3.2 Secondary endpoints: Overall survival

Analysis of the all-comer population from the efficacy and safety update (August 2023) shows better OS in pembrolizumab + CT, as median OS was not reached, compared to a median OS of 32.2 months in placebo + CT. The OS hazard ratio was 0.74 (95% CI: 0.57, 0.97, p=0.0153), representing a clinically meaningful 26% reduction in the risk of death, in favour of pembrolizumab + CT. OS rates were

higher in the pembrolizumab + CT arm at all timepoints (6, 12, 18, 24, 30, 36, 42 months), but these differences were not significant (CS Document B, Section B.2.6.2 and Table 11). OS rates were higher in the pembrolizumab + CT arm than the placebo + CT arm in the all-comer population. The EAG suggest this analysis is appropriate.

3.2.3.3 Objective response rate

Analysis of the all-comer population from the efficacy and safety update (August 2023) shows 319 patients in the pembrolizumab + CT and 334 patients in the placebo + CT arm had measurable disease and were included in the objective response rate (ORR) analysis. There was an improvement in ORR in the pembrolizumab + CT arm (75.2%) compared to placebo + CT (62.6%), with a clinically meaningful estimated difference in treatment of 12.4% (95% CI: 5.4, 19.4, p= 0.00029).

The company note the increase in ORR was influenced by a higher proportion of complete responses in pembrolizumab + CT arm compared to placebo + CT arm. Complete responses were available for 19.4% in the pembrolizumab + CT arm and 9.9% in the placebo + CT arm (CS Document B, Section B.2.6.2 and Table 12). There was a significant improvement in ORR in patients in the pembrolizumab + CT arm.

The EAG note the high rate of incomplete responses. This creates uncertainty around the results regarding the robustness of the observed treatment benefit in the pembrolizumab + CT arm. While there is a clear improvement in ORR and a notable increase in complete responses, the relatively high proportion of partial responses raises questions about the long-term durability and clinical significance of these outcomes. Further analysis of follow-up data may be warranted to fully assess the extent of benefit in the pembrolizumab group and to determine if the advantage in ORR translates into improvements in outcomes such as PFS or OS. Additionally, the predominance of partial responses could imply a potentially limited durability of response, as patients with incomplete responses may face a higher likelihood of disease progression. This has implications for patient quality of life, as partial responders may continue to experience symptoms or require additional treatments

over time. Moreover, the low complete response rate might limit the expected long-term survival benefits and increase the need for further interventions, adding to the potential burden of treatment and impacting both cost-effectiveness and patient management. Thus, while the ORR improvement is promising, the observed partial response rate suggests a need for cautious interpretation of the clinical significance and sustainability of these outcomes.

3.2.3.4 Duration of response

Analysis of the DOR in the all-comer population from the efficacy and safety update (August 2023) showed that duration of response amongst patients with measurable disease was 5.9 months longer in the pembrolizumab + CT arm (12.1 months) compared to placebo + CT arm (6.2 months).

More patients receiving pembrolizumab + CT had a response last 6 months or longer (80.7%) and 12 months or longer (50.7%) compared to those receiving placebo + CT (53.0% and 20.8% respectively). The median time to response was 2.3 months in both groups (CS Document B, Section B.2.6.2 and Table 14). Overall, patients in the pembrolizumab + CT arm showed a longer duration of response than those in the placebo + CT arm. The EAG suggest this analysis is appropriate.

3.2.3.5 Exploratory endpoints: PFS on next-line therapy

The CS defines PFS on next-line therapy (PFS2) as the time from randomisation to disease progression on subsequent anticancer therapy.

Analysis of all-comer population from the efficacy and safety update (August 2023) showed a greater reduction of disease progression or death (an improvement in PFS2) in patients in the pembrolizumab + CT arm (median PFS2 [redacted]) than in the placebo + CT arm (median PFS2 [redacted]). The hazard ratio for PSF2 was [redacted] representing a statistically significant [redacted] reduction in the risk of disease progression or death in the pembrolizumab + CT arm on subsequent anticancer therapy (CS Document B, Section B.2.6.3). Rates of PFS2 were higher in the pembrolizumab + CT arm at all timepoints (6, 12, 18, 24, 30, 36

and 42 months), but PFS2 appears to plateau at later timepoints (CS Document B, Table 15). The EAG suggest this analysis is appropriate.

3.2.3.6 Patient-reported outcomes (pMMR cohort):

Patient-reported outcome (PRO) data was collected on patients in the pMMR cohort only. PRO data was collected at weeks 0, 6, 18, 30 and 54 in line with key timepoints in the trial (CS Document B, Section B.2.6.4). The following PRO instruments were used: PROMIS-Fatigue Scale (short form), PROMIS-Physical Function Scale (short form), FACT-En-TOI (Functional Assessment of Cancer Therapy- Endometrial) and FACT/ Gynaecological Oncology Group-Neurotoxicity (GOG-Ntx). Completion rates of all instruments was high in both pembrolizumab + CT and placebo + CT arms, but completion rates decreased over time due to discontinuation from the study. PRO data is presented from the interim analysis data cut (December 2022).

EAG comment: The EAG note that PROs were assessed in pMMR cohort only using data from the interim analysis data cut. This choice was queried during the clarification phase (Clarification question A10). The company's explanation for limiting HRQoL/PRO analyses to the pMMR cohort cites a lack of sufficient statistical power in the dMMR group due to a smaller sample size. At the time of the interim efficacy analysis, the statistical power for detecting meaningful differences in HRQoL outcomes was estimated to be 58% for the pMMR cohort and only 50% for the dMMR cohort (CS Document B, Table 8). The EAG consider that these relatively low power levels suggest that even with the sample sizes of n=586 for pMMR and n=223 for dMMR at the final analysis (CS Document B Table 6), the study may have struggled to detect statistically significant HRQoL changes, especially in the dMMR group at the interim analysis stage.

The reduced power indicates a higher risk of type II errors (failing to detect a true effect), which could have informed the decision to focus HRQoL analyses on the pMMR group. Nonetheless, given the final sample sizes at the August 2023 data-cut, uncertainty remains as to whether additional efforts to improve power or conduct exploratory analyses in the dMMR group would have provided valuable insights (even if the findings were less conclusive). However, the EAG recognised that whilst

the HRQoL analyses may be underpowered during the interim analysis, for completeness the study sponsor (as MSD was not the sponsor of KEYNOTE-868 (NRG-GY018)) could have still investigated HRQOL in the dMMR population with caveats around limited interpretation of results.

3.2.3.6.1 PROMIS-Fatigue Scale (short form):

Baseline PROMIS-Fatigue Scale scores were [redacted] between the pembrolizumb + CT and placebo + CT arms in the pMMR cohort. At week 18 both arms showed [redacted] of fatigue, with [redacted] in the pembrolizumab + CT arm ([redacted]) compared to the placebo + CT arm ([redacted]). Despite initially worsening, by [redacted] (CS Document B, Section B.2.6.4).

3.2.3.6.2 PROMIS-Physical Function Scale (short form):

Baseline PROMIS-Physical Function Scale scores were [redacted] between the pembrolizumb + CT and placebo + CT arms in the pMMR cohort. At week 18 both arms showed [redacted] of physical function of approximately 2 points. There was [redacted]. [redacted] (CS Document B, Section B.2.6.4).

3.2.3.6.3 FACT-En-TOI:

Baseline FACT-En-TOI scores were [redacted] between the pembrolizumb + CT and placebo + CT arms in the pMMR cohort. At week 18 both arms showed [redacted] of quality of life, with [redacted] (less worsening) in the placebo + CT arm (last square mean change [redacted]) compared to pembrolizumab + CT arm (last square mean change [redacted]), however the [redacted] (CS Document B, Section B.2.6.4).

3.2.3.6.4 Exploratory PRO endpoints: FACT-GOG-Ntx:

Baseline FACT-GOG-Ntx scores were [redacted] between the pembrolizumb + CT and placebo + CT arms in the pMMR cohort. At week 18 both arms showed [redacted] of quality of life, but [redacted] (CS Document B, B.2.6.4).

3.2.3.6.5 Summary of PRO:

Overall, the EAG note a [redacted] was seen in both pembrolizumab + CT and placebo + CT arms, in the FACT-En-TOI, PROMIS-Physical Function Scale (short form) and PROMIS-Fatigue Scale (short form) scores. With [redacted] in quality of life, physical function or fatigue scores between the two arms (CS Document B, Section B.2.6.4).

3.2.4 Safety results of KEYNOTE-868 (NRG-GY018)

3.2.4.1 Adverse Events (AEs):

Safety analysis focuses on 779 patients in the All Participants as Treated population who received at least one dose of pembrolizumab + CT (n=391) or one dose of placebo + CT (n=388). Analysis of all-comer population from the efficacy and safety update (August 2023) showed almost all patients in both arms experienced at least one AE, with both arms being well balanced in frequency: 379 (96.9%) in pembrolizumab + CT arm compared to 373 (96.1%) in placebo + CT arm. Three patients (0.8%) died from drug-related AEs in pembrolizumab + CT arm and two patients (0.5%) died from drug-related AEs in placebo + CT arm (CS Document B, Section B.2.10).

EAG comment: The EAG note that no new safety concerns were identified, and AE type and frequency were reported to be generally consistent with established safety profiles of the treatments (CS Document B, Section B.2.10). EAG clinical experts

were consulted and confirmed that the AEs reported were what they would expect to see. AE inputs into the economic model are described in Section 4.2.8.4. EAG notes that only anaemia and hypertension were included in modelling.

3.2.4.2 Treatment exposure:

The median duration of treatment on pembrolizumab + CT was longer than on placebo + CT. After adjusting for exposure time, event rates of AEs were [redacted] in the two arms (CS Document B, Section B.2.10.1).

3.2.4.3 Any grade adverse events:

The EAG note that the type and frequency of AEs appear well balanced between the two arms of the trial. Detail was provided in CS Document B, Section B.2.10.2.

Frequency of AEs were often slightly higher in the pembrolizumab + CT arm compared to the placebo + CT arm, which the exception of a few AEs that were more commonly reported in the placebo + CT arm. These included Alopecia (n=223 (57.5%) in placebo + CT compared to n=215 (55%) in pembrolizumab + CT arm), Peripheral sensory neuropathy (n=158 (40.7%) in placebo + CT compared to n=146 (37.3%) in pembrolizumab + CT arm), Arthralgia (n=140 (36.1%) in placebo + CT compared to n=128 (32.7%) in pembrolizumab + CT arm), Neutrophil count decreased (n=114 (29.4%) in placebo + CT compared to n=111 (28.4%) in pembrolizumab + CT arm), Decreased appetite (n=89 (22.9%) in placebo + CT compared to n=88 (22.5%) in pembrolizumab + CT arm), Hypokalaemia (n=76 (19.6%) in placebo + CT compared to n=62 (15.9%) in pembrolizumab + CT arm) and Dysgeusia (n=43 (11.1%) in placebo + CT compared to n=41 (10.5%) in pembrolizumab + CT arm) (CS Document B, Table 21).

The most frequently reported AEs in both arms (occurring in >50% cases) were Fatigue (n=275 (70.3%) in pembrolizumab + CT and n=248 (63.9%) in placebo + CT arm), Anaemia (n=234 (59.8%) in pembrolizumab + CT and n=220 (56.7%) in placebo + CT arm), Alopecia (n=215 (55%) in pembrolizumab + CT and n=223 (57.5%) in placebo + CT arm) and Nausea (n=200 (51.2%) in pembrolizumab + CT

and n=178 (45.9%) in placebo + CT arm) (CS Document B, Section B.2.10.2 and Table 21).

3.2.4.4 Grade 3-5 adverse events:

The EAG note that the type and frequency of Grade 3-5 AEs appear relatively well balanced between the two groups. Detail was provided in CS Document B, Section B.2.10.3.

Rates were largely slightly higher in the pembrolizumab + CT arm compared to placebo + CT arm, with the exception of two where higher frequencies were reported in placebo + CT arm. These were Neutrophil count decreased (n=56 (14.4%) in placebo + CT compared to n=55 (14.1%) in pembrolizumab + CT arm) and Fatigue (n=10 (2.6%) in placebo + CT compared to n=6 (1.5%) in pembrolizumab + CT arm). Frequency of Syncope (n=16 (4.1%)) and Hypokalaemia (n=14 (3.6%) were equal in both pembrolizumab + CT and placebo + CT arms.

The most frequently reported Grade 3-5 AEs (occurring in >10% cases) were Anaemia (n=66 (16.9%) in pembrolizumab + CT and n=45 (11.6%) in placebo + CT arm) and Neutrophil count decreased (n=55 (14.1%) in pembrolizumab + CT and n=56 (14.4%) in placebo + CT arm) (CS Document B, Table 22).

Importantly the type and frequency of drug-related Grade 3-5 AEs were well balanced between the two arms. The most frequently reported drug-related Grade 3-5 AEs (occurring in >10% cases) were Anaemia (n=60 (15.3%) in pembrolizumab + CT and n=34 (8.8%) in placebo + CT arm) and Neutrophil count decreased (n=45 (11.5%) in pembrolizumab + CT and n=45 (11.6%) in placebo + CT arm). Drug-related Grade 3-5 AEs were largely consistent with Grade 3-5 AEs reported.

3.2.4.5 Adverse events of special interest:

The company state that AEs of special interest are based on a list of preferred AEs that are potentially linked to immune response or reactions to infusions, casually associated with pembrolizumab (CS Document B, Section B.2.10.4). The frequency of the AEs of special interest were balanced between the two arms. EAG clinical experts were in agreement that AEs of special interest were as expected.

The most frequently reported AEs of special interest (occurring in >10% cases) were Infusion related reaction ([redacted] in pembrolizumab + CT and n=[redacted] in placebo + CT arms) and Hypothyroidism (n=[redacted] in pembrolizumab + CT and n=[redacted] in placebo + CT arms).

3.2.4.6 Summary of AEs:

The EAG note that AEs, Grade 3-5 AEs, drug-related Grade 3-5 AEs and AEs of special interest were similar between the two treatment groups.

The frequency was often [redacted] in the pembrolizumab + CT arm, but there were no AEs reported that were not also seen in the placebo + CT arm, suggesting there were no concerning effects caused by the introduction of pembrolizumab + CT. No new indication-specific AEs of special interest were identified with the introduction of pembrolizumab + CT, and any that did arise were managed with corticosteroids or ceasing treatment (CS Document B, Section B.2.10.4), and [redacted] in either arm (CS Document B, Table 24).

3.2.4.7 Summary of all-comer population outcomes:

Pembrolizumab + CT showed a [redacted] in all outcomes (PFS, OS, ORR, DOR, PFS2) compared to placebo + CT in the KEYNOTE-868 (NRG-GY018) trial, apart from measures of PROs which showed a [redacted] in both arms, and [redacted] between arms. The type and frequency of AEs were similar in both arms, with the introduction of no new AEs unique to the pembrolizumab + CT arm.

3.2.5 Subsequent therapies

The company provide a table of subsequent treatments following discontinuation of study treatment. A wide range of subsequent treatment was adopted by study participants, with 394 of 819 participants receiving some form of subsequent treatment (CS Document B, Table 18).

The company acknowledge that as some of the treatments identified as subsequently used are not used in UK clinical practice, these were adjusted and validated to exclude treatments not used in England and Wales, or not representative of UK clinical practice (CS Document B, Section B.2.6.5). The EAG consulted clinical experts on this who suggested that pembrolizumab is not given as a monotherapy after 1L chemotherapy in UK clinical practice. This point is discussed in Section 4.2.8.2.

For patients in the placebo + CT arm that received a subsequent therapy 165/248 (66.5%) received pembrolizumab + CT as a later-line therapy (CS Document B, Table 18 and clarification response to Clarification question A6 from company).

3.2.6 Sub-group analysis:

The company present subgroup analysis based on MMR status of participants. Data is reported largely from the Efficacy and Safety Update in August 2023, with some data from the interim analysis in December 2022, and consisted of pMMR population (n=597) and dMMR population (n=222).

[redacted] (CS Document B, Section B.2.7).

EAG comment: The EAG note that the sub-groups examined in the KEYNOTE-868 (NRG-GY018) trial were narrower than the sub-groups identified in the NICE scope. The CS (and the KEYNOTE-868 (NRG-GY018) trial) does not examine how pembrolizumab performs in local versus metastatic cases or in patients with versus without prior debulking surgeries (The company previously confirmed it was not possible to present analyses based on these subgroups due to a lack of systematic data collection on these characteristics in the KEYNOTE-868 (NRG-GY018) trial).Consequently, the EAG clinical advisors note that treatment indications for pembrolizumab could be *reasonably broad*, as enrolled patients may have been those unsuitable for other therapies.

3.2.6.1 Primary endpoint: PFS

Interim analysis

The company report PFS from the interim analysis (December 2022 data-cut) in the dMMR and pMMR cohort. In both cohorts, pembrolizumab + CT showed a statistically significant improvement compared to placebo + CT. In the pMMR cohort, the hazard ratio was 0.57 (95% CI: 0.44, 0.74) in favour of pembrolizumab + CT (representing a 43% reduction in the risk of disease progression or death). In the dMMR cohort, the hazard ratio was 43% (95% CI: 0.22, 0.53) representing a 66% reduction in the risk of disease progression or death, in favour of pembrolizumab + CT (CS Document B, Section B.2.6.1). Both cohorts showed a greater reduction of disease progression or death in the pembrolizumab + CT arm. The EAG suggest this analysis is appropriate.

Efficacy and safety update

PFS is also reported from the efficacy and safety update in August 2023 in the dMMR and pMMR cohorts. Pembrolizumab + CT showed an [redacted] in PFS compared to placebo + CT arm. The median PFS was [redacted] in both cohorts ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] months in pMMR pembrolizumab + CT and [redacted] months in pMMR placebo + CT arms). In the dMMR cohort, the hazard ratio was [redacted] in favour of pembrolizumab + CT (representing a statistically significant [redacted]). In the pMMR cohort, the hazard ratio was [redacted] of pembrolizumab + CT (representing a [redacted] in the risk of disease progression or death).

[redacted] (CS Appendix E, Section E.2.1 and Table 7). The EAG suggest this analysis is appropriate.

3.2.6.2 Secondary outcomes: OS

Interim analysis

The company report OS from the interim analysis (December 2022 data-cut) in the dMMR and pMMR cohort. There was similar survival in pembrolizumab + CT and placebo + CT in both cohorts at all timepoints. Median survival for the dMMR cohort was the same in both pembrolizumab + CT and placebo + CT (Not reached), and in the pMMR cohort median survival was slightly longer in placebo + CT arm (median OS of 27.96 months) compared to pembrolizumab + CT arm (median OS of 27.37 months) (CS Appendix E, Section E.4.2). OS was similar between pembrolizumab + CT and placebo + CT arms in both cohorts, at the interim analysis. The EAG suggest this analysis is appropriate.

Safety and Efficacy update

OS from the Safety and Efficacy update (August 2023 data-cut) in the dMMR and pMMR cohort shows better median survival in dMMR cohort, and better median survival in pembrolizumab + CT arm than placebo + CT (median survival was not reached in dMMR pembrolizumab + CT, and was 42.7 months in dMMR placebo + CT. Median survival was 28.9 months in pMMR pembrolizumab + CT and 28.7 months in pMMR placebo + CT) (CS Appendix E, Table 8).

In the dMMR cohort, the hazard ratio was 0.57 (95% CI: 0.31, 1.04, p=0.0323), representing a clinically meaningful 43% reduction in death, in favour of pembrolizumab + CT. In the pMMR cohort, the hazard ratio was 0.80 (95% CI: 0.59, 1.08, p=0.0683), representing a 20% reduction in death in favour of placebo + CT (although this was not significant p=0.0683). Overall survival was similar between pMMR and dMMR cohorts at 6,12 and 18 months, but survival in the dMMR cohort was higher at 24, 30 and 36 months, and placebo + CT had a higher OS rate than pembrolizumab + CT in the pMMR cohort at all timepoints, but these differences were not significant (CS Appendix E, Table 8).

3.2.6.3 Objective response rate:

ORR from the Safety and Efficacy Update analysis (August 2023 data-cut) is reported in the dMMR and pMMR cohort. There was an improvement in ORR in the pembrolizumab + CT arm in the dMMR cohort (82.1%) compared to placebo + CT arm (71.6%), with a statistically significant estimated difference in treatment of 10.2% (95% CI: -1.9, 22.2, p=0.04954). There was also an improvement in ORR in the pembrolizumab + CT arm in the pMMR cohort (72.3%) compared to placebo + CT arm (59.0%), with a statistically significant estimated difference of treatment of 13.3% (95% CI: 4.6, 21.7, p=0.00138). The pembrolizumab + CT arm showed a greater improvement of ORR in both cohorts, but more improvement was seen in the pMMR cohort. The EAG suggest this analysis is appropriate.

3.2.6.4 Duration of response:

DOR from the Safety and Efficacy Update analysis (August 2023 data-cut) is reported in the dMMR and pMMR cohort. Duration of response in the dMMR was longer in placebo + CT arm (median response was not reached) than the pembrolizumab + CT arm (4.8 months). The median response duration in the pMMR cohort was longer in the placebo + CT arm (8.1 months) compared to the pembrolizumab + CT arm (6.4 months). There were higher proportions of patients in the placebo + CT arm in both the dMMR and pMMR cohorts, with extended response duration at all timepoints (CS Appendix E, Table 10). Overall, there were longer response times in placebo + CT compared to pembrolizumab + CT in both cohorts, suggesting a less favourable outcome in the pembrolizumab + CT treatment arm.

3.2.6.5 Exploratory endpoints: PFS on next-line therapy:

The company report PFS on next-line therapy (PFS2) from the Efficacy and Safety Update analysis (August 2023 data-cut) in the dMMR and pMMR cohort. In both cohorts, pembrolizumab + CT showed an [redacted] compared to placebo + CT. The median PFS2 was [redacted] in dMMR pembrolizumab + CT and [redacted] months in dMMR placebo + CT, and was [redacted] months in pMMR pembrlizumab + CT and [redacted] months in pMMR placebo + CT. In the dMMR cohort the hazard ratio was

[redacted], representing a statistically significant [redacted] in favour of pembrolizumab + CT arm on subsequent anticancer therapy (CS Appendix E, Table 11). In the pMMR cohort the hazard ratio was [redacted], representing a statistically significant [redacted] of disease progression or death in [redacted] of pembrolizumab + CT arm on subsequent anticancer therapy (CS Appendix E, Table 11). PFS2 was consistently [redacted] in the pembrolizumab + CT arm compared to the placebo + CT arm in both cohorts, at all timepoints (6, 12, 18, 24, 30 and 36 months). Reduction in the risk of progression of disease or death on subsequent anticancer therapy was [redacted] in the dMMR cohort. The EAG suggest this analysis is appropriate.

3.2.7 Adverse events for dMMR/pMMR cohorts:

AEs in sub-group analysis were based on efficacy and safety update (August 2023). The number of AEs reported, and the number of drug-related AEs were similar across treatment arms and dMMR and pMMR cohorts (CS Document B, Table 13).

3.2.7.1.1 Most frequently reported adverse events:

The most frequently reported AEs in both arms (occurring in >50% cases) were Fatigue; with [redacted] reported by patients in the dMMR cohort ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT arms, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). [redacted] patients in dMMR cohort reported Alopecia, with [redacted] cases reported in both placebo arms than treatment arms ([redacted] in dMMR pembrolozumab + CT and [redacted] in placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms) (CS Document B, Table 13).

3.2.7.1.2 Grade 3-5 adverse events:

The most frequently reported Grade 3-5 AEs in both arms (occurring in >10% cases) were Anaemia; with [redacted] reported by patients in the dMMR cohort ([redacted] in

dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT arms, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). [redacted] patients in the pMMR cohort reported Neutrophil count decreased [redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). [redacted] patients in the pMMR pembrolizumab + CT arm than dMMR cohort reported White blood cell count decreased, but [redacted] in the dMMR placebo + CT arm overall [redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms) (CS Document B, Table 14).

3.2.7.1.3 Drug-related Grade 3-5 adverse events:

[redacted] drug-related Grade 3-5 AEs were reported in pembrolizumab + CT arms in both dMMR and pMMR cohorts compared to placebo + CT arms. A [redacted] proportion of cases were reported in dMMR and pMMR cohorts ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). The most commonly reported drug-related Grade 3-5 AEs (occurring in >10% cases) were Anaemia; with [redacted] reported by patients in dMMR receiving pembrolizumab + CT than in pMMR cohort or in placebo + CT arm ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). [redacted] patients in pMMR cohort receiving pembrolizumab + CT reported Neutrophil count decreased ([redacted] in dMMR pembrolizumab + CT and n=12 (11.4%) in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms) (CS Document B, Table 15).

3.2.7.1.4 Adverse events of special interest:

A [redacted] number of AEs of special interest were reported across both cohorts, with [redacted] reported in pembrolizumab + CT than placebo + CT arms. The most frequently reported AEs of special interest in both arms (occurring in >10% cases) were Infusion related reaction, [redacted] between the two cohorts, and [redacted] in

pembrolizumab + CT than placebo + CT ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms). Frequency of hypothyroidism were [redacted] between dMMR and pMMR cohorts, with pembrolizimub + CT arms reporting [redacted] events than placebo + CT in both cohorts ([redacted] in dMMR pembrolizumab + CT and [redacted] in dMMR placebo + CT, and [redacted] in pMMR pembrolizumab + CT and [redacted] in pMMR placebo + CT arms).

3.2.7.2 Summary of AEs in sub-group analysis:

A [redacted] number of AEs and drug-related AEs were reported in the sub-group analysis. [redacted] events were often reported in the pembrolizumab + CT arm compared to placebo + CT arm, but as with the all-comer population, no new AEs were reported as a result of pembrolizumab + CT that were not reported in the placebo + CT arm.

3.2.7.3 Summary of outcomes in sub-group analysis:

Pembrolizumab + CT showed a clinically meaningful [redacted] in PFS, OS, ORR and PFS2 compared to placebo + CT, with the dMMR cohort often showing [redacted] improvements than pMMR cohort. Placebo + CT showed [redacted] improvement in DOR than pembrolizumab + CT arm. The number of AEs and drug-related AEs were [redacted] between treatment arms and between pMMR and dMMR cohorts. The majority of outcomes in the pMMR and dMMR cohorts were based on the Safety and Efficacy update analysis (August 2023 data cut), with PFS and OS also being available at the interim analysis (December 2022 data cut). PRO data was presented from the Interim analysis (December 2022).

3.2.7.4 Summary of outcomes of KEYNOTE-868 (NRG-GY018):

Evidence of the clinical effectiveness of pembrolizumab + CT came from the KEYNOTE-868 (NRG-GY018) trial. Comparisons with placebo + CT arm in the all-comer population at the August 2023 data cut showed [redacted] in all outcomes (PFS, OS, ORR, DOR, PFS2) following treatment with pembrolizumab + CT.

Sub-group analysis compared cohorts of patients with dMMR and pMMR status (largely at the August 2023 data cut) and showed [redacted], with dMMR cohorts often showing greater improvements than pMMR cohort (PFS, OS, PSF2). Improvements in ORR [redacted]

For patient reported outcomes (PROs), there was a [redacted] overall in both pembrolizumab + CT and placebo + CT arms, in the FACT-En-TOI, PROMIS-Physical Function Scale (short form) and PROMIS-Fatigue Scale (short form) scores. There were [redacted] differences in quality of life, physical function or fatigue scores between the two arms.

Overall, the type and frequency of AEs and drug-related AEs reported appear reasonable and were [redacted]. AEs were often slightly [redacted] common in the pembrolizumab + CT arm, but there were no unique AEs that were not also seen in the placebo + CT arm, suggesting no concerning effects caused by the introduction of pembrolizumab + CT. Any AEs that did arise were managed with corticosteroids or ceasing treatment.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 Indirect Treatment Comparison (ITC) and Meta-Analysis:

In section B.2.8 and B.2.9 of the CS, the company stated that no meta-analysis or indirect treatment comparison (ITC) was conducted due to the absence of other relevant studies fitting the scope, paclitaxel + carboplatin being the only relevant comparator for pembrolizumab + carboplatin + paclitaxel, and that the KEYNOTE-868 (NRG-GY018) study is the only direct comparison. Thus, a network meta-analysis (NMA) was not required.

The EAG note that while this rationale may be reasonable, under certain circumstances, it is important to consider the broader implications for the robustness of the clinical effectiveness evidence from a single study, particularly when these results inform the economic evaluation (see Section 4.2.4).

3.3.2 Implications of not conducting ITC or Meta-Analysis:

From the EAG perspective, there are some pros and cons to not conducting any ITC which we have summarised below.

- The reliance on the direct comparison from the KEYNOTE-868 (NRG-GY018) trial only, ensures that there is no additional uncertainty introduced by assumptions inherent in an indirect comparison, such as potentially high heterogeneity between studies. The data directly compares the treatment arms of interest without reliance on cross-trial comparisons, which could potentially introduce bias. In indirect treatment comparisons, data from different trials are often combined to compare interventions that have not been studied head-to-head. However, these trials may vary in important aspects, such as patient populations, endpoints, study designs, dosing regimens, or even follow-up periods, leading to potential heterogeneity and inconsistency. Such differences require complex adjustments and assumptions to approximate comparability, which can increase uncertainty and introduce bias into the analysis. If no other studies directly comparable in terms of final scope, conducting an ITC or meta-analysis could lead to inappropriate or misleading conclusions.
- The lack of ITC means the evidence base remains narrow, relying on a single randomised controlled trial for clinical effectiveness. This limits the generalisability of the findings, particularly since indirect comparisons with other potentially relevant treatments or subpopulations cannot be made.
    - It is possible that studies, though not directly comparing pembrolizumab + CT to CT alone, may have compared other relevant treatments in a broader network of therapies for advanced or recurrent EC. If such studies exist but were excluded from consideration, this will limit the robustness of the comparative evidence. However, as detailed

in Section 3.1 the EAG consider the SLR to be appropriate and do not consider potential studies to be missing.

- To provide assurance for committee, the EAG assessed the list of studies the company excluded and found studies to have been excluded appropriately. We also undertook a targeted search of relevant studies for health utility data, and searched for potentially relevant RCTs using the Epistemonikos database and did not find any relevant studies for inclusion in the ITC. This further supports the company's rationale, though the absence of broader comparative data still constrains the reliability and depth of the economic model.

3.4 Additional work on clinical effectiveness undertaken by the EAG

No additional work on clinical effectiveness was undertaken by the EAG. The EAG's survival modelling can be found in Section 4.2.6.4.

3.5 Conclusions of the clinical effectiveness section

- The company SLR searches and methods were appropriate. Clinical evidence for the safety and effectiveness of pembrolizumab presented in the CS was obtained by one source, the KEYNOTE-868 (NRG-GY018) study.[2]
- Due to the SLR including one study only, no ITC was possible, and evidence on clinical effectiveness was based on the one study. The CS presents evidence from one included study: the KEYNOTE-868 (NRG-GY018) trial,[2] a Phase III double-blind, placebo controlled, randomised trial, investigating the safety and effectiveness of pembrolizumab + CT compared with placebo + CT in patients 18 years and over with advanced stage or recurrent endometrial cancer.
- The EAG note that KEYNOTE-868 (NRG-GY018) contained no UK patients and query the representativeness of the KEYNOTE-868 (NRG-GY018) trial baseline characteristics to patients in UK clinical practice.

Alignment of service delivery may not be comparable between UK and health systems represented in the trial.

- The KEYNOTE-868 (NRG-GY018) trial consisted of a maximum of 30 weeks in the combination phase, followed by maximum of 84 weeks in the maintenance phase (equating to approximately 2.2 years). The EAG note the short follow-up data available in the KEYNOTE-868 (NRG-GY018) trial (median follow up data of [redacted] to inform economic modelling).
- At the efficacy and safety update analysis (August 2023), analysis of the all-comer population showed a clinically meaningful[redacted] in the pembrolizumab + CT arm compared to the placebo + CT arm, and sub-group analysis showed improvements in pembrolizumab + CT arms in most outcomes, with dMMR cohorts often showing greater improvements than pMMR cohort. Improvements in ORR were greater in the pMMR cohort, and DOR showed greater improvements in the placebo + CT arm over the pembrolizumab + CT arm.
- HRQoL outcomes were only assessed in the pMMR cohort, and there was a [redacted] overall in both pembrolizumab + CT and placebo + CT arms, in PRO measures. There were [redacted] differences in quality of life, physical function or fatigue scores between the two arms. The EAG has some concerns about the lack of HRQoL assessment in the dMMR cohort. Assessment of HRQoL in both cohorts would have allowed completeness of data.
- Overall, the type and frequency of AEs and drug-related AEs reported were similar between treatment arms and cohorts. There were no unique AEs that were not also seen in the placebo + CT arm.
- The EAG note differences in intervention, comparator and sub-groups between the KEYNOTE-868 (NRG-GY018) trial and the NICE scope, however evidence provided in the submission for pembrolizumab is largely aligned with the decision problem population
- The EAG note caution in the use of post-hoc analyses of the all-comer population, which might not be entirely representative of the original trial's

intended population (i.e., separate cohorts for dMMR and pMMR patients) and may introduce potential bias and risks overgeneralising the results of the all-comer population (the post hoc analysis). The company provided analyses for the dMMR and pMMR cohorts separately, in addition to the all-comer population, as per the trial design.

- The EAG note the high numbers of discontinuation in the KEYNOTE-868 (NRG-GY018) trial.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

4.1.1 Search strategies

Separate searches were carried out to identify cost-effectiveness, health-related quality of life (HRQoL) and cost and healthcare resource identification, measurement and valuation evidence (CS Appendix G.1, H.1 and I.1). The original searches for the cost-effectiveness and cost and healthcare resource identification, measurement and valuation SLRs were carried out on the 29th May 2019 and updated on the 5th January 2021, 8th November 2021 and the 16th March 2024 (CS Appendix G.1 and I.1). The HRQoL search was carried out on the 3rd June 2019 and updated on the 6th January 2021, 8th November 2021, 19th July 2022 and the 15th March 2024 (CS Appendix H.1). A broad and appropriate range of sources were searched including bibliographic databases and manual searches of HTA agencies (CS Appendix G.1.1, G.1.2 Table 24). The HTA searches of the International HTA Database (INAHTA) and manual searches focussed on 'EU-4 countries (Italy, Spain, France and Germany) and the UK and Canada', which could introduce geographic bias (CS Appendix G.1.2, Table 24).[42] A targeted literature search was also carried out on the Health Economics and Research Centre (HERC) Database of Mapping Studies (CS Appendix P.3 Table 87). The searches were limited to the date period of 1999 and a rationale for limiting by date is not provided. The searches were not limited by language.

The EAG has concerns about the reporting of the Embase and Medline searches for economic modelling, health related quality of life (HRQoL) AND cost and resource use and utility. The CS states that the database searches were run via Ovid (CS Appendix G.1.1) but the reported syntax for all database searches are incompatible with this platform. The free-text search lines for the population (lines 1-3) of the Embase, Medline-In-Process and EconLit searches do not include the search field operator characters, so it is not clear which fields were searched. The EAG note that searching Title, Abstract and Keyword fields would be optimal (CS Appendix G.1.1, H.1. and I.1.1) During FAC the company confirmed that there was an error in the CS

in terms of the platform specified in the economic SLR, and confirmed that Embase.com was used to search Medline and Embase and not Ovid.

The search terms for the population terms for each database are reasonable; they include a range of free-text synonyms and the most appropriate thesaurus terms for the disease. Unlike with the clinical effectiveness searches, a concept of disease stage is included in the Embase and EconLit searches, which could potentially restrict the search results (CS Appendix G.1 Table 19, Table 21, H.1 Table 31, Table 33, I.1 Table 40, Table 43). The CS states that the eligibility criteria was amended to include early-stage endometrial cancer and this concept was added to the update searches (CS Appendix G.1, G.2 Table 19, lines 22 and 23, H.1 Table 31 Lines 19, 21 and 23 and I.1 Table 40 Line 23). Due to the unclear reporting, it is not clear if searches for second-line and third-line were searched for the periods 1999 onwards or limited to studies published from 2021 onwards (CS Appendix G.1.1 Table 19 and 20 H.1.1. Table 31 and 32 and I.1.1 Table 40 and 41). The EAG would recommend not including search terms for disease stage, particularly if the inclusion criteria has been broadened, to ensure that studies relating to endometrial cancer that do not refer to disease stage are not missed.

The search terms for cost-effectiveness, economic models for the Medline and HRQoL and cost and healthcare resource identification, measurement and valuation for the Embase, Medline-In-Process and EconLit searches appear to have been derived from search filters and are suitable and comprehensive, including a broad range of database-specific indexing and free text terms (CS Appendix G.1.1, H.1.1 and I.1.1).

The EAG query whether the Embase searches for economic models, utility studies and cost and resource contain an error in the use of a Boolean operator, as the search lines for second-line and third-line are combined using the Boolean operator AND. The EAG note that the concepts for second and third-line should be combined using the Boolean operator OR, or ideally that search terms for disease stage were not included (CS Appendix G.1 Table 19 search line 17, H.1.1. Table 31 line 16 and I.1 Table 40 line 17).

The Embase and EconLit searches also contains a few typos in the population search terms, for example ‘51arcino*’ (CS Appendix G.1 Table 19, Table 21).

The CS reports that Medline searches were carried out on Medline-In-Process only via Ovid (CS Appendix G.1 Table 20, H.1 Table 32 and I.1 Table 41 Medline In-process search for). Medline-In-Process contains a small proportion of the overall MEDLINE database as it contains records that are undergoing indexing and the vast majority of articles in MEDLINE are fully indexed with Medical Subject Headings (MeSH) terms. Search lines 7 and 8 limit the results to the most recently added PubMed in process and citations not indexed for Medline results. This may have been applied to find unique content only, as Medline and Embase contain the same journals. However, the EAG consider this to be insufficient and would recommend that Embase and Medline are searched separately as they contain different thesauri and the same searches and can result in different search results.[43]

The EconLit searches includes search terms to identify economic models, cost utilities and cost and resource use (CS Appendix G.1 Table 21. H.1 Table 33 and I.1 Table 41). The search results for the population terms alone were relatively small; therefore the EAG would recommend searching for the population terms only, as per the search carried out on the Centre for Reviews of Dissemination database (CS Appendix G.1 Table 22, Table 34 and Table 43 NHSEED and HTAD for economic modelling, cost and resource use and utility) to ensure that a sensitive search was carried out, as the main focus of this database are studies related to economic and cost studies. The fourth update search of the CRD database is amended slightly to not include exploded indexing terms but the rationale for doing so is not provided (CS Appendix G.1 Table 22, Table 34 and Table 43 NHSEED and HTAD for economic modelling, cost & resource use and utility).

Four conferences were searched from the conference websites directly and the search is reported clearly and transparently including the numbers of results and included studies (CS Appendix G.1.2 Table 23).

The CS states that reference checking of key systematic review and meta-analysis articles was carried out and the PRISMA flow-diagram reports that one study was identified via ‘Bibliography Searches’ (CS Appendix G.3, Figure 16: PRISMA flow diagram of initial and 2021 updates SLRs for economic studies in patients with EC); however, the company’s clarification response states that ‘no SLRs/HTAs identified during the SLR that were hand-searched to identify any additional, relevant studies for inclusion in the reviews’ (Clarification question B.1.) The Embase searches also

includes a search line (line 7) to remove reviews, which could remove this study type from the search results (CS Appendix G.1.1 Table 19, H.1.1. Table 31 and I.1.1 Table 40).

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The eligibility criteria were suitable for the SLR performed. The SLR search strategies were comprehensive enough despite some limitations highlighted above. However, a targeted literature search for health-related utility data performed by the EAG retrieved a paper citing utility values from KEYNOTE-158 that was not included in company's search, despite the company also using KEYNOTE-158 data as the primary data source for utilities.[44] It is not clear to the EAG why this paper was not included in the company's review as it also used the UK value set. Noteworthy, the reported utility values for stable and progressed disease in that study are lower than those included in the company's model. The EAG provides a more detailed discussion in section 4.2.7.3.

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist is presented in Table 6.

Table 6: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between	Yes

	the technologies being compared	
Synthesis of evidence on health effects	Based on systematic review	Yes
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.	Yes. However, EQ-5D data was not collected in pivotal trial (KEYNOTE-868 (NRG-GY018)) but based on subgroup of KEYNOTE-158 trial population
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, but based on external data (same comment as above).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company used a de-novo cost-utility partitioned survival model with a weekly cycle length and time horizon of 35 years. The model has three health states: progression free survival (PFS), progressed disease (PD) and death (absorbing state). All patients begin in the PFS state (receive treatment with pembrolizumab + CT, or CT only) and remain there until disease progression or death. Patients in the PD health state remain there until death as shown in Figure 1 below.

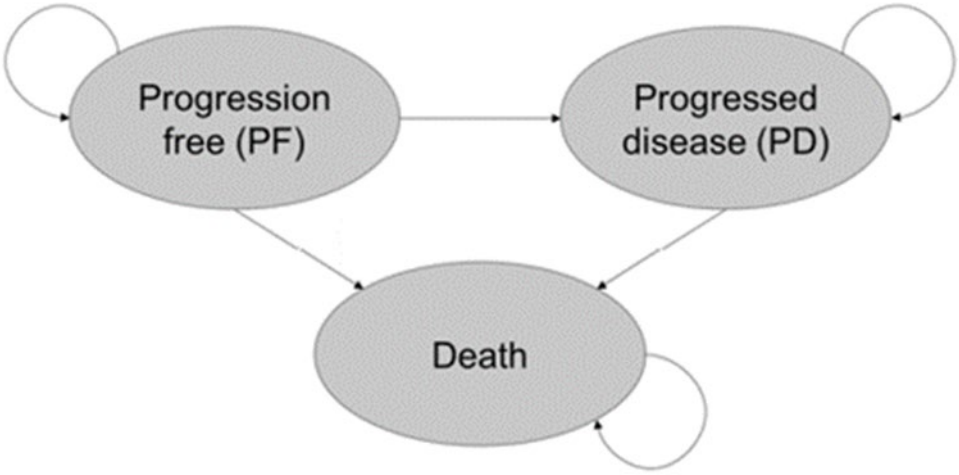


Figure 1 Model Structure (Company Submission -Figure 14)

The partitioned survival method model uses “area under the curve” approach, where the number of patients in each state at a given time point is taken directly from survival curves fitted to the clinical data. The PFS curves show at a given time point, the proportion of patients who have not progressed or died, whilst the OS curves show the proportion of patients who are alive at a given time point. The proportion of the patients in the PD state was calculated as the difference between the proportion of living patients (OS health state) and the proportion of patients who are both living and pre-progression (PFS health state). The modelled OS and PFS curves were based on KEYNOTE-868 (NRG-GY018) data and the approach used is described in detail in section 4.2.6. Actual Kaplan-Meier (KM) data were used to estimate time to discontinuation (TTD).

In the company’s base-case analysis, no treatment effect waning was assumed following pembrolizumab + CT discontinuation, with rationale provided on pg. 125 CS Document B. The company explored a scenario assuming gradual treatment waning in the OS curve five years after stopping treatment in 24.8% of patients who did not attain ORR, citing KEYNOTE-006 trial (pembrolizumab versus ipilimumab in advanced

melanoma), in which treatment waning was not observed during the 7-year follow-up period as justification.

EAG Comments

- The model structure allowed the two clinical efficacy endpoints, PFS and OS, to be modelled directly from the KEYNOTE-868 (NRG-GY018) data. Ample evidence was provided to justify model choice, including its widespread use in oncology modelling and application in previous technology appraisals.
- The weekly cycle length was short enough to capture changes over the relevant time interval.
- The 35-year time horizon was long enough to capture important differences in costs and clinical outcomes.
- TTD was based on actual KM data, reflecting actual treatment use observed in the trial.
- Clinical advice to the EAG suggests that *"the discussion regarding treatment waning is relevant to all immunotherapy*" and with the trial's limited follow-up, there is no evidence to suggest that treatment waning does not occur.

4.2.3 Population

Pembrolizumab (KETRUDA) does not currently have a marketing authorisation in the UK for the indication under consideration. The patient population considered in the model is in line with the anticipated MHRA marketing authorisation: "KEYTRUDA, in combination with carboplatin and paclitaxel, for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults." Treatment outcome data were available by MMR status (i.e., patients with dMMR disease and patients with pMMR disease), allowing analysis for the all-comer (combined) population. The pivotal trial provided data on safety and time on treatment and baseline characteristics of the population were derived from baseline characteristics of the KEYNOTE-868 (NRG-GY018) population (i.e., mean age: 65.40 years; baseline body weight: [redacted]kg; baseline BSA: [redacted]m^2 (CS Document B, Table 60).

The CS states that KEYNOTE-868 (NRG-GY018) trial population is *'broadly similar'* to patients seen in real-world clinical practice. The EAG's clinical advisors indicated

that in real life, the patients are likely older with less good performance status (Section 3.2.1.3 for further details). The clinical expert for the EAG advised that a mean starting age of 70 years is likely more representative of the population with this indication. The EAG sought alternative data sources, retrieved through the cost-analysis and cost-effectiveness literature, for data to inform alternative starting age that would be more appropriate for this appraisal. Table 7 summarises the sources retrieved and mean age of the population.

Table 7: Overview of sources for starting age in economic model

Source	Median/ Mean age (yrs)	Population	EAG comments
KEYNOTE-868 (NRG-GY018) **(Company submission)**	Mean age - 65.4	All-comer population (n= 819)	No patients recruited from UK sites. EAG clinical experts' opinion likely younger population than seen in UK practice.
Alternative sources			
Pennington (2016) [45]	Mean age - 67.1	Participants enrolled in UKCTOCS subsequently diagnosed with advanced stage III and IV EC patients (n=39)	Relevant population to England & Wales although small sample size. Supports EAG clinical experts' opinion of higher starting age.
Zhang (2024) Endometrial Cancer Health Outcomes-Europe (ECHO-EU) study[46]	Mean age – 68.3 Median age - 69	Retrospective chart review (3 years) of patients with recurrent or advanced endometrial cancer in Europe who progressed after prior first-line systemic therapy (n= 475; 101 from the UK) & 89.5% - stage III or IV	Relevant population to UK and large sample size. Both pMMR and dMMR patients included. Supports EAG's clinical opinion of a mean age of 70 years and population less healthy population (higher ECOG scores)
Heffernan (2022)[47]	65.5	GSK-funded retrospective	Relevant population to

Source	Median/ Mean age (yrs)	Population	EAG comments
		review of patients diagnosed with recurrent/advanced endometrial cancer between 1 January 2013 and 31 December 2018 in England (n= 999 for immune checkpoint inhibitor-eligible second-line cohort)	England but not current appraisal as it reports on a previously treated (second-line cohort). Missing data on relevant characteristics e.g., ECOG, MMR status, progression status within datasets used
Ingles Russo Garces et al (2023)[48]	*Median age - 67.9* (entire immune checkpoint inhibitor (ICI)-eligible 1L cohort) (n=2,376) *Median age -66.6* (subpopulation of ICI-eligible 1L cohort who received solely carboplatin-paclitaxel (n=902)	GSK-funded retrospective review of patients diagnosed with recurrent/advanced endometrial cancer between 1 January 2013 and 31 December 2019 in England (n= 2,376 for immune checkpoint inhibitor-eligible first-line cohort)	Conference presentation based on same study reported by Heffernan (2022) above but with a focus on first line cohort (Reflects population under consideration for this appraisal). Inclusion criteria do not completely match current appraisal as patients included in review matched to inclusion criteria for RUBY trial e.g., for ECOG performance status
Sorbe (2008)[49]	Mean age - 67.9	Prospective, phase II, multicentre study of patients with primary advanced and recurrent EC. Treatment with Carboplatin and paclitaxel (n=66)	Small sample population but European population and relevant to decision problem. Median follow-up of 57 months
TA 963[50]	Mean age - 67.1	Adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary	dMMR population only. Committee determined 67.1 years to be the most appropriate

Source	Median/ Mean age (yrs)	Population	EAG comments
		advanced or recurrent endometrial cancer (EC)	age for use in model
Clinical expert for EAG	Mean age - Approx. 70	EC patients undergoing treatment in England NHS Trust	Expert opinion indicates that real world population seen in clinical practice (rather than those included in trials) is generally older and less healthy. Mean age approximately 70 years

Except for Heffernan et al. (2022)[47], all the additional studies in table 7 above reported mean ages >66 years for patients with primary advanced or recurrent EC (stage III/IV). This is higher than the starting age (65.4 years) used in the company's economic model and based on data from KEYNOTE-868 (NRG-GY018). The study by Heffernan and colleagues was a retrospective review of patients diagnosed with recurrent/advanced endometrial cancer between 1 January 2013 and 31 December 2018 in England (n= 999 for immune checkpoint inhibitor-eligible (ICI) second-line cohort).[47] The study was commissioned by GSK to observe 'real-world' treatment patterns in England. Although, the population is relevant to England and Wales, the study reports on a previously treated second-line cohort therefore does not fully match the NICE decision problem for this appraisal. In addition, the authors did note that relevant baseline characteristics e.g., ECOG status, disease stage and MMR status were mostly missing.

Ingles Russo Garces et al (2023)[48] reports on a first-line advanced or recurrent EC cohort in England. The analysis is based on the GSK-commissioned study reported above but using data from 1 January 2013 and 31 December 2019 in England (n= 2,376 for immune checkpoint inhibitor-eligible first-line cohort). The study population is relevant to England and Wales and matches the NICE decision problem for this appraisal. However, inclusion criteria do not completely match current appraisal as

patients included in review matched to inclusion criteria for RUBY trial. For example, only patients with ECOG performance status of 0,1 were included but the current appraisal includes patients with ECOG performance status of 0,1,2. The authors report median ages for the entire ICI-1L eligible cohort (i.e., all patients who would be eligible to receive ICI as 67.9 years. Median ages for a subpopulation of the ICI-1L cohort (i.e., those who received only carboplatin-paclitaxel) was reported as 66.6 years.

Zhang and colleagues conducted a retrospective chart review of patients with recurrent/advanced endometrial cancer who progressed between 1 July 2016 and 30 June 2019 following prior first-line systemic therapy.[46] Baseline characteristics of patients included in the review were reported and indicate a higher mean and median age at primary diagnosis and distribution of ECOG scores that support EAG's clinical experts' opinions of older and less healthy population than reported in KEYNOTE-868 (NRG-GY018). The review included 101 patients from the UK and observed "real-world" data. The EAG considers the starting age more representative of patients seen in the NHS though results were not reported specifically by country.

Pennington and colleagues[45] estimated long-term secondary care costs of EC using data from a prospective cohort study nested within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The study included women participating in UKCTOCS and diagnosed with EC following enrolment (2001-2005) and prior to 31st Dec 2009. Thirty-four of the patients were diagnosed at stage III and five at stage IV. The mean ages of these patients were 66.8years and 69.4 years for stage III and stage IV respectively. Though the sample size was small (n=39), all patients were from England hence the data are also likely representative of NHS population. The study by Sorbe and colleagues, though small sample-sized,[49] was relevant to the decision problem and indicated a higher mean age at diagnosis than reported in company submission for patients with primary advanced/ recurrent EC receiving treatment with carboplatin-paclitaxel combination therapy.

Based on these findings, the EAG believes the starting age at baseline might be somewhere between Zhang and colleagues' estimates (also close to EAG's experts' opinion) and the company's estimates. Previous NICE appraisal committees[27] have accepted 67.1 years as a more representative starting age of patients in the economic model for patients with this indication. The EAG has thus chosen this value to use in its base case and performed a range of sensitivity analyses using different starting ages as informed by the external evidence in Table 7. When starting age in the model was implemented at 67.1 years the company ICER increased by [redacted] to [redacted] per QALY.

EAG comments:

- The population included in CEM aligns with the population specified in the NICE scope
- The baseline starting age used in the CEM appears too young and unlikely representative of patients seen in real world clinical practice in England and Wales. Alternative evidence on average starting age (mean or median), sourced through the literature (Table 7), supports the EAG clinical experts' opinions.

4.2.4 Interventions and comparators

The final scope issued by NICE as seen in Table 1 of the company submission includes hormone therapy in addition to the comparator considered in this appraisal (carboplatin + paclitaxel). The company excluded hormone therapy because it is typically used when "*all other treatment options are exhausted, or if chemotherapy is not suitable for patients*." The EAG's clinical experts confirmed that although hormone therapy would be considered for subgroups of patients e.g., where tumours are ER/PR+, there is lack of randomised data on use of hormone therapy and none using modern immunohistochemistry. The EAG agree that carboplatin/paclitaxel is the fairer comparator as discussed in Table 3.

4.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. In the base case, costs and benefits were discounted at an annual rate of 3.5% in line with NICE reference case. The 35-year time horizon is sufficient to capture the extrapolated OS curves given the model cohort age.

4.2.6 Treatment effectiveness and extrapolation

This section critiques the company's modelling approach for long-term estimates of PFS and OS, and potentially for TTD. The EAG fit our own survival models in a manner consistent with the company to come up with the most plausible estimates of these outcomes.

4.2.6.1 Critique of clinical evidence included in the economic model

As noted in Table 3 of CS Document B, PFS and OS results from KEYNOTE-868 (NRG-GY018) were incorporated in the economic model. This section focuses on these outcomes only and includes the survival analysis modelling of PFS and OS to estimate long-term PFS and OS probabilities, beyond the timescale of KEYNOTE-868 (NRG-GY018). The TTD outcome was also included in the survival analysis section of the CS, thus it will be covered in this section of the EAG report also, however no survival curves were fit by the company, only the Kaplan-Meier data were used. This will also be discussed. All of the EAG's analysis was conducted using the 'flexsurv' package in R.

4.2.6.2 Survival analysis methods

The company used the patient-level data available to them from KEYNOTE-868 (NRG-GY018) to model PFS and OS beyond the timeframe of the study. With a median follow-up of [redacted] months in the pembrolizumab + CT arm and [redacted] months in the CT only arm, three survival analysis techniques were used so that long-term survival probabilities could be obtained. In tables 34, 35, 39 and 40 of the CS Document B, key timepoints to be extrapolated were two, five, ten and 20 years, all of which are beyond the [redacted] months of median follow-up in KEYNOTE-868 (NRG-GY018).

4.2.6.2.1 In response to clarification question C5, the company confirmed that no covariates were adjusted for in any of the survival analysis models. The main reasons stated were that KEYNOTE-868 (NRG-GY018) is an RCT so, by the very nature of the study design, both treatment groups were likely to be balanced, the clinicians consulted confirmed the trial population was broadly similar to that of the UK setting, and subgroup analyses found no significant treatment effect modifier. The EAG inspected the results of the subgroup analyses in Figure 12 and Figure 13 of the CS Document B. For the PFS outcome in Figure 12, there [redacted] Smooth parametric models

Standard parametric models were fit to the observed KM data. These are fit from time zero until the end of the study and beyond. These models provide a continuous, smooth representation of survival data and feature no breaks in between unlike the other two methods used. The parametric models fitted were the exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, and gamma models. Each of these models offers different assumptions about the underlying hazard function, allowing for flexibility in capturing a range of survival patterns observed in KEYNOTE-868 (NRG-GY018) and are often preferred for their ability to provide stable and interpretable projections. Briefly:

- Exponential: assumes a constant hazard over time, thus the risk of an event is the same throughout.
- Weibull: allows for a hazard rate that can either increase or decrease over time.
- Log-normal: assumes the log of survival times follows a normal distribution.
- Log-logistic: similar to log-normal, but assumed time follows a logistic distribution, allowing for hazards that increase and then decrease.
- Gompertz: assumes hazard increases exponentially over time.

- Generalized gamma: a highly-flexible model that can accommodate various hazard shapes.
- Gamma: assumes survival time follows a gamma distribution, similar to the Weibull model but with a different shape for the hazard function.

4.2.6.2.2 Two-stage piece-wise models

The company identified the optimum cut-off point by investigating the hazard profile, and used the Chow test to single-out inflection points in the hazards, choosing the earliest key inflection point to maintain sufficient statistical power.

The Chow test is a method used to determine whether there is a significant change in the hazards, in this case, at a specific point in time, to check if the data before and after this time point follows a different pattern. If the Chow test finds a significant change, or inflection point, it suggests that the data should be analysed differently either side of this time point.

As the company investigated the hazards between groups, a single cut-off point was identified for each group for each outcome, thus the pembrolizumab + CT and CT only models were modelled with the same cut-off point for each outcome, [redacted] for PFS and [redacted] for OS, though the smooth parametric curve was selected for the OS control group. It is also possible to investigate how the hazards of each group change themselves, therefore obtaining different cut-off points for the intervention and control groups. This approach was explored independently by the EAG as part of an expanded analysis, but it is acknowledged that the company's considerations already incorporated hazard profiles in their approach.

The EAG asked the company during the clarification stage if any other cut-off points were explored. The company responded in responses C3 and C4 that while other methods and cut-off points were explored and modelled, the chosen cut-off points identified using the Chow test were the most appropriate and ensured extrapolations were made based on a sufficiently large sample size.

4.2.6.2.3 Cubic splines

Cubic splines, as described by Royston and Palmer 2002,[51] were also used. Analyses were performed using 1, 2, and 3-knot spline models on three different scales: normal, odds and hazards. Knots represent the points along the timeline

where the behaviour of the data can change, therefore different models are fit to the points before the knot and after the knot. Unless it is specified in the model code and manually changed, knots split the data equally, so a one-knot spline model splits the data in half, two knots splits the data into thirds, and three knots splits the data into quarters.

The three scales refer to how the data is transformed for the model. The normal scale assumes the data is normally distributed (bell curve), the odds scales focuses on the probability of an event happening relative to it not happening, and the hazards scale models the risk of the event occurring at a specific time point.

4.2.6.2.4 Assumptions and model fit

The selection of the models used in the economic base case was based on a few factors listed in CS Document B, Section B.3.3.2, including an assessment of proportional hazards using Schoenfeld's residuals, time-dependent hazard ratio and cumulative hazard plots, visual fit to the Kaplan-Meier plot, and goodness-of-fit statistics (Akaike information criterion (AIC) and Bayesian information criterion (BIC)). Additionally, the underlying hazard functions and the clinical plausibility of the extrapolated outcomes were evaluated. Other good-fitting models were included in scenario analyses.

The company clarified in Clarification question C6 that all analyses were conducted using the 'flexsurv' package in R.

4.2.6.3 Company's chosen models

The chosen models for the company's economic base case are described and justified in Table 41 of the CS, and is discussed in this section.

For each outcome, different models were fitted for the intervention and control groups. Since there is evidence that the proportional hazards assumption is violated, and due to the reasons stated by the company, this seems a sensible approach. Fitting different models for each treatment group lets you capture the different shapes of the survival curves between groups, particularly so when they exhibit varying hazards over time.

4.2.6.3.1 PFS

The company selected the [redacted] model using the cut-off at [redacted] weeks for the pembrolizumab group, and the [redacted] for the CT only group.

In terms of visual fit, the [redacted] and look to be unrealistic given the almost 200 weeks of PFS data from KEYNOTE-868 (NRG-GY018). The two-piece models look to be a better fit to the observed data but go below the KM data, except for the [redacted] model which initially looks in line with the KM data, but then stays constant throughout, which is unrealistic. The [redacted] is the next model which has the highest PFS estimates after the [redacted]. As for the spline models, the [redacted] underestimate long-term PFS considerable, while the other six models look to be a better fit. The CT only group tells a similar story, except that the spline models are more together and seem more plausible when assessed visually.

The [redacted] had the third-lowest AIC and BIC, after the [redacted] and [redacted], however both AIC and BIC were within five of the lowest AIC and BIC, suggesting no significant difference.

It should be noted that the company presented the average of AIC and BIC as well, applying an equal weighting between the two. This did not have a huge effect on the conclusions in this submission but in general is not appropriate as AIC and BIC are distinct model selection criteria with different goals and different penalties for model complexity. While AIC has a fixed penalty for each additional parameter, the BIC penalty increases as sample size increases (log(n)). Thus, BIC will favour more parsimonious models as sample size increases compared to AIC.

The company justified the choice of the [redacted] in the pembrolizumab group by stating “clinical plausible with landmark estimates in line with UK clinical experts’” and similarly for the [redacted] in the CT only group.

In the pembrolizumab group, all of the [redacted] provide closer estimates to the experts with the [redacted] providing the closest estimates to the experts, thus the [redacted] would be at-best the seventh best model.

For the CT only group, there are different criterions to compare the estimates to, therefore choosing the best model in terms of survival estimates is trickier. However, the model which provides the best estimates is likely to be [redacted] first and then the [redacted], and then the company's chosen model, the [redacted] However, all four of these models provide close estimates, unlike in the pembrolizumab arm where estimates are not very close, suggesting that the chosen model for pembrolizumab may not accurately reflect expected patient outcomes and could potentially misinform clinical or policy decisions if adopted without further validation against expert assessments.

4.2.6.3.2 OS

The company selected the 3-knot spline model on the odds scale model for the pembrolizumab group, and the standard log-logistic model for the CT only group.

The standard parametric models fit the observed KM data well when overlayed and only after the study period do the curves drastically change in terms of long-term estimates. This applies to both treatment groups.

The company only presented the plots for the piecewise and spline models for the pembrolizumab + CT group as the parametric models were deemed a good-enough fit alone. The piecewise models also fit the KM data well, and only after the study period do we see large deviations in estimates. The Gompertz being the most optimistic and the gamma and exponential models being the most pessimistic for OS. The spline models were the same also, with the 1-knot hazard models being very pessimistic.

The chosen model, 3-knot odds, had an AIC only three more than the lowest AIC which is from the 1-knot normal model. However, its BIC was 11 more than the lowest BIC, also from the 1-knot normal model, which signifies a significant difference.[52] If AIC was the key criterion used for statistical fit, then the choice of the 3-knot odds model is justified. If BIC was the key, then it should not be chosen based on statistical fit alone. As mentioned above, the equal weighting of AIC and BIC should not be done.

For the pembrolizumab group, the expected OS probabilities vary considerably between the two experts. For example, the 5-year expected OS from the TA963 is 59%, the same percentage from the weighted average of dMMR with PD-1 inhibitor

+ CT and pMMR with CT only at 2-years (CS Table 40). Plus, the 20-year OS estimate from TA963 is 38%, more than the 5-year estimate of the weighted average estimates at 27%, a full 15-year gap. Therefore, choosing which expert to conform to is a delicate matter and should be subjected to a consensus of other independent experts.

Most of the models provide landmark estimates somewhere between the estimates provided by both experts, so it is conceivable that multiple models are a good fit when using the long-term estimates as a criterion, this includes the chosen 3-knot odds model which provides plausible estimates.

For the CT model, the chosen log-logistic model produces estimates inline with the experts, although the 10 and 20 year estimates are lower, this is the case for the exponential and log-normal models. It could be argued that any of these three models are the best fitting in this criterion.

4.2.6.3.3 Scenario analysis models

The company also tested different survival curves in scenario analyses which are presented in CS Document B, Table 65, and have provided the justification for these scenarios therein.

One scenario for PFS:

- Pembrolizumab: [redacted]; CT: [redacted]

The [redacted] of the pembrolizumab group has the second-lowest AIC and BIC from the piecewise models, but these values are lower than the base case model. The [redacted] model is slightly pessimistic compared to the base case model, but only by between [redacted]% in each estimate.

The [redacted] for the CT group has the third-lowest AIC and BIC in the two-piece models, and is slightly more optimistic compared to the base case model, [redacted], between [redacted]% higher.

Five scenarios for OS:

- Pembrolizumab: as base case; CT: standard generalised gamma

Compared to the log-logistic used in the company's base case, the generalised gamma model had a similar AIC but a slightly higher BIC (by six), indicating a similar statistical fit. The generalised gamma model is more pessimistic compared to the log-log model, estimating 1% survival at 20-years compared to 4%.

- Pembrolizumab: as base case; CT: standard log-normal

Compared to the log-logistic used in the company's base case, the log-normal model had a similar AIC and BIC, indicating a similar statistical fit. The log-normal model is more optimistic compared to the log-log model, estimating a 5% survival rate at 20-years compared to the 4% from the log-log model.

- Pembrolizumab: two-piece log-normal; CT: as base case

The two-piece log-normal model is more optimistic compared to the 3-knot odds model, estimating 18% survival at 20-years compared to 13%.

- Pembrolizumab: two-piece log-logistic; CT: as base case

The two-piece log-logistic model is slightly more pessimistic compared to the 3-knot odds model, estimating 12% survival at 20-years compared to 13%.

- Pembrolizumab: 2-knot odds; CT: as base case

Compared to the 3-knot odds model used in the company's base case, the 2-knot odds model had slightly lower AIC and BIC, indicating a similar, albiet slighltly better, statistical fit. The 2-knot odds model estimates a 1%-higher survival at 2-years but then estimates lower survival thereafter, ending with 10% survival at 20-years compared to 13% for the base case model.

For overall survival, the company compared a range of long-term survival extrapolations, models which esitmate both higher and lower OS comapred to the base case, which is a sensible approach. For progression-free survival, the company only explored more pessimistic estimates for the pembrolizumab arm and more optimistic estimates for the control arm, leaving out exploring more optimistic curves for the pembrolizumab arm and more pessimistic curves for the control arm.

There could be justification in erring on the side of caution by overestimating the responses control arm and underestimating those in the pembrolizumab arm as this leads to conservative, and potentially worse-case, estimates and avoids overstating

the potential benefit of pembrolizumab until its effects are seen in clinical practice. However a truly conservative analysis should explore the full spectrum of scenarios for both pembrolizumab + CT and CT only which will provide a more balanced view and allowing for a broader understanding of the comparative effectiveness of these treatments.

4.2.6.4 The EAG's survival analysis

In this section, the EAG details our modelling approach, which is consistent with the company's, and presents the main results and EAG's chosen models. The detailed survival modelling is presented in Appendix 2.

4.2.6.4.1 Receiving the data and digitising the Kaplan-Meier plots

Using Figure 5 and Figure 6 of the CS Document B, the EAG digitised the Kaplan-Meier plots for the all-comer PFS and OS outcomes, respectively, using the methods described by Guyot et al.[53] However, due to the nature of the presented figures, the digitising method was not wholly accurate. For example, for the PFS outcome there were [redacted] events in the pembrolizumab arm and [redacted] events in the control arm. Using the digitised figures, the EAG were only able to account for [redacted] and [redacted] PFS events in each group, respectively. Reasons as to why the KM plots were inadequate were the size of the censoring bars and the control arm being dashed instead of a solid line.

Therefore, the EAG requested new Kaplan-Meier plots for PFS and OS from the company in Clarification question C1 which were of a higher quality than what was already provided by the company in CS Document B, and the individualised Kaplan-Meier patient-data in Clarification question C2. In the company's clarification responses, the response was that they have already provided that data in the economic model, namely in the 'KM data' sheet which provides the proportion remaining at each cycle, with each cycle being a week, for PFS, OS, and TTD in the all-comer, pMMR, and dMMR populations.

Since the Kaplan-Meier survival data provided by the company is aggregated in weekly intervals, we only know the proportion of individuals surviving at the end of each week (week 1, week 2, etc.). When reconstructing individual patient data from this grouped data, we inevitably lose some level of precision. Specifically, individuals who die within the same week are treated as if they experienced the event at the

same time, without capturing the exact day of the event. It may not make a huge difference but weekly data aggregration can result in minor imprecision when reconstructing the KM Individual participant data (IPD) as it slightly reduces the fidelity of survival curves. It's not expected to have a large impact but does contribute to small discrepancies in survival estimates that could accumulate over time. Including this detail clarifies why the EAG prefers exact IPD for the most accurate reconstruction. This results in less accurate survival estimates compared to having the actual Individual participant data IPD, where each event would be recorded with its exact timing, and was preferred by the EAG.

Furthermore, attempting to reconstruct the OS data using the data provided in the 'KM data' sheet of the economic model looked visually similar to Figure 6 of the CS Document B, but resulted in too many observations being censored instead of dying in the pembrolizumab arm. For instance, there were 94 OS events in this arm. When reconstructing the data based on the 'KM data' sheet of the economic model, there were only 51 events while reconstructing based on digitising Figure 6 of Document B, there were 92 events in the reconstructed KM IPD dataset. The observed discrepancy likely results from the limitations of reconstructing exact patient event times from weekly data intervals, rather than an issue with the data provided. Since the aggregated data does not reflect individual patient events precisely, some events are counted as censored rather than deaths, which slightly underestimates the actual number of OS events in the pembrolizumab arm. While we documented this as a reconstruction limitation, we do not interpret it as a sign of incorrect data.

Therefore, PFS and TTD were reconstructed based on the 'KM data' sheet only. For OS, the pembrolizumab arm was reconstructed using the digitised pembrolizumab arm of CS Document B Figure 6 while the control arm was reconstructed using the 'KM data' sheet of the economic model.

4.2.6.4.2 EAG's preferred PFS model

Based on the EAG's experts and the company's expert estimates listed in Tables 34 and 35 of the CS, the EAG's preferred base case model is the same as the company's base case models for both the pembrolizumab and control arms.

The EAG also explored two scenario analyses for each treatment arm. These models were models with good fit to the experts' estimates and provide survival estimates either higher (optimistic) or lower (pessimistic) compared to the base case at 20 years. For the pembrolizumab arm, the scenario analysis models are the [redacted] and the [redacted]. For the control arm, the scenario analysis models are the [redacted] and the [redacted]*Pembrolizumab arm*

Figure 2 plots the six best-fitting models to the pembrolizumab arm of the observed Kaplan-Meier data. Over the trial period, the models closely follow the observed KM line and start to diverge after around 30 months. Figure 3 shows how these models predict PFS up to 20 years, and there is a clear difference in PFS estimates in the long-term.

Figure 2. Visual fit of the six best-fitting models in the EAG's survival analysis for PFS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the pembrolizumab arm only

Figure 3. Visual fit of the six best-fitting models in the EAG's survival analysis for PFS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the pembrolizumab arm only

Table 8 compares different survival models for projecting progression-free survival rates at 2, 5, 10, and 20 years for endometrial cancer patients treated with pembrolizumab plus chemotherapy. These are evaluated against the expert benchmark estimates from NICE TA963 for an alternative treatment (dostarlimab plus chemotherapy) used in the company submission.

Using mean average error (MAE), where the average difference between modelled estimates and the NICE TA963 experts' expectations, the EAG ranked the models from 1=best to 7=worst, where the lower values of MAE were ranked better. The best models based on MAE were the [redacted], and then the [redacted]. The company's chosen model, based on MAE of their reported extrapolations, is [redacted] best.

It needs to be noted that the NICE TA963 and EAG advisor's mean shown in the first row specifically for 1L dMMR EC patients receiving dostarlimab + chemotherapy (CT). This subgroup is expected to have better outcomes because dMMR tumors tend to respond more favourably to immunotherapies. The modelled estimates apply to a broader dataset that includes both dMMR and pMMR patients. Therefore, it is crucial to account for the differences in patient population and treatment specificity.

Table 8: Comparison of long-term PFS extrapolations between the EAG's potential models and the company's base case in the pembrolizumab + CT arm

Pembrolizumab + CT	**2 years**	**5 years**	**10 years**	**20 years**
NICE TA963 company and EAG advisors' mean for 1L dMMR EC patients receiving dostarlimab + CT	60.0	42.0%	33.0%	27.0%
EAG				
Two-piece log-logistic with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece generalised gamma with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
Company				
Two-piece log-normal with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]

CT only

Figure 4 plots the six best-fitting models to the control arm of the observed Kaplan-Meier data. Over the trial period, the models closely follow the observed KM line and start to diverge after near the end of KEYNOTE-868 (NRG-GY018) follow-up. Figure 5 shows how these models predict PFS up to 20 years, and there is a clear difference in PFS estimates in the long-term.

Figure 4. Visual fit of the five best-fitting models in the EAG's survival analysis for PFS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the control arm only

Figure 5. Visual fit of the five best-fitting models in the EAG's survival analysis for PFS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the control arm only

Using MAE in the extrapolations presented in Table 9 where the average difference between modelled estimates and the NICE TA963 experts' expectations, the best-ranked models were the [redacted] and then the [redacted]. Using the NICE TA963 expectations, the

best-ranked models were the [redacted] and then the [redacted]. However, the issues with the NICE TA963 estimates have been previously mentioned. The EAG's clinical experts believe the clinical experts' estimates via weighted calculation to be appropriate criterion of the two.

Table 9: Comparison of long-term PFS extrapolations between the EAG's potential models and the company's base case in the placebo + CT arm

Placebo + CT	**2 years**	**5 years**	**10 years**	**20 years**
Company's clinical expert – weighted calculation of estimates for all-comers	11.0%	3-5%	2-3%	
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	23.0%	9.0%	7.0%	6.0%
EAG				
Two-piece log-logistic with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log- logistic with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
Company				
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]

4.2.6.4.3 EAG's preferred OS model

Based on the EAG's experts and the company's estimates listed in Tables 38 and 39 of the CS, the EAG's preferred base case model is the two-piece log-logistic model with a 9.4-week data cut for the pembrolizumab arm, and the same model as the company's base case model for the control arm.

The EAG also explored two scenario analyses for each treatment arm. These were the two-piece log-normal model with 40-week data cut and the 1-knot odds model for the pembrolizumab arm, and the 1-knot odds and 1-knot normal model for the control arm.

Pembrolizumab

Figure 6 and Figure 7 present the potential models chosen by the EAG to model long-term OS using the data from the pembrolizumab arm of KEYNOTE-868 (NRG-GY018), and how the company's chosen model compares (in purple). Near the end of KEYNOTE-868 (NRG-GY018), all the fitted models look to underestimate OS, however this may be due to the plateau after around 30 months. When considering the model estimates over 20 years, the two-stage log-normal model with a 40-week cut is the most optimistic while the two spline models are the most pessimistic. The company's chosen model sits in between the two extremes.

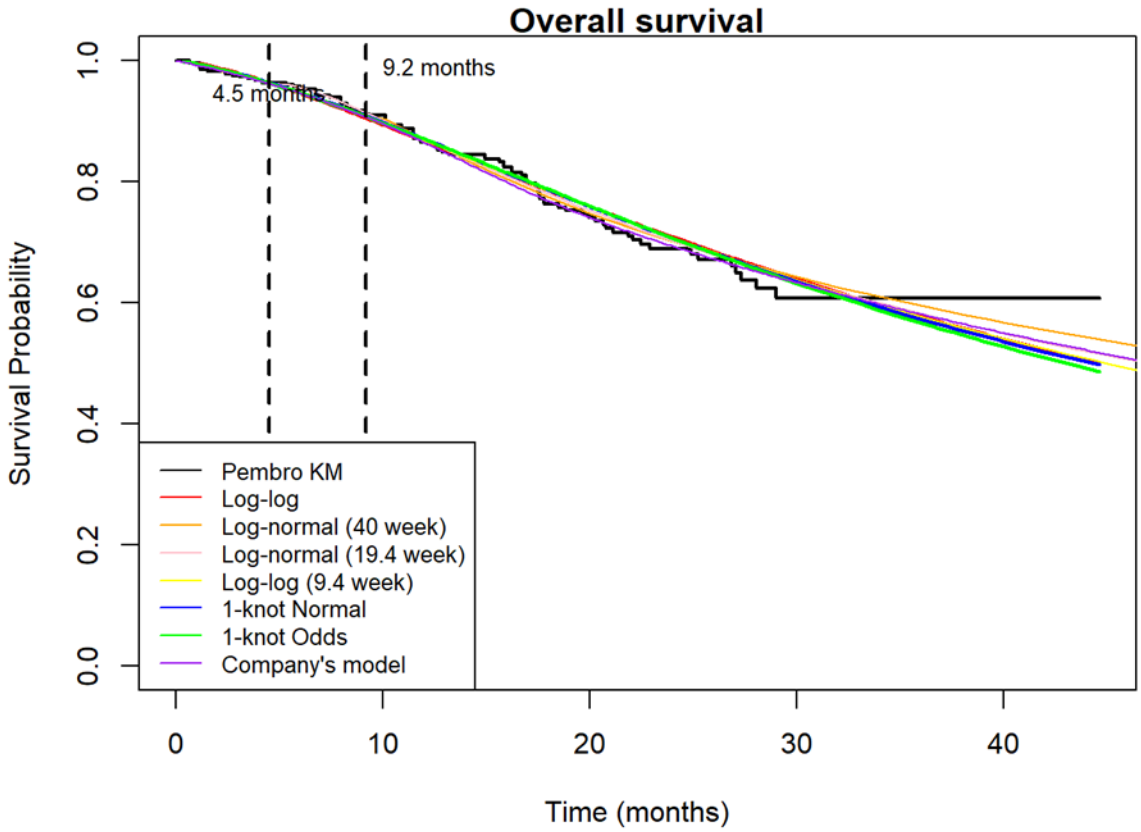


Figure 6. Visual fit of the six best-fitting models in the EAG's survival analysis for OS over the trial period of KEYNOTE-868 (NRG-GY018) (3-knot odds was the company's chosen model) for the pembrolizumab arm only

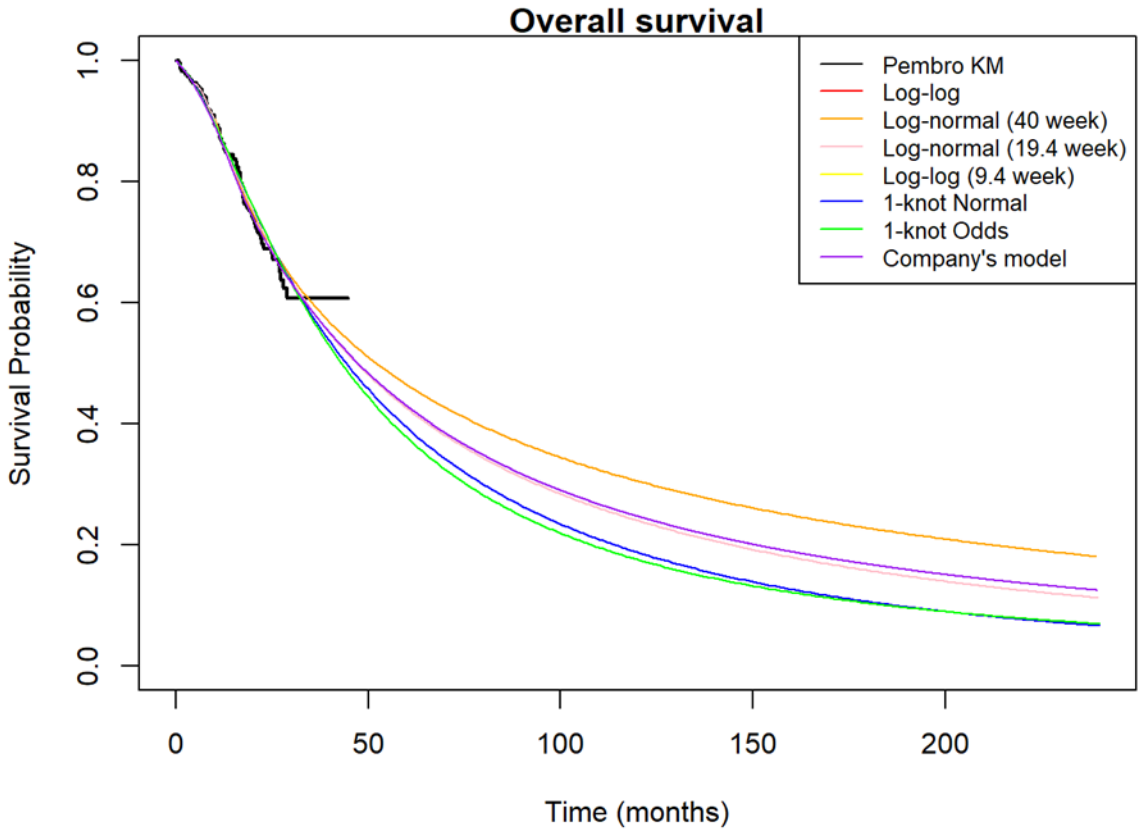


Figure 7. Visual fit of the six best-fitting models in the EAG's survival analysis for OS over 240 weeks (3-knot odds was the company's chosen model) for the pembrolizumab arm only

Table 10 presents the milestone OS estimates and compares them to two sets of experts presented in the company submission. The company's chosen model, the 3-knot odds model, provides the second-closest estimates for the first experts' OS estimates, however this is based solely on dMMR patients, and sixth-best for the weighted average estimate. The log-normal model with a 40-week cut provides the closest estimates for the first set of experts' estimates, and the log-logistic model with 9.4-week cut for the second set.

Table 10: Comparison of long-term OS extrapolations between the EAG's potential models and the company's base case in the pembrolizumab arm

Pembrolizumab + CT	2 years	5 years	10 years	20 years
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving PD-1 Inhibitor + CT	82%	59%	46%	38%
Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR	59%	27%	16%	10%

with CT only (from company's clinical experts)				
EAG				
Log-logistic	70.9%	39.8%	19.7%	8.4%
Log-normal model with 40.0-week cut	74.2%	51.8%	35.0%	21.1
Log-normal model with 19.4-week cut	70.5%	43.7%	25.1%	11.9%
Log- logistic model with 9.4-week cut	70.6%	40.4%	20.9%	9.4%
1-knot normal spline	70.7%	39.4%	18.8%	6.7%
1-knot odds spline	70.7%	37.8%	17.6%	7.0%
Company				
3-knot odds spline	69%	43%	25%	13%

CT only

Figure 8 and Figure 9 shows how the models estimate OS in the control group of KEYNOTE-868 (NRG-GY018). Due to the limited number of participants near the end of the study, the steps in the KM plot are more pronounced, and thus by the end of the study the fitted survival models look to overestimate OS. By 240 weeks, there is a range of OS estimates between the models where some models predict almost no survivors, while other models estimate at least a few survivors.

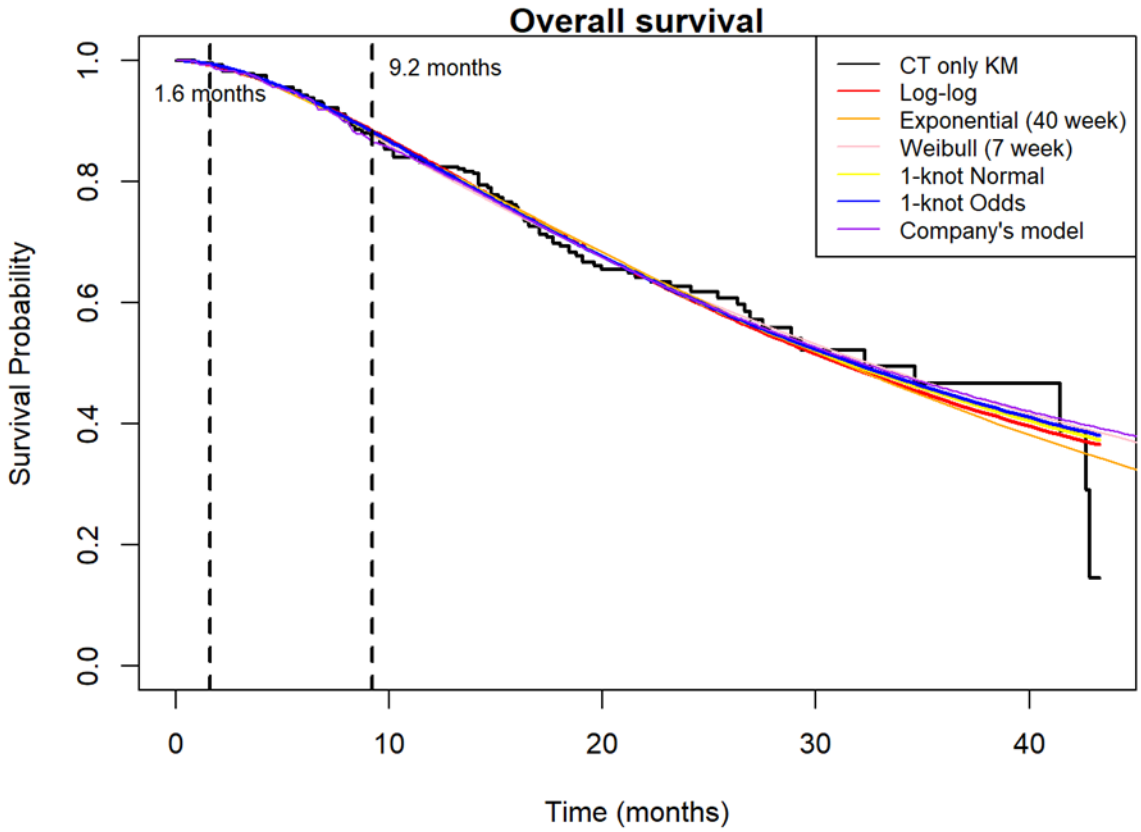


Figure 8. Visual fit of the five best-fitting models in the EAG's survival analysis for OS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the control arm only

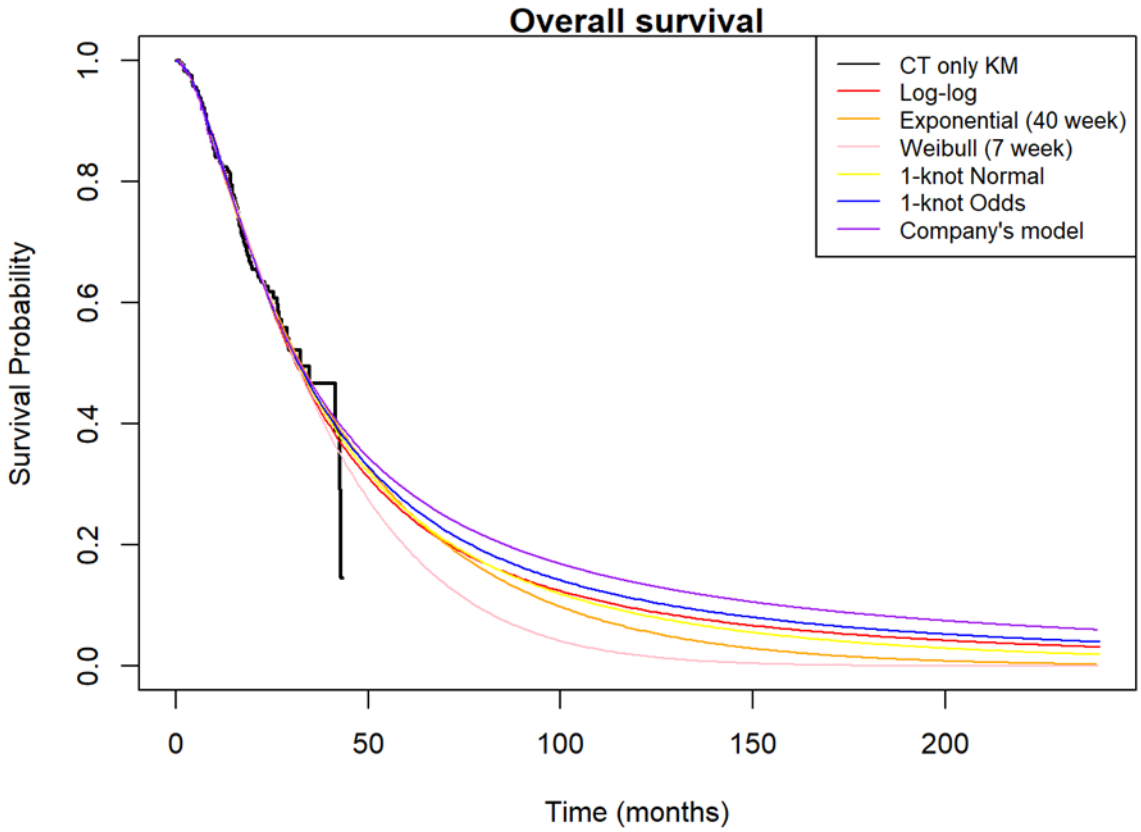


Figure 9. Visual fit of the five best-fitting models in the EAG's survival analysis for OS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the CT only arm only

Table 11 provides the estimates OS in the control arm between the EAG's possible chosen model and the company's base case. The model whose estimates are most aligned with the first set of experts (in the first row of the table) is the 1-knot normal spline model, and the model most aligned with the second set of experts is the 1-knot odds spline model.

Table 11: Comparison of long-term OS extrapolations between the EAG's potential models and the company's base case in the control arm

Placebo + CT	**2 years**	**5 years**	**10 years**	**20 years**
Company's Clinical Expert – weighted calculation of estimates for all-comers	54-57%	21-25%	9%	-
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	58%	30%	17%	13%
EAG				
Log-logistic	60.7%	25.0%	9.5%	3.2%

Exponential model with 40-week cut	56.3%	28.9%	9.5%	1.0%
Weibull model with 7-week cut	61.0%	15.3%	0.6%	0.0%
1-knot normal spline	60.9%	25.6%	8.7%	1.9%
1-knot odds splines	61.0%	27.0%	11.1	4.0%
Company				
Log-logistic	61%	26%	10%	4%

4.2.6.4.4 EAG's preferred TTD model

The company also included time to treatment discontinuation in the economic model. Since the Kaplan-Meier data is available up to the end of the pembrolizumab treatment period, the company used these estimates to inform the economic model as no future TTD extrapolations are necessary. Furthermore, the observed data realistically reflects the different treatment discontinuation dynamics that were observed in KEYNOTE-868 (NRG-GY018).

The EAG agreed with this approach and considered the KM data for TTD as the base case. As a sensitivity analysis, the EAG also fit smooth parametric curves to each treatment group as KM estimates are stepwise, with more pronounced steps near the end of the study when the sample size has decreased due to attrition. Parametric models provide a smoother representation, which can help reduce variability near the end of the study.

Therefore, the EAG's base case is the KM estimates, and the Gompertz model for the pembrolizumab arm and the gamma model for the CT only arm is included as a sensitivity. These models were chosen based on visual and statistical fit only.

4.2.6.5 Survival modelling summary

Table 12 summarises the EAG's chosen base case and scenario models, justification for the choice of these models and the long-term survival estimates up to 20 years.

Table 12: EAG's chosen models and milestone survival estimates

Outcome	Group	Model type	Chosen model	Justification	2-year	5-year	10-year	20-year
PFS	Pembro	Base case	(Company's) Two-piece log-normal with [redacted] cut	Best fitting model to long-term estimates that were chosen by EAG experts	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 1	3-knot odds	Best overall fitting model to both set of experts and more optimistic compared to the base case	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 2	Two-piece log-normal with [redacted] cut	Only model more pessimistic compared to the base case, decent fit	[redacted]	[redacted]	[redacted]	[redacted]
	CT	Base case	(Company's) 1-knot hazards spline	Best fitting model to long-term estimates that were chosen by EAG experts	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 1	1-knot odds	Best overall fit, slightly more pessimistic compared to the base case with similar OS at the end	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario 2	Two-piece log-logistic with [redacted] cut	Preferred by experts, more optimistic	[redacted]	[redacted]	[redacted]	[redacted]
OS	Pembro	Base case	Log- logistic model with 9.4-week cut	Best fitting model to long-term estimates that were chosen by EAG experts	68.10%	39.00%	20.20%	9.00%
		Scenario 1	Log-normal model with 40.0-week cut	Best fitting overall, more optimistic	61.70%	43.00%	29.10%	17.50%

		Scenario 2	1-knot odds spline	Decent fit, more pessimistic	70.70%	37.80%	17.60%	7.00%
	CT	Base case	(Company's) Log-logistic	Preferred by EAG experts	61.00%	26.00%	10.00%	4.00%
		Scenario 1	1-knot odds splines	Good fit according to EAG experts, more optimistic	61.00%	27.00%	11.10%	4.00%
		Scenario 2	1-knot normal spline	Good fit according to EAG experts, more pessimistic	60.90%	25.60%	8.70%	1.90%
TTD	Pembro	Base case	(Company's) KM data	Long-term extrapolations not needed as both arms available for treatment period	NA	NA	NA	NA
		Scenario 1	Gompertz	Best statistical fit	NA	NA	NA	NA
	CT	Base case	(Company's) KM data	Long-term extrapolations not needed as both arms available for treatment period	NA	NA	NA	NA
		Scenario 1	Gamma	Best statistical fit	NA	NA	NA	NA

4.2.7 Health related quality of life

As outlined in section 3.2.3.6, KEYNOTE-868 (NRG-GY018) assessed HRQoL using several PRO instruments including FACT-En-TOI, FACT/Gynecologic Oncology Group-Neurotoxicity (GOG-NTX), PROMIS-Fatigue Scale (short form), and PROMIS-Physical Function Scale (short form) in the pMMR subgroup only. Given that there was no EQ-5D data available from the trial, health state utilities were derived from alternative data sources for this appraisal. The health state utility values and AE disutilities applied in the CEM are summarised in Table 13 and Table 14.

4.2.7.1 Summary of company's base case approach

In the base case analysis, the company used health state utilities based on progression status (PFS or PD). Grade 3+ adverse event-related disutilities occurring in more than 5% of patients and age-related utility decrements were applied to the utility estimates.

On pg. 129 CS Document B, the company stated that the health state utility values were based on EQ-5D-3L data taken from [redacted] patients in the endometrial cancer subgroup in KEYNOTE-158 and analysed using a UK value set. [54] Although it was not referenced in the company submission, the EAG assumes that the 3L value set currently recommended by NICE was used to convert the responses into utility scores.[55] The company assumed that the health state utility values from KEYNOTE-158 would likely underestimate the QoL of patients in the pivotal trial, given that KEYNOTE-158 patients had failed a prior line of standard therapy and their HRQoL is expected to decrease as they move from 1L to 2L therapy.

The EAG notes that the statistical methods for deriving the utility values from KEYNOTE-158 are limited. Estimating base-case utilities from a small sample of [redacted] patients is challenging and may limit the robustness of the economic model. A sample of this size has limited generalisability, as individual variations can heavily influence mean utility scores, making them less representative of the broader population. Additionally, small sample sizes are statistically unstable, with wide confidence intervals that could lead to under- or overestimated utility values, thereby affecting the accuracy of the model. Sampling bias is also a risk, as a small group may not reflect the characteristics and quality-of-life scores of a larger, more representative patient

population. Thus, while it provides preliminary estimates, the sample size may be insufficient for deriving reliable utility values.

Beyond descriptive analysis, the company could have applied several statistical methods to derive more robust utility estimates. Mixed-effects modelling, for example, can account for intra-patient variability and improve reliability in small samples by capturing individual differences. Bayesian methods could incorporate data from similar populations to stabilise estimates, and bootstrapping could generate confidence intervals to better understand the estimate's variability. Regression-based mapping from other HRQoL measures or multiple imputation for missing data could further strengthen the utility values used in the model, particularly given the limited sample size. However, MSD explored a range of alternative utility sources in scenario analyses to mitigate the uncertainty from the small sample size.

A utility value of [redacted] was applied to the progression-free health state and a value of [redacted] was applied to the progressed disease health state. In the economic model, QALY estimates were obtained in each cycle by multiplying the health state utility weights to the corresponding health state occupancy and then applying the cycle discount rate.

Table 13: EQ-5D-3L values used in CEM

Health state	(N=[redacted]) Mean (SE)	95% CI	Source
Progression-free	[redacted]	[redacted]	KEYNOTE-158
Progressed	[redacted]	[redacted]	KEYNOTE-158

Source: Table 42, pg.130, CS document B

In the CEM, the company included a one-off AE utility decrement associated with grade 3+ AEs with an incidence of >5% in the pivotal trial, citing previous oncology STAs as justification for using this approach.[24, 56] The company considered the average number of AE events per subject to "*accurately capture the impact of AEs*" and assumed AEs occur immediately following treatment and require only acute care.[27, 56, 57] The disutility was calculated as the "*product of the incidence rate, disutility associated with the AE and duration of the AE*" and applied as a one-off QALY decrement in the first cycle of the model, resulting in a QALY loss of [redacted] for patients in the Pembrolizumab +CT arm versus [redacted] for patients in the CT arm. The utility

estimates were adjusted by age to account for the natural decline in QoL using the general female population utility values from Hernández Alava et al.[58]

Table 14: Adverse event disutilities used in CEM

Adverse Event	Disutility	Source (disutility)
Neutrophil count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
White blood cell count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Lymphocyte count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Hypertension	-0.02	NICE TA963
Anaemia	-0.119	NICE TA963

Source: Table 46, pg.137, CS document B

EAG comments:

The EAG considers using the progression status approach rather than the time-to-death approach to be in line with best practice however, they would have preferred that health state utilities be estimated directly from the pivotal trial data, particularly given that KEYNOTE-158 only recruited MSI-H/dMMR endometrial cancer patients, which accounts for just 27% of KEYNOTE-868 (NRG-GY018) participants and had a smaller sample size of [redacted] participants. In response to clarification question B3, the company provided the baseline characteristics for KEYNOTE-158 endometrial cancer patients, confirming that there were differences between the two populations. Patients in KEYNOTE-158 were slightly younger (mean age of [redacted]), had a lower average weight ([redacted] and BSA ([redacted]). Clinical advice to the EAG suggests that despite KEYNOTE-158 recruiting a younger subgroup, participants were receiving 2L therapy due to having progressed disease, which may have contributed to a decline in their QoL.

The EAG questioned why patients in the pMMR subgroup should be assumed to have the same QoL as patients in the dMMR subgroup, given that treatment response could be influenced by MMR status. Clinical advice to the EAG agreed that there could be differences in the HRQoL of pMMR and dMMR cohort, as there is a *higher response*

rate to treatment with dMMR and they will likely be on treatment for longer. In addition, *pMMR endometrial cancer does not respond as well to immunotherapy so one might assume that this cohort will have a less good quality of life as they are more likely to have active/progressive disease*. Several trials have shown that IOs have limited efficacy in the pMMR population, with higher ORRs observed in dMMR compared to pMMR patients.[59-61] Clinical advice to the EAG in TA904 also indicated that prognosis and treatment are likely to vary for patients based on their MMR status.[24]

The EAG also sought clarification on whether separate utility values were considered for people in a progression-free health state (on treatment) and those in a progression-free health state (off-treatment). The company confirmed that health utility values in the model did not separately consider PFS (on-treatment) from PFS (off-treatment) due to data paucity and stated that the "profiles of the pembrolizumab + CT group and the placebo + CT group in KEYNOTE-868 (NRG-GY018) were comparable, indicating that most AEs are driven by the CT portion of the combination treatment". The company assumed equal utility benefit whether on or off treatment, with the justification that it was accepted in TA963, a recent STA in the 1L EC population. Clinical advice to the EAG acknowledges that although "*most of the haematological toxicity is driven by chemotherapy, important toxicity as AKI, diarrhoea, glycemia and abnormal liver function is driven by IO*".

Following clarification with the company, the EAG noted that there were [redacted] patients in the endometrial cancer subgroup that had received 1 prior line of therapy in KEYNOTE-158 however, as per pg.129 CS Document B, only [redacted] were included in the utility analysis.

Overall, the EAG is satisfied with how the progression-based utilities, AE and age-related disutilities were applied in the model

4.2.7.2 Summary of company's scenario analyses

The company explored several scenario analyses using EQ-5D data from KEYNOTE-826[62] and KEYNOTE-775. KEYNOTE-826 assessed pembrolizumab + CT versus CT

as 1L therapy in treating patients with untreated persistent, recurrent or metastatic cervical cancer. KEYNOTE-775 examined the use of pembrolizumab in combination with lenvatinib for previously-treated advanced EC.

In one scenario, the company estimated progression-based utilities from KEYNOTE-826 by mapping ED-5D-5L data from [redacted] patients to EQ-5D-3L using the mapping function from Hernandez Alava, in accordance with NICE guidance.[63, 64] Mixed linear effects regression models were fitted including variables such as the mapped utility estimates, progression status, presence of grade 3+ adverse events, and treatment group and the model with the lowest AIC was selected as the final model. The analyses were conducted using 7228 EQ-5D records from [redacted] patients. In another scenario, the company used time-to-death utilities from KEYNOTE-826, calculated as the time between the EQ-5D observation and the time of death. Time-to-death utilities collected in KEYNOTE-158 from the EC patient subgroup who received prior 1L therapy were not explored in a scenario analysis, with the justification that they were unable to perform a robust regression analysis due to a lack of sufficient statistical power in the EC cohort. Additional scenario analyses involved using EQ-5D scores from KEYNOTE-775 to derive utility progression-based utility estimates based on an Australian and Swedish scoring algorithm.[65, 66] The scenario analyses utility values are summarised in Table 15.

Table 15: Summary of utility values for scenario analyses

Source	State	Utility value: mean (SE)	Reference
Time-to-death utilities	360+ days	[redacted]	**KEYNOTE-826**
	180-359 days	[redacted]	
	90-179 days	[redacted]	
	30-89 days	[redacted]	
	<30 days	[redacted]	
Progression-based utilities	Progression-free	[redacted]	
	Progressed	[redacted]	
	Progression-free	0.736	**PBAC_Pembrolizumab 2022[101]/KEYNOTE-775**
	Progressed	0.700	
	Progression-free	0.851	

	Progressed	0.817	**Ralph 2024[102]/KEYNOTE-775**

Source: Table 48, pg.139, CS document B

4.2.7.3 Alternative methods considered for calculating health-state utilities

1. *Mapping health-reported patient outcomes from KEYNOTE-868(NRG-GY018) to EQ-5D*

As patient EQ-5D-3L data was not collected in the pivotal KEYNOTE-868 (NRG-GY018) trial, the company explored alternative methods for identifying appropriate utility data to be used in the appraisal. Mapping patient-reported health outcomes collected in the trial to EQ-5D-3L was one of the approaches the company explored for identifying potential utility values. The company conducted a targeted literature review to identify existing validated mapping algorithms integrating the QoL instruments collected in the trial and EQ-5D however, they were unable to find an appropriate algorithm. The EAG conducted a search for mapping algorithms and can confirm that there is no appropriate algorithm available for this purpose.

2. *Literature search for utility values*

The company has access to unpublished utility values from KEYNOTE-775 (pembrolizumab + lenvatinib for previously treated advanced EC) however, they state that this data cannot be made available for this appraisal due to contractual obligations with a third party. In a targeted literature search, the EAG identified an additional cost-effectiveness study of pembrolizumab for previously treated MSI-H/dMMR solid tumours in the UK. This study was not included in the HRQoL publications summary table in Appendix H, despite citing utility values derived from KEYNOTE-158, the same trial the company used to estimate base case utility values. Notably, the company's utility values for stable and progressed disease are higher than those reported in the paper. This difference may be explained by the fact the company's values relate specifically to patients who had received only 1 prior line of therapy, while the study included patients with 1 or more lines of therapy, and therefore may have further

progressed disease. Since the paper does not provide sufficient detail on how these utilities were derived, the values were not included in the EAG's preferred assumptions and are instead explored only in scenario analyses.[44]

4.2.8 Resources and costs

Cost evaluation in the model was based on cost of the technology (Pembrolizumab + CT) and its comparator (Placebo + CT). Costs included drug acquisition and administration costs, treatment-related costs (subsequent treatments, adverse events, and terminal care costs) and resource utilisation costs in each health state. Costing was conducted from the perspective of the NHS and PSS.

4.2.8.1 Intervention and comparators costs

The primary treatment costs were calculated for Pembrolizumab + CT, and the Placebo + CT based on the drug acquisition cost per dose and the administration costs. The dosing schedule for Pembrolizumab + CT was applied in the model according to the anticipated European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation and the KEYNOTE-868 (NRG-GY018) trial protocol. Carboplatin and Paclitaxel were implemented in the model as per their licenced dose. A body surface area (BSA) of [redacted] m^2 which is the average mean baseline characteristics of the patients in the KEYNOTE-868 (NRG-GY018) was used to calculate the dose of Paclitaxel. The list price of £2,630 per 100mg for Pembrolizumab was obtained from the British National Formulary (BNF)[67] and that of Paclitaxel (£24.23/300mg, £3.88/30mg) and Carboplatin (£48.09/450mg, £20.22/150mg) were obtained from the electronic market information tool (eMIT).[68]

In the model, the company applied the unit cost of the best vial options for each drug that makes up the dose per cycle of treatment and assumed no vial sharing. For example, carboplatin comes in unit packs of 1000mg, 600mg, 450mg, 150mg, and 50mg. The company used 2 vials of 150mg and 1 vi
al of 450mg to obtain the dose of 750mg of carboplatin required per cycle. A commercial access agreement (CAA) is in place for pembrolizumab and was applied

in the model (details are provided in CS document B, Appendix K). The drug acquisition costs, and administration costs were calculated for patients in each arm based on the modelled time on treatment (TOT) that was observed in the KEYNOTE-868 (NRG-GY018) trial. The costs were estimated per component, considering the relative dose intensity (RDI) of each component per treatment as obtained from the trial. The RDI was applied to the drug acquisition costs to account for interruptions and reductions in treatment doses per cycle. Table 16 and Table 17 (obtained from Table 49, 50 and 51 CS Document B) below shows the dosing regimen, and the drug acquisition costs for pembrolizumab + CT and CT + placebo respectively. There was an error with the costs per cycle for initial treatment with pembrolizumab + CT (£5,056 instead of £5,068) and carboplatin + paclitaxel (£106 instead of £118.90) in CS (Table 51). The EAG noted that the costs were applied correctly in the economic model and did not affect the results of the analysis.

Table 16: Dosage regimen and drug acquisition costs Pembrolizumab + CT

Drug	Dosage	Dosing frequency	Vial options	Unit costs	Costs per cycle	RDI	Reference
Initial treatment							
Pembrolizumab	200mg	Every 3 weeks (up to 6 cycles)	2 x 100mg	£2630 (without CAA)	£5,068	94.1%	BNF online Accessed 25/09/2024
Carboplatin	750mg	Every 3 weeks (up to 6 cycles)	2 x 150mg 1 x 450mg	£20.22 £48.09		98.1%	eMIT
Paclitaxel	175mg/m^2	Every 3 weeks (up to 6 cycles)	2 x 30mg 1 x 300mg	£3.88 £24.43		98%	eMIT
Maintenance							
Pembrolizumab	400mg	Every 6 weeks (from cycles 7-14)	4 x 100mg	£2630 (without CAA)	£9,899	94.1%	BNF online Accessed 25/09/2024
Source- Table 49, 50 & 51, CS document B pg. 141-142							

RDI, relative dose intensity; BNF, British national formulary; eMIT, electronic market information tool.

Table 17: Dosage regimen and drug acquisition costs Placebo + CT

Drug	Dosage	Dosing frequency	Vial options	Unit costs	Costs per cycle	RDI	Reference
Carboplatin	750mg	Every 3 weeks (up to 6 cycles)	2 x 150mg 1 x 450mg	£20.22 £48.09	£118.90	98.6%	eMIT
Paclitaxel	175mg/m^2	Every 3 weeks (up to 6 cycles)	2 x 30mg 1 x 300mg	£3.88 £24.43		98.2%	eMIT
Source- Table 49, 50 & 51, CS document B pg. 141-142							

RDI, relative dose intensity; BNF, British national formulary; eMIT, electronic market information tool.

In the economic model, the drug administration costs were accrued for the duration of treatment in both arms. The administration cost which is in line with the planned treatment schedule for each drug was sourced from the NHS reference cost 2022/23 (Table 18) (obtained from table 52 CS Document B).[69] A different cost was assigned for infusing monotherapy and for combination therapy. The company assigned the costs of simple chemotherapy to monotherapy with pembrolizumab and complex chemotherapy to combination therapy with pembrolizumab + CT and for CT alone. This was considered appropriate by the EAG. According to the compulsory Summary of Product Characteristics (SmPC) for paclitaxel, patients are administered corticosteroids, antihistamines and H_2 receptor antagonists as a prophylaxis against hypersensitivity reactions, but these pre- medication costs were eliminated in the model as they were applicable to both arms.

Table 18: Drug administration costs per cycle

Administration type	Cost per administration	Drug	Assumption	Reference

Complex chemotherapy	£277	Pembrolizumab + CT	Deliver more Complex Parenteral Chemotherapy at First Attendance, outpatient	NHS Reference costs 2022/23 (SB13Z)
	£277	CT alone		
Simple chemotherapy	£217	Pembrolizumab maintenance	Deliver Simple Parenteral Chemotherapy at First Attendance, outpatient	NHS Reference costs 2022/23 (SB12Z)
Source: Table 52 CS document B, pg. 143				

CT, chemotherapy

4.2.8.2 Costs of subsequent treatments

In the CS the patients receive further line of therapy following progression on any of the modelled treatments. This was calculated as a one-off cost on entry into the progressed diseased (PD) state in the model. The total average cost per patient of subsequent therapies is estimated by considering the proportion of patients receiving subsequent treatment, average time on treatment, the distribution of each subsequent treatment, drug acquisition and administration costs of each therapy. The CS stated that the proportion of patients receiving subsequent treatment were obtained from KEYNOTE-868 (NRG-GY018) trial and were adjusted/ validated by UK clinicians to account for records that reflects UK clinical practice. The EAG's clinical experts advised that giving pembrolizumab monotherapy as subsequent treatment is not standard UK practice. NICE has recently advised that pembrolizumab +Lenvatinib is a suitable second line treatment option for patients with advanced or recurring EC that have progressed during or after platinum-based chemotherapy.[24] For dMMR patients with advanced or recurrent endometrial cancer who have progressed after platinum-based treatment and are ineligible for curative surgery or radiotherapy, pembrolizumab monotherapy is another recommended option.[56] To explore uncertainty around the subsequent treatment mix, the EAG performed a scenario analysis where patients who were supposed to receive

pembrolizumab as per the company's model were all assigned to receive pembrolizumab + lenvatinib. The analysis led to a slight decrease in the company's base case ICER. The company performed a scenario analyses, exploring a scenario in which dostarlimab takes the place of pembrolizumab as a second-line treatment, and incorporating the treatment mix from trial that led to a decrease in the ICER in the first scenario and an increase in the second scenario.

Table 19 (obtained from Table 55 CS Document B) shows the mean duration (obtained from KEYNOTE-868 (NRG-GY018)) and the share of each subsequent treatment following progression on any of the modelled treatments. The EAG was uncertain about the duration measurement units in the CS, but the company incorporated the mean duration in days into the economic model.

The dose, frequency of administration, unit costs and how costs of each treatment was obtained per week are presented in Table 20 (obtained from Table 56 CS Document B) and the total cost of each drug regimen as used in the model are presented in Table 21 (obtained from CS model). The EAG observed discrepancies in the cost per weekly values of subsequent treatment report in the CS Document B (Table 56). For example, the cost of carboplatin per week was £26.72 instead of £29.51, costs of carboplatin + paclitaxel per week was £35.99 instead of £40.24, Doxorubicin was £9.49 instead of £10.71, and paclitaxel 80mg/m^{2}every week at £12.72 instead of 80mg/m^2 every three weeks at £5.63. On inspecting the model, the EAG saw that the correct values have been applied in the model and does not affect the results of the analysis.

Table 19: Duration and distribution of subsequent therapies

Subsequent treatment	**Pembrolizumab + CT**			**CT**	
	% share	**Mean duration in weeks**		**% share**	**Mean duration in weeks**
Carboplatin	1.65%	[redacted]		1.84%	[redacted]
Carboplatin +paclitaxel	14.31%	[redacted]		11.34%	[redacted]

Doxorubicin	13.69%	[redacted]		1.22%	[redacted]
Letrozole	7.31%	[redacted]		4.60%	[redacted]
Megestrol	0.00%	[redacted]		1.84%	[redacted]
Paclitaxel	8.27%	[redacted]		8.98%	[redacted]
Pembrolizumab	0.00%	[redacted]		16.76%	[redacted]
Pembrolizumab + Lenvatinib	0.00%	[redacted]		23.95%	[redacted]
Radiotherapy	23.06%	[redacted]		11.68%	[redacted]
No treatment	31.72%	[redacted]		17.78%	[redacted]
Source: Table 55 CS document B, pg. 148					

Table 20: Posology and cost per week of subsequent treatments

Subsequent treatment	Drug component	Dosage Strength	Dosage frequency	Vials/tabs used	Unit costs per vial, per tablet	Total cost per week	Reference
Carboplatin	Carboplatin	750mg IV	Every 3 weeks	2 x150mg 1 x 450mg	£20.22 £48.09	£29.51	eMIT
Carboplatin + paclitaxel	Carboplatin	750mg IV	Every 3 weeks	2 x150mg 1 x 450mg	£20.22 £48.09	£40.24	eMIT
	Paclitaxel	175mg/m^2 IV	Every 3 weeks	2 x 30mg 1x 300mg	£3.88 £24.43		
Doxorubicin	Doxorubicin	60mg/m^2 IV	Every 3 weeks	2 x 10mg 2 x 50mg	£3.91 £12.15	£10.71	eMIT
Letrozole	Letrozole	17.5mg PO	Every week	7 tabs x 2.5mg	£0.03	£0.22	eMIT
Megestrol	Megestrol	1,120mg PO	Every week	7tabs x 160mg	£0.65	£4.55	BNF
Paclitaxel	Paclitaxel	80mg/m^2 IV	Every 3 week	2 x30mg 1 x 100mg	£3.88 £9.13	£5.63	eMIT
Pembrolizumab monotherapy	Pembrolizumab	200mg IV	Every 3 weeks	2 x 100mg	£2630 (without CAA)	£1753.33	BNF online Accessed 25/09/2024
		400mg IV (maintenance dose)	Every 6 weeks	4 x 100mg		£1753.33	

Pembrolizumab+ Lenvatinib	Pembrolizumab	200mg	Every 3 weeks	2 x100mg	£2630 (without CAA)	£2,423.93	BNF online Accessed 25/09/2024
	Lenvatinib	140mg PO	Every week	14 x 10mg	£47.90		
	Pembrolizumab (maintenance)	400mg IV	Every 6 weeks	4 x 100mg	£2630 (without CAA)	£2,423.93	BNF online Accessed 25/09/2024
	Lenvatinib (maintenance)	140mg PO	Every week	14 x 10mg	£47.90		
Source: Table 56 CS document B, pg.149							

BNF, British National Formulary; eMITelectronic market information tool; CAA, Commercial Access Agreement; IV, Intravenous; PO, per os

Table 21: Total costs of subsequent treatment as used in the model

Subsequent treatment	Total cost of drug regimen
Carboplatin	[redacted]
Carboplatin + paclitaxel	[redacted]
Dostarlimab	[redacted]
Doxorubicin	[redacted]
Letrozole	[redacted]
Megestrol	[redacted]
Paclitaxel	[redacted]
Pembrolizumab	[redacted]
Pembrolizumab+ Lenvatinib	[redacted]
Radiotherapy	[redacted]
No treatment	[redacted]
Source: CS model work sheet, subsequent treatment costs	

4.2.8.3 Health state resource use and costs

The model assumed three health states for the patients; the progression free survival (PFS), progressed disease (PD) and death. In the model, the cost of managing the disease, monitoring and following up of the patients were included. Resource uses were assumed to differ between the PFS and PD states. Different resource use was also assumed depending on whether the patients were on treatment or off treatment in the PFS. To estimate the costs in each health state, unit costs were applied to the levels of resource used and values were summed up across all the resources in accordance with the time spent in the health state. The unit costs were sourced from the personal and social services research unit (PSSRU) or the NHS reference costs 2022/23.[70] As MMR testing is routinely performed in the NHS (NICE diagnostic guidance DG42)[21] for patients diagnosed of EC to detect tumours with dMMR, this resource use and costs were not included in the economic model (CS Document B, Section B.3.5.4 pg. 151).

The CS mentioned that resource levels for PFS and PD were determined by consulting clinical experts, utilising an advisory board, and conducting a manual search of HTAs in similar cancers. Clinical experts contacted by the EAG validated the items in the CS but faced difficulty confirming all frequencies. However, the clinical experts consulted by the EAG stated that patients undergo a series of blood

tests at the beginning of each chemotherapy cycle and patients on immunotherapy would in addition, have regular thyroid function and glucose levels tests to identify and treat any concerns of toxicity. This is further substantiated by literature.[71]

Since the company have excluded all immune related AEs (irAEs) like hyper/hypothyroidism and others resulting from electrolyte deficiency like hypokalaemia in their economic model (see Section 4.2.8.4) which have clinical and costs implications as informed by the EAG's clinical experts, the EAG has considered that the health resource use and costs of monitoring the patients in the pembrolizumab +CT are underestimated in the company's economic model. The EAG sought alternative sources, clinical experts' opinion and past HTAs to determine the resource use levels that would reflect use observed in clinical practice both on-treatment and off-treatment during the initial treatment phase and pembrolizumab maintenance phase. The values obtained by the EAG and the sources are presented in Table 22 and Table 23. Scenario analyses performed with these estimates increased the company's base case ICER by [redacted] for values sourced from clinical opinion and [redacted] for values obtained from TA963. For the TA963 data analysis, the company's base case values were maintained for the resource use off treatment.

Table 22 presents the resource use and Table 23 shows the costs used in the company's economic model associated with each health state. (obtained from table 54 CS Document B).

Table 22: Resource use for pembrolizumab +CT arm (PFS) obtained by the EAG

Health state	Resource	Frequency per week	Source	Frequency per week	Source
		Scenario 1		**Scenario 2**	
PFS (on treatment)	Blood tests	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.33 (up to cycle 18) 0.22 (cycle 19+)	TA963
	Outpatient visits	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.30 (up to cycle 18) 0.13 (cycle19+)	TA963
PFS (off treatment)	Blood tests	0.08	EAG clinical expert	0.17	Company base case

Health state	Resource	Frequency per week	Source	Frequency per week	Source
		Scenario 1		**Scenario 2**	
	Outpatient visits	0.08	EAG clinical expert	0.06	Company base case

EAG, External Assessment Group; PFS, progression-free survival

Table 23: Unit costs of resource use associated with model health states

Health State	Resource	Cost	Reference
PFS (on treatment) Pembrolizumab +CT	CT scan	£160.83	NHS Reference Costs 2022/23- RD22Z- CT scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	£179.00	NHS Reference Costs 2022/23: Gynaecological Oncology service - service code 503
	Blood test	£5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PFS (off treatment) Pembrolizumab + CT	CT scan	£160.83	NHS Reference Costs 2022/23: RD22Z- CT scan of one area, with pre and post contrast (outpatient)
	Outpatient visit	£179.00	NHS Reference Costs 2022/23: Gynaecological Oncology service - service code 503
	Blood test	£5.00	NHS Reference Costs 2022/23: Haematology (DAPS05) board
PFS (on treatment) CT	CT scan	£160.83	NHS Reference Costs 2022/23: RD22Z- CT scan of one area, with pre and post contrast (outpatient) board
	Outpatient visit	£179.00	NHS Reference Costs 2022/23: Gynaecological Oncology service - service code 503visory board
	Blood test	£5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)
PFS (off treatment) CT	CT scan	£160.83	NHS Reference Costs 2022/23: RD22Z- CT scan of one area, with pre and post contrast (outpatient)
	Outpatient	£179.00	NHS Reference Costs 2022/23: Gynaecological Oncology service - service code 503
	Blood test	£5.00	NHS Reference Costs 2022/23: Haematology (DAPS05)

CT, chemotherapy; CT scan, computed tomography; NHS, National Health Service; PD, progressed disease; PFS, progression-free survival

4.2.8.4 Treatment of adverse event costs

In the model, the costs of adverse event management were applied as a one-off cost in the first cycle. All adverse events (AEs) of grade 3+ that occur in greater than 5% of the patients in either arm of the KEYNOTE-868 (NRG-GY018) trial were included in the model. Anaemia and hypertension are the only AEs included. The costs of adverse events were estimated as a product of the rate of AE per subject, number of AE episodes per subject, and the cost of each AE episode. Unit cost for the adverse event episodes were obtained from the NHS reference costs 2022/23[69] and assumed to be the costs of a non-elective short stay (NES) and from the TA904 for Pembrolizumab with Lenvatinib in previously treated advanced or recurrent endometrial cancer.[24]

Table 24 (obtained from table 57 CS Document B) presents the unit costs of AE per episode. The EAG accepts the methodology, and the assumptions used to derive the AE cost per episode, however the CS reported adverse events of grade 3+ observe in ≥ 2% in all comer population but excluded the costs in their base case analysis not meeting the ≥ 5% criteria. This approach used by the company was considered by the EAG to have underestimated the costs of AEs observed in the patients. Supporting this, the EAG clinical advisors view immune-related AEs (irAEs) reported in ≥ 2% of the trial's all-comer population as toxicities that need clinical management. After considering exploratory analysis, the EAG sourced costs estimates for the additional AEs, and maintained the costs values already provided in the company's model (see Appendix: Supplementary table 30). The analysis showed that including these AEs in the model only minimally raised the company's base case ICER.

Table 24: Costs of adverse events of grade 3+ used in the model 26

Adverse Event	Cost per episode	Reference
Neutrophil count decreased	£0.00	NICE TA904
White blood cell counts decreased	£0.00	NICE TA904
Lymphocyte count decreased	£0.00	Assumed no cost
Anaemia	£565.40	NHS reference costs 2022/23: weighted average of SA03G, SA03H, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J, SA08G, SA08H, SA08J.
Hypertension	£735.07	NHS Reference costs 2022/23: EB04Z(NES)- Hypertension
Source: Table 57 CS Document B, pg. 151		

4.2.8.5 Terminal care costs

In the model, terminal care costs were included as a one-off cost at the end of a patient's life on entry into the death state. The cost reflects the costs of people in the last ninety days of life, and it was sourced from Georghiou et al, (2014).[72] This was estimated to be £7,287.99 from the sum of the costs of GP contacts, community nursing, local authority-funded social care and institutional hospice care and hospitals. The CS stated that this cost was an uprated value using 2023 PSSRU but the EAG noted that the uprated value differed from what the company has stated. At clarification, the company provided the uprated end-of-life cost of £8,829.07 (Clarification question B10). The EAG has updated the costs of terminal care in the model to reflect these costs.

4.2.8.6 EAG Summary and critique of the resource use and costs

The EAG deems the resource use, cost, assumptions made and their integration into the economic model as suitable. However, there were some issues of concern.

- First, considering that patients with EC undergo series of blood tests at the beginning of each chemotherapy cycle (EAG clinical expert's confirmation) and several other tests for patients on IO, the blood tests and outpatient visits frequency per week for patients who received the intervention was thought to have been underestimated in the model.
- Secondly, the CS stated that 16.76% of patients received pembrolizumab in the Placebo + CT arm as subsequent therapy but EAG's clinical expert confirmed that this is not a UK clinical practice. Patients given 1L chemotherapy do not receive immunotherapy monotherapy as subsequent treatment. There remains uncertainty around the 2L treatment as scenario analyses showed significant differences to the company's base case ICER.
- Thirdly, the CS included only AEs of grade 3+ observed in ≥ 5% in their base case analysis. The EAG's clinical advisor is of the opinion that the AEs of grade 3+ observed in ≥ 2% are also toxicities that should be considered when managing cancer patients especially the irAEs resulting from the use of Immunotherapies (IOs), however the CS has excluded these AEs which would have underestimated the costs of managing AEs in the economic model.
- Lastly, terminal costs were found not to have been uprated to 2023 by the company as stated in the CS. The company have used a value of £7,287.99 instead of £8,829.07. This was clarified by the company at the clarification stage, and it was agreed that the uprated terminal cost is £8,829.07. The end-of-life costs has been updated in the company's model.

4.2.8.7 EAG summary of the methods for identifying healthcare resource use and costs

The company performed a SLR to identify published studies on cost and HCRU in adult patients with advanced/recurrent EC with search strategy later updated to include early-stage EC (see CS Appendix I). Most of the studies that were retrieved were US studies with paucity of UK data relevant to the model inputs. The company resulted to using costs and HCRU values from UK clinical expert's opinions, the British National Formulary,[67] drug and pharmaceuticals electronic market information tool,[68], NHS National costs collection[69] and NICE technology appraisal (TA904)[24]

Costs were for 2022/23 cost year and uprated where necessary using the PSSRU inflation indices annual percentage increase for adult services.[70]

All the costs included in the economic model correctly captured the range of resource use for the indication and levels of resource used were appropriately valued using the available data sources.

Costs included in the economic model comprised:

- Intervention, comparators and subsequent treatment costs and resource use.
  - Drug acquisition costs
  - Subsequent therapy drug acquisition cost
  - Drug administration costs

- Health state resource use costs (monitoring and follow-up)
  - Disease management costs
  - Terminal care costs

- Adverse events unit costs and resource use

The company excluded:

- Monitoring costs for intervention, comparators and subsequent treatment (was captured in the health state costs).
- MMR diagnostic testing costs to identify tumours with dMMR in patients with endometrial cancer (routinely performed to identify dMMR tumours).

The EAG has regarded the approach used by the company to obtain costs and HCRU to be suitable.

4.2.9 Severity

When evaluating treatments for patients with severe disease, the appraisal committees can apply additional weighting to QALY gains for severe diseases, based on NICE's new severity-based decision modifier approach. Under this

approach, two different – but related – measures of disease severity are calculated: absolute QALY shortfall (AS) and proportional QALY shortfall (PS). Absolute shortfall represents the number of future QALYs that are lost by people living with the disease and *on current standard of care* whilst proportional shortfall represents the proportion of future QALYs that are lost by people living with the disease and *on current standard of care*. The severity modifier reflects a spectrum of disease severity and allows a QALY weight of (x1, x1.2 and x1.7) to apply depending on the QALY shortfall (AS or PS) (Table 24). The multiplier is applied to the incremental QALYs associated with a technology before the calculation of ICERs implying the £20,000 to £30,000 threshold is retained regardless of QALY weight chosen.

Table 25 below shows the cut-off levels for AS and PS used to guide the QALY weights for adjusting the QALYs in the reference case.

Table 25: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

In its submission, the company could not provide evidence that a QALY weighting should be applied for this appraisal. The company's QALY shortfall analysis followed the NICE's Health Technology Evaluations manual.[64] The number of QALYs that the general population living without the condition would be expected to accrue for the rest of their lifetime was estimated to be 10.99 and was based on the characteristics of the KEYNOTE-868 (NRG-GY018) trial population i.e., age = 65.40 years and proportion females = 100%. The remaining QALYs accrued by people with primary advanced/recurrent EC and on current standard of care were [redacted] and estimated using the company's base case cost-effectiveness model. The resulting QALY shortfalls (absolute and proportional) are shown in Table 26 below. Since the absolute QALY shortfall is below 12 and the proportional QALY shortfall less than 85%, the company appropriately concluded that a multiplier for disease severity was not appropriate for this appraisal as per NICE guidance.

Table 26: Summary of QALY shortfall analysis (table 59 CS)

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
10.99	[redacted]	[redacted]	[redacted]	x1

EAG comments:

- The company appropriately estimated the absolute and proportional QALY shortfalls, using preferred value sets (i.e.,[63] to crosswalk from EQ-5D-5L to EQ-5D-3L).
- The EAG was able to replicate the QALY shortfall values in the company submission.
- The EAG recalculated the QALY shortfalls based on EAG's base case assumptions and arrived at the same conclusions as the company i.e., a severity weighting does not apply for this appraisal.

5 [redacted]COST EFFECTIVENESS RESULTS

The company reported deterministic, sensitivity and scenario analysis results for the comparison between pembrolizumab + CT versus placebo + CT using list prices. Main outcomes are reported in terms of costs, life-years and QALYs, with the overall results reported in the form of an ICER expressed as cost per life-year gained net health benefit at willingness-to-pay thresholds of £20,000 and £30,000.

5.1 Company's cost effectiveness results

The results in Table 27 shows that pembrolizumab + CT is [redacted] more costly than treatment with CT and is expected to yield an additional [redacted] LY and 1.33 QALYs, which equated to an ICER of [redacted] per QALY.

Table 27: Company's deterministic base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)

CT	[redacted]	3.79	[redacted]	-	-	-	-
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.33	[redacted]
CT, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years							

In Table 28 the company's results are reported in terms of net health benefit. These results show that at WTP thresholds of £20,000 and £30,000, the net health benefits are [redacted] and [redacted], respectively.

Table 28: Company's results based on the net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Pembrolizumab + CT	[redacted]	[redacted]	-	-	-	-
CT	[redacted]	[redacted]	[redacted]	1.33	[redacted]	[redacted]
CT, carboplatin and paclitaxel; NHB, net health benefit; QALY, quality-adjusted life years						

5.2 [redacted]Company's sensitivity analyses

Probabilistic sensitivity analysis (PSA) was undertaken for the outcomes LYs, QALYs, cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions, for example gamma and beta distributions were applied to resource use and costs and utility values. The PSA results were reported in tabular form (see Table 29), and the 1000 iterations presented on scatterplots (Figure 10) and their corresponding cost-effectiveness acceptability curves (CEACs) (Figure 11).

The PSA results show that the ranking of the technologies remained the same as the deterministic results. The PSA estimates a higher QALY gain than the deterministic analysis leading to an ICER of [redacted] per QALY.

Table 29: Company's probabilistic sensitivity analysis results

Treatment	Total costs (£)	Total Lys	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)

Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-
CT	[redacted]	3.79	[redacted]	[redacted]	[redacted]	1.43	[redacted]

Figure 10 shows the company's PSA results for the comparison between pembrolizumab + CT and CT. These results show that there is a wide variation in terms of incremental QALYs and less so for the incremental costs. The majority of the iterations were in the north-east quadrant, indicating that pembrolizumab + CT was more costly and effective than CT. Based on the WTP threshold denoted by the green dashed diagonal line going through the point of origin, majority of the iterations are at and below this line, indicating probability of pembrolizumab + CT being cost-effective versus CT alone. Also, as can be seen that some of the iterations were in the north-west quadrant, indicating that in a small number of iterations pembrolizumab + CT was likely to be more expensive than CT and less effective.

[redacted]

Figure 10: Incremental scatterplot for the comparison between pembrolizumab + CT versus CT (obtained from CS document B, pg48)

In Figure 11, the PSA results are plotted in the form of a cost-effectiveness acceptability curve (CEAC), and these show the probability that pembrolizumab + CT is cost-effective at various WTP thresholds. At WTP thresholds of £20,000 per QALY, pembrolizumab + CT [redacted]

Figure 11: Cost-effectiveness acceptability curve

Deterministic sensitivity analysis

The company undertook one-way sensitivity analysis by varying key input parameters based on their upper and lower limits, or by an arbitrary +/-20% of its standard error in the absence of these limits. Results of the 10 most influential parameters were plotted on a tornado diagram based on the cost per QALY (see Figure 12). The company also undertook sensitivity analysis based on the incremental net monetary benefit.

One-way sensitivity analysis results showed

Figure 12: Tornado diagram for the comparison between pembrolizumab + CT versus CT

Scenario analysis results

The company undertook several scenario analyses, with the results presented in Table 31. Scenario analyses were undertaken around key aspects of the model including, time horizon, discount rate, utility values, adverse event treatment costs and disutilities, subsequent treatment, resource use and costs and overall survival. These results showed that implementing a 10-year time horizon, choosing the standard log-normal CT OS curve, or two-phase piecewise log-normal pembrolizumab + CT OS curve had the greatest impact to the base-case ICER.

Table 30: Company's scenario analysis results

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
-	Base case				[redacted]	-
1	Time horizon	35	10	Estimating impact if a shorter time-horizon is selected	[redacted]	[redacted]
2		35	20		[redacted]	[redacted]
3	Discount rate (costs and utilities)	3.5%	1.5%	As per NICE guidance	[redacted]	[redacted]
4	Impact of AE (cost and disutilities)	Include	Exclude	Remove potential double counting of impact of AEs	[redacted]	[redacted]
5	Utility values	KN-158	KN-826 TTD	Explore a wide range of utility sources given that trial-based EQ-5D was not available from KEYNOTE-868 (NRG-GY018)	[redacted]	[redacted]
6		KN-158	KN-826 progression-based		[redacted]	[redacted]
7		KN-158	KN-775 (Swedish value set)		[redacted]	[redacted]
8		KN-158	KN-775 (Australian value set)		[redacted]	[redacted]
9	Subsequent treatment	Re-weighted trial-based treatment mix based on UK clinician inputs	Per KEYNOTE-868 (NRG-GY018)	Understand the impact of using different subsequent treatment composition in the UK, including IO	[redacted]	[redacted]
10	Subsequent treatment (CT): dostarlimab	Dostarlimab: 0.00%	Dostarlimab takes pembrolizumab monotherapy share: = 20.71%	Estimate impact of a scenario where dostarlimab becomes standard of care for 2L	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
11	Healthcare resource utilisation	UK clinician inputs	Healthcare resource use reported in TA963	Estimate impact of a different healthcare resource utilisation pattern	[redacted]	[redacted]
12	OS extrapolation	Pembrolizumab + CT: 3-knot odds CT: standard log-logistic	Pembrolizumab + CT: 3-knot odds CT: standard generalised gamma	CT: standard generalised gamma model as it had acceptable visual fit and concordance with landmark estimates, but with a more pessimistic survival in the CT arm	[redacted]	[redacted]
13			Pembrolizumab + CT: 3-knot odds CT: standard log-normal	CT: standard log-normal model as it had third best statistical fit, close alignment with observed hazards, and acceptable concordance with landmark estimates from UK experts but with a more optimistic long-term survival in the CT arm	[redacted]	[redacted]
14			Pembrolizumab + CT: two-piece log-normal CT: standard log-logistic	Pembrolizumab + CT: two-piece log-normal. Best statistical fit (AIC) among two-piece models, good visual fit to both the KM data and hazard (past 40 weeks). Good visual fit to the tail of the observed HR over time	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
15			Pembrolizumab + CT: two-piece log-logistic CT: standard log-logistic	Pembrolizumab + CT: two-piece log-logistic model, as it had the third best statistical fit among two-piece models with relatively close fit to observed KM, and provided a more pessimistic estimate of long-term survival in the pembrolizumab + CT arm	[redacted]	[redacted]
16			Pembrolizumab + CT: 2-knot (odds) CT: standard log-logistic	Pembrolizumab + CT: 2-knot odds spline, as it had good statistical fit, captured the turning point in the hazard profile, and provided a more pessimistic estimate of long-term survival	[redacted]	[redacted]
17	PFS extrapolation	Pembrolizumab + CT: two-piece log-normal CT: 1-knot (hazard)	Pembrolizumab + CT: two-piece log-logistic CT: two-piece log-normal	Pembrolizumab + CT: Reasonable statistical and visual hazards fit, represents a conservative survival estimate compared to base case CT: Reasonable statistical fit, represents a more optimistic estimate for the CT arm	[redacted]	[redacted]
18	Treatment waning	No waning	Applied to 24.8% of pembrolizumab + CT of patients. Assumed start	In accordance with previous IO therapies, waning is applied to patients who did not have an ORR. It is applied from 7 years based on the long-term follow-up reported in KEYNOTE-006	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER	Percentage change
			at 7 years (post treatment initiation) for 2 years before effect of CT is assumed	where no evidence of treatment effect waning is observed.		
19	TTD extrapolation	Pembrolizumab + CT: Observed KM CT: Observed KM	Pembrolizumab + CT: Standard generalised gamma CT: Standard Weibull	Exploring a scenario where TTD is based on best-fitting extrapolations	[redacted]	[redacted]

2L, second-line; AE, adverse event; CT, paclitaxel + carboplatin; IO, immunotherapy; ICER, incremental cost effectiveness ratio; ITT, intention to treat; KM, Kaplan–Meier; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; TTD, time to treatment discontinuation

Subgroup analysis

The company presented analyses for the pMMR and dMMR subgroups based on the KEYNOTE-868 (NRG-GY018) trial design. For the dMMR subgroup, these results showed that treatment with pembrolizumab + CT is [redacted] more costly than treatment with CT and expected to yield an additional [redacted] LYs and 2.14 QALYs, resulting in an ICER of [redacted]. For the pMMR subgroup, treatment with pembrolizumab + CT is [redacted] more costly that CT and expected to yield [redacted] LYs and 1.18 QALYs, resulting in an ICER of [redacted] per QALY.

EAG summary

The EAG considers that the company's base-case results reported in the CS Document B report to be reflective of the results shown in the model; however, there were some concerns. First, during clarification stage the company accepted that the costs associated with end-of-life care was not uprated to current prices as stated in CS Document B. It should be noted that the company did not provide a new model incorporating this change into the company base-case. Additionally, in the model 'Health state utility' worksheet the utility value for progressed disease was 0.85 and stable disease was 0.82. However, when the EAG checked the reference, we noted that the utility value for progressed disease was 0.82 and stable disease was 0.85, so the results for the scenario analyses based on KEYNOTE-775 (Sweden) utility values are not accurate. Applying the correct utility values for progressed vs. stable disease resulted in a decrease in the ICER from [redacted] to [redacted]. Because there were more people with progressed disease in the placebo +CT arm, the lowered (correct utility value) for progressed disease drives the ICER change observed.

5.3 Model validation and face validity check

The EAG conducted an extensive review of the model submitted by the company. The model appears to reflect the assumptions made by the company and contained clinical aspects necessary to address the decision problem. The EAG sought clinical validation of (i) the model assumptions (both EAG and company's) and (ii) model's output ((LYG, QALYs) and relevant economic outcomes (e.g., treatment costs)).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Changes to company's base case ICER (after clarification)

The EAG has updated the costs of terminal care in the model to £8,829.07 to reflect the correct, uprated costs preferred by the company in response to Clarification question B10. Any changes to the ICER when undertaking EAG's exploratory analyses will be based on this updated base case ICER of [redacted] (hereon ICER after clarifications).

6.2 Exploratory and sensitivity analyses undertaken by the EAG

Based on our critique of the company's economic model, the EAG made changes to the company's model to explore the impact of individual changes to the company's base case results. The suggested changes along with the EAG's justifications are presented below:

- Higher starting age in the model (67.1 years) to better reflect the NHS population

This exploratory analysis draws on the EAG's additional literature search (Table 7) for data to inform alternative starting age that would be more appropriate for this appraisal and is representative of the NHS population. Full details of our critique are presented in Section 4.2.3.

- A different approach to extrapolating PFS

Section 4.2.6.4.2 provided an in-depth justification for EAG's preferred PFS extrapolations to reflect EAG's clinical experts' opinions of what would be a more plausible clinical benefit of the technologies and also the best fitting models according to EAG's assessments. The EAG preferred the company's chosen extrapolations for its base case therefore no changes to the base case ICER were observed. Sensitivity analyses were run to show the impact of choosing extrapolations that were good fit to the experts' estimates but were (i) most optimistic (i.e., provided survival estimates higher than the base case at 20 years) or (ii) most pessimistic (i.e., provided survival estimates lower than the base case at 20 years).

For the pembrolizumab arm, the scenario analyses models are (i) the 3-knot odds model and (ii) the two-piece log-normal with 6.5-month data cut. For the control arm, the scenario analysis models are: (i) the 1-knot odds model and (ii) the two-piece log-logistic model with 38-week data cut.

- A different approach to extrapolating OS

This exploratory analysis draws on EAG's clinical experts' opinions of what would be considered a clinically plausible benefit (long-term survival) at different years alongside the EAG's assessment of best fitting models. Detailed critique and justification for model choice are provided in Sections 4.2.6.3.2 and 4.2.6.4.3

Briefly, the EAG's experts' opinion indicated that benefit of pembrolizumab +CT was likely overestimated and they preferred EAG's extrapolations with lower survival benefit at 20 years. Therefore, the EAG chose a different approach to the extrapolation of OS. The EAG's preferred base case model is the two-piece log-logistic model with a 9.4-week data cut for the pembrolizumab arm, and the same model as the company's base case model for the control arm. The EAG also explored two scenario analyses for each treatment arm. These were the two-piece log-normal model with 40-week data cut and the 1-knot odds model for the pembrolizumab arm, and the 1-knot odds and 1-knot normal model for the control arm.

- Exploring more conservative treatment waning effect assumptions

As detailed in Section 4.2.2, clinical advice to the EAG maintains that treatment waning does occur in immunotherapies and due to the trial's short follow-up period, there is insufficient evidence to confirm that treatment effect is sustained overtime. In previous NICE technology appraisals for immunotherapies in HNSCC for pembrolizumab (TA661) and nivolumab (TA655), committees have accepted that it is plausible for treatment effect to be sustained for three to five years after discontinuing IO therapy after two years.[50, 73, 74]

Thus, the EAG has explored scenarios in which treatment waning is applied to the pembrolizumab + CT OS curve at specific time points for a duration of two years. In

the first scenario, waning starts in year 5 and ends in year 7, while in the second scenario, it starts in year 6 and finishes in year 8. The EAG acknowledges that there is no evidence available to support the conservative assumption and as a result, it has not been included in the EAG's preferred assumptions.

- Health-state utility values from McCarthy et al. (2024)[44] based on UK value set

The EAG explored a scenario using lower utility values retrieved from an alternative cost-effectiveness study based on EQ-5D-3L questionnaires from KEYNOTE-158 and a UK value set. These utilities are not included in the EAG's preferred assumptions as the paper does not explicitly specify the methods for deriving the utilities. A more detailed discussion can be found in section 4.2.7.3.

- Exploring uncertainty around the resource utilisation for blood tests and outpatient visits per week in the intervention arm.

As explained in Section 4.2.8.3, EAG clinical experts emphasised that patients in the pembrolizumab + CT arm will typically have more blood tests and outpatient appointments. Two scenario analyses were conducted to gauge the uncertainty level of the company's values. Scenario 1 relied on data provided by the EAG's clinical experts and scenario 2 used data sourced from TA963.

- Evaluate the impact of including a broader range of adverse events in the model.

In Section 4.2.8.4, it was highlighted that the costs of AEs incorporated into the model was underestimated by the company considering only the AEs of grade 3+ occurring in ≥ 5% of patients in the trial. An analysis was conducted to consider a scenario where other AEs of grade 3+ occurred in ≥ 2% of patients, aiming to evaluate the effect of associated costs and disutilities in the model. This assumption was not included in the EAG base case analysis because of certain conservative assumptions.

- Estimating the uncertainty of the subsequent treatments mix received by the patients who have previously received chemotherapy as 1L therapy.

As discussed in Section 4.2.8.2, EAG clinical experts disagreed with the use of pembrolizumab monotherapy as a subsequent treatment for patients in the CT arm. Analysis was explored were all patients that received pembrolizumab monotherapy as subsequent therapy after progression were allocated to receive pembrolizumab + Lenvatinib.

The EAG's main exploratory analyses (Table 31) informed the base case (described below in Section 6.4).

Table 31: EAG Exploratory analyses table

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
MSD base case (post clarifications)				[redacted]	1.33	[redacted]	[redacted]
Baseline starting age	65.40	67.1 [27, 45]	Estimating impact when baseline age is reflective of population seen in UK clinical practice.	[redacted]	1.30	[redacted]	[redacted]
		67.9[49]		[redacted]	1.28	[redacted]	[redacted]
		69[46]		[redacted]	1.27	[redacted]	[redacted]
OS extrapolation							
	Pembrolizumab + CT: 3-knot odds	**OS Scenario 1**	Best fitting model to model long-term	[redacted]	1.05	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
	CT: standard log-logistic	Pembrolizumab + CT: two-piece Log- logistic model with 9.4-week cut CT: Company's standard log-logistic model	survival chosen by EAG experts				
		OS Scenario 2 Pembrolizumab + CT: two-piece Log- normal model with 40-week cut CT: 1-knot odds spline	Pembrolizumab +CT: Best fitting overall, more optimistic CT: Good fit, more optimistic model	[redacted]	2.09	[redacted]	[redacted]
		OS Scenario 3 Pembrolizumab + CT: 1-knot odds spline	Pembrolizumab+CT: Decent fit, more pessimistic	[redacted]	0.94	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		CT: 1-knot normal spline	CT: Good fit, more pessimistic				
PFS extrapolation	Pembrolizumab + CT: Two-piece log-normal with 38-week cut CT: 1-knot hazards spline						
		Scenario 1 PFS Pembrolizumab + CT: Two-piece log-normal with 38-week cut (company's base case) CT: 1-knot hazards spline (company's base case)	Company' base case assumptions chosen as best fitting model to long-term estimates by EAG experts	[redacted]	1.33	[redacted]	[redacted]
		Scenario 2 PFS Pembrolizumab + CT: 3-knot odds spline	Pembrolizumab +CT: Best overall fitting model and more optimistic compared to the base case	[redacted] [redacted]	1.35 [redacted]	[redacted] [redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		CT: Two-piece log-logistic with 38-week cut	**CT:** Preferred by experts, more optimistic				
		Scenario 3 PFS Pembrolizumab + CT: Two-piece log-normal with 6.5-months cut CT: 1-knot odds spline	Pembrolizumab +CT: Only model more pessimistic compared to the base case, decent fit **CT:** Best overall fit, slightly more pessimistic compared to the base case with similar OS at the end	[redacted]	1.32 [redacted]	[redacted]	[redacted]
TTD	KM estimates	TTD Pembrolizumab arm, Gompertz model	Smoother parametric curves to help reduce variability near end of study when sample size is small	[redacted]	1.33	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		TTD CT arm, Gamma model	Models conservatively chosen based on statistical and visual fit only				
Treatment waning in OS	No treatment waning assumed	**Scenario 1** 3 years after discontinuing pembrolizumab + CT	Precedent in previous NICE appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.23	[redacted]	[redacted]
		Scenario 2 4 years after discontinuing pembrolizumab + CT		[redacted]	1.23	[redacted]	[redacted]
HSU from McCarthy et al 2024	PFS: [redacted] PD: [redacted]	**PFS:** 0.72 **PD:** 0.67	Utilities were estimated based on progression status and tumour site data from KEYNOTE-158 using a UK value set.	[redacted]	1.33	[redacted]	[redacted]
Resource use frequency per week of blood	PFS (on treatment): Blood tests - 0.17,	**Scenario 1** PFS (on treatment):	EAG Clinical experts most	[redacted]	1.33	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
tests and outpatient visits in the pembrolizumab + CT arm	outpatient visits - 0.17 PFS (off treatment) - Bood test – 0.17 Outpatient visits – 0.06	Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+) Outpatient visits – 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08 Outpatient visits – 0.08	appropriate estimates.				
		Scenario 2 PFS (on treatment): Blood test – 0.33 (up to cycle 18), 0.22 (cycle 19+) Outpatient visits – 0.30 (up to	Explore data from TA963 to assess uncertainty.	[redacted]	1.33	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		cycle 18), 0.13 (cycle 19+) PFS (off treatment): Blood tests – 0.17 (company's base case) Outpatient visits – 0.06 (company's base case)					
Adverse events of grade 3+ in ≥ 5% of patients	All costs and disutilities associated with adverse events of grade 3+ in ≥ 5% of patients	All costs and disutilities associated with adverse events of grade 3+ in ≥ 2% of patients	Assess the impact of including a broader range of AEs in the model	[redacted]	1.33	[redacted]	[redacted]
Subsequent treatment mix after CT	Pembrolizumab – 16.76% Pembrolizumab + Lenvatinib 23.95%	Pembrolizumab 0.00% Pembrolizumab+ Lenvatinib 40.71%	Adjusting the subsequent treatment mix to reflect treatments received by UK patients based on	[redacted]	1,33	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
			EAG clinical expert's opinion.				

[redacted]

The EAG's exploratory analyses results presented in Table 31 demonstrate that changing the OS extrapolation method had the greatest impact to the company's base case ICER. The EAG's base case (preferred by EAG experts and denoted as scenario 1), resulted in an increase in the ICER of [redacted] due to the decreased overall QALY benefits of Pembrolizumab + CT. The most optimistic scenario explored by the EAG resulted in a decrease in the ICER of [redacted] whilst the more pessimistic scenario increased the ICER by [redacted]. Except for TTD, PFS (optimistic scenario) and subsequent treatment mix, the other scenario analyses explored by the EAG all [redacted] the company's base case ICER.

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The main issues highlighted by the EAG throughout this report that could impact the cost-effectiveness of pembrolizumab +CT are summarised in Table 32**.**

It shows the expected direction of bias introduced by these issues and whether these are examined in any exploratory analyses or incorporated in the EAG base-case.

Table 32: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses
Representativeness of some baseline characteristics of KEYNOTE-868			
Trial population appears healthier and younger than observed in real world clinical practice	+ (and unknown)	Base case (varied age only)	No
Treatment effectiveness and extrapolation			
Overly optimistic OS extrapolation for pembrolizumab + CT	+	Base case Scenarios	Scenarios. However, alternative OS extrapolations explored to reflect EAG clinical experts' preferences
Resource use and cost and Adverse Events			
Insufficient capture of AE cost and monitoring	+	Sensitivity analyses	No
Utility values			
Health state utilities applied in economic model that are unlikely representative of all-comer population as utilities sourced from dMMR population only	+/-	None (lack of data availability)	Scenarios. However, error in scenario analyses for KN775 (see section 5.1; EAG summary). EAG considers KN775 a more appropriate data source if UK value set is used.
'+/-' indicates that the bias introduced by the issue is unclear to the EAG; while '+' indicates that the EAG believes this issue likely induces bias in favour of the technology versus comparator and '+and -' indicates the EAG believes the potential bias can be positive or negative depending on the assumptions used.			

6.4 EAG's preferred assumptions

The adjustments made by the EAG to the company's model are summarised below, and the effects of each change are shown in Table 33**.**

EAG 01: Starting age at baseline is increased from 65.40 to 67.1 years to reflect EAG clinical experts' opinion, previous NICE appraisal committee's preference and relevant evidence from the literature (see 4.2.3 and Table 7).

EAG 02: A different approach to the extrapolation of OS for pembrolizumab +CT. The EAG applies a Two-piece log-logistic model with 9.4 week cut as the best fitting to model long term estimates as chosen by the EAG experts

EAG03: The EAG maintain the company's log-logistic extrapolation for Placebo +CT as the best fitting model preferred by EAG experts

Table 33: EAG's preferred model assumptions

Preferred assumption	Section in EAG report	ICER £/QALY (Individual impact on company base case ICER)
Company base-case		[redacted]
EAG 01: Starting age at baseline 67.1 years.	4.2.3	[redacted]
EAG 02: OS extrapolation for pembrolizumab +CT using a piecewise approach (log-logistic model with 9.4 week cut)	4.2.6.4.32	[redacted]
EAG03: OS extrapolation for placebo+CT. EAG maintains company's log-logistic model	4.2.6.4.3	[redacted]
EAG Base Case (Applied all changes cumulatively)		[redacted]

Table 34 below shows the results of the deterministic cost-effectiveness analysis, based on EAG's preferred base case assumptions. The ICER increased from £[redacted] (Company's base case) to £[redacted] (EAG's base case). The main driver of the increased ICER was the OS extrapolation approach for pembrolizumab +CT.

Table 34: EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab

Technologies	Costs	LYG	QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Pembrolizumab + Carboplatin + Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Carboplatin + Paclitaxel	[redacted]	3.77	[redacted]	[redacted]	[redacted]	1.04	[redacted]

EAG's probabilistic base case cost-effectiveness analysis

Probabilistic sensitivity analysis was performed on the EAG base case using 1000 iterations drawn from parametric assumptions in the adapted economic model (ID6381_Pembro_1LEC_Model_v1.0_EAG [CON]). Incremental costs were [redacted] and incremental QALYs 1.02 resulting in an ICER of [redacted]*(Table 36). At a £30,000 WTP threshold pembrolizumab +CT return an iNMB of [redacted] and iNHB of 0.15 under EAG base case assumptions. The iNMB and iNHB at £20,000 WTP threshold under EAG base case assumptions are [redacted] and [redacted] respectively.

Table 35: EAG Probabilistic base case cost-effectiveness analysis (with PAS price used for pembrolizumab) 37

Treatment	Pembrolizumab + Carboplatin + Paclitaxel	Carboplatin + Paclitaxel
Costs	[redacted]	[redacted]
LYG	[redacted]	3.80
QALYs	[redacted]	[redacted]
Incremental costs		[redacted]
Incremental LYG		[redacted]
Incremental QALYs		1.02
ICER		[redacted]

Figure 13 shows the PSA results for the comparison between pembrolizumab + CT and CT in a scatterplot, for the EAG's base case. These results show a narrower variation in terms of incremental QALYs (compared to the company's base case). However, variation in QALYs is still wider than for the incremental costs as observed in company's base case analysis. Most of the iterations were in the north-east quadrant, indicating that pembrolizumab + CT was more costly and effective than CT. The WTP threshold at £30,000/QALY (denoted by the green dashed diagonal line going through the point of origin), shows most of the iterations appear to be at or below this line. This indicates that the probability of pembrolizumab + CT being cost-effective versus CT alone is greater than 50%.

Figure 13: Incremental scatterplot for the comparison between pembrolizumab + CT versus CT

In Figure 14 below, the PSA results are plotted in the form of a cost-effectiveness acceptability curve (CEAC), showing the probability that pembrolizumab + CT is cost-effective at various WTP thresholds. At WTP thresholds of £20,000 per QALY, pembrolizumab + CT

Figure 14: Cost-effectiveness acceptability curve

6.5 Conclusions of the cost effectiveness section

In summary, the model constructed by the company appears to be logical.

The EAG has the following concerns regarding the cost-effectiveness analysis (as detailed in 1.5):

- the extent of the OS benefit associated with pembrolizumab +CT
- the starting age of the population in the economic model

However, additional unresolved uncertainties around health state utilities applied within the economic model, resource usage in the pembrolizumab+CT arm and uncertain subsequent treatment patterns should also be considered.

The EAG have presented scenarios with a preferred base-case analysis. The ICER has mostly [redacted] compared with the CS.

7 SEVERITY MODIFIERS

As discussed in Section 4.2.9, the company did not submit a case for a 'severity modifier' to be applied. The EAG is in full agreement that a severity weighting does not apply for this appraisal, so nothing further was explored.

8 [redacted]References

1. NICE. Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer ID6381 Final scope. London: National Institute for Health and Care Excellence; 2024. URL: https://www.nice.org.uk/guidance/gid-ta11461/documents/final-scope (Accessed 23rd October 2024).

2. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med 2023;388(23):2159-70. http://dx.doi.org/10.1056/NEJMoa2302312

3. Cancer Research UK. What is womb cancer? 2024. URL: https://www.cancerresearchuk.org/about-cancer/womb-cancer/about (Accessed 13 June 2024).

4. Cancer Research UK. Uterine cancer incidence. 2024. URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero (Accessed 07 May 2024).

5. Cleveland Clinic. Uterine Cancer (Endometrial Cancer). 2023. URL: https://my.clevelandclinic.org/health/diseases/16409-uterine-cancer (Accessed 14 June 2024).

6. Cancer Research UK. Uterine cancer mortality statistics. 2022. URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/mortality#heading-Zero (Accessed 07 May 2024).

7. Cancer Research UK. Risks and causes of womb cancer. Cancer Research UK; 2024. URL: https://www.cancerresearchuk.org/about-cancer/womb-cancer/risks-causes (Accessed 23rd October 2024).

8. Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Caruso G, et al. Endometrial carcinosarcoma. Int J Gynecol Cancer 2023;33(2):147-74. http://dx.doi.org/10.1136/ijgc-2022-004073

9. Hong R, Liu W, DeLair D, Razavian N, Fenyo D. Predicting endometrial cancer subtypes and molecular features from histopathology images using multi-resolution deep learning models. Cell Rep Med 2021;2(9):100400. http://dx.doi.org/10.1016/j.xcrm.2021.100400

10. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162(2):383-94. http://dx.doi.org/10.1002/ijgo.14923

11. Leon-Castillo A. Update in the molecular classification of endometrial carcinoma. Int J Gynecol Cancer 2023;33(3):333-42. http://dx.doi.org/10.1136/ijgc-2022-003772

12. NHS. Symptoms - womb (uterus) cancer. 2021. URL: https://www.nhs.uk/conditions/womb-cancer/symptoms/ (Accessed 13 June 2024).

13. Cancer Research UK. Symptoms of womb cancer. 2024. URL: https://www.cancerresearchuk.org/about-cancer/womb-cancer/symptoms (Accessed 13 June 2024).

14. American Cancer Society. Signs and Symptoms of Endometrial Cancer. 2019. URL: https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/signs-and-symptoms.html (Accessed 13 June 2024).

15. Zandbergen N, de Rooij BH, Vos MC, Pijnenborg JMA, Boll D, Kruitwagen R, et al. Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis. Acta Oncol 2019;58(5):790-800. http://dx.doi.org/10.1080/0284186X.2018.1560498

16. Gil-Ibanez B, Davies-Oliveira J, Lopez G, Diaz-Feijoo B, Tejerizo-Garcia A, Sehouli J. Impact of gynecological cancers on health-related quality of life: historical context, measurement instruments, and current knowledge. Int J Gynecol Cancer 2023;33(11):1800-6. http://dx.doi.org/10.1136/ijgc-2023-004804

17. Shisler R, Sinnott JA, Wang V, Hebert C, Salani R, Felix AS. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecologic Oncology 2018;148(2):403-13. http://dx.doi.org/10.1016/j.ygyno.2017.11.007

18. Jonsdottir B, Wikman A, Sundstrom Poromaa I, Stalberg K. Advanced gynecological cancer: Quality of life one year after diagnosis. PLoS One 2023;18(6):e0287562. http://dx.doi.org/10.1371/journal.pone.0287562

19. NICE. Suspected cancer: recognition and referral. National Institute for Health and Care Excellence 2023. URL: https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer (Accessed 18 July).

20. Cancer Research UK. Tests for womb cancer. 2024. URL: https://www.cancerresearchuk.org/about-cancer/womb-cancer/getting-diagnosed/tests-womb-cancer (Accessed 14 June 2024).

21. NICE. Testing strategies for Lynch syndrome in people with endometrial cancer. National Institute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/dg42 (Accessed 17 June 2024).

22. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol 2022;270:50-89. http://dx.doi.org/10.1016/j.ejogrb.2021.11.423

23. Rütten H, Verhoef C, van Weelden WJ, Smits A, Dhanis J, Ottevanger N, et al. Recurrent Endometrial Cancer: Local and Systemic Treatment Options. Cancers (Basel) 2021;13(24). http://dx.doi.org/10.3390/cancers13246275

24. NICE. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. National Institute for Health and Care Excellence 2023. URL: https://www.nice.org.uk/guidance/TA904 (Accessed 18 June 2024).

25. McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: Not your grandmother's cancer. Cancer 2016;122(18):2787-98. http://dx.doi.org/10.1002/cncr.30094

26. Cao SY, Fan Y, Zhang YF, Ruan JY, Mu Y, Li JK. Recurrence and survival of patients with stage III endometrial cancer after radical surgery followed by adjuvant chemo- or chemoradiotherapy: a systematic review and meta-analysis. BMC Cancer 2023;23(1):31. http://dx.doi.org/10.1186/s12885-022-10482-x

27. NICE. Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. National Institute for Health and Care Excellence; 2024. URL: https://www.nice.org.uk/guidance/ta963 (Accessed 07 May 2024).

28. Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. Br J Cancer 2022;126(12):1765-73. http://dx.doi.org/10.1038/s41416-022-01718-5

29. Eskander R, Sill M, Beffa L, Moore R, Hope J, Musa F, et al. Overall survival and progression-free survival by PD-L1 status among endometrial cancer patients treated with pembrolizumab plus carboplatin/paclitaxel as compared to carboplatin/paclitaxel plus placebo in the NRG GY018 trial. Gynecologic Oncology

2024;190(Supplement 1):S5. http://dx.doi.org/https://dx.doi.org/10.1016/j.ygyno.2024.07.015

30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. http://dx.doi.org/10.1136/bmj.n71

31. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). 2024. URL: www.training.cochrane.org/handbook (Accessed 21 October 2024).

32. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;69:225-34. http://dx.doi.org/10.1016/j.jclinepi.2015.06.005

33. SIGN. Search filters. Scottish Intercollegiate Guidelines Network (SIGN); 2021. URL: https://www.sign.ac.uk/using-our-guidelines/methodology/search-filters/ (Accessed 21st October 2024).

34. Eskander R, Sill M, Beffa L, Moore R, Hope J, Musa F, et al. Pembrolizumab versus placebo in addition to carboplatin and paclitaxel for measurable stage 3 or 4a, stage 4b or recurrent endometrial cancer: The phase 3, NRG GY018 study (LBA 10). Gynecologic Oncology 2023;176:S42-S3. http://dx.doi.org/10.1016/j.ygyno.2023.06.523

35. Eskander RN, Sill M, Miller A, Beffa L, Moore R, Hope J, et al. LBA43 Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial. Annals of Oncology 2023;34:S1284. http://dx.doi.org/10.1016/j.annonc.2023.10.037

36. Merck. Statistical Report Efficacy Update Report of NRG-GY018/KEYNOTE-868 Primary advanced or recurrent endometrial cancer; 2024.

37. Eskander R, Sill M, Miller A, Beffa L, Moore R, Hope J. Overall survival, progression-free survival by PD-L1 status, and blinded independent central review results with pembrolizumab plus carboplatin/paclitaxel (CP) versus placebo plus CP

in patients with endometrial cancer: results from the NRG GY018 trial. Society of Gynecologic Oncology 2024 Annual Meeting for Womens Cancer, abstract no. 428.

38. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. http://dx.doi.org/10.1136/bmj.l4898

39. National Cancer Institute (NCI). Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer. 2023. URL: https://classic.clinicaltrials.gov/ct2/show/NCT03914612 (Accessed 19 June 2024).

40. MSD. Protocol 868: Pembrolizumab (MK-3475) in Combination with Paclitaxel and Carboplatin - Efficacy (All-comer Participants Population). 2024.

41. 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. http://dx.doi.org/10.1016/j.ejca.2008.10.026

42. Skopec M, Issa H, Reed J, Harris M. The role of geographic bias in knowledge diffusion: a systematic review and narrative synthesis. Research Integrity and Peer Review 2020;5(1):2. http://dx.doi.org/10.1186/s41073-019-0088-0

43. Calrivate. Embase vs MEDLINE: FAQ. 2024. URL: https://clarivate.com/blog/embase-vs-medline-faq/ (Accessed 23rd October 2024).

44. McCarthy G, Young K, Madin-Warburton M, Mantaian T, Brook E, Metcalfe K, et al. Cost-effectiveness of pembrolizumab for previously treated MSI-H/dMMR solid tumours in the UK. J Med Econ 2024;27(1):279-91. http://dx.doi.org/10.1080/13696998.2024.2311507

45. Pennington M, Gentry-Maharaj A, Karpinskyj C, Miners A, Taylor J, Manchanda R, 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):e0165539. http://dx.doi.org/10.1371/journal.pone.0165539

46. Zhang J, Kelkar SS, Prabhu VS, Qiao Y, Grall V, Miles N, et al. Real-world treatment patterns and clinical outcomes from a retrospective chart review study of

patients with recurrent or advanced endometrial cancer who progressed following prior systemic therapy in Europe. BMJ Open 2024;14(4):e079447. http://dx.doi.org/10.1136/bmjopen-2023-079447

47. 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. http://dx.doi.org/10.1016/j.ygyno.2022.06.011

48. Alvaro Ingles Russo Garces. Demographics and Survival Outcomes in Patients with Advanced or Recurrent Endometrial Cancer in the English Real-World Setting. 2023. URL: https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/0214cb59-a124-470f-af22-724a2e9bcb91/0214cb59-a124-470f-af22-724a2e9bcb91_viewable_rendition__v.pdf?REF--ALL-004799 (Accessed 10 July 2024).

49. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer 2008;18(4):803-8. http://dx.doi.org/10.1111/j.1525-1438.2007.01094.x

50. NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency 2021. National Institute for Health and Care Excellence 2022. URL: https://www.nice.org.uk/guidance/ta779 (Accessed 24 July 2024).

51. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21(15):2175-97. http://dx.doi.org/10.1002/sim.1203

52. Burnham KP, Anderson DR. Model selection and multimodel inference: a practical information-theoretic approach. 2nd edn. New York: Springer; 2002. http://dx.doi.org/10.1007/b97636

53. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012;12(1):9. http://dx.doi.org/10.1186/1471-2288-12-9

54. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38(1):1-10. http://dx.doi.org/10.1200/jco.19.02105

55. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-108. http://dx.doi.org/10.1097/00005650-199711000-00002

56. NICE. Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency TA914. National Institute for Health and Care Excellence; 2023. URL: https://www.nice.org.uk/guidance/ta914 (Accessed 24 July 2024).

57. NICE. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. National Institute for Health and Care Excellence 2024. URL: https://www.nice.org.uk/guidance/TA962 (Accessed 23 July 2024).

58. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. 2022. URL: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d (Accessed June 2024).

59. Di Dio C, Bogani G, Di Donato V, Cuccu I, Muzii L, Musacchio L, et al. The role of immunotherapy in advanced and recurrent MMR deficient and proficient endometrial carcinoma. Gynecologic Oncology 2023;169:27-33. http://dx.doi.org/10.1016/j.ygyno.2022.11.031

60. Ott PA, Bang YJ, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS, et al. Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1-Positive Endometrial Cancer: Results From the KEYNOTE-028 Study. J Clin Oncol 2017;35(22):2535-41. http://dx.doi.org/10.1200/jco.2017.72.5952

61. Antill Y, Kok PS, Robledo K, Yip S, Cummins M, Smith D, et al. Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. J Immunother Cancer 2021;9(6). http://dx.doi.org/10.1136/jitc-2020-002255

62. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med 2021;385(20):1856-67. http://dx.doi.org/10.1056/NEJMoa2112435

63. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics 2023;41(2):199-207. http://dx.doi.org/10.1007/s40273-022-01218-7

64. NICE. NICE Health Technology Evaluations: the Manual. National Institute for Health and Care Excellence; 2022. URL: https://www.nice.org.uk/process/pmg36 (Accessed 17 June 2024).

65. Pharmaceutical Benefits Advisory Committee. Pembrolizumab (Endometrial cancer): Solution concentrate for I.V. infusion 100 mg in 4 mL. 2022. URL: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-03/pembrolizumab-endometrial-cancer-solution-concentrate-for-iv-infusion (Accessed 24 July 2024).

66. Ralph L, Young K, Upadhyay N, Prabhu VS, Ljungcrantz C, Massaad R, et al. Cost effectiveness of pembrolizumab plus lenvatinib compared with chemotherapy for treating previously treated advanced endometrial cancer in Sweden. J Med Econ 2024;27(1):483-91. http://dx.doi.org/10.1080/13696998.2024.2329022

67. British National Formulary. Pembrolizumab [Specialist drug]. 2024. URL: https://bnf.nice.org.uk/drugs/pembrolizumab-specialist-drug/ (Accessed June 2024).

68. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2011. URL: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (Accessed June 2024).

69. NHS. 2022/23 National Cost Collection Data. 2024. URL: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (Accessed July 2024).

70. Jones KCaW, Helen and Birch, Sarah and Castelli, Adriana and Chalkley, Martin and Dargan, Alan and Forder, Julien E. and Gao, Minyue and Hinde, Seb and

Markham, Sarah and Premji, Shainur and Findlay, D. and Teo, H. Unit Costs of Health and Social Care 2023 Manual. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2024. http://dx.doi.org/10.22024/UniKent/01.02.105685

71. Cancer Insitute NSW. Immunotherapy blood test recommendations. 2023. URL: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/immunological/3549-immunotherapy-blood-test-monitoring-recommend#blood-tests-for-monitoring-when-on-immunotherapy-a (Accessed 06th November 2024).

72. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014. URL: https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life (Accessed June 2024).

73. NICE. Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma - TA661. National Institute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/TA661).

74. NICE. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy - TA655. National Institute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/ta655).

9 Appendices

9.1 Appendix 1: ROBIS assessment

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably yes**	The CS clearly states that the review was conducted to identify evidence of the efficacy and safety of interventions used in the UK for the first-line treatment of advanced or recurrent endometrial cancer. The CS provides eligibility criteria on most elements (CS Appendix D, Table 4). The EAG requested

		information on publication type and country of study. This was provided in the company's response to Clarification question A3.
1.2 Were the eligibility criteria appropriate for the review question?	**Probably not**	The eligibility criteria were narrower than the NICE scope. The NICE scope includes more comparators that are not included in the CS: (Hormone therapy (such as medroxyprogesterone acetate and megestrol), Best supportive care). Additional sub-groups are in the NICE scope that are not included in the CS: Local vs metastatic recurrence.
1.3 Were eligibility criteria unambiguous?	**Yes**	Eligibility criteria were clear.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Probably yes**	Restrictions were generally appropriate, but no explanation on restrictions on study design. These were probably appropriate restrictions.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Yes**	No language or time restrictions were included.
Concerns regarding specification of study eligibility criteria	**Low concern**	The EAG are happy that effort has been made to clearly specify the review question and appropriate eligibility criteria.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**	Search included an appropriate range of databases and four conference proceedings. The United States (US) National Institutes of Health Clinical Trial Registry, ClinicalTrials.gov was also searched.
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**	Four conference proceedings were searched – the search terms and numbers of results were provided in the clarification responses. The United States (US) National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) was searched to identify completed

		clinical trials with empirical data that had not yet been published. The search terms were provided in the clarification responses.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably yes**	The database, trial registry and conference searches included search terms for the population only, which increases the sensitivity. It did not include additional terms for endometrial cancer including (but not limited to) womb or uterus cancer. The database searches did not include search terms for disease stage; however, the conference abstracts searches via Northerm Lights did (Tables 2 and 3 CS Clarification response).
2.4 Were restrictions based on date, publication format, or language appropriate?	**Yes**	Restricted to randomised controlled trials. Appropriate to do so. Language and date limits not applied to database searches. Date limit of 2022 applied to conference abstract searches, appropriate to do so to capture studies that are yet to be published.
2.5 Were efforts made to minimise errors in selection of studies?	**Yes**	Two reviewers independently screened all abstracts and full texts, and any discrepancies were resolved by a third reviewer.
Concerns regarding methods used to identify and/or select studies	**Low concerns**	Attempts were made to identify as many relevant studies as possible, using an appropriate approach.
3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Standardised form used, extraction by two reviewers for the final list of included studies and a third reviewer to reach consensus for any remaining discrepancies
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Yes**	Characteristics of one study with similar baseline characteristics to the KEYNOTE-868 [NRG-GY018]) trial was performed. At clarification, the company provided additional information on the baseline characteristics and outcomes, but it was not clear whether patients on hormone therapy were included

		thus meeting the decision problem. The other included studies were also tabulated.
3.3 Were all relevant study results collected for use in the synthesis?	**Yes**	Only one study (An RCT) was selected after conducting the SLR. The other studies were excluded at full text based on study design, population, intervention, outcome, and duplicates in line with comparators only of interest as per NICE decision problem.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	As there were no non-randomised studies included, the included randomised controlled trial was assessed using the recommended Cochrane risk of bias tool. However, a narrative of the ratings was not provided. The EAG conducted another ROB with a narrative of the ratings and rated the study as low risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes**	All quality and risk of bias assessment were validated by two independent reviewers and conflicts resolved by a third reviewer.
Concerns regarding methods used to collect data and appraise studies	**Low concern**	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted in line with the scope.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	**Yes**	The company included all the relevant studies
4.2 Were all predefined analyses followed or departures explained?	**No information**	There were no pre-defined analyses specified in the CS. No mention of the review being registered with PROSPERO or similar.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and	**Not applicable**	The company had only identified one eligible head-to-head comparison RCT to inform the clinical evidence. Therefore, no indirect treatment comparisons

outcomes across included studies?		were conducted for this submission.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Not applicable**	See above
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**Not applicable, see 4.3.**	Not applicable
4.6 Were biases in primary studies minimal or addressed in the synthesis?	**Yes**	The review makes reference to the risk of bias pertaining to overestimation of PFS for the placebo + CT arm which may introduce bias in favour of the CT arm.
Concerns regarding the synthesis and findings	**Some concern**	The narrative synthesis did not discuss the ROB in the results.
Risk of bias		
A. Did the interpretation of findings address all of the concerns identified in the Phase 2 assessment?	**Unclear concern**	Differences in comparators were probably appropriate, but differences in sub-groups were not explained. The review did not discuss RoB in the results.
B. Was the relevance of identified studies to the review's research question appropriately considered?	**Yes**	The included study was relevant to the review's research question.
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	**Yes**	Results of the review include both statistically significant and non-significant findings. The CS presents data from the clinical effectiveness evidence from the KEYNOTE-868 (NRG-GY018) trial (included in the SLR) that includes both significant and non-significant results.

9.2 Appendix 2: EAG modelling

9.2.1 Progression-free Survival modelling

9.2.1.1 Source of Kaplan-Meier data

The source of the Kaplan-Meier data for this outcome, progression-free survival, comes from the 'KM data' sheet to MSD's economic model. The KM data was provided where the proportion of people without a PFS event were given at each week, and using the methods described in Guyot et al., the survival IPD was estimated.

9.2.1.2 Descriptive analysis

Supplementary table 1: Results of the reconstructed PFS KM data

	Pembrolizumab + CT	**Placebo + CT**
Total Number	[redacted]	[redacted]
Number of events (%)	[redacted]	[redacted]
Chi2 p-value	[redacted]	
Median PFS in months	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
P-value	[redacted]	
PFS at 6 months	[redacted]	[redacted]
PFS at 12 months	[redacted]	[redacted]
PFS at 18 months	[redacted]	[redacted]
PFS at 24 months	[redacted]	[redacted]
PFS at 30 months	[redacted]	[redacted]

PFS at 36 months	[redacted]	[redacted]

Compared to the results in Table 10 of CS document B, the digitised sample identified five fewer events in the pembrolizumab arm, and seven fewer in the control group, which will affect the results going forward. This is reflected in the slightly lower HR ([redacted]) and slightly different PFS rates at difference months, however these differences are not significant, and should result in similar conclusions regarding the survival modelling.

9.2.1.3 Kaplan-Meier plot

The reconstructed KM plot looks like the one presented in document B (see Supplementary figure 1), however there are differences in the numbers at risk and the censoring bars. These are a result of the nature of the KM data provided by the company that was used for the EAG's reconstruction and survival modelling.


[redacted]

Supplementary figure 1. PFS Kaplan-Meier plot; replication of Figure 5 using 'KM data' from MSD's economic model

9.2.1.4 Proportional hazards testing

9.2.1.4.1 Schoenfeld residuals

The plots of Schoenfeld residuals and time-dependent hazard ratio using the reconstructed KM data looks reasonably like the plot presented in Figure 15 of the CS. Also, the cumulative and log-cumulative hazard plots in Supplementary figure 2 cross. All of which provide sufficient evidence to [redacted] the proportional hazards assumptions, like the company.

Supplementary figure 2. PFS cumulative hazard function

9.2.1.5 Smooth parametric modelling

9.2.1.5.1 Pembrolizumab arm

Supplementary figure 3 fits the seven standard parametric curves to the pembrolizumab arm of the reconstructed KM data. After around [redacted] months, all the curves clearly [redacted] PFS.

Supplementary figure 3. Fitting smooth parametric curves to the pembrolizumab group using reconstructed PFS data

The survival extrapolations from the [redacted] model falls most in-line with the estimates of the NICE TA963 company and EAG advisors. The [redacted] has the best statistical fit. For both models, PFS is [redacted] compared to expectations.36

Supplementary table 2. Long-term extrapolations and model fit for the pembrolizumab arm (standard parametric model)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	60	42	33	27		
Parametric						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.5.2 Control arm

Supplementary Figure 4 fits the seven standard parametric curves to the control arm of the reconstructed KM data. Similarly, after around [redacted] months, all the curves clearly [redacted] PFS

[redacted]

Supplementary Figure 4. Fitting smooth parametric curves to the CT group using reconstructed PFS data

The survival extrapolations from the [redacted] model falls most in-line with the estimates of the MSD and NICE TA963 experts, respectively. The [redacted] has the lowest AIC and the [redacted] has the lowest BIC. However, assessing the survival estimates for these three models shows that, from [redacted] years onwards, these models [redacted] PFS considerably.

Supplementary Table 3. Long-term extrapolations and model fit for the CT arm (standard parametric model)

	2 years	5 years	10 years	20 years	AIC	BIC

MSD experts	11	3-5	2.3	-		
NICE TA963	23	9	7	6		
Parametric						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6 Piece-wise models

9.2.1.6.1 Company's chosen cut-off point

The company identified the cut-off point for the two-piece model by investigating where the hazards for each group start to meaningfully change in the original Kaplan-Meier plot. The company used the Chow test, which is used to determine any structural breaks in a dataset. Using this test, they identified the cut-off point at [redacted] weeks due to the presence of an inflection point at this time, and as that is the earlier of the inflection points; the other being at [redacted] weeks. This was done to preserve statistical power.

9.2.1.6.2 EAG's chosen cut-off points

The EAG investigated the potential for other cut-off points, and how they would affect results. First, the EAG verified the company's cut-off point based on meaningful changes in the Kaplan-Meier plot. Additionally, the EAG also examined the log-cumulative hazard function of each treatment arm. One cut-off point was based on where the two log-CH curves start to diverge from each other, and the other cut-off point was when meaningful changes in each individual curve occurred. Therefore, the third set of piecewise modelling had different cut-off points between the pembrolizumab and placebo arms.

37 Supplementary table 4. Chosen cut-off points for the EAG's piecewise modelling of PFS

Piecewise model	Pembrolizumab + CT	Placebo + CT	Reasoning
1	[redacted]	[redacted]	Replicate MSD's chosen point
2	[redacted]	[redacted]	Assess log CH plot for divergence
3	[redacted]	[redacted]	Assess log CH curves separately

9.2.1.6.3 PW1: Pembrolizumab with cut-off at [redacted] weeks

The EAG first fit the piecewise curves using the company's chosen cut-off of [redacted] weeks. Assuming a year has 365.25 days, [redacted] weeks translates to around [redacted] months. At this cut, the survival probability is [redacted]%. From Supplementary figure 5, the piecewise model is clearly a better fit to the KM data compared to the smooth parametric models from the first part of the modelling, while the [redacted] curve is clearly a poor fit.

Supplementary Figure 5. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 38 weeks

The survival extrapolations from the [redacted] model, using MAE, falls most in-line with the estimates of the NICE TA963 company advisors. However, due to the nature of the [redacted] model, this model will extrapolate to a PFS-free proportion of [redacted]% beyond the 20 years, which is not valid. The [redacted] model is, therefore, the best model based on survival extrapolation. The [redacted] model had the lowest AIC and BIC, while the [redacted] was not significantly worse as the difference in AIC and BIC was around one. Furthermore, the [redacted] model was the company's chosen model.

Supplementary Table 5. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 1)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	60	42	33	27		
PW with 38w cut						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6.4 PW1: CT with cut-off at [redacted] weeks

Compared to the full smooth parametric curves fitted before, the two-piece models in the control arm appear to fit [redacted] nearer the end of the study. At this cut, the survival probability is [redacted]%.

[redacted]

Supplementary Figure 6. Two-stage parametric model fit on the reconstructed CT arm

The best-fitting model based on the MSD experts is the [redacted] model, however this assumes a [redacted]% survival from ten years onwards which is not realistic. The best-fitting model based on the NICE TA963 experts is a [redacted] model which is a

more reasonable fit. The [redacted] model has the lowest AIC and BIC., however the estimated survival at 20 years is [redacted] compared to expectations.

Supplementary table 6. Long-term extrapolations and model fit for the CT arm (piecewise models 1)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
MSD experts	11	3-5	2.3	-		
NICE TA963	23	9	7	6		
PW with 38w cut						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6.5 PW2: Pembrolizumab with cut-off at [redacted] months

At this cut, the survival probability is [redacted]%. From Supplementary Figure 7, the piecewise model is clearly a better fit to the data compared to the smooth parametric models and similar to that of the first piecewise models

Supplementary Figure 7. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 6.5 months

In terms of both statistical fit and survival estimates, the [redacted] was the best fitting model when using the [redacted] month cut. However, as mentioned above, the [redacted] will not decrease below [redacted]% in this case and so is not a valid model to select. The next best model is the [redacted].

Supplementary Table 7. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 2)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	60	42	33	27		
PW with 6.5m cut						
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]

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6.6 PW2: CT with cut-off at [redacted] months

Compared to the full smooth parametric curves fitted before, the two-piece models in the control arm appear to fit better nearer the end of the study. At this cut, the survival probability is [redacted]%.

[redacted]

Supplementary figure 8. Two-stage parametric model fit on the reconstructed CT arm

The best-fitting model based on the MSD experts is the [redacted] model, however this again assumes a [redacted]% survival from ten years onwards which is not realistic. The best-fitting model based on the NICE TA963 experts is a [redacted] model which is a more reasonable fit. The [redacted] model has the lowest AIC and BIC, however this model assumes [redacted]% survival well beyond 20 years.

Supplementary table 8. Long-term extrapolations and model fit for the CT arm (piecewise models 2)

	2 years	5 years	10 years	20 years	AIC	BIC

MSD experts	11	3-5	2.3	-		
NICE TA963	23	9	7	6		
PW with 6.5m cut						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6.7 PW3: Pembrolizumab with cut-off at [redacted] months

At this cut, the survival probability is [redacted]%. Visually, the models with a [redacted] month cut-point fits worse compared to later cut-off points of [redacted] weeks or [redacted] months.

Supplementary Figure 9. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 2.4 months

In terms of both statistical fit and survival estimates, the [redacted] was the best fitting model when using the [redacted] month cut. However, as mentioned above, the [redacted] will not decrease below [redacted]% in this case and so is not a valid model to select. The next best models are either the [redacted] or the [redacted].

Supplementary Table 9. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 3)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	60	42	33	27		
PW with 2.4m cut						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.6.8 PW3: CT with cut-off at [redacted] months

At this cut, the survival probability is [redacted]. Similar to the pembrolizumab arm of the third piecewise modelling analysis, these curves [redacted] PFS after around [redacted] months.

[redacted]

Supplementary Figure 10. Two-stage parametric model fit on the reconstructed CT arm

The best-fitting model based on the MSD experts is the [redacted] model, however this again assumes a [redacted]% survival from ten years onwards which is not realistic. The best-fitting model based on the NICE TA963 experts is a [redacted] model. The [redacted] model has the lowest AIC and the [redacted] the lowest BIC.

Supplementary Table 10. Long-term extrapolations and model fit for the CT arm (piecewise models 3)

38	**2 years**	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**

MSD experts	11	3-5	2.3	-		
NICE TA963	23	9	7	6		
PW with 2.6m cut						
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]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.7 Restricted cubic splines

9.2.1.7.1 Pembrolizumab arm

From Supplementary Figure 11, all the spline models where k>1 fit well, the [redacted] [redacted] PFS at around [redacted] months.

Supplementary Figure 11. Natural cubic splines fit on the pembrolizumab arm KM data

The [redacted] model has the lowest AIC and BIC, while the [redacted] model fits the NICE TA963 experts' opinions best.

Supplementary table 11. Long-term extrapolations and model fit for the pembrolizumab arm (splines)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	60	42	33	27		
Cubic splines						
1-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.7.2 Control arm

Similarly, the models with more than one knot look to be good fits visually to the observed KM data I the control group.

Supplementary Figure 12. Natural cubic splines fit on the control arm KM data

The [redacted] model had the lowest AIC and BIC. Compared to the MSD experts, the [redacted] is the best-fitting, however visually, it [redacted] the observed KM data. Compared to the NICE TA963 experts, the [redacted] model is the best fitting.

Supplementary Table 12. Long-term extrapolations and model fit for the CT arm (splines)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
MSD experts	11	3-5	2.3	-		

NICE TA963	23	9	7	6		
Cubic splines						
1-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.8 Comparing the best-fitting models

Supplementary table 13 shows the best-fitting models by a combination of visual fit, statistical fit, and long-term PFS extrapolations for PFS. In this section, the EAG compared visual fit and long-term PFS extrapolations in conjunction with the EAG's clinical experts to come up with the EAG's base case model.

Supplementary Table 13. Final models assessed for the EAG base case and MSD's chosen model for PFS

	Pembrolizumab + CT	**Placebo + CT**
EAG assessment		
Standard parametric	NA	NA
Piecewise 1 (38-week cut)	Log-logistic Log-normal	Log-logistic
Piecewise 2 (6.5-month cut)	Log-normal Generalised gamma	Log-normal Log-logistic
Splines	2-knot hazards	2-knot normal

	3-knot odds	1-knot odds
Company's preferred	Two-piece log-normal (38 week cut)	1-knot hazards

9.2.1.8.1 Pembrolizumab + CT group

Supplementary Figure 13 plots the six best-fitting models to the pembrolizumab arm of the observed Kaplan-Meier data. Over the trial period, the models closely follow the observed KM line and start to diverge after around 30 months. Supplementary figure 14 shows how these models predict PFS up to 20 years, and there is a clear difference in PFS estimates in the long-term.

Supplementary Figure 13. Visual fit of the six best-fitting models in the EAG's survival analysis for PFS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the pembrolizumab arm only

Supplementary Figure 14. Visual fit of the six best-fitting models in the EAG's survival analysis for PFS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the pembrolizumab arm only

Supplementary table 14 compares different survival models for projecting progression-free survival rates at 2, 5, 10, and 20 years for endometrial cancer patients treated with pembrolizumab plus chemotherapy. These are evaluated against the expert benchmark estimates from NICE TA963 for an alternative treatment (dostarlimab plus chemotherapy).

Using mean average error (MAE), where the average difference between modelled estimates and the NICE TA963 experts' expectations, the EAG ranked the models from 1=best to 7=worst, where the lower values of MAE were ranked better. The best models based on MAE were the [redacted] spline model, and then the [redacted] model. The company's chosen model, based on MAE of their reported extrapolations, is [redacted] best.

It needs to be noted that the NICE TA963 and EAG advisor's mean shown in the first row specifically for 1L dMMR EC patients receiving dostarlimab + chemotherapy (CT). This subgroup is expected to have better outcomes because dMMR tumors tend to respond more favourably to immunotherapies. The modelled estimates apply to a broader dataset that includes both dMMR and pMMR patients. Therefore, it is crucial to account for the differences in patient population and treatment specificity.

Supplementary Table 14. Comparison of long-term PFS extrapolations between the EAG's potential models and the company's base case in the pembrolizumab + CT arm

Pembrolizumab + CT	**2 years**	**5 years**	**10 years**	**20 years**
NICE TA963 company and EAG advisors' mean for 1L dMMR EC patients receiving dostarlimab + CT	60.0%	42.0%	33.0%	27.0%
EAG				
Two-piece log-logistic with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece generalised gamma with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
Company				
Two-piece log-normal with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]

9.2.1.8.2 CT only

Supplementary Figure 15 plots the six best-fitting models to the control arm of the observed Kaplan-Meier data. Over the trial period, the models closely follow the observed KM line and start to diverge after nearing the [redacted] of KEYNOTE-868 (NRG-GY018) follow-up. Supplementary figure 16 shows how these models predict PFS up to 20 years, and there is a clear difference in PFS estimates in the long-term.

Supplementary Figure 15. Visual fit of the five best-fitting models in the EAG's survival analysis for PFS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the control arm only

Supplementary Figure 16. Visual fit of the five best-fitting models in the EAG's survival analysis for PFS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the control arm only

Using MAE in the extrapolations presented in Supplementary table 15, where the average difference between modelled estimates and the NICE TA963 experts' expectations, the best-ranked models were the [redacted] model and then the [redacted] model with a [redacted] cut. Using the NICE TA963 expectations, the best-ranked models were the [redacted] and then the [redacted] model. However, the issues with the NICE TA963 estimates

have been previously mentioned. The EAG's clinical experts believe the clinical experts' estimates via weighted calculation to be appropriate.

Supplementary Table 15. Comparison of long-term PFS extrapolations between the EAG's potential models and the company's base case in the placebo + CT arm

Placebo + CT	**2 years**	**5 years**	**10 years**	**20 years**
Clinical expert – weighted calculation of estimates for all-comers	11.0%	3-5%	2-3%	
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	23.0%	9.0%	7.0%	6.0%
EAG				
Two-piece log-logistic with 38-week cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log-normal with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece log- logistic with 6.5-months cut	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
Company				
1-knot hazards	[redacted]	[redacted]	[redacted]	[redacted]

9.2.2 Overall Survival modelling

9.2.2.1 Source of Kaplan-Meier data

The source of the Kaplan-Meier data for this outcome, overall survival, comes from two sources: Figure 6 of CS document B and the 'KM data' sheet to MSD's economic model. For the pembrolizumab arm, the intervention arm of the Kaplan-Meier plot was digitised, and for the control group, KM data was provided where the proportion of people without an OS event were given at each week, and using the methods described in Guyot et al., the survival IPD was estimated. The KM data provided by the company in the economic model was not used for the pembrolizumab arm as this provided wildly different results to the number of actual deaths in this arm (94 actual deaths vs 51 reconstructed deaths).

9.2.2.2 Descriptive analysis

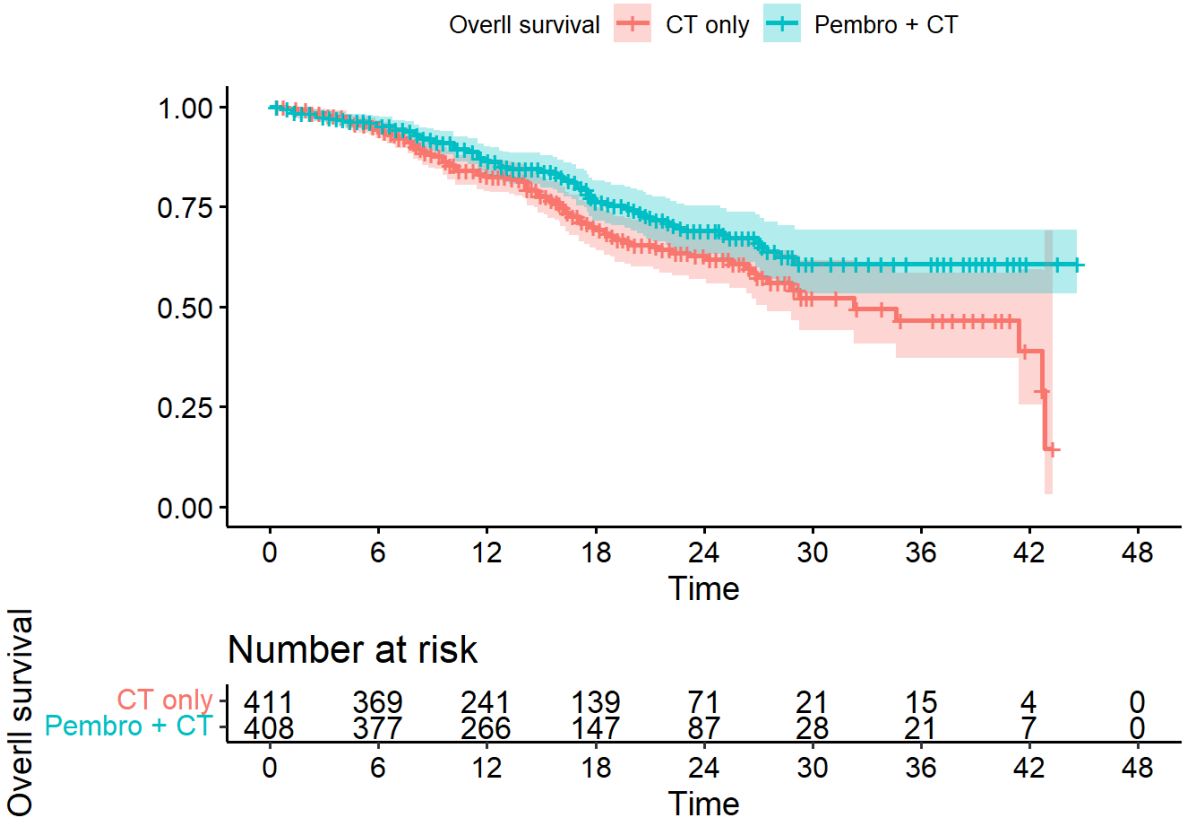
Supplementary Table 16. Results of the reconstructed PFS KM data

	Pembrolizumab + CT	**Placebo + CT**
Total Number	408	411
Number of events (%)	92 (22.5%)	119 (29.0%)
Chi2 p-value	0.04383	
Median OS in months	Not reached	32.3
Hazard ratio (95% CI)	0.71 (0.54, 0.93)	
P-value	0.0141	
OS at 6 months	95.8	94.2
OS at 12 months	86.5	82.8
OS at 18 months	76.3	69.8
OS at 24 months	68.9	62.7
OS at 30 months	60.8	52.2
OS at 36 months	60.8	46.6

Compared to the results in Table 11 of CS document B, the digitised sample identified two fewer event in the pembrolizumab arm, and the same number of OS events in the control group, which will affect the results going forward. This is reflected in the slightly lower HR (0.71 vs 0.74) and slightly different OS rates at difference months; however these differences are not significant, and should result in similar conclusions regarding the survival modelling.

9.2.2.3 Kaplan-Meier plot

The reconstructed KM plot looks similar to the one presented in document B (see Supplementary figure 17), however there are differences in the numbers at risk and the censoring bars. These are a result of the nature of the KM data and the reconstruction process.

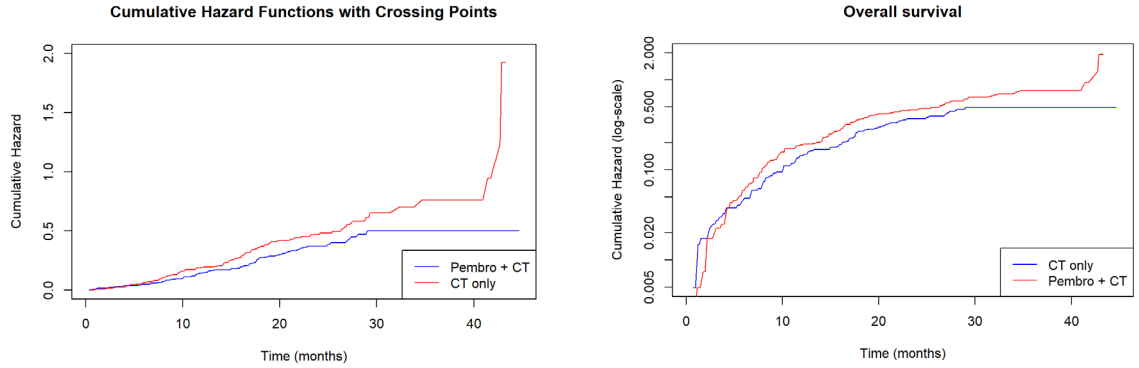


Supplementary Figure 17. OS Kaplan-Meier plot; replication of Figure 6 using 'KM data' from MSD's economic model (control) or digitising Figure 6 (pembrolizumab)

9.2.2.4 Proportional hazards testing

9.2.2.4.1 Schoenfeld residuals

The plots of Schoenfeld residuals and time-dependent hazard ratio using the reconstructed KM data looks reasonably similar to the plot presented in Figure 32 and Figure 33 of the CS. Also, the cumulative and log-cumulative hazard plots in Supplementary figure 18 cross. All of which provide sufficient evidence to reject the proportional hazards assumptions, similar to the company.

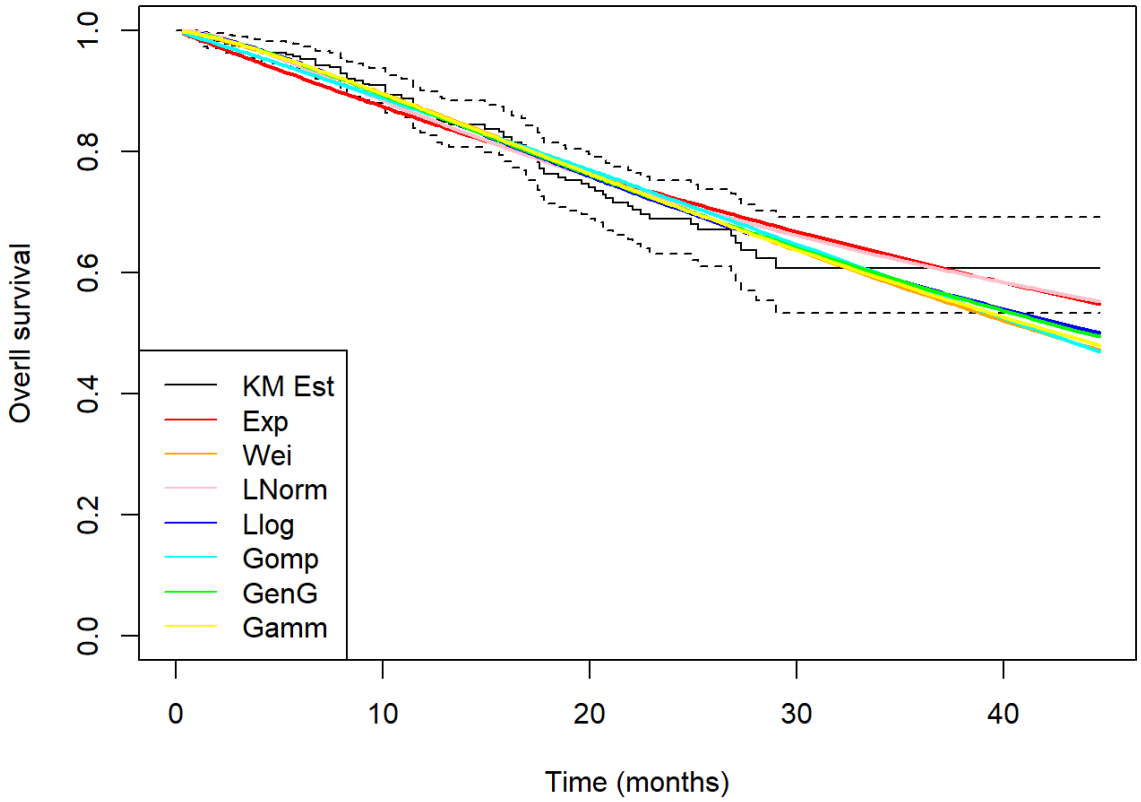


Supplementary Figure 18. OS cumulative hazard function

9.2.2.5 Smooth parametric modelling

9.2.2.5.1 Pembrolizumab arm

Supplementary Figure 19 fits the seven standard parametric curves to the pembrolizumab arm of the reconstructed KM data. Near the end of the trial, by around 35 months, every curve underestimates OS.



Supplementary Figure 19. Fitting smooth parametric curves to the pembrolizumab group using reconstructed OS data

The log-logistic model had both the lowest AIC and BIC. From the two experts estimates the company presented in Table 40 of the CS, NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving PD-1 Inhibitor + CT, and Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from clinical experts), the log-normal model was the best for the former and the log-logistic for the latter.

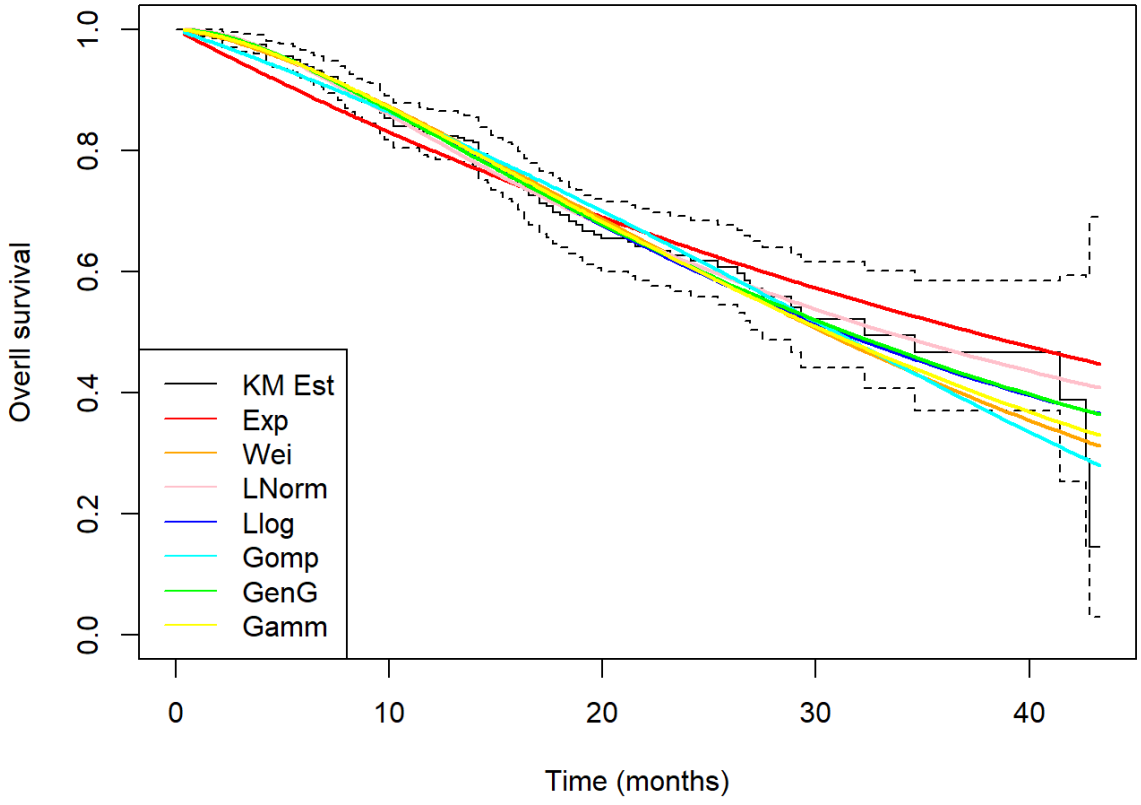
Supplementary Table 17. Long-term extrapolations and model fit for the pembrolizumab arm (standard parametric model)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	82.0	59.0	46.0	38.0		
TA963 and company's clinical experts	59.0	27.0	16.0	10.0		
Parametric						

Exponential	72.4	44.6	19.9	4.0	978.95	982.96
Weibull	71.3	33.4	6.9	0.2	973.88	981.90
Log-normal	71.7	47.0	28.5	14.5	976.68	984.70
Log-logistic	70.9	39.8	19.7	8.4	972.45	980.47
Gompertz	72.1	30.1	0.7	0.0	978.23	986.25
Generalised gamma	71.2	37.6	13.1	1.8	975.29	987.32
Gamma	71.2	35.2	9.5	0.6	973.46	981.48

9.2.2.5.2 Control arm

Supplementary Figure 20 fits the seven standard parametric curves to the control arm of the reconstructed KM data. These curves fit the KM curve of the placebo + CT arm well until the end due to the big drops in the KM curve.



Supplementary Figure 20. Fitting smooth parametric curves to the CT group using reconstructed OS data

The log-logistic model has the lowest AIC and BIC in the control arm and is also the second best fit for both of the company's experts in terms of survival extrapolations at key timepoints over 20 years. The best model for the company's clinical experts is the generalised gamma, and for the NICE TA963 advisors is the log-normal.

Supplementary Table 18. Long-term extrapolations and model fit for the CT arm (standard parametric model)

39	**2 years**	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
Company Experts	55.5	23.0	9.0			
NICE TA963	58.0	30.0	17.0	13.0		
Parametric						
Exponential	64.1	32.9	10.8	1.2	1189.19	1193.21
Weibull	61.3	15.3	0.6	0.0	1169.68	1177.71
Log-normal	61.6	30.1	12.7	3.9	1169.17	1177.21
Log-logistic	60.7	25.0	9.5	3.2	1168.30	1176.34
Gompertz	62.8	7.4	0.0	0.0	1175.67	1186.70
Generalised gamma	61.1	23.6	5.6	0.5	1169.50	1181.56
Gamma	61.0	18.4	1.8	0.0	1168.35	1176.39

9.2.2.6 Piece-wise models

9.2.2.6.1 Company's chosen cut-off point

The company identified the cut-off point for the two-piece model by investigating where the hazards for each group start to meaningfully change in the original Kaplan-Meier plot. The company used the Chow test, which is used to determine any structural breaks in a dataset. Using this test, they identified the cut-off point at 40 weeks due to the presence of an inflection point at this time, and as that is the earlier of the inflection points; the other being at 80 weeks. This was done to preserve statistical power.

9.2.2.6.2 EAG's chosen cut-off points

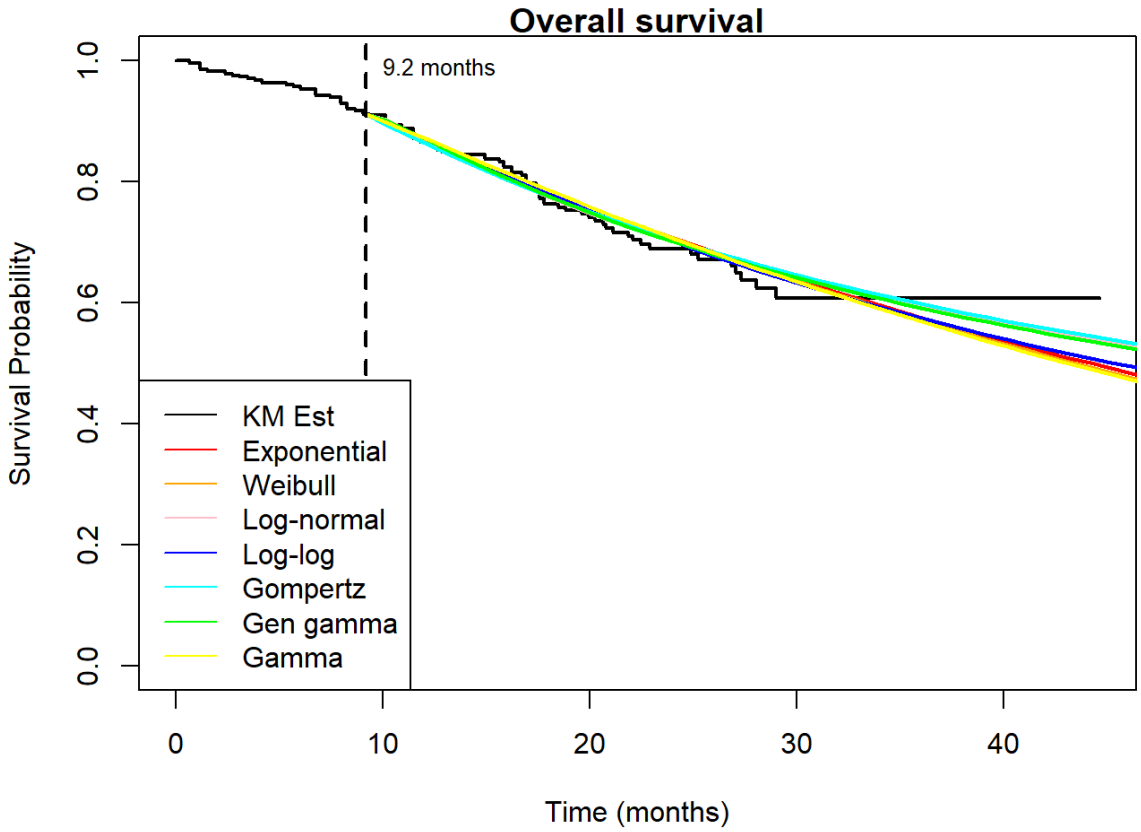
The EAG investigated the potential for other cut-off points, and how they would affect results. First, the EAG verified the company's cut-off point based on meaningful changes in the Kaplan-Meier plot. Additionally, the EAG also examined the log-cumulative hazard function of each treatment arm. One cut-off point was based on where the two log-CH curves start to diverge from each other, and the other cut-off point was when meaningful changes in each individual curve occurred. Therefore, the third set of piecewise modelling had different cut-off points between the pembrolizumab and placebo arms.

Supplementary Table 19. Chosen cut-off points for the EAG's piecewise modelling of OS

Piecewise model	Pembrolizumab + CT	Placebo + CT	Reasoning
1	40 weeks	40 weeks	Replicate MSD's chosen point
2	19.4 weeks	19.4 weeks	Assess log CH plot for divergence
3	9.4 weeks	7.0 weeks	Assess log CH curves separately

9.2.2.6.3 PW1: Pembrolizumab with cut-off at 40 weeks

The EAG first fit the piecewise curves using the company's chosen cut-off of 40 weeks. Assuming a year has 365.25 days, 40 weeks translates to around 9.2 months. At this cut, the survival probability is 91.1%. From Supplementary 21, the piecewise model seem to fit similar to the smooth parametric curves.



Supplementary Figure 21. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 40 weeks

The log-normal model has the lowest AIC, and the exponential model has the lowest BIC. The Gompertz model is the best fit against the NICE TA963 criteria, and the log-logistic model is the best fit against the TA963 criteria.

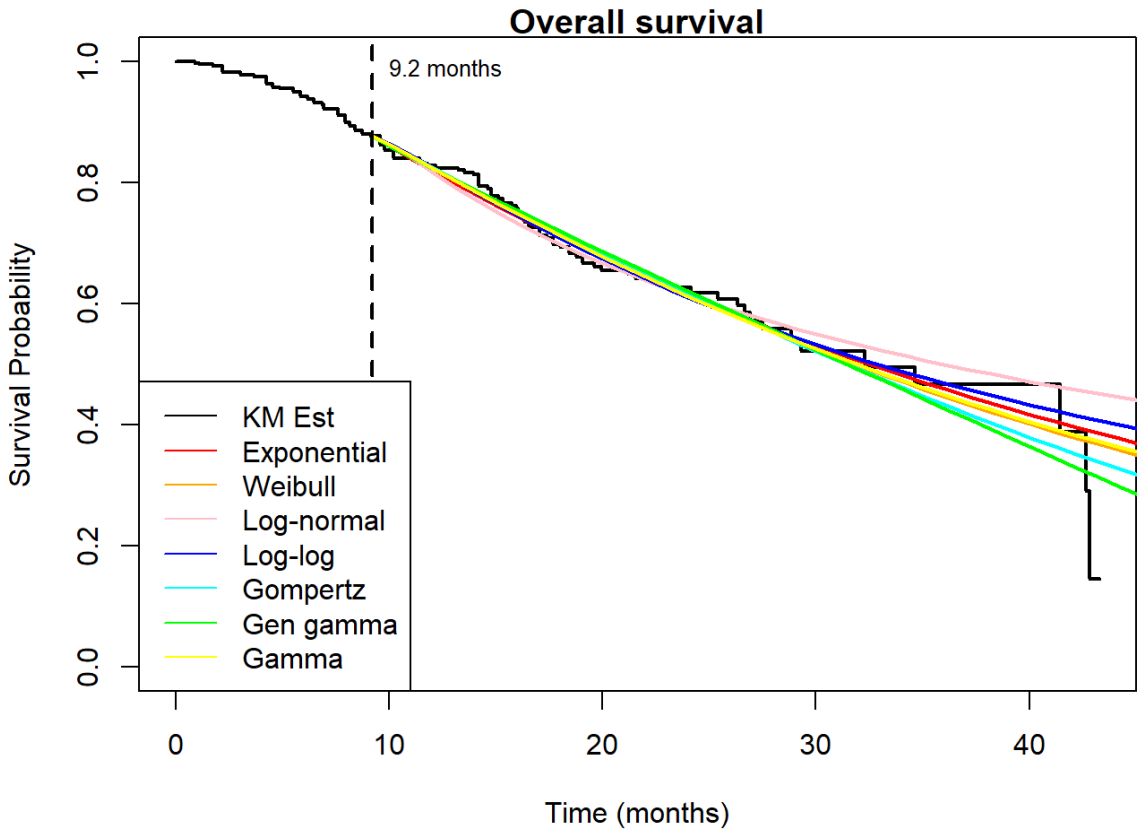
Supplementary Table 20. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 1)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	82.0	59.0	46.0	38.0		
TA963 and company's clinical experts	59.0	27.0	16.0	10.0		
PW with 40w cut						
Exponential	60.4	32.6	11.7	1.5	589.68	593.44
Weibull	60.1	31.4	10.5	1.1	591.63	599.16

Log-normal	61.7	43.0	29.1	17.5	589.06	596.59
Log-logistic	60.1	37.4	21.8	11.5	589.90	597.43
Gompertz	62.0	44.1	34.6	31.0	590.78	598.31
Generalised gamma	61.4	41.8	27.1	15.2	591.01	602.30
Gamma	59.9	30.9	10.1	1.1	591.54	599.07

9.2.2.6.4 PW1: CT with cut-off at 40 weeks

Compared to the full smooth parametric curves fitted before, the two-piece models in the control arm appear to fit in a similar manner. At this cut, the survival probability is 87.7%.



Supplementary Figure 22. Two-stage parametric model fit on the reconstructed CT arm with 40 week cut

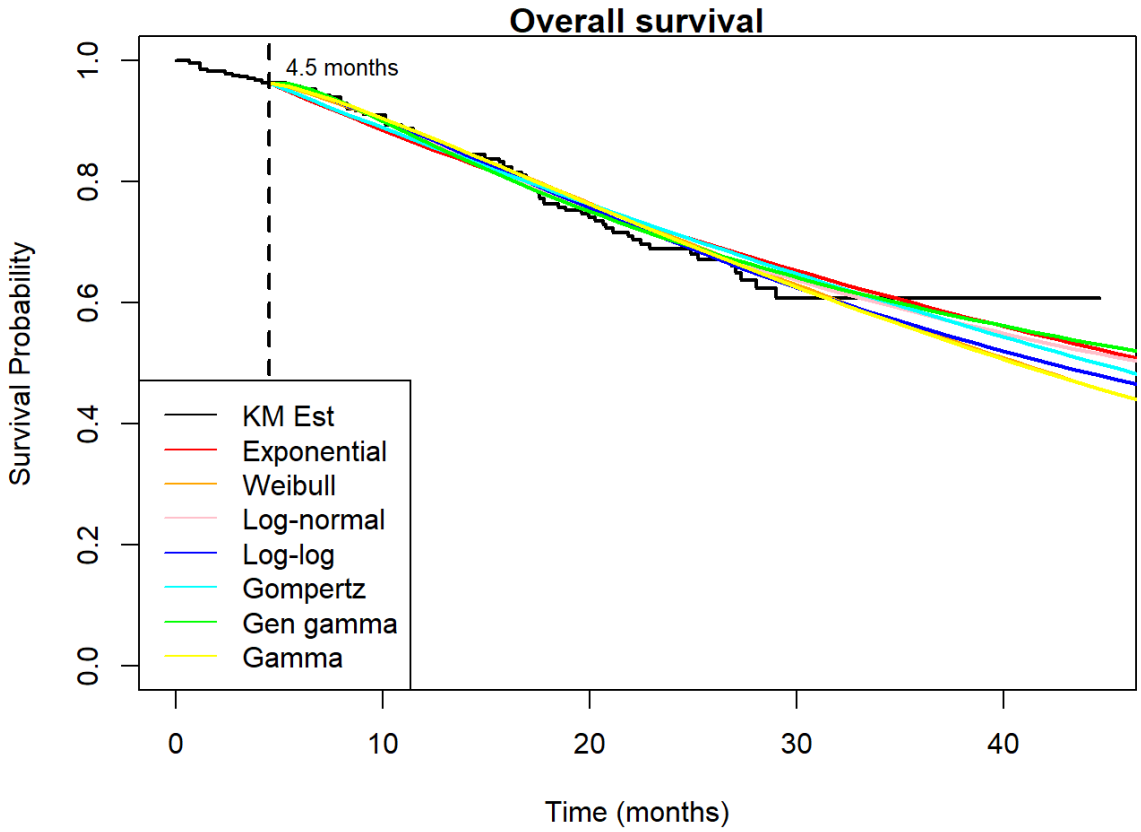
The exponential model has the lowest AIC and lowest BIC. The exponential model is the best fit against the NICE TA963 criteria, and the log-normal model is the best fit against the TA963 criteria.

Supplementary Table 21. Long-term extrapolations and model fit for the CT arm (piecewise models 1)

	2 years	5 years	10 years	20 years	AIC	BIC
Company's experts	55.5	23.0	9.0			
NICE TA963	58.0	30.0	17.0	13.0		
PW with 40w cut						
Exponential	49.2	20.7	4.9	0.3	682.59	686.30
Weibull	48.2	18.0	3.2	0.1	684.22	691.63
Log-normal	52.2	33.7	21.2	11.8	690.67	698.08
Log-logistic	49.7	27.1	14.6	7.2	685.90	693.31
Gompertz	47.4	10.7	0.0	0.0	683.72	691.13
Generalised gamma	47.2	0.1	0.0	0.0	685.28	696.41
Gamma	48.8	18.8	3.8	0.2	684.30	691.71

9.2.2.6.5 PW2: Pembrolizumab with cut-off at 19.4 weeks

At this cut, the survival probability is 96.3%. From Supplementary figure 23, the piecewise models similarly look to fit well until near the end of the trial where they appear to underestimate OS.



Supplementary Figure 23. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 19.4 weeks

The log-normal model has the lowest AIC and BIC. The generalised gamma model is the best fit against the NICE TA963 criteria, and the log-logistic model is the best fit against the TA963 criteria.

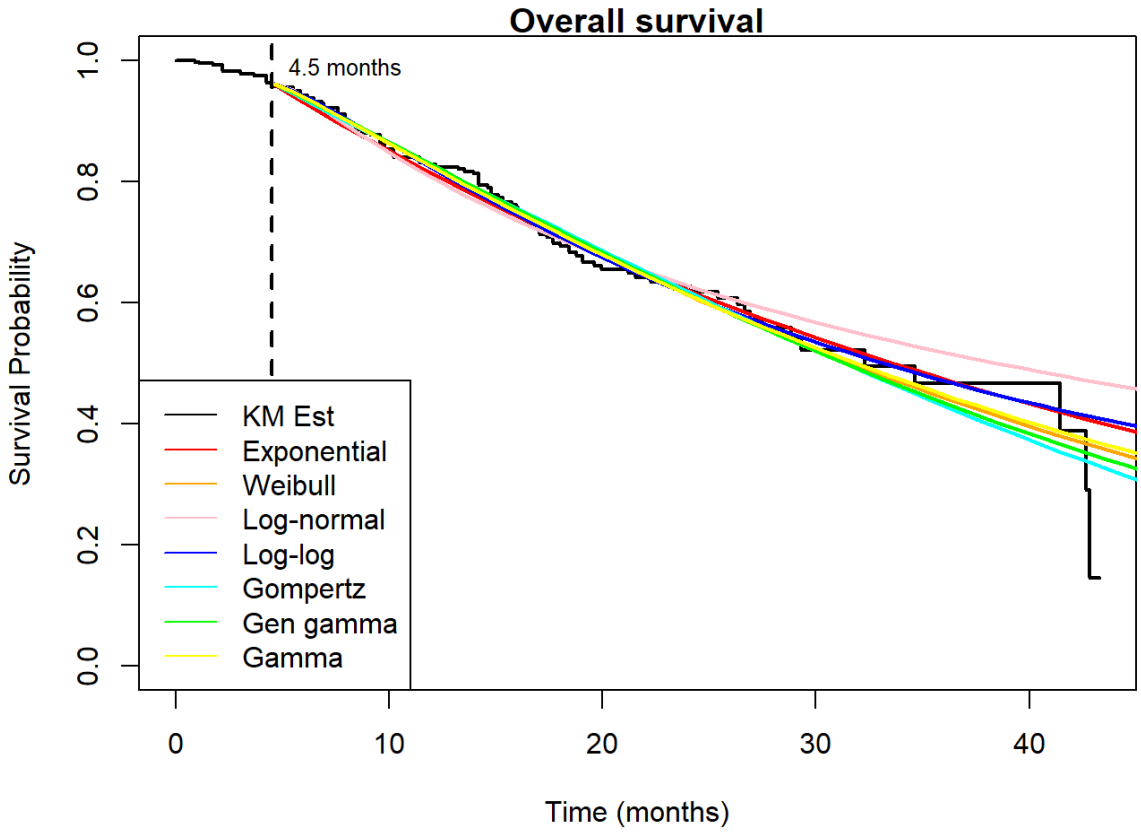
Supplementary Table 22. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 2)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	82.0	59.0	46.0	38.0		
TA963 and Company's clinical experts	59.0	27.0	16.0	10.0		
PW with 19.4w cut						
Exponential	66.8	38.7	15.5	2.5	800.71	804.65

Weibull	64.9	28.6	5.6	0.1	798.31	806.20
Log-normal	65.3	40.5	23.2	11.0	792.28	800.17
Log-logistic	64.3	35.1	17.4	7.6	795.23	803.12
Gompertz	66.5	33.6	6.9	0.0	802.48	810.37
Generalised gamma	65.6	43.2	27.6	15.7	794.03	805.86
Gamma	64.6	29.2	6.9	0.3	797.25	805.15

9.2.2.6.6 PW2: CT with cut-off at 19.4 weeks

At this cut, the survival probability is 96.3%, similar to the pembrolizumab arm at this timepoint.



Supplementary Figure 24. Two-stage parametric model fit on the reconstructed CT arm

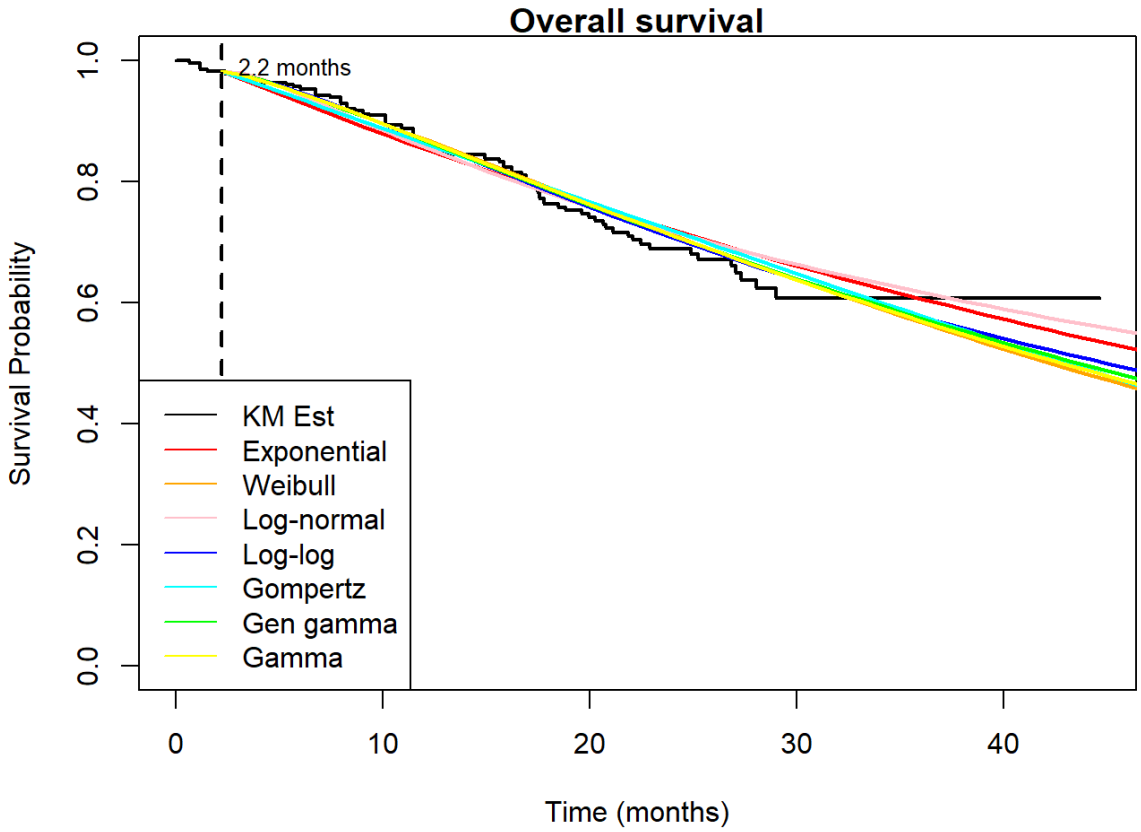
The Gompertz model has the lowest AIC, and the exponential model has the lowest BIC. The exponential model is the best fit against the NICE TA963 criteria, and the log-logistic model is the best fit against the TA963 criteria.

Supplementary Table 23. Long-term extrapolations and model fit for the CT arm (piecewise models 2)

	2 years	5 years	10 years	20 years	AIC	BIC
Company's experts	55.5	23.0	9.0			
NICE TA963	58.0	30.0	17.0	13.0		
PW with 6.5m cut						
Exponential	56.1	25.0	6.5	0.4	999.45	1003.39
Weibull	54.4	19.3	2.8	0.0	999.29	1007.17
Log-normal	58.2	36.6	22.3	11.8	1013.19	1021.08
Log-logistic	55.3	28.7	14.5	6.6	1001.02	1008.91
Gompertz	54.5	12.1	0.0	0.0	999.27	1007.16
Generalised gamma	54.3	16.3	1.1	0.0	1001.13	1012.96
Gamma	54.6	20.7	3.8	0.1	999.46	1007.34

9.2.2.6.7 PW3: Pembrolizumab with cut-off at 9.4 weeks

At this cut, the survival probability is 98.3%. Visually, the models with a 9.4-week cut-point reasonably well but looks to underestimate OS in the long-term.



Supplementary Figure 25. Two-stage parametric model fit on the reconstructed pembrolizumab arm at 9.4 weeks cut

The log-logistic model has the lowest AIC, and the exponential model has the lowest BIC. The log-normal model is the best fit against the NICE TA963 criteria, and the log-logistic model is the best fit against the TA963 criteria.

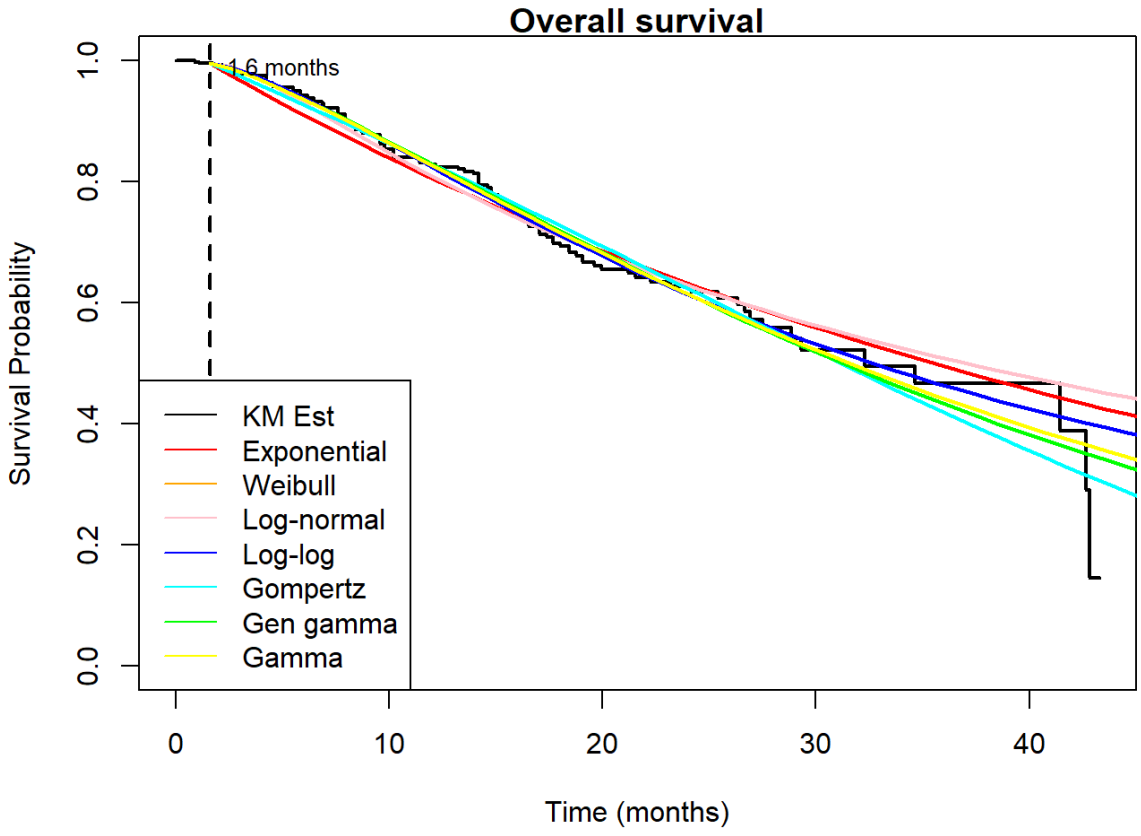
Supplementary table 24. Long-term extrapolations and model fit for the pembrolizumab arm (piecewise models 3)

	2 years	**5 years**	**10 years**	**20 years**	**AIC**	**BIC**
NICE TA963	82.0	59.0	46.0	38.0		
TA963 and Company's clinical experts	59.0	27.0	16.0	10.0		
PW with 9.5w cut						
Exponential	69.8	41.8	17.7	3.2	894.53	898.51

Weibull	68.5	32.6	7.6	0.3	892.35	900.31
Log-normal	69.7	57.2	30.2	16.7	897.83	905.79
Log-logistic	68.1	39.0	20.2	9.0	890.99	898.94
Gompertz	69.3	31.2	2.3	0.0	895.35	903.31
Generalised gamma	68.3	35.6	12.0	1.5	983.99	905.93
Gamma	68.4	34.0	9.6	0.7	892.08	900.04

9.2.2.6.8 PW3: CT with cut-off at 7 weeks

At this cut, the survival probability is 99.5%.



Supplementary Figure 26. Two-stage parametric model fit on the reconstructed CT arm

The Weibull model has the lowest AIC and BIC. The gamma model is the best fit against the NICE TA963 criteria, and the log-normal model is the best fit against the TA963 criteria.

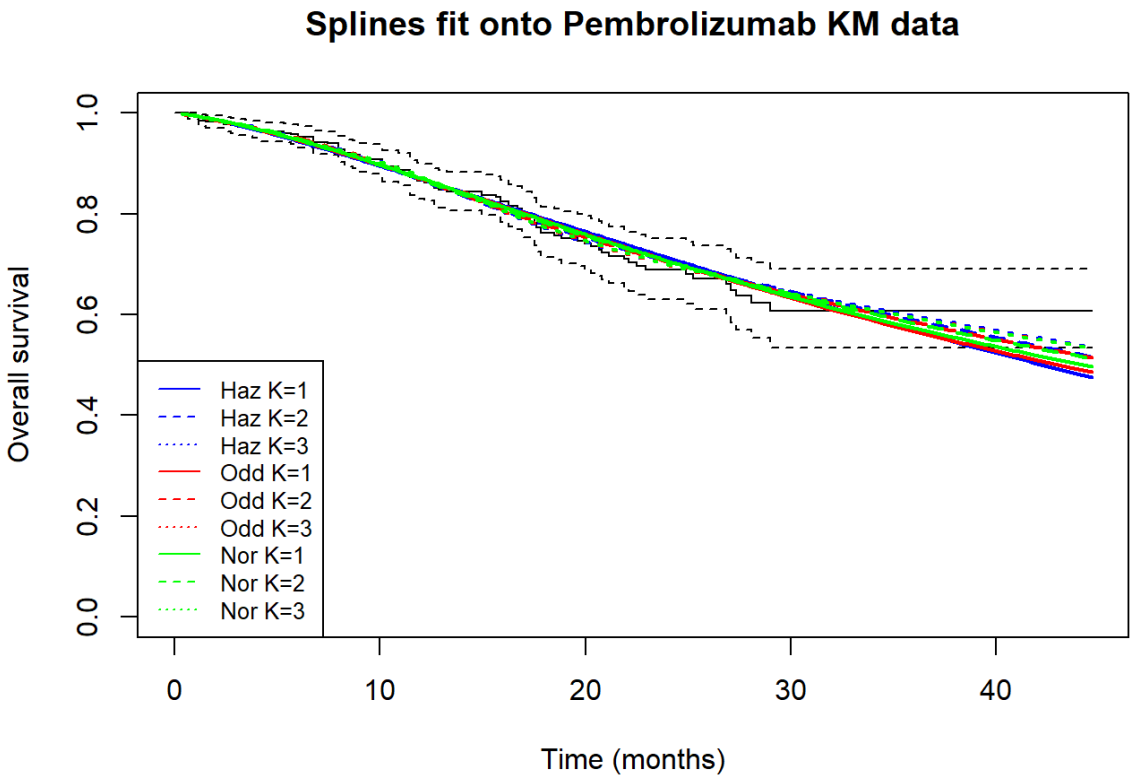
Supplementary Table 25. Long-term extrapolations and model fit for the CT arm (piecewise models 3)

	2 years	5 years	10 years	20 years	AIC	BIC
Company's experts	55.5	23.0	9.0			
NICE TA963	58.0	30.0	17.0	13.0		
PW with 2.6m cut						
Exponential	61.2	29.5	8.7	0.8	1148.10	1152.10
Weibull	58.8	18.4	1.7	0.0	1141.55	1149.55
Log-normal	61.0	35.2	19.0	8.4	1152.30	1160.30
Log-logistic	59.0	28.1	12.7	5.1	1142.69	1150.70
Gompertz	59.6	9.9	0.0	0.0	1143.78	1151.78
Generalised gamma	58.8	18.4	1.7	0.0	1143.55	1155.55
Gamma	58.9	20.8	3.2	0.1	1141.70	1149.70

9.2.2.7 Restricted cubic splines

9.2.2.7.1 Pembrolizumab arm

From Supplementary 27, all the spline models underestimate OS after around 32 months.



Supplementary Figure 27. Natural cubic splines fit on the pembrolizumab arm KM data

The 1-knot normal model has the lowest AIC and BIC and is the second best model based on the estimates from TA963 and clinical experts. The 3-knot odds model is the best fit against the NICE TA963 criteria but the worst fit against the other criteria, while the 1-knot odds model is the best based on the TA963 and clinical experts criteria.

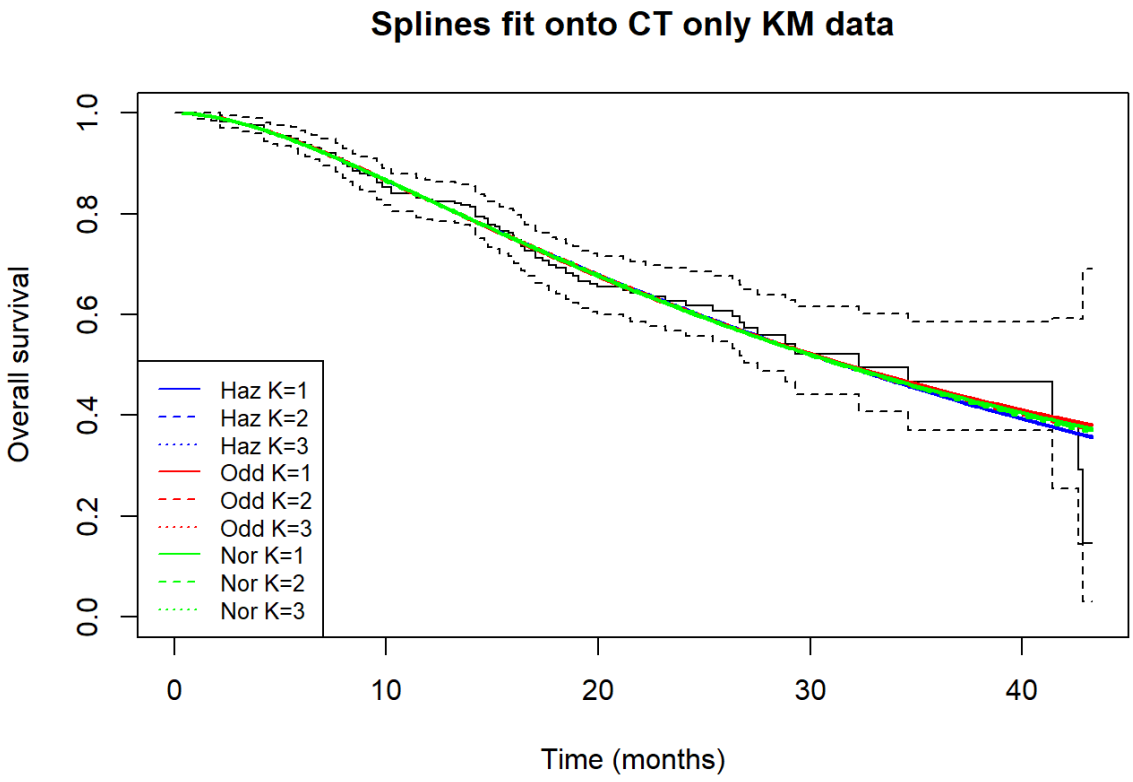
Supplementary Table 26. Long-term extrapolations and model fit for the pembrolizumab arm (splines)

	2 years	5 years	10 years	20 years	AIC	BIC
NICE TA963	82.0	59.0	46.0	38.0		
TA963 and Company's clinical experts	59.0	27.0	16.0	10.0		
Cubic splines						

1-knot Hazards	71.3	33.9	7.4	0.2	975.86	987.90
2-knot Hazards	70.7	40.8	16.0	2.4	975.62	991.67
3-knot Hazards	69.9	44.5	22.4	6.3	976.39	996.45
1-knot Odds	70.7	37.8	17.6	7.0	974.08	986.11
2-knot Odds	70.5	42.0	22.7	10.6	975.09	991.13
3-knot Odds	69.9	45.1	27.3	14.6	976.13	996.19
1-knot Normal	70.7	39.4	18.8	6.7	973.20	985.23
2-knot Normal	70.7	41.6	21.7	8.8	974.98	991.03
3-knot Normal	70.0	45.1	27.0	13.6	975.81	995.87

9.2.2.7.2 Control arm

All nine spline models look to fit the control arm reasonably well.



Supplementary Figure 28. Natural cubic splines fit on the control arm KM data

The 1-knot hazards model has the lowest AIC and BIC but is among the worst models based on both estimates. The 2-knot normal model is the best fit according to clinical experts' estimates. The 1-knot odds model is the best fit according to the NICE TA963 but also the worst fit compared to the other criteria.

Supplementary table 27. Long-term extrapolations and model fit for the CT arm (splines)

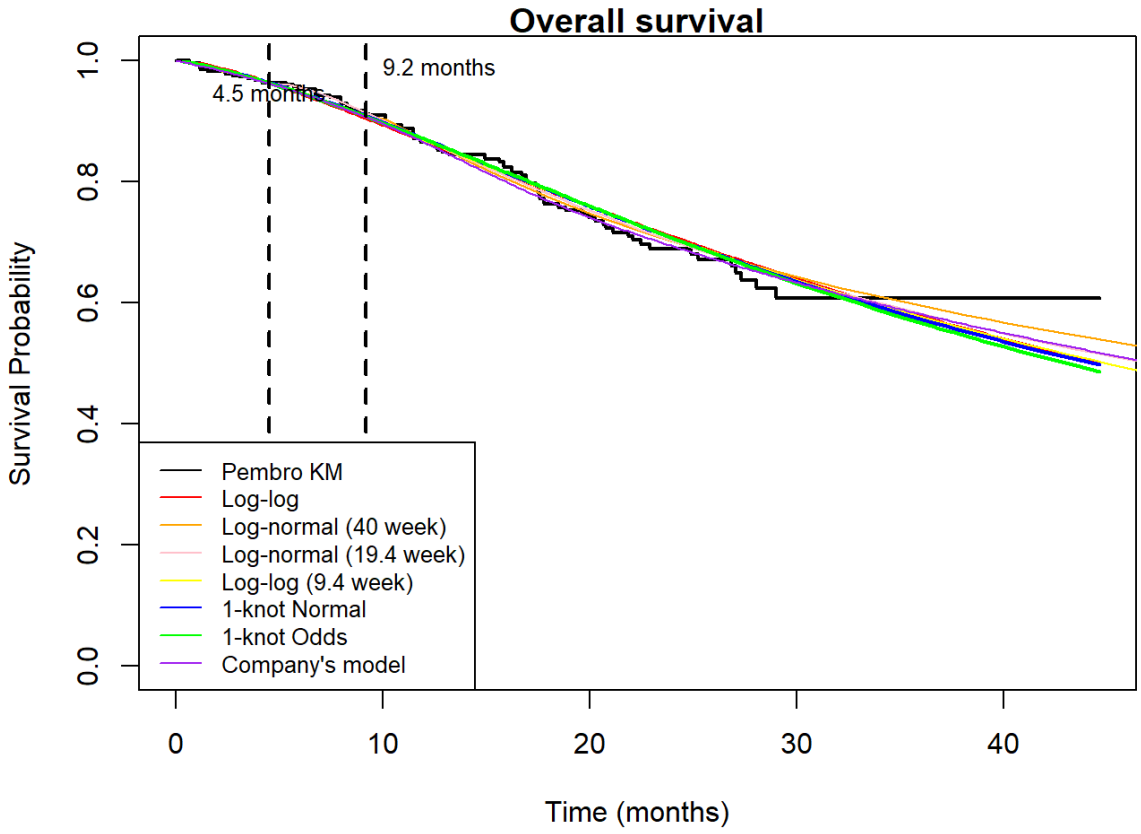
	2 years	5 years	10 years	20 years	AIC	BIC
Company's experts	55.5	23.0	9.0			
NICE TA963	58.0	30.0	17.0	13.0		
Cubic splines						
1-knot Hazards	61.2	21.4	2.6	0.0	1169.28	1181.34
1-knot Hazards	61.3	21.3	2.5	0.0	1171.29	1187.36
2-knot Hazards	61.3	21.4	2.6	0.0	1173.28	1193.37
3-knot Hazards	61.0	27.0	11.1	4.0	1169.96	1182.02
1-knot Odds	61.1	25.6	9.9	3.4	1171.84	1187.91
2-knot Odds	61.1	25.5	9.7	3.2	1173.86	1193.96
1-knot Normal	60.9	25.6	8.7	1.9	1169.63	1181.69
2-knot Normal	61.0	25.1	8.2	1.7	1171.60	1187.67
3-knot Normal	61.2	24.5	7.5	1.5	1173.50	1193.60

9.2.2.8 Comparing the best-fitting models

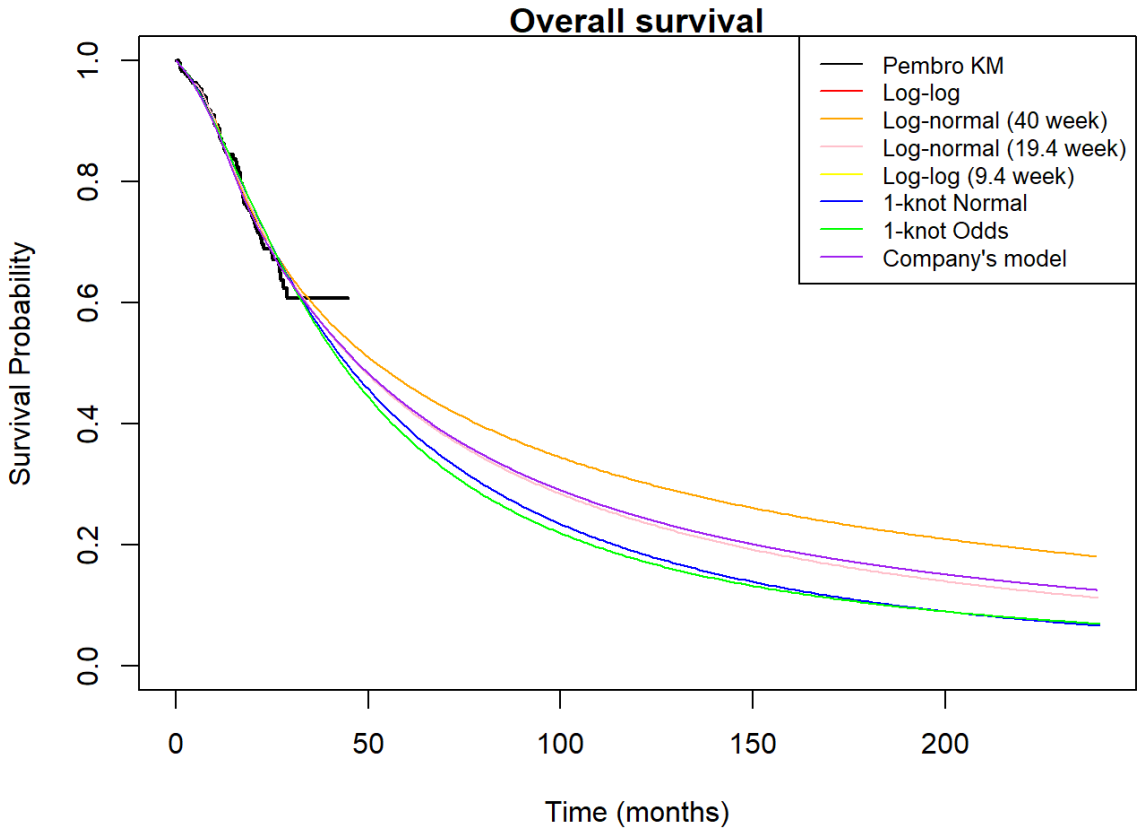
9.2.2.8.1 Pembrolizumab

Supplementary 29 and Supplementary 30 present the potential models chosen by the EAG to model long-term OS using the data from the pembrolizumab arm of KEYNOTE-868 (NRG-GY018), and how the company's chosen model compares (in purple). Near the end of KEYNOTE-868 (NRG-GY018), all the fitted models look to underestimate OS, however this may be due to the plateau after around 30 months. When considering the model estimates over 20 years, the two-stage log-normal

model with a 40-week cut is the most optimistic while the two spline models are the most pessimistic. The company's chosen model sits in between the two extremes.



Supplementary Figure 29. Visual fit of the six best-fitting models in the EAG's survival analysis for OS over the trial period of KEYNOTE-868 (NRG-GY018) (3-knot odds was the company's chosen model) for the pembrolizumab arm only



Supplementary Figure 30. Visual fit of the six best-fitting models in the EAG's survival analysis for OS over 240 weeks (3-knot odds was the company's chosen model) for the pembrolizumab arm only

Supplementary 28 presents the milestone OS estimates and compares them to two sets of experts presented in the company submission. The company's chosen model, the 3-knot odds model, provides the second-closest estimates for the first experts' OS estimates, however this is based solely on dMMR patients, and sixth-best for the weighted average estimate. The log-normal model with a 40-week cut provides the closest estimates for the first set of experts' estimates, and the log-logistic model with 9.4-week cut for the second set.

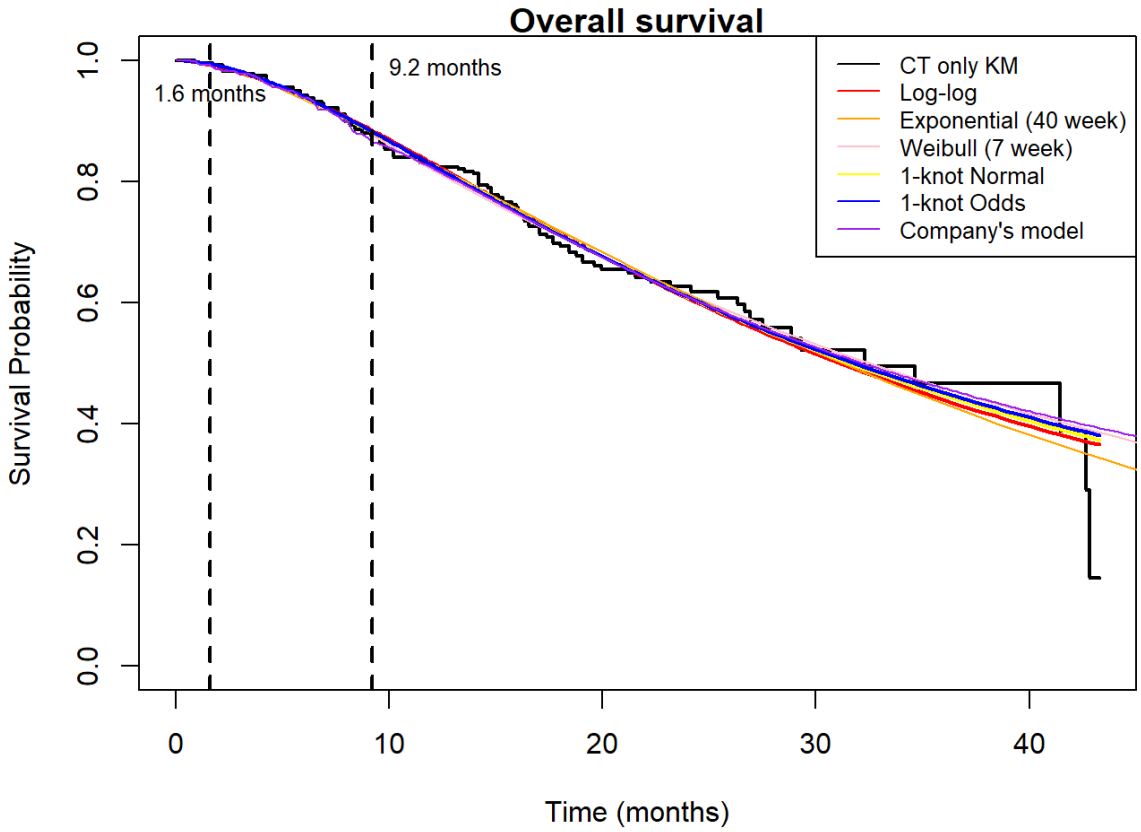
Supplementary Table 28. Comparison of long-term OS extrapolations between the EAG's potential models and the company's base case in the pembrolizumab arm

Pembrolizumab + CT	2 years	5 years	10 years	20 years
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving PD-1 Inhibitor + CT	82%	59%	46%	38%

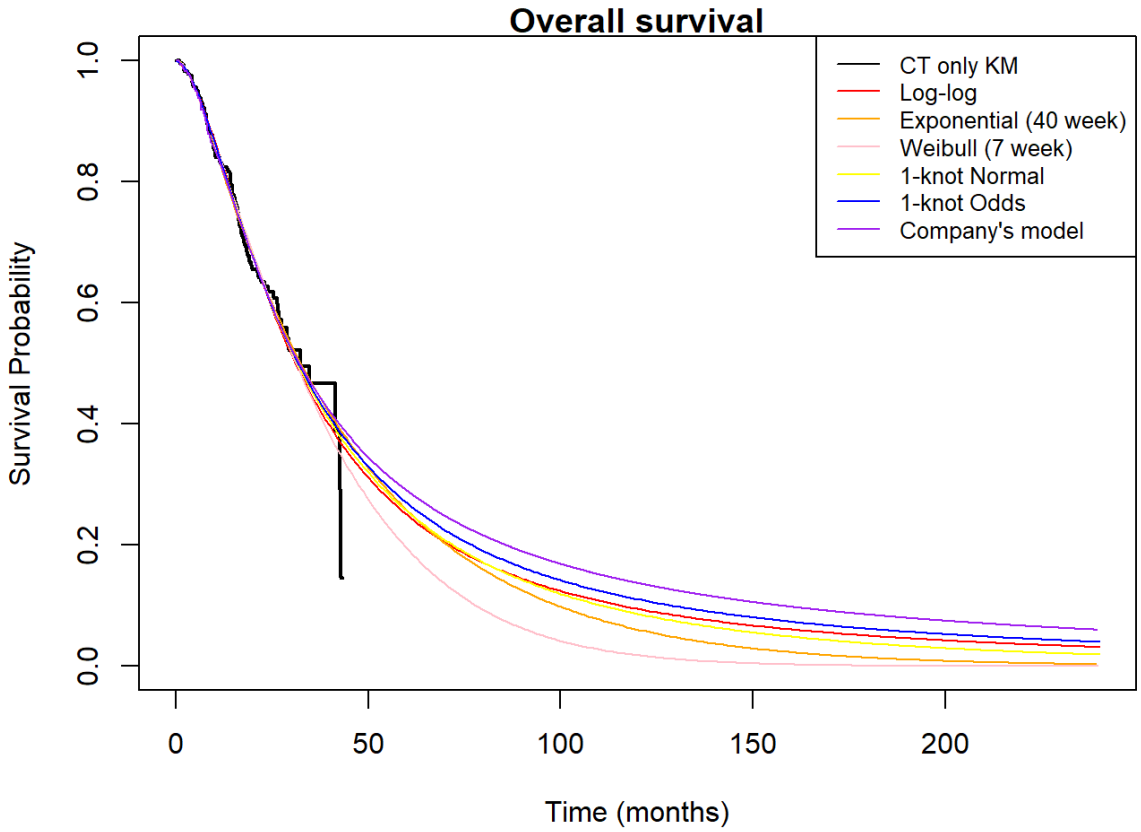
Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from company's clinical experts)*	59%	27%	16%	10%***
EAG				
Log-logistic	70.9%	39.8%	19.7%	8.4%
Log-normal model with 40.0-week cut	61.7%	43.0%	29.1%	17.5%
Log-normal model with 19.4-week cut	65.3%	40.5%	23.2%	11.0%
Log- logistic model with 9.4-week cut	68.1%	39.0%	20.2%	9.0%
1-knot normal spline	70.7%	39.4%	18.8%	6.7%
1-knot odds spline	70.7%	37.8%	17.6%	7.0%
Company				
3-knot odds spline	69%	43%	25%	13%

9.2.2.8.2 CT only

Supplementary 31 and Supplementary 32 shows how the models estimate OS in the control group of KEYNOTE-868 (NRG-GY018). Due to the limited number of participants near the end of the study, the steps in the KM plot are more pronounced, and thus by the end of the study the fitted survival models look to overestimate OS. By 240 weeks, there is a range of OS estimates between the models where some models predict almost no survivors, while other models estimate at least a few survivors.



Supplementary Figure 31. Visual fit of the five best-fitting models in the EAG's survival analysis for OS over the trial period of KEYNOTE-868 (NRG-GY018) (38-week two-piece log-normal was the company's chosen model) for the control arm only



Supplementary Figure 32. Visual fit of the five best-fitting models in the EAG's survival analysis for OS over 240 weeks (38-week two-piece log-normal was the company's chosen model) for the CT only arm only

Supplemental Table 29 provides the estimates OS in the control arm between the EAG's possible chosen model and the company's base case. The model whose estimates are most aligned with the first set of experts (in the first row of the table) is the 1-knot normal spline model, and the model most aligned with the second set of experts is the 1-knot odds spline model.

Supplementary Table 29. Comparison of long-term OS extrapolations between the EAG's potential models and the company's base case in the control arm

Placebo + CT	**2 years**	**5 years**	**10 years**	**20 years**
Company's Clinical Expert – weighted calculation of estimates for all-comers	54-57%	21-25%	9%	-
NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT	58%	30%	17%	13%
EAG				

Log-logistic	60.7%	25.0%	9.5%	3.2%
Exponential model with 40-week cut	49.2%	20.7%	4.9%	0.3%
Weibull model with 7-week cut	58.8%	18.4%	1.7%	0.0%
1-knot normal spline	60.9%	25.6%	8.7%	1.9%
1-knot odds splines	61.0%	27.0%	11.1%	4.0%
Company				
Log-logistic	61%	26%	10%	4%

Supplementary table 30: Costs of additional adverse events experienced in ≥2% of patients in the all-comer population included in the model

Adverse event category	Cost per episode	Source
Pulmonary embolism	£2,077.99	Company's estimate
Hypokalaemia	£1,081.00	NHS reference costs 2022/23. Weighted average of FD04A, FD04B (Nutritional disorders with intervention)
Diarrhoea	£545.34	Company's estimate
Neutropenia	£1,667.58	Company's estimate

9.3 Appendix 3: Confidential appendix

Appendix 3 is the confidential appendix and is provided separately.

9.4 Appendix 4: Confidential appendix supplementary document

Appendix 4 summarises the contents of the confidential appendix and is provided separately.

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **19 November 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Reference to the CAA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 120: EAG report states "A commercial access agreement (CAA) is in place for pembrolizumab (XXX%) and was applied in the model"	Remove (XXX%). If needed, please cross-refer to the relevant CS document B appendix.	MSD request that the details of the CAA are removed from the report to reduce the risk of unintentional data leaks and breach of confidentiality.	We have removed the (XXX%) as requested and cross-referred to CS document B, appendix K by including the statement "details are provided in CS document B, Appendix K"

Issue 2 Implementation of the EAG base case in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Potential error in the plotting of EAGs two-piece curves (PFS and OS, for both arms) in the Excel model sheet <EAG Model Extrapolations>	MSD request the EAG to double check the plots, especially with consideration to the break point for the two-piece curves	At the point where the two-piece curves switch from the KM data to the fitted curve, there seems to be an unrealistic drop in the KM curves: • For the EAG's OS base case, this drop is relatively small (2%), but a 2% drop in a single week still seems clinically implausible. • For the EAG's OS 'Scenario 1' curve, the drop at the two-piece	The EAG noted a slight issue with the R code which has now been resolved. All figures and tables in report have been updated to reflect the revised estimates used. See: Issue 5

		cut point at 40 weeks is 15% in a single week. This does not seem clinically plausible.
		• This drop is seen in all other two-piece EAG curves included in the Excel model, specifically:
		  ○ Pembrolizumab + CT PFS scenario 2
		  ○ CT PFS scenario 2
			Table 1: EAG Exploratory analyses (OS extrapolation)
			Table 2: EAG's preferred model assumptions (EAG02)
			Table 3: EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab
			Figure 1: Incremental scatterplot for the comparison between pembrolizumab + CT versus CT
			Figure 2: Cost-effectiveness acceptability curve

Implementation of the EAG curves into the model engine is producing incorrect long term survival estimates, typically	MSD requests that the EAG re-run the analysis using curve extrapolations with the greatest precision possible (in terms of decimal places). When these	The EAG's fitted curves in <EAG Model Extrapolations> are static values, with many rounded to 3dp (Columns D,G,H,I). This rounding means the weekly hazard/risk of	As above, the EAG has now updated all analyses using the revised estimates with the greatest precision possible

overestimating mortality or progression. This in turn impacts the model ICER	curves have been updated in the <EAG Model Extrapolations> sheet, the current EAG macros can be used as normal to run the scenarios again	death is not a smooth, continuous function. The weekly hazard function is made up of high weekly hazards followed by weeks of low/zero hazard (see Figure 1 in the Appendix of this document for a clearer demonstration of the issue regarding the hazard function related to the pembrolizumab EAG OS base case). At the macroscale this averages out to produce a smooth looking curve, but at the microscale (weekly) the KM becomes steplike (weeks of constant OS followed by single large drops of survival). When these weekly hazards are run through the model engine (<trace_treatment1> for pembrolizumab or <trace_treatment2> for CT curves), the application of background general mortality unduly affects the OS leading to much higher rates of mortality than expected. This is most notable from week 300 onwards when, for many cycles (weeks), the risk of mortality for the EAG's OS curve is 0 as the rounding of the values has likely	

		hidden small changes in OS. In these cycles, background mortality further pushes down the KM curve, leading to something akin to double counting of hazards. MSD looked to reanalyse the EAG pembrolizumab OS base case correcting for both the sudden drop in OS at the two-piece cut point and to smooth out the hazard function by using the model parameters provided by the EAG. When this was done the EAG's corrected base case resulted in an extra ≈ 0.63 incremental undiscounted LYs (≈ 0.39 discounted LYs). This in turn will result in updated QALYs and ICERs, therefore correcting this is important to ensure the cost-effectiveness results are accurate. See Figure ***2*** in the Appendix of this document for a clearer demonstration of the difference between the implementation of the curves.	

		For clarity, this will affect all curves that have been rounded to 3 dp, not just the pembrolizumab EAG base case OS curve described in this example.	

Issue 3 Trial Descriptor

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the trial which informs the CS is referred to as "*KEYNOTE-868*"	As per the CS, we request the EAG refer to the trial as "*KEYNOTE-868 (NRG-GY018)*" consistently throughout the EAG report	This is a non-MSD sponsored study. Guidance received by MSD when preparing the CS was that the correct terminology to use when referring to the study is "KEYNOTE-868 (NRG-GY018)"	We have amended references to KEYNOTE-868 (NRG-GY018) throughout.

Issue 4 Reference to "statistical significance" association with results from analysis of the all-comer population, generated post-hoc

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In multiple instances throughout the EAG report, reference is made to [redacted] of results based on analysis of the all-comer population,	In line with the wording used throughout the CS when referring to results in the all-comer population generated through post-hoc analyses, we request that the EAG revise references to	Statistical significance cannot be attributed to results generated through post-hoc analyses, as such analyses were not associated with any formal hypotheses testing.	This wording had been amended in the EAG report on pages 12, 57, 58, 68, 72 and 75.

generated through post-hoc analyses Page 12: EAG report states "*analysis of the all-comer population showed a [redacted] improvement*…." Page 57: EAG report states *"….representing a statistically significant [redacted] relative [redacted] in the risk of disease progression or death following treatment with pembrolizumab + CT…*" Page 57: EAG report states "*The OS hazard ratio was 0.74 (95% CI: 0.57, 0.97, p=0.0153), representing a statistically significant 26% reduction in the risk of death*"	"[redacted]" and replace with "*clinically meaningful"*	The only analyses associated with formal hypothesis testing (and therefore where statistical significance can be stated) were the PFS analyses in the dMMR and pMMR cohorts at the IA (Dec 2022 data cut).	

Page 58: EAG report states "*There was an improvement in ORR in the pembrolizumab + CT arm (75.2%) compared to placebo + CT (62.6%), with a statistically significant estimated difference in treatment…*" Page 68: EAG report states "*In the dMMR cohort, the hazard ratio was 0.57 (95% CI: 0.31, 1.04, p=0.0323), representing a statistically significant…*" Page 72: EAG report states "*Comparisons with placebo + CT arm in the all-comer population at the August 2023 data cut showed* [redacted] *in all outcomes*" Page 75: EAG report states " • At the efficacy and safety update analysis (August			

2023), analysis of the all-comer population showed a [redacted] …"			
Page 16 EAG report (Table of Issue 1), first row states "…*This introduces potential bias, reduces statistical validity…*" And Page 34: EAG report states *"…conducting post-hoc analyses of the all-comer population in the KEYNOTE-868 trial introduces potential bias, reduces statistical validity, and risks overgeneralising the results*…" And Page 76: EAG report states *"…(i.e., separate cohorts for dMMR and pMMR patients) and may introduce potential bias, reduce statistical validity…*"	Please remove "*reduces statistical validity*" from these sentences.	No formal hypothesis testing took place with respect to the post-hoc analyses conducted to generate all-comer population data based on the August 2023 data cut, as the primary objective was met at IA1; so all subsequent statistical testing would be considered nominal, regardless of whether conducted post hoc or not.	We have implemented these changes to the EAG report.

Issue 5 Lack of clarity regarding which clinical experts are being referred to in some sections of the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In various sections of the EAG report (detailed below), reference is made to advice/preferences provided by "clinical experts". In such instances, the current wording does not make clear if it is the company's clinical experts, the EAG's clinical experts, or the clinical experts consulted in TA963, who are being referred to. Page 13: EAG report states *"….when OS extrapolations assumptions and starting age in economic model are changed to reflect EAG's preferences as advised by clinical experts"* Page 21 (issue 6): EAG report states "*Starting age at baseline is increased from*	We suggest that for each sentence, it should be made clear whether it is the company's or EAG's clinical experts being referred to.	For the avoidance of misinterpretation and to provide clarity to the reader on the origin of certain assumptions/preferences.	For all instances where clinical experts are mentioned, we have amended the text to clarify which experts are being referred to.

65.4 to 67.1 years to reflect clinical expert opinion…" Page 22 (issue 7): EAG report states "*Clinical expert opinion indicates that utilities will likely differ between pMMR and dMMR patients…"* Page 23 (Issue 8): EAG report states "…*for patients receiving IO and chemotherapy combination from clinical experts*…" Page 55: EAG report states "…*with trial population potentially being healthier and younger than patients that clinical experts might expect to see in their patients in the UK*." Page 84: EAG report states "*Supports clinical expert*			

opinion of higher starting age" Page 87: EAG report states: "*Alternative evidence on mean starting age, sourced through the literature (Table 7), supports the clinical experts' opinions*" Page 103: EAG report states: "*Clinical expert – weighted calculation of estimates for all-comers*" Page 108: EAG report states: "*Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from clinical experts)*" Page 110: EAG report states: "*Clinical Expert – weighted calculation of estimates for all-comers*"			

Page 127: EAG report states "*However, the clinical experts consulted stated that patients undergo a series of blood tests at the beginning of each chemotherapy cycle…."* Page 134: EAG report states: "*First, considering that patients with EC undergo series of blood tests at the beginning of each chemotherapy cycle (clinical expert confirmation)…"* Page 147: The EAG report states: "*This exploratory analysis draws on clinical experts' opinions of what would be considered a clinically plausible benefit…*" Page 148: The EAG report states: "…*clinical experts emphasised that patients in the pembrolizumab + CT*			

arm will typically have more blood tests and outpatient appointments." Page 156: The EAG report states: "*Adjusting the subsequent treatment mix to reflect treatments received by UK patients based on clinical expert opinion*." Page 158: The EAG report states: "*Starting age at baseline is increased from 65.40 to 67.1 years to reflect clinical expert opinion*…" Page 206, 210, 213, 216, 219: The EAG report states: "*Experts*" Page 208, 211, 214, 217: The EAG report states: "*TA963 and clinical experts*" Page 222: The EAG report states: "*Weighted average*			

*of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from clinical experts)**" Page 224: The EAG report states: "*Clinical Expert – weighted calculation of estimates for all-comers*"			

Issue 6 OS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: EAG report states "*The company prefers OS extrapolations for pembrolizumab +CT that predicts large (benefit) in terms of survival for the technology".*	MSD requests that the statement be removed.	MSD had chosen the OS extrapolations with scientific rigour. As detailed in the CS, the base-case OS curve was selected not only based on statistical and visual fit, but also corroborated with a weighted average of: the weighted average landmark estimates for dostarlimab + CT for the dMMR cohort provided by company and EAG clinical experts as part of TA963; and pMMR estimates for patients receiving CT by MSD clinical	We have amended the statement to: The company's selected OS extrapolations for pembrolizumab +CT predicts large (benefit) in terms of survival for the technology compared to the comparator.

		experts, based on the dMMR and pMMR proportions in KEYNOTE-868 (NRG-GY018). Since this approach assumes that pembrolizumab + CT has no benefit in the pMMR group, these estimates are highly conservative and should be considered the lower bound. Landmark estimates from the selected 3-knot odds curve yielded a moderate estimate of treatment effect amongst all possible curves across all time points. The EAG's statement is therefore a misrepresentation of the deliberate selection that was conducted by MSD. In addition, this statement contradicts a further assessment made by the EAG, where in page 93, the EAG opined that "*it is conceivable that multiple models are a good fit when using the long-term estimates as a criterion, this includes the chosen 3-knot odds model which provides plausible estimates.*"	

Issue 7 Representativeness of the post-hoc analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16: In the table outlining Issue 1, against the subheading "What alternative approach has the EAG suggested?", the EAG report states "*Stratified analyses to maintain the all-comer analysis while preserving the separation between dMMR and pMMR patients, allowing for clearer insights into treatment effects. Subgroup analyses should further explore progression-free survival (PFS), as differences between dMMR and pMMR were seen in PFS but not overall survival.* *Additionally, propensity score matching could be used to adjust for imbalances between the two cohorts, ensuring more accurate comparisons when combining them*."	MSD requests that the following sentence is removed: *"Subgroup analyses should further explore progression-free survival (PFS), as differences between dMMR and pMMR were seen in PFS but not overall survival."*	In the CS (section B.3.12) and Appendices (E and O), MSD presented clinical and cost-effectiveness analyses based on dMMR and pMMR cohorts separately, in line with the trial design. The forest plots (Figures 12 and 13 in the CS) show the stratification factors, one of which was MMR status. MSD would like to highlight that KEYNOTE-868 (NRG GY018) is a randomised trial, and the two cohorts (dMMR and pMMR), will already be balanced; therefore propensity matching would not be appropriate. Both the dMMR and pMMR cohorts in the trial were powered independently. Enrolment in the trial had two stages. First the patient's MMR status was used to assign to the dMMR or pMMR group. Then the assignment to the pembrolizumab arm or placebo arm was made.	The EAG acknowledges the company's rationale regarding the randomisation process and cohort balancing in the KEYNOTE-868 trial. However, the suggestion to explore further PFS subgroup analyses was made to highlight the potential for additional insights, especially as the EAG observed differences in PFS between the dMMR and pMMR cohorts. While acknowledging that the trial design inherently balances the cohorts, we still believe that a closer look at PFS differences could provide further understanding of the treatment effect across these subgroups. We also note that MSD has already accounted for these differences in its analyses. Therefore no amendments have been made to this statement as this is not a factual inaccuracy.

Issue 8 Sub-groups examined

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17: Outline of issue 2 in the EAG report states *"The KEYNOTE-868 (NRG-GY018) trial[2] did not systematically collect data on the site of recurrence (local vs. metastatic) or on prior debulking surgery, limiting subgroup analyses which were outlined in the NICE scope*" without providing any context of responses on this issue previously provided by MSD Page 66 of EAG report states "*The CS (and the KEYNOTE-868 trial) does not examine how pembrolizumab performs in local versus metastatic cases or in patients with versus without prior debulking surgeries*."	We request the statements on pages 17 and 66 are amended as follows, in particular because KEYNOTE-868 (NGR-GY018) was a non-MSD sponsored study: Page 17: *The KEYNOTE-868 (NRG-GY018) trial[2] did not systematically collect data on the site of recurrence (local vs. metastatic) or on prior debulking surgery,* ***which limited the feasibility of the company being able to conduct*** *subgroup analyses which were outlined in the NICE scope*" Page 66: *The CS (and the KEYNOTE-868* ***(NRG-GY018)*** *trial) does not*	Please see the following explanation previously provided in response to scoping consultation and in the CS (Table 1: The decision problem): "*Information concerning site of recurrence was not systematically collected in the KEYNOTE-868 (NRG-GY018) trial. Forest plots available in the CSR make a distinction between subgroups based on whether patients had recurrent or primary advanced disease at the start of the trial, but not explicitly based on site of recurrence (local versus metastatic). Although the CSR for KEYNOTE-868 (NRG-GY018) does have indirect data points with regards to details about the site of recurrence, identification and prior therapies, which could potentially be used to assess some of the site-relevant information for recurrent patients, more detailed data may have*	The EAG acknowledges that the company was unable to *systematically collect data on the site of recurrence (local vs. metastatic) or on prior debulking surgery.* However, the limited feasibility was not mentioned in the CS decision problem. Therefore, no amendments have been made to page 17 as this is not a factual inaccuracy. The EAG have made this change to p66 of the EAG report

	examine how pembrolizumab performs in local versus metastatic cases or in patients with versus without prior debulking surgeries. ***The company previously confirmed it was not possible to present analyses based on these subgroups due to a lack of systematic data collection on these characteristics in the KEYNOTE-868 (NRG-GY018) trial.***	*gaps and will likely be subject to limitations when attempting to interpret the data. Therefore, evidence does not allow for the consideration of the local versus metastatic recurrence subgroups.* *Information concerning proportion of people who had primary debulking surgery versus those who have not had surgery was also not systematically collected in the KEYNOTE-868 (NRG-GY018) trial."*	
Page 147: Under the subgroup analysis subheading, EAG report states "*The company undertook exploratory analyses for the pMMR and dMMR subgroups*"	We request the sentence is amended to *"The company presented analyses for the pMMR and dMMR subgroups based on the KEYNOTE-868 (NRG-GY018) trial design*"	The two cohorts based on MMR status were each powered and prespecified in the KEYNOTE-868 (NRG-GY018) trial.	We have implemented the requested change (p150).

Issue 9 Short duration of follow-up

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18: Outline of issue 3 in the EAG report states *"Longer follow-up of participants (beyond median 16.3 months) would inform the impact of treatment and would strengthen the clinical effectiveness evidence."* No reference is made to the fact that MSD had already confirmed in the CS and in response to a clarification question that additional follow up data, beyond the August 2023 data cut, is currently unavailable.	We request the sentence is amended to state "*Longer follow-up of participants (beyond median 16.3 months) would inform the impact of treatment and would strengthen the clinical effectiveness evidence.* ***The company has previously confirmed in response to clarification questions that further data from the KEYNOTE-868 (NRG-GY018) trial will only be available following Final Analysis, which is currently planned for*** [redacted]*"*	In response to CQ A8, MSD had provided the following information: "*The August 2023 data cut presented in the submission is the most recent data cut from the trial. The next planned data cut for this trial is Final Analysis, with outputs due in* [redacted]". We consider it important that this additional context is provided in the EAG report.	The EAG have made this change to the report.

Issue 10 Health-related quality of life (HRQoL) assessed in mismatch repair proficient (pMMR) cohort only

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19: EAG report states *"Given the final sample sizes (pMMR n=597, dMMR n=222), it may be reasonable to expect additional efforts to improve power and/or conduct exploratory analyses in the dMMR group would have provided valuable insights and completeness of data if included in the CS, even with caveats that finding are less conclusive*".	MSD requests this sentence is removed.	MSD wishes to re-state that there were no PROs collected for the patients with dMMR in the KEYNOTE-868 (NRG-GY018) trial; therefore it is not possible to have investigated the HRQoL in these patients. Lorusso et al (2023) reported on the HRQoL in the KEYNOTE-775 study (pembrolizumab plus lenvatinib for advanced endometrial cancer). The EORTC QLQ-C30 and EQ-5D-5L results at baseline were similar for all comers (pMMR and dMMR) and pMMR only populations.	This is not a factual inaccuracy. The EAG included this point to highlight our concerns regarding the absence of HRQoL/PROs data for the dMMR subgroup in the KEYNOTE-868 trial. Whilst we understand MSD's explanation regarding the lack of data, we felt that additional efforts could have been made to include this data for the dMMR group, particularly as HRQoL is an important outcome measure. Since HRQoL data were collected for the pMMR cohort, it seemed reasonable to question why similar efforts weren't made for the dMMR subgroup,

			especially when such data could have provided valuable insights into treatment effects across both populations. For this reason, the EAG have not made the changes requested by the company.
Page 56: EAG report states "*PRO data was presented from the Interim analysis (December 2022).”*	At the end of this sentence add "PRO data was not available from the Safety and Efficacy update analysis (August 2023 data cut)"	To provide clarity to the reader that the most recent PRO data available has been included in the CS.	These changes have been implemented in the EAG report.
Page 60: EAG report states "*However, the EAG recognised that whilst the HRQoL analyses may be underpowered during the interim analysis, for completeness the company could have still investigated HRQOL in the dMMR population with caveats around limited interpretation of results*"	MSD suggests that either this sentence should be deleted, or clarified by amending as follows: "*However, the EAG recognised that whilst the HRQoL analyses may be underpowered during the interim analysis, for completeness the* ***study sponsor,*** *could have still investigated HRQOL in the dMMR population with caveats around limited interpretation of results.* ***The submitting company, MSD, was not the sponsor of the KEYNOTE-868 (NRG-GY018) trial”***	MSD was not the sponsor of the KEYNOTE-868 (NRG-GY018) trial. Again, MSD wishes to clarify there were no PROs collected for the patients with dMMR in the KEYNOTE-868 (NRG-GY018) trial; therefore it is not possible to have investigated the HRQoL in these patients.	As with the previous response two rows above, the point made by the EAG was not to attribute the lack of HRQoL to the company but rather highlight the opportunity for the sponsor of the trial to have included HRQoL data for the dMMR group, even with caveats around the potential limitations in interpretation. We

			acknowledge MSD's point that HRQoL data were not collected for the dMMR group and appreciate the clarification regarding the company's role. Therefore, we have made the proposed amendment in the EAG report.
Page 115: EAG report states "*Beyond descriptive analysis, the company could have applied several statistical methods to derive more robust utility estimates...*"	MSD requests that this paragraph is amended to also state that a range of alternative utility sources were explored in scenario analyses.	MSD presented a range of scenario analyses using alternative sources of utility values to explore the impact of utility estimates on the results of the economic analysis, which mitigates any uncertainty related to the small sample size.	The EAG have amended the paragraph to the following so that it acknowledged the company's scenario analyses: *... Regression-based mapping from other HRQoL measures or multiple imputation for missing data could further strengthen the utility values used in the model, particularly given the limited sample size.* ***However, MSD explored a range of***

			alternative utility sources in scenario analyses to mitigate the uncertainty from the small sample size.

Issue 11 Position of pembrolizumab + chemotherapy in the clinical pathway

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30: EAG report states "*In the UK, NICE recommends a suspected cancer pathway referral for women ≥ 55 years or ≤ 55 years with post-menopausal bleeding*"	MSD suggests amending the wording to *"NICE recommends a suspected cancer pathway referral for women ≥ 55 years and a referral to be considered for those < 55 years with post-menopausal bleeding."*	The NICE Guideline 12 (NG12) states: 1.5.10: **Refer** women using a suspected cancer pathway referral for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause). [2015] 1.5.11: **Consider** a suspected cancer pathway referral for endometrial cancer in women aged under 55 with	The EAG have made this change in the report to highlight "considered or those < 55 years with post-menopausal bleeding"

		post-menopausal bleeding. [2015] It infers a referral should be made for those 55 and over, and for under 55 a consideration, rather than automatic referral. ***Bold is MSD emphasis*** NICE guidelines do not cover the entirety of the UK. Also "≥ 55 years or ≤ 55 years" means that women who are 55 fall into both categories	

Issue 12 Line of treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36: EAG report states "*The EAG clinical advisors also noted that weekly paclitaxel, Caelyx (doxorubicin), or topotecan*	MSD suggested that this text should be removed from the EAG report.	The technology under consideration in this appraisal is a first-line treatment option; consequently, second-line treatments are not appropriate	The EAG acknowledges the company's justification for amendment. However, this is not a factual inaccuracy and has not been amended.

*can be used as second-line therapies and are considered appropriate comparator*s"		comparators. It is unclear what value is added by this text being included in the report, when it relates to a different line of therapy, outside the scope of this appraisal.	The EAG provides a broader perspective/ context of what the EAG clinical advisors stated in addition to the current treatment pathway in the UK.
Page 31: EAG report states *"The EAG clinical experts provided several corrections to the proposed treatment pathway for EC in the UK.* • *For early-stage EC, they clarified that neoadjuvant radiotherapy (RT), or chemotherapy (CT) would not be given, and after surgery, patients may receive adjuvant RT with or without CT.* • *In advanced EC, for locally advanced cases, surgery would be followed by adjuvant treatment, which could include RT and/or CT.*	MSD request removal of the text against bullet point 2.	Bullet point 2 regarding surgery +/- adjuvant chemotherapy or radiotherapy is already included in Figure 3 of the CS.	The EAG acknowledges the company's justification for amendment. However, this is not a factual inaccuracy and has not been amended. While the company included that "s*urgery **may be considered** +/- adjuvant chemotherapy or radiotherapy*" to Figure 3 of CS, the EAG clinical experts statement was that "*In advanced EC, for locally advanced cases, surgery would be followed by adjuvant treatment, which could include RT and/or CT*" which is what the EAG have captured.

• *For inoperable, locally advanced cases, neoadjuvant CT and/or RT may be considered. “*			
Pg 39: “Clinical advice to the EAG emphasized that systemic treatment in the UK is typically reserved for multisite or extra-abdominal recurrence, and without this information, it is unclear how pembrolizumab performs in local versus metastatic cases or in patients with prior surgeries”	MSD proposes that BGCS guidelines and comments from TA963 are also referenced in this section, highlighting they do not specify suitability for systemic treatment is guided by the site or spread of disease	BGCS does not specify the site or dissemination of the disease (i.e. multisite or extra-abdominal), thus, systemic treatment (i.e. 1L pembrolizumab + CT or CT alone as per KN-868), is an appropriate SoC for patients with advanced or recurrent disease without further delineation of site. Although efficacy outcomes are not delineated by local vs. metastatic primary disease, patients had to have measurable stage III, measurable stage IVA or stage IVB (measurable or non-measurable). These are advanced patients and thus would receive SoC systemic therapy (carboplatin + paclitaxel) as per BGCS guidelines, thus, the same cohort of patients would be	The EAG acknowledges the company’s justification for the proposed amendment. However, this is not considered a factual inaccuracy. The statement was provided by the EAG clinical experts to reflect current UK practice, and as such has not been amended. Furthermore, while the company proposes the inclusion of the BGCS guidelines and comments from TA963, NICE highlights the need to consider various subgroups in the decision problem. Therefore, on this page, the EAG has provided a critique of the decision problem in alignment with what NICE stipulates and

		suitable for pembrolizumab + carboplatin + paclitaxel. BGCS guidance also does not vocalize different first-line treatment decisions for locally advanced or metastatic disease. We do not believe the introduction of pembrolizumab would change that. Similarly, within TA963 Committee papers page 20: "*The EAG clinical advisor confirmed that there is no objective criteria and that clinical judgement is used depending on factors including the characteristics of the patient, their disease and their clinical status and the anticipated clinical benefit / intention of the systemic therapy*". This again does not make any delineation with regards to site and spread.	not the BGCS guidelines and comments from TA963.

Issue 13 Unmet need

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32: EAG report states "*However, the EAG notes that some of this data may be more generalized to uterine cancers,[28] and not specific to endometrial cancer"*	MSD suggests it should be clarified that endometrial cancers make up 95% of uterine cancers, as stated in section 2.2.1.	The current wording implies the information provided by the company is not relevant.	The EAG acknowledge the company's proposed ammendment. However, while relevant and highlighted in section 2.2.1, the EAG reviewed the evidence submitted and noted this observation. Therefore, this is not considered a factual innacuracy and no ammendments have been made.
Page 32: EAG report states "*Additionally, some information may not be accurate; for instance, the CS states that 18% of endometrial cancer patients experience recurrence, while the actual paper cited indicates that 17% of patients across all four molecular groups (POLEmut, MMRd,*	MSD request that this paragraph is removed.	The 18% figure is taken from the introduction of the referenced paper "*About 18% of endometrial cancer patients experience recurrence, the majority during the first two years after primary surgical treatment*" This statement as currently written implies that this text in the CS is inaccurate.	The EAG do not consider this to be a factual inaccuracy. We acknowledge that the CS obtained the 18% figure from the introduction of the cited paper, while the EAG reviewed the primary data within the same paper, which report a recurrence rate of 17% across all molecular groups. To ensure clarity, we have amended the wording in

p53abn, and NSMP) experience recurrence[29]"			the report to accurately reflect this context.

Issue 14 Evidence presented in the CS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Various sections of the EAG report may give the impression that analyses have only been presented in the CS for the pooled all-comer population, when in fact analyses were also presented for the dMMR and pMMR cohorts separately, as per trial design. Page 52: EAG report states "*By combining the cohorts as in the CS, this could obscure insights necessary for informed treatment decisions in these distinct groups*."	In each of the sentences highlighted, we request the EAG to make it clear that the company has also provided analyses in the dMMR and pMMR cohorts separately, in addition to the all-comer population.	To make it clear to the reader that the CS and appendices presents clinical and cost-effectiveness analyses in the all-comer population as well as by cohort based on MMR status (dMMR and pMMR) as per the trial design.	The EAG has amended the report to include "**The company also provided analyses for the dMMR and pMMR cohorts separately, in addition to the all-comer population, as per the trial design**." in each section.

Page 52-53: EAG report states "*Though KEYNOTE-868 was designed to assess the outcomes in two separate cohorts depending on MMR status (dMMR and pMMR), the results of the all-comer population, comprising of both cohorts, were presented as the company felt this a more appropriate population to reflect the decision problem*." Page 53: EAG report states *"While the post-hoc results of the all-comer population feeds into the company's economic model, (on the company premise that this reflects the anticipated NHS population), it increases uncertainty in the results*" Page 76: *EAG report states "• The EAG note caution in the use of post-hoc analyses*			

of the all-comer population….”			

Issue 15 Imbalance in discontinuation rate between treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57: EAG report states “*The EAG note that this imbalance in discontinuation rate may bias the PFS for the placebo + CT arm and may possibly lead to an overestimation of PFS in placebo + CT arm…”*	MSD suggests a corresponding statement should be added to the Overall survival section that follows in the report (3.2.3.2)	The imbalance in discontinuation rate mentioned may possibly also lead to an overestimation of OS in the placebo + CT arm.	Added to the highlighted paragraph that this possible overestimation can also apply to the OS section.

Issue 16 Economic SLR searches

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 77: EAG report states “*CS states that the database searches were run via Ovid (CS Appendix G.1.1) but the reported syntax for all database*	MSD request that the paragraph is amended to state that the Company has clarified that the searches for the economic, HRQoL and cost/resource use SLRs were conducted via the	MSD would like to clarify that the there was an error in the CS in terms of the platform specified for running the search	This is not a factual accurarcy, however the EAG have added a comment in Sectin 4.1 1.1.1 of the EAG report stating that ‘during FAC

searches are incompatible with this platform.”	corresponding search platforms for each database.	terms for the economic SLR (Ovid was not used). Embase.com, PubMed.com, Ebsco.com, CRD and INAHTA were the platforms used depending on the database searched. The list of databases in section G.1.1 are correct • Embase® and MEDLINE (using Embase.com) • MEDLINE® In-Process (using PubMed.com) • EconLit™ (using Ebsco.com) • Centre for Reviews and Dissemination (CRD), York • INAHTA	the company confirmed that there was an error in the CS in terms of the platform specified in the economic SLR, and confirmed that Embase.com was used to search Medline and Embase and not Ovid.

Issue 17 Pembrolizumab marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83: EAG report states "*Pembrolizumab (KETRUDA) does not currently have a marketing authorisation in the UK*"	Amend to "*Pembrolizumab (KE**Y**TRUDA) does not currently have a marketing authorisation in the UK **for the indication under consideration***" (emphasis added)	Current wording states that the product has no marketing authorisation in the UK. This could be misinterpreted as meaning it is a non-licensed product, when in fact the sentence only relates to the indication under consideration.	Amended as requested

Issue 18 Model population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 84: Table 7 of the EAG report lists various sources that report the mean age of UK EC cohorts	Please state that Zhang (2024) reports on a previously treated (i.e. second line) cohort.	Zhang (2024) reports on a previously treated (i.e. second line) advanced or recurrent EC cohort, therefore this does not fully match the population in the current NICE decision problem. This should be stated for transparency and to avoid misinterpretation.	Not a factual inaccuracy. The EAG already state the patients included in the review by Zhang (2024) had progressed following prior first line systemic therapy in the text. However, we have added similar text to table 7.

	MSD request that the median age (66.6 years) reported by Ingles Russo Garces et al (2023), as referenced in the CS, is added to the table. All cells in the second column will then need to be updated to indicate whether each age represents the mean or the median age of the study cohorts.	Ingles Russo Garces et al (2023) reports on a first-line advanced or recurrent EC cohort in England, which aligns with the population in the current NICE decision problem. This is the largest study available (n=902) that directly reflects the population under consideration, and therefore this study should be presented for completeness and transparency.	We have included the study by Ingles Russo Garces et al (2023) and indicated that it draws from the same study by Heffernan et al. (2022). We have also noted that the median age for the entire immune checkpoint inhibitor (ICI)-eligible 1L cohort was 67.9 years as reported by the study authors (n=2,376). The median age of 66.6 years reported by the company was for the subpopulation of ICI-eligible 1L cohort who received solely carboplatin-paclitaxel. Also, worth noting that only patients with ECOG performance status of 0,1 were included to mirror inclusion criteria of RUBY trial (NCT03981796; evaluating ICI dostarlimab + carboplatin-paclitaxel in patients with primary advanced or first-recurrent EC). However, the inclusion

			criteria for the current appraisal includes patients with ECOG performance status of 0,1,2.
Page 84: *The EAG report states: "Table 7 summarises the sources retrieved and mean age of the population*."	"Table 7 summarises the sources retrieved and **average (mean or median)** age of the population"	Assuming Ingles Russo Garces et al (2023) is added to Table 7 as requested above, this sentence should be updated to reflect the values presented in the table.	Amended as requested

Issue 19 Survival Analysis methods

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 89: EAG report states "*The company identified the optimum cut-off point by investigating where the Kaplan-Meier plots of the two treatments group start to significantly diverge from each other, and used the Chow test to single-out inflection points in the hazards, choosing the*	MSD requests that the text on page 80 should potentially be amended to: *"The company identified the optimum cut-off point by investigating the hazard profile, and used the Chow test to single-out inflection points in the hazards, choosing the earliest key inflection point to maintain sufficient statistical power."*	The first statement is factually inaccurate. Divergence of KM data between arms was not a consideration in MSD's decision making regarding the optimum cut-off point. Within our response to clarification questions (C3 and C4) we highlighted that not only the Chow test was used to determine the cut point.	The EAG have made this change.

earliest key inflection point to maintain sufficient statistical power." Page 90: EAG report states "*It is also possible to investigate how the hazards of each group change themselves, therefore obtaining different cut-off points for the intervention and control groups, which is something the EAG explored*."	MSD proposes that the text on page 90 should be removed	Two statisticians assessed the KM curves, hazard profile, number of events and number at risk to determine the most appropriate cut-off points. Chow test statistics were also conducted to support the choice of cut-off points. Both statisticians considered the cut-off points presented in the submission to be the most appropriate given the observed data across all treatment arms/outcomes. Number of events and number at risk were considered to ensure that past the cut-off point extrapolations were being made based on a sufficient sample size. We believe the second statement is also misleading as the hazard profile was already used by MSD in our considerations. For PFS the CT arm had no turning point and for the pembrolizumab arm the hazard turning point coincided with the Chow test.	Regarding the paragraph on page 90: The EAG appreciates the company's clarification regarding the methods used to determine cut-off points and acknowledges that both the hazard profile and additional considerations (Chow test, number of events, and number at risk) were factored into their decision-making process. However, the text on page 90 was not intended to critique or misrepresent the company's approach but to highlight alternative methodologies for determining cut-off points, particularly as these considerations were not detailed in the

			main submission and arose during the clarification stage. To avoid potential misinterpretation, the EAG have made the following revision: “It is also possible to investigate how the hazards of each group change themselves, therefore obtaining different cut-off points for the intervention and control groups. This approach was explored independently by the EAG as part of an expanded analysis, but it is acknowledged that the company’s considerations already incorporated hazard profiles in their approach.”

Issue 20 Company's chosen models

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92: EAG report states *"In the pembrolizumab group, all of the 2-knot and 3-knot models provide closer estimates to the experts with the 3-knot hazard model providing the closest estimates to the experts, thus the log-normal would be at-best the seventh best model*." Page 92: EAG report states *"...unlike in the pembrolizumab arm where estimates are not very close, suggesting that the chosen model for pembrolizumab may not accurately reflect expected patient outcomes and could potentially misinform clinical or policy decisions if adopted without further*	MSD requests that these statements from pages 92-93 of the EAG report are removed	We believe the EAG may have misinterpreted some of the clinician based landmark figures used to validate both the PFS and OS curves in the CS. For pembrolizumab PFS, these act as an absolute upper bound as they are based on the dMMR population, who are expected to benefit most from pembrolizumab. This means ranking curves on closeness to this is not appropriate. Likewise, using the distance extrapolations are from clinical opinion to question accuracy may not be appropriate; the aim was to select curves with long term extrapolations below these dMMR estimates, not necessarily close to these estimates. Similar to pembrolizumab PFS, for pembrolizumab OS modelling we attempted to create 2 bounds: • The first set of clinician estimates in CS (Table 40) represent	We acknowledge MSD's clarification on the bounding of the PFS and OS extrapolations are between two sets of clinician estimates. However, our critique focuses on the clinical plausibility of the selected models for the all-comer population and their alignment with broader expert expectations. Therefore we have not amended these statements.

validation against expert assessments" Page 93: EAG report states "*For the pembrolizumab group, the expected OS probabilities vary considerably between the two experts. For example, the 5-year expected OS from the TA963 is 59%, the same percentage from the weighted average of dMMR with PD-1 inhibitor + CT and pMMR with CT only at 2-years (CS Table 40). Plus, the 20-year OS estimate from TA963 is 38%, more than the 5-year estimate of the weighted average estimates at 27%, a full 15-year gap. Therefore, choosing which expert to conform to is a delicate matter and should be subjected to a consensus of other independent experts."*		landmarks for dMMR patients, who are expected to have greater OS than the all comer population. • The second set of estimates (CS Table 40) attempts to create a lower bound by using the dMMR estimates from TA963 to estimate the dMMR OS and using the advisory board pMMR **CT** OS estimates. These are then combined to make a weighted OS average for all-comer population. In this scenario we are conservatively assuming that pembrolizumab would have **no** additional OS benefit in the pMMR population (which corresponds to ~75% of allcomers), hence we consider this to be a strict lower limit. MSD's curve selection was then guided by curves that sit between these two bounds, as opposed to trying to pick curves close to either one or the other.	

Issue 21 EAG's survival analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report: Section 4.2.6.4.1	MSD is requesting the EAG revisit curve selection rationale for both PFS/OS pembrolizumab outcomes in light of the clarification provided.	As has been highlighted in Issue 20, there has possibly been some misinterpretation of the definition and purpose of the presented clinician estimates, especially for the pembrolizumab arm. These estimates were used as upper or lower bounds for long term extrapolation, in which closeness to estimates was not the aim of MSD's selection process. MSD are concerned that for the pembrolizumab OS extrapolations the EAG has used the lower bound estimates to inform model selection. This lower bound works on an assumption that the pMMR population receives **no** additional benefit from the addition of pembrolizumab. The EAG's rationale for picking the loglogistic curves appears to be based solely on the comparison against this lower bound. Given the long-term OS extrapolations	The EAG appreciates MSD's clarification but would like to highlight that the clinical expert estimates used for selecting the extrapolation models were primarily those of the EAG's own clinical experts, with the company's expert estimates considered as secondary guidance. These estimates were not used as strict upper or lower bounds but rather as a secondary point of comparison to help inform the overall plausibility of the selected curves. OS extrapolation: The EAG's choice of the log-logistic model for OS in the intervention group was based on statistical fit, visual inspection, and expert input, with a focus on plausible long-term outcomes. The

		actually fall below the lower bound estimates, it makes the implicit assumption that pembrolizumab has a detrimental long term OS effect on the pMMR population, which is contradictory to the results observed in this population in the KEYNOTE-868 (NRG-GY018) trial.	selected model for the pembrolizumab arm falls between the upper and lower bounds proposed by MSD, except at 20 years where the EAG's model predicts 9% survival, which is slightly lower than MSD's lower bound of 10%. For the control group, the EAG used the company's fitted log-logistic model, which predicts 4% survival at 20 years, which is below the company's upper bound estimate of 13% at 20 years, with no stated lower bound. This discrepancy was not interpreted as an indication of incorrect data but rather reflects the inherent limitations of survival extrapolation, particularly with long-term follow-up and different model selection methods.

EAG report: Section 4.2.6.4.3	MSD requests that the EAG clarify the selection method and rationale for presented scenarios compared against the company submission.	MSD considers that the EAG has not provided a clear rationale for picking specific curves. e.g. for Pembrolizumab OS, the 9.4 week two-piece log-logistic curve has been selected but it is unclear why. A comparison to one set of clinician inputs was referenced, but these were a lower bound, and the selected curve is below these in the long term. There is no other mention of the rationale for selecting this curve (goodness of fit, plausibility of hazard profile etc), even though it has been identified by the EAG as the main driver of effectiveness in the model. No rationale has been provided for why the EAG's fitted two-piece model has been preferred over other methods such as the splines that have been fitted by the Company to the individual patient data as opposed to data digitised by the EAG.	The EAG selected the two-piece log-logistic model with a 9.4-week data cut for pembrolizumab after considering both statistical fit and EAG's expert input. This model provides a reasonable balance between long-term survival expectations and clinical plausibility, despite being slightly below the clinical experts' lower bound in the long term. The model's fit with the data and its realistic survival trajectory were key factors in its selection. The EAG also considered multiple alternative models in scenario analyses but found the two-piece log-logistic to be the most consistent with the available data and clinical expectations. For the control arm, the EAG adopted the company's log-logistic model, as it provided a reasonable fit, despite a lower long-term extrapolation.

			While MSD raised concerns about the model selection, the EAG believes the chosen models offer the most plausible and balanced extrapolation based on the available data and expert input.

Issue 22 Interpretation of the pembrolizumab long term clinician estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report: Tables 8, 10 and supplementary tables 2, 5, 7, 9, 11, 14, 17, 20, 22, 24, 26, 28 and accompanying commentary	MSD proposes that all mentions to these clinician estimates highlight that these represent bounds, not targets. We request that tables 8, 10 and supplementary tables 2, 5, 7, 9, 11, 14, 17, 20, 22, 24, 26, 28 also highlight that these estimates are upper or lower bounds. Proposed amendments: For the PFS tables: "NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT (Upper bound)" For the OS tables	Please see rationale for Issue 20	The EAG does not consider these to be factual inaccuracies as the company did not explicitly state these are upper bounds in the CS. Therefore, no change has been made to this point. Moreover, the EAG's model choice was primarily based on the EAG's experts' opinions.

	"NICE TA963 advisors' mean for 1L dMMR EC patients receiving CT (Upper bound)" "MSD Clinical Expert – weighted calculation of estimates for all-comers (Lower bound)"		
EAG report: Tables 18,21, 23, 25, 27	Please amend to reflect that the MSD advisory board clinicians did not give estimates, removing the reference to 0%	For clarity, clinicians did not provide landmark PFS/OS estimates for the 20 year landmarks. The highlighted tables imply that an estimate of 0% was given	Amended as requested
EAG report: Section 4.2.6.4	MSD asks that the EAG update tables 10, 11 and supplementary tables 17, 18, 20 – 29 to reflect general background mortality adjustments	It is unclear to MSD, but it seems that during curve selection the EAG have compared curve fits that are not adjusted for general background mortality to clinician estimates. This may have led to ruling out otherwise well-fitting curves on the basis that they had long, flat tails that would subsequently have been adjusted downwards in the model engine once background mortality is applied	The EAG have updated the long-term piecewise estimates in Tables 10 and 11; background mortality is adjusted for in the economic model and the EAG does not believe it double-counted removing the effects of background mortality.

Issue 23 Interpretation of the cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 139: EAG report states "*The PSA results show that the ranking of the technologies remained the same as the deterministic results; however, the PSA results slightly overestimated the results in terms of QALYs*. Hence, reducing the PSA ICER to £XX per QALY.""	MSD request that this statement be removed, or otherwise only comment on the difference **relative to the deterministic results**.	MSD consider this comment to be misleading. It is not true to claim the PSA "overestimated" the QALYs (as the true QALYs are unknown), but rather that the PSA estimates a higher QALY gain than the deterministic analysis.	The statement has been amended to: "The PSA estimates a higher QALY gain than the deterministic analysis leading to an ICER of XXXX per QALY"
Page 139: EAG report states "*Also, as can be seen that some of the iterations were in the north-east quadrant, indicating that pembrolizumab + CT was likely to be more expensive than CT but less effective*."	MSD request that the wording be amended to the as follows: "*Also, as can be seen that some of the iterations were in the north-east quadrant, indicating that in a small number of iterations pembrolizumab + CT was more expensive than CT but less effective*."	The phrasing of this comment is potentially misleading as it suggests that the conclusions of the PSA overall is that pembrolizumab was likely more expensive but less effective, rather than just in the small number of iterations	Amended as requested.

Issue 24 Waning

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 148: EAG report states "*Thus, the EAG has explored scenarios in which treatment waning is applied to the pembrolizumab + CT OS curve at specific time points: three years post-discontinuation (between years 3 and 5) and four years post-discontinuation (between years 4 and six), while maintaining the company's assumption that treatment effect wanes completely after two years.*"	MSD request that the statement referencing the company's assumption that treatment effect wanes completely after two years is removed. "*Thus, the EAG has explored scenarios in which treatment waning is applied to the pembrolizumab + CT OS curve at specific time points: three years post-discontinuation (between years 3 and 5) and four years post-discontinuation (between years 4 and six)*."	This is a factual inaccuracy. MSD's base case does not incorporate a treatment waning effect; the impact of treatment effect waning was explored by MSD in a scenario analysis only. MSD would like to reaffirm our position that, across many studies of pembrolizumab in metastatic cancers, long term data supports a sustained treatment effect.	We have made the requested changes to the statement.
Page 147: EAG report states "*Thus, the EAG has explored scenarios in which treatment waning is applied to the pembrolizumab + CT OS curve at specific time points: three years post-discontinuation (between years 3 and 5) and four*	Could the EAG clarify when waning has been applied, stating both the post discontinuation time and the model time point to avoid any doubt.	We assume that this statement means that waning starts in year 5 of the model and finishes in year 7 (or year 6 to 8) as pembrolizumab treatment is continued for up to 2 years, however it is not completely clear from the current wording in the report.	This statement has been revised for clarity and now reads "Thus, the EAG *explored scenarios in which treatment waning is applied to the pembrolizumab + CT OS curve at specific time points for a duration of two years. In*

years post-discontinuation (between years 4 and six)," Table 32: Rows referencing waning			*the first scenario, waning starts in year 5 and ends in year 7, while in the second scenario, it starts in year 6 and finishes in year 8."*
Table 32: Base case column relating to waning	Please update the base case column relating to waning to reflect that MSD's base case did not apply treatment waning.	The table suggests that MSD's base case was to apply waning from year 7 to 9 of the model, but this was only a scenario analysis. The base case did not include treatment waning.	The table has been amended with the correct base case assumption.

Issue 25 Resource use

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Table 32. Resource use scenarios	Please clarify the resource input assumptions used in scenario analysis.	The values stated in the resource use scenario rows of Table 32 do not match the values reported in section 4.2.8.3 (Table 22). In Table 32 it is stated that blood tests and outpatient visits would be conducted 0.5 times a cycle (i.e. once every	The resource use values in Table 32 have been corrected to match those on Table 22, section 4.2.8.3 of the EAG report.

		2 weeks). Given this does not align with the administration schedule of pembrolizumab + CT or CT alone, this resource use schedule seems improbable and MSD consider that this may be an error in the report.	

Issue 26 EAG results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 157: EAG report states "*The EAG's exploratory analyses results presented in Table 32 demonstrate that changing the OS extrapolation method had the greatest impact to the company's base case ICER, with an increase by XX % due to the decreased overall QALY benefits of Pembrolizumab + CT. Except for TTD, PFS (optimistic scenario) and subsequent treatment mix, the scenario analyses*	When describing uncertainty, please report on the impact of all scenarios, no matter if the ICER sits above or below a given threshold.	The EAG explored 3 OS curve scenarios, but there is no mention within the text in the report that 2 of the 3 scenarios explored produced ICERs below £30,000/QALY. This risks misrepresenting the uncertainty within the model.	This has been amended to indicated the change in ICER across all the OS scenarios explored.

explored by the EAG all increased the company's base case ICER."			
Table 33: Treatment effectiveness and extrapolation "Scenarios - Not satisfactorily"	Further clarification/justification as to why the scenarios were "not satisfactory" is requested.	MSD consider that the EAG should provide a rationale for this claim. MSD provided 5 OS scenario analyses beyond the base case analysis. The EAG also provided 3 scenarios with alternative OS extrapolations. This statement in Table 33 could be misinterpreted as a lack of thorough interrogation into this issue of uncertainty, when in fact, between the company and EAG, 9 OS scenarios have been run of which 8 scenarios produced ICERs below £30,000/QALY.	This has been amended to indicate that alternative scenarios using EAG clinical experts' preferences were included.
Page: 159 "*At a £20,000 WTP threshold pembrolizumab +CT return an incremental net monetary benefit (iNMB) of -£ XX under EAG base case assumptions*."	Please include iNMB at £30,000	We believe the iNMB results using both the £20,000 and £30,000 thresholds should be presented together to represent the range across NICE's willingness to pay thresholds.	iNMB values at £20,000 threshold have been included.

Issue 27 Subsequent treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 123: EAG report states "*The EAG's clinical experts advised that giving pembrolizumab monotherapy as subsequent treatment is not standard UK practice. Now, there are no NICE recommended 2L drug treatments for advanced EC and the EAG's assessment shows uncertainty regarding the 2L treatment options used for these patients in the company's analysis*" Page 134: "*Secondly, the CS stated that 16.76% of patients received pembrolizumab in the Placebo + CT arm as subsequent therapy but EAG's clinical expert confirmed that this is not a UK clinical practice*"	The text should be corrected to reflect current NICE recommendations.	As reflected in current NICE guidance, both pembrolizumab + lenvatinib (TA904) and pembrolizumab monotherapy (dMMR only, TA914) are recommended by NICE as options for routine use in the 2L setting. MSD's assumption is that the extent of pembrolizumab monotherapy usage in clinical practice may be impacted by the availability of dostarlimab (via the CDF, TA779). Regardless of the outcome of the CDF guidance review for dostarlimab (TA779), a PD-1 inhibitor monotherapy would be available to clinicians in the 2L dMMR population. Hence, we explored scenarios with both pembrolizumab and dostarlimab for the dMMR population	The EAG has revised the text to accurately reflect the NICE recommendations in TA904 and TA914.

Issue 28 Quality of life

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 119: EAG report states "*This study was not included in the HRQoL publications summary table in Appendix H, despite citing utility values derived from KEYNOTE-158, the same trial the company used to estimate base case utility values. Notably, the company's utility values for stable and progressed disease are lower than those reported in the paper*."	*"This study was not included in the HRQoL publications summary table in Appendix H, despite citing utility values derived from KEYNOTE-158, the same trial the company used to estimate base case utility values. The company's utility values for stable and progressed disease are* ***higher*** *than those reported in the paper.* *This difference may be explained by the fact the company's values relate specifically to patients who had received only 1 prior line of therapy, while the study included patients with 1 or more lines of therapy, and therefore may have further progressed disease."*	The paper by McCarthy et al (2024) reports a pre-progression utility of 0.72 and a progressed utility of 0.67 for the endometrial cohort of the KEYNOTE-158 trial. The utility values used in MSD's base case are higher than these values, not lower. The KEYNOTE-158 utilities used by MSD in the base case relate specifically to the subgroup of patients that had received only 1 prior line of treatment. This was an attempt to focus on patients at the earliest possible stage of disease to best match the 1L population of the current decision problem. By contrast, the utilities reported by McCarthy et al reflect all EC patients in the KEYNOTE-158 trial which	The EAG have made this change to the report.

		included patients with more than 1 prior line of therapy. It is to be expected that utility values relating to patients that have only had 1 line of therapy would be higher than the overall KEYNOTE 158 EC population that include patients that have had multiple progressions and lines of treatments.	

Issue 29 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 45: EAG report states "*The searches across the ASMO and ESMO conferences*"	Amend "*ASMO*" to "***ASCO***"	Typographical error	Thank you, we have corrected this typo.
Page 49: EAG report states "…*participants were randomised in a 1:1 ration…*"	Amend "*ration*" to "*ratio*"	Typographical error	Thank you, we have corrected this typo.

Page 51: EAG report states "*The population separation may have been conducted so that it is line with the population identified in the NICE scope…"*	Amend "*population separation*" to "*population* ***pooling***"	Typographical error	Thank you, we have corrected this typo.
Page 51: EAG report states *"(see Table 3"*	Amend "*(see Table 3*" to "*(see Table 3)"*	Closing bracket missing	Thank you, we have corrected this typo.
Page 54: EAG report states *"• Clinical experts felt that serious EC was overrepresented in the trial population (compared to UK clinical practice), but this may be attributed to trial eligibility, and the relatively high proportion of Black and African American participants who have a higher rate of serious endometrial cancers (CS Document B, Table 6)"*	Amend "serious" to "**serous**" (two instances)	Typographical error	Thank you, we have corrected this typo in two instances.
Page 72: Section 3.2.7.3 of the EAG report states "with the pMMR cohort often	Amend sentence: pMMR and dMMR should be swapped in this sentence	Typographical error	Thank you, we have corrected this typo.

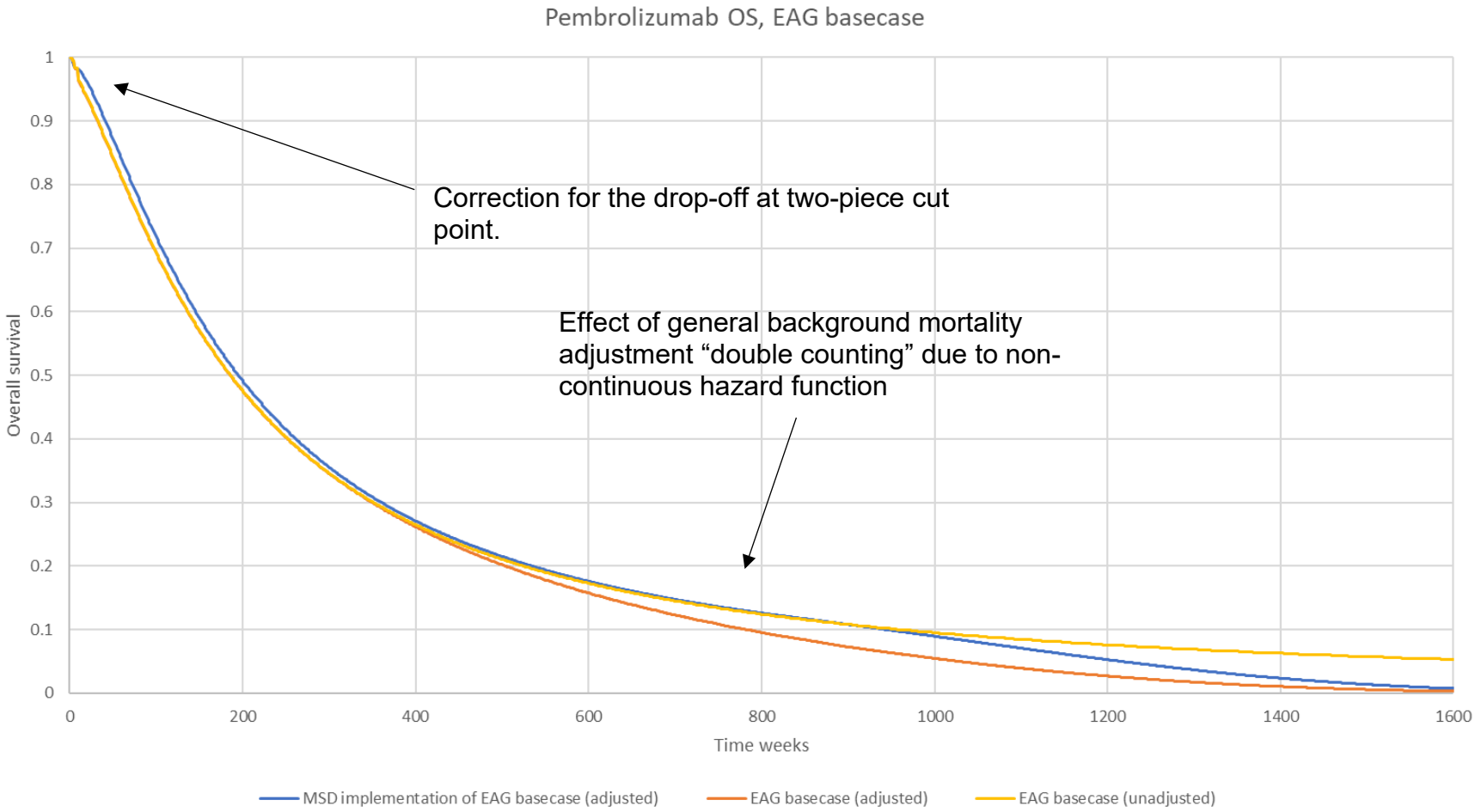
showing [redacted] improvements than dMMR cohort.”			
Page 222: Table 28	Missing footnote	Missing footnote	Thank you. Footnote has been added.
Page 83: EAG report states “*Pembrolizumab (KETRUDA) does not currently have a marketing authorisation in the UK”*	Amend to: “*Pembrolizumab (KE**Y**TRUDA) does not currently have a marketing authorisation in the UK **for the indication under consideration***”	Typographical error	Thank you we have corrected this.
Page 123: “*The company performed a scenario analyses, exploring a scenario in which dorstalimab”*	Amend to: “*The company performed a scenario analyses, exploring a scenario in which dost**ar**limab”*	Typographical error	Thank you, we have corrected this typo.
Table 32 Column 2 title “*Base case value”*	Can the EAG clarify it is MSD’s basecase	Clarification	Thank you we have amended this.
Supplementary table 16	Row names labelled with “PFS” when should be “OS”	Typographical error	Thank you we have corrected this.
Page 116: “*49 patients*”	Amend to “*47 patients”*	Typographical error	Thank you we have corrected this.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 21	This table should be redacted as they can be used to back calculate the time on treatment figures within the model	Redaction required	Table has been redacted
Page 181: "…by mapping ED-5D-5L data from 545 patients to EQ-5D-3L using the mapping function from Hernandez Alava,…"	Redact [redacted]	Redact [redacted] (not currently marked as confidential in EAG report)	Thank you. This has been corrected.
Page 181: "…the model with the lowest AIC was selected as the final model. The analyses were conducted using 7228 EQ-5D records from 545 patients. In another scenario, the company used time-to-death utilities…"	Redact [redacted]	Redact [redacted] (not currently marked as confidential in EAG report)	Thank you. This has been corrected.

Appendix

Figure 3: EAG Pembrolizumab OS hazard plot

Figure 4: Comparisons of EAG OS base case implementations within the Excel model



Footnote: adjusted/unadjusted refers to the adjustment for general background mortality that is applied in the model trace, sheet <trace_treatment1>. The blue "MSD" curve also corrects for the sudden drop in OS at the two-piece cut off.

MSD implementation refers to MSDs interpretation of how the curve should have been plotted. The parameters provided in ‘EAG Model Parameters’!E8:F8 were used to plot the new curve, continuing from the KM data starting at week 10. This curve was not rounded (left at 15 dp) and replaced the curve in ‘EAG Model Extrapolations’!H4:H2145. The macros added by the EAG in ‘Model Settings’ were then used as normal to assess the EAG scenarios. No additional work was done for the general background mortality adjustment, this is applied within ‘trace_treatment1’ as standard, by comparing the weekly hazard from the curve against UK life tables. The parameters for plotting the EAG curve had been fitted to data that used months as the time scale (opposed to weeks), the conversion factor used to go from months to weeks was 365.25 / 7 / 12

References:

Lorusso et al (2023): Health-Related Quality of Life in Patients With Advanced Endometrial Cancer Treated With Lenvatinib Plus Pembrolizumab or Treatment of Physician's Choice. Eur J Cancer. 2023 Jun;186:172-184.

External Assessment Group's supplementary report for pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381] – Subgroup analyses

Produced by	*Warwick Evidence*
Authors	***Mandy Maredza**, Senior Research Fellow (Health Economics)*[1] ***Mubarak Patel**, Research Fellow*[1] ***Aziza Osman**, Research Associate in Health Economics*[1] ***Christiana Anyebe**, Research Associate in Health Economics*[1] ***Naila Dracup,** Information Specialist*[1] ***Dr Sarah Kitson** Clinical Lecturer and Honorary Consultant Gynae-oncologist*[2] ***Dr Melanie Powell**, Consultant Clinical Oncologist*[3] ***Jo Parsons,** Assistant Professor of Health Science Research*[1] [1]*Warwick Evidence, Warwick Applied Health, Warwick Medical School, University of Warwick, Coventry, CV4 7AL* [2]*Division of Cancer Services, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PL* [3]*St Bartholomew's Hospital, London, EC1A 7BE*
Correspondence to	*Dr Jo Parsons* *Warwick Applied Health* *Warwick Medical School* *University of Warwick* *Coventry, CV4 7AL*
Date completed	*28th February 2025*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR169037.

Declared competing interests of the authors
The authors declare no competing interests.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This supplemental report should be referenced as follows:
Maredza M, Patel M, Osman A, Anyebe C, Dracup N, Kitson S, Powell M, Parsons J. Supplementary report for pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381] – Subgroup analyses. EAG report: A Single Technology Appraisal. Warwick Evidence. 2025.

Contributions of authors
Mandy Maredza provided oversight of the critique of the cost-effectiveness evidence and EAG's modelling for the subgroup analyses. Mubarak Patel critiqued the statistical analysis. Aziza Osman and Christiana Anyebe critiqued the cost-effectiveness evidence for each of the subgroups. Naila Dracup provided information specialist support with citations. Sarah Kitson provided clinical expertise. Melanie Powell provided clinical expertise. Jo Parsons coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

1 Background

This document presents the deterministic base case and probabilistic sensitivity analysis (PSA) results separately for the dMMR and pMMR subgroups and supplements the EAG's post-factual accuracy check (FAC) report. Except for survival extrapolations critique presented in detail in this document, and changes to the EAG's chosen starting age in model, all other critiques align with what was previously presented in the EAG's report.

Two accompanying models are provided alongside the document, saved with the EAG's chosen assumptions for the base case as described below for each MMR subgroup (sections 8.1 and 8.2). No modifications to the company's model structure were applied. Exploratory analyses are also presented for treatment waning, health state utilities and resource use.

2 Curve selection and extrapolation

2.1 Modelling approaches

2.1.1 Company

The company provided survival extrapolations and curve selection for the MMR subgroups individually in CS section O.2. Table 59 of appendix O presents the preferred models for the pembrolizumab+CT and CT only arms of KEYNOTE-868 (NRG-GY018) for PFS and OS outcomes across both the dMMR and pMMR subgroups (a total of eight models) with justification for the chosen models. The approach for choosing the models followed a similar methodological approach as the all-comer models in the main company submission document.

These models were fit in a similar manner to the all-comer PFS and OS curves the company provided in the original submission. Parametric, piecewise, and spline models were fit and then assessed for visual fit to the observed KM data and hazards plots, statistical fit using Akaike's information criterion (AIC) and Bayesian information criterion (BIC), and clinical plausibility. In some cases, two-piece models were not considered or preferred due to an already low sample size, mainly in the dMMR subgroup. However, the PFS-CT model in the dMMR subgroup did use a two-

piece model, which begs the question as to why they were not considered for the other three models in the dMMR subgroup outside of the standard parametric models providing “reasonable”, “good”, or “acceptable” visual fit, as the company stated in Table 59.

2.1.2 EAG

In the absence of Kaplan-Meier (KM) IPD, the EAG digitised the PFS and OS plots for the MMR subgroups presented in CS section E.2. and reconstructed pseudo-IPD using the same approach as described in the EAG’s report.

Similar to the company, the EAG selected the most plausible model based on a combination of statistical fit, visual fit, and clinical plausibility. Models with an AIC and/or BIC within five points of the AIC or BIC of the best-fitting model were investigated further for visual fit to the observed KM data and the observed hazard plot, and the EAG’s clinical experts were consulted as to the model with the most plausible survival extrapolations up to 20 years.

Due to time constraints, the EAG first fit and assessed parametric models only. If they were deemed to be a poor fit, then more complicated models such as splines or piecewise models were considered. Additional to the time constraint, due to the low sample size in the dMMR subgroup, piecewise models were not explored in order to maximise sample size in this subgroup.

Table 1 lists the potential models chosen as the EAG’s preferred models for each subgroup, treatment arm, and outcome. In all cases, the potential models were chosen based on good statistical and visual fit to both KM and hazard plots. These potential models were then judged by how plausible the long-term survival extrapolations were compared to the EAG’s clinical experts’ opinions. In cases where multiple models were reasonable and resulted in similar PFS or OS estimates, the simpler of the models were chosen. Table 2 and Table 3 summarise the preferred model choices and the survival extrapolations at key time points by subgroup.

Table 1. EAG's justification for chosen model

Population/outcome	Potential models	Justification
dMMR, CT only, PFS	**Gen Gamma** 2-knot hazards 2-knot normal	Parametric models acceptable visual fit, however pessimistic near KEYNOTE-868 (NRG-GY018) EOS and possibly beyond Spline models better visual fit, more reasonable hazard functions, but much more optimistic over long-term
dMMR, CT only, OS	**Exponential** Log-normal	Parametric and spline models both have reasonable visual fit
dMMR, Pembro + CT, PFS	**Log-logistic** 2-knot normal	Parametric and spline models both have reasonable visual fit, but parametric models looked to be pessimistic beyond KEYNOTE-868 (NRG-GY018)EOS.
dMMR, Pembro + CT, OS	Weibull **Log-logistic** Gamma	Parametric and spline models both have reasonable visual fit
pMMR, CT only, PFS	**2-knot hazards** 2-knot odds 2-knot normal	Parametric models have good visual fit to observed KM data, hazard plots reasonable except the Gompertz model Splines show improved visual fit to data, with reasonable hazards for >1-knot models 2-knot models best fitting
pMMR, CT only, OS	Weibull Log-normal Log-logistic Gamma **1-knot hazards**	Parametric models have decent to good visual fit to observed KM data, hazard plots reasonable except the Gompertz model Spline models fit similarly well
pMMR, Pembro + CT, PFS	**1-knot hazards** 1-knot odds 1-knot normal 2-knot hazards 2-knot odds 2-knot normal	Parametric models too pessimistic near KEYNOTE-868 (NRG-GY018) EOS and beyond Spline models with showing better fit to KM and hazards, with 2-knot models fitting the best visually
pMMR, Pembro + CT, OS	Weibull Log-logistic Gamma 1-knot odds **1-knot normal**	Parametric models have acceptable fit to observed KM data with reasonable hazards except for the Gompertz model Odds and normal spline models fit well
Chosen model denoted in **bold**		

2.2 Summary – curve selection and survival extrapolations

2.2.1 Selected models

Table 2. Summary of the preferred model by company and EAG

Subgroup	Treatment	Outcome	Company	EAG
dMMR	CT only	PFS	Two-piece gamma with 27-week cut	Generalised gamma
		OS	Exponential	Exponential
	Pembrolizumab + CT	PFS	Generalised gamma	Log-logistic
		OS	Log-logistic	Log-logistic
pMMR	CT only	PFS	1-knot odds spline	2-knot hazards
		OS	Gamma	1-knot hazards
	Pembrolizumab + CT	PFS	37-week two-piece generalised gamma	1-knot hazards
		OS	Log-logistic	1-knot normal

2.2.2 Survival extrapolations

Table 3. Survival extrapolations at key timepoints (%)

Model	**2Y**	**5Y**	**10Y**	**20Y**	**Model**	**2Y**	**5Y**	**10Y**	**20Y**
Cycle	**104**	**260**	**520**	**1040**	**Cycle**	**104**	**260**	**520**	**1040**
dMMR; CT only; PFS					**pMMR; CT only; PFS**				
Company	[redacted]				Company	[redacted]			
EAG	[redacted]				EAG	[redacted]			
dMMR; CT only; OS					**pMMR; CT only; OS**				
Company	72	44	19	4	Company	56	13	1	0
EAG	72	44	19	4	EAG	56	14	1	0
dMMR; Pembrolizumab + CT; PFS					**pMMR; Pembrolizumab + CT; PFS**				
Company	[redacted]				Company	[redacted]			
EAG	[redacted]				EAG	[redacted]			
dMMR; Pembrolizumab + CT; OS					**pMMR; Pembrolizumab + CT; OS**				

Company	83	64	42	25	Company	64	31	14	5
EAG	83	64	42	25	EAG	64	28	10	2
Survival extrapolations for both company and EAG retrieved from the company's economic model									

3 Population

In the main report, the EAG proposed a different baseline starting age for the model in the all-comer population based on the EAG's clinical expert advice and external evidence reviewed. However, post AC1, the EAG received CDF data on baseline characteristics (age) of endometrial cancer patients who receive immunotherapy (summarised in Table 4). The data on advanced/ metastatic endometrial cancer patients (previously untreated in advanced setting) who receive dostarlimab plus chemotherapy appears most relevant to the decision problem. Both the population (untreated in advanced setting) and intervention (immunotherapy plus CT) are more closely aligned to the current appraisal with the caveat that it is only for dMMR patients. That data indicates that the company's current chosen values for age in dMMR patients (65.7 years) aligns closely to that reported for patients receiving dostarlimab+CT. Thus, the EAG believes that the company's values used in model and obtained in KEYNOTE-868 (NRG-GY018) are likely a close reflection of starting ages observed in practice. Since that data is specifically for pembrolizumb plus chemotherapy, it appears more reasonable to maintain the current values in model for both dMMR and pMMR.

Table 4: Overview of CDF data on patients with endometrial cancer having immunotherapy

Immunotherapy	Median/ Mean age (yrs)	Population	EAG comments
Pembrolizumab plus lenvatinib (PEMB23)	Mean age – 67.5 Median - 69	Patients previously treated with platinum-containing therapy given in any setting (neoadjuvant, adjuvant, chemo-radiotherapy, 1L for	Reports on previously treated population. Does not align with current appraisal

Immunotherapy	Median/ Mean age (yrs)	Population	EAG comments
		advanced/metastatic disease)	
Dostarlimab monotherapy (DOS 1)	Mean -66 Median 67	Patients with advanced/ metastatic dMMR endometrial cancer previously treated in the advanced/metastatic disease setting with chemotherapy	Reports on a previously treated population
Dostarlimab plus chemotherapy (DOS 2)[1]	Mean – 65.4 Median -66	Patients with advanced/ metastatic dMMR endometrial cancer previously untreated in the advanced/metastatic disease setting	Immunotherapy plus CT and in previously untreated advanced setting therefore more closely aligns with current appraisal. Caveat: dMMR population only
Dostarlimab plus chemotherapy (DOS 2 – excluding EAMS/Post-EAMS)	Mean – 65.58 Median -67	Patients with advanced/ metastatic dMMR endometrial cancer previously untreated in the advanced/metastatic disease setting	Immunotherapy plus CT and in previously untreated advanced setting therefore more closely aligns with current appraisal. Caveat: dMMR population only

[1] This includes 60 Early Access to Medicines Scheme (EAMS) and post-EAMS approvals

4 Health-related quality of life

As with the all-comer population analysis, for the subgroup analysis, the company relied on health state utilities from KEYNOTE-158 based on patients with MSI-H/dMMR endometrial cancer who had previously failed standard therapy. Utility values of [redacted] and [redacted] were applied to the progression-free and progressed disease health states respectively. A one-off QALY decrement associated with grade

3+ AEs with an incidence of >5% in the trial was applied in the first cycle of the model for each intervention arm. For the dMMR subgroup, the utility decrement was -[redacted] for patients in the Pembrolizumab +CT arm versus -[redacted] for patients in the CT arm. In the pMMR subgroup, a utility decrement of -[redacted] was estimated for patients in the Pembrolizumab +CT arm and -[redacted] for patients in the CT arm. The utility estimates were adjusted by age to account for the natural decline in QoL using the general female population utility values from Hernández Alava et al.[1] The base-case health-state utilities and adverse event disutilities applied in the economic model are presented in Table 5 and Table 6 below.

Table 5: EQ-5D-3L values used in CEM

Health state	(N=[redacted]) Mean (SE)	95% CI	Source
Progression-free	[redacted]	[redacted]	KEYNOTE-158
Progressed	[redacted]	[redacted]	KEYNOTE-158

Source: Table 42, pg.130, CS document B

Table 6: Adverse event disutilities used in CEM

Adverse Event	Disutility	Source (disutility)
Neutrophil count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
White blood cell count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Lymphocyte count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Hypertension	-0.020	NICE TA963
Anaemia	-0.119	NICE TA963

Source: Table 46, pg.137, CS document B

In line with the all-comer population analysis, the company estimated utilities from a range of different sources to explore the impact on the ICER, given that there was no EQ-5D data available from KEYNOTE-868 (NRG-GY018). These scenarios included using TTD and progression-based utilities from KEYNOTE-826 and progression-based utilities from KEYNOTE-775 based on the Swedish and Australian value set.

On pg. 128 CS Document B, the company states that utility values from KEYNOTE-775 based on the UK value set could not be disclosed for the purpose of this appraisal due to contractual obligations with a third party. KEYNOTE-826 assessed pembrolizumab + CT versus CT as 1L therapy in treating patients with untreated persistent, recurrent or metastatic cervical cancer. KEYNOTE-775 examined the use of pembrolizumab in combination with lenvatinib for previously treated advanced EC. The utilities used in the scenario analyses are presented in Table 7.

Table 7: Summary of utility values for scenario analyses

Source	State	Utility value: mean (SE)	Reference
Time-to-death utilities	360+ days	[redacted]	KEYNOTE-826
	180-359 days	[redacted]	
	90-179 days	[redacted]	
	30-89 days	[redacted]	
	<30 days	[redacted]	
Progression-based utilities	Progression-free	[redacted]	
	Progressed	[redacted]	
	Progression-free	0.736	PBAC_Pembrolizumab 2022/KEYNOTE-775
	Progressed	0.700	
	Progression-free	0.851	Ralph 2024/KEYNOTE-775
	Progressed	0.817	

Source: Table 48, pg.139, CS document B

EAG comments:

The EAG maintains that the health state utilities used in economic model may not be representative of patients with pMMR given the trial only recruited MSI-H/dMMR endometrial cancer patients. Clinical advice to the EAG suggests that there could be differences in the HRQoL of pMMR and dMMR cohort, as there is a *higher response rate to treatment with dMMR and they will likely be on treatment for longer*. In addition, *pMMR endometrial cancer does not respond as well to immunotherapy so one might assume that this cohort will have a less good quality of life as they are more likely to have active/progressive disease*. This is supported by clinical advice in TA904, which indicates 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.[2] Previous clinical trials have shown that immunotherapies have limited efficacy in the pMMR population, with higher ORRs observed in dMMR compared to pMMR patients[3-5] This uncertainty remains unresolved due to a lack of data available from the pivotal trial, as well as the literature on patients with pMMR endometrial cancer.

5 Treatment waning

In the subgroup analysis, no treatment waning was assumed in the base-case analysis. A scenario assuming gradual treatment waning in the OS curve was applied to 24.8% of patients who did not attain ORR. In accordance with KEYNOTE-006, treatment waning was assumed to start 7 years after starting treatment (or five years post-discontinuation). The EAG maintains its previous position that due to the trial's short follow-up, there is insufficient evidence to support that treatment effect is sustained for such a long period. Previous NICE committees on immunotherapy appraisals have excepted more pessimistic treatment waning assumptions of three to five years post-discontinuation.[6-8]

6 Resource use and costs

6.1 Intervention and comparators' costs and resource use

The primary treatment costs calculated for Pembrolizumab + CT, and Placebo + CT from the drug acquisition costs and the administration costs have been explained explicitly in the EAG report. All assumptions made for the all-comer population applies to the dMMR and pMMR subgroups considered in the KEYNOTE-868 (NRG-GY018) trial. The EAG has considered the assumptions to be appropriate.

6.2 Health state resource use and costs

The costs of managing the disease, monitoring and following up the patients in the health states were estimated in the model for the pMMR and the dMMR subgroups. The resource use was assumed to differ between the PFS (progression free state) and the PD (progressed disease) state and based on treatment status. The

assumptions used for the frequency of resource used by patients were obtained by consulting clinical experts, advisory board and through HTA search of similar cancers. On consultation with the EAG clinical experts, the resource used by the CS was thought to be underestimated for the Pembrolizumab + CT arm as the expert advised that EC patients on immunotherapy undergo series of blood tests (details of this can be found in the EAG report). The EAG presents its preferred assumptions, based on consultation with clinical experts and sourcing from TA963, in Table 8. These values are the same for both subgroups as the resource use is determined by patient health states and treatment status. Table 9 presents the company's values for MMR subgroups resource use, which are the same for the all-comer analysis. All unit costs were sourced from NHS reference costs 2022/23 and are presented in the EAG report, Table 23.

Table 8: Resource use for Pembrolizumab + CT arm obtained by the EAG

Health state	Resource	Frequency per week	source	Frequency per week	source
		Scenario 1		**Scenario 2**	
PFS (on treatment)	Blood tests	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.33 (up to cycle 18) 0.22 (cycle 19+)	TA963
	Outpatient visits	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.30 (up to cycle 18) 0.13 (cycle19+)	TA963
PFS (off treatment)	Blood tests	0.08	EAG clinical expert	0.17	Company base case
	Outpatient visits	0.08	EAG clinical expert	0.06	Company base case

Table 9: Heath state resource use for the pMMR and dMMR Subgoups (Company's assumptions)

Health state	Resource	Frequency per week		Source
		pMMR	**dMMR**	
PFS (on treatment) pembrolizumab + CT	Ct scan	0.08	0.08	Advisory board
	Outpatient visits	0.17	0.17	Advisory board
	Blood test	0.17	0.17	Advisory board
PFS (off treatment) pembrolizumab + CT	Ct scan	0.08	0.08	Advisory board
	Outpatient visit	0.06	0.06	Advisory board
	Blood test	0.17	0.17	Advisory board
PFS (On treatment): CT	Ct scan	0.09	0.09	Advisory board

	Outpatient visits	0.29	0.29	Advisory board
	Blood test	0.29	0.29	Advisory board
PFS (Off treatment): CT	Ct scan	0.08	0.08	Advisory board
	Outpatient	0.06	0.06	Advisory board
	Blood test	0.00	0.00	Advisory board
PD	Ct scan	0.04	0.04	Advisory board
	Outpatient visit	0.11	0.11	Advisory board
	Blood test	0.11	0.11	Advisory board
Source: CS model, worksheets disease management costs in PFS and PD				

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy; Ct, computed tomography; PFS, progression-free state; PD, progressed disease

6.3Costs of subsequent treatments

The subsequent treatment costs were estimated per patient by considering the proportion of patients receiving subsequent treatment, average time on treatment, the distribution of each subsequent treatment, and drug acquisition and administration costs of each therapy. These costs were calculated as a one-off cost upon entry into the PD state in the economic model. The same approach was taken for obtaining the proportion of patients on subsequent treatment as described for the all-comer population. Data obtained from the KEYNOTE-868 (NRG-GY018) trial were adjusted and validated to reflect UK clinical practice.

The proportions of patients receiving subsequent treatments in the pMMR and dMMR alongside the all-comer population are presented in Table 10. The dosage and costs per week of subsequent treatments are the same for the all-comer population and presented in Table 20 of the EAG report. All the assumptions surrounding the proportion of subsequent treatment are deemed appropriate by the EAG.

Table 10: Subsequent treatment mix for the for the pMMR and dMMR subgoups

Subsequent treatment	**ALL-comer population**	**pMMR**	**dMMR**
Pembrolizumab +CT arm			
Carboplatin	1.65%	0.00%	8.93%
Carboplatin + paclitaxel	14.31%	11.50%	26.79%
Doxorubicin	13.69%	14.78%	8.93%
Letrozole	7.31%	4.93%	17.86%
Megestrol	0.00%	0.00%	0.00%

Paclitaxel	8.27%	10.14%	0.00%
Pembrolizumab	0.00%	0.00%	0.00%
Pembrolizumab + Lenvatinib	0.00%	0.00%	0.00%
Radiotherapy	23.06%	26.28%	8.93%
No active treatment	31.72%	32.37%	28.57%
CT arm			
Carboplatin	1.84%	2.50%	0.00%
Carboplatin + paclitaxel	11.34%	14.17%	3.51%
Doxorubicin	1.22%	1.67%	0.00%
Letrozole	4.60%	5.00%	3.51%
Megestrol	1.84%	2.50%	0.00%
Paclitaxel	8.98%	12.22%	0.00%
Pembrolizumab	16.76%	0.00%	63.10%
Pembrolizumab + Lenvatinib	23.95%	32.59%	0.00%
Radiotherapy	11.68%	10.83%	14.02%
No active treatment	17.78%	18.52%	15.87%
Source: CS economic model, subsequent treatment worksheet			

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy

6.4 Treatment of adverse events costs

The costs of adverse events were estimated as a one-off cost in the first model cycle as the product of the rate of AE per subject, number of episodes of AEs per subject, and the unit cost of the AE. The assumptions for estimating the costs of adverse events are considered appropriate by the EAG. In its report, the EAG indicated that immune-related AEs (irAEs) reported in ≥ 2% of the trial's all-comer population are toxicities that need clinical management, and their exclusion likely underestimates costs of AEs. Whilst the EAG maintains this argument, the inclusion of AEs of grade 3+ occurring in ≥ 2% in the EAG's exploratory analysis for the all-comer population yielded only a minimal change to the company base case ICER. But it is worth noting that only neutropenia and anaemia were costed in the model for the two subgroups, although hypertension was listed in the AEs occurring in ≥ 5% as seen in table 12 and neutropenia was not. The EAG questions the exclusion of hypertension and inclusion of neutropenia. However, there seems to be an apparent mismatch between the values reported in table 12, and those in the model. The model values indicate that neutropenia and anaemia are the two AEs with cost attached that occurred in ≥ 5% of patients and Hypokalaemia ([redacted] of dMMR patients) had no cost. The impact on the company's base case ICER was negligible when hypertension was used instead of neutropenia and when hypokalaemia was costed for the dMMR

subgroup. Table 11 presents the AEs included in the subgroup analyses as implemented in the economic model and Table 12 shows the proportion of patients with grade 3+ AEs in the subgroups.

Table 11: Adverse events costs for pMMR and dMMR subgroups applied in the model

Adverse events	Cost per episode (£)	Source
Lymphocyte count decreased	0.00	Assumed no cost
White blood cell counts decreased	0.00	NICE TA904
Neutrophil count decreased	0.00	NICE TA904
Neutropenia	1,667.58	NHS Reference costs 2022/23
Anaemia	565.40	NHS Reference costs 2022/23
Source: CS B Table 57 and Model, adverse events costs worksheet		

Table 12: Adverse events of grade 3+ occurring in ≥ 5% of patients in pMMR and dMMR cohorts

Adverse events	**pMMR**	**dMMR**
Pembrolizumab + CT arm		
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
CT arm		
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Source: Table 57 CS Appendix O, pg.183		

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy

7 EAG summary and critique of resource use and cost

The EAG considers the resource use, cost assumptions, and their integration into the MMR subgroup cohorts' economic model appropriate. Resource allocation for the pembrolizumab +CT arm remains the EAG's main concern as detailed in the EAG report. Another area of concern with minimal impact on ICER is the exclusion of hypertension from AE costs despite meeting the established criteria. However, it is likely that there was an error in reporting of AEs in ±Ï ¦ Þ¼ as explained above.

8 Cost-effectiveness results

8.1 dMMR subgroup

The EAG's adjustments to the company's base case model are presented in Table 13, showing the individual effect of each change as well as the combined effect of all changes cumulatively for dMMR subgroup. Table 14 and Table 15 show the EAG's estimated deterministic and probabilistic ICERs respectively.

The EAG's deterministic ICER for the dMMR subgroup was [redacted], representing a 6% increase from the company's base case ICER. The most influential adjustment was the EAG clinical experts' resource use assumption, followed by the selection of the standard log-logistic model for PFS extrapolation in the pembrolizumab + CT arm. The probabilistic ICER was [redacted].

Table 13: EAG preferred model assumptions, dMMR

Preferred assumption	Section in EAG report	ICER £/QALY (Individual impact on company base case ICER)	Percentage change in ICER
Company base-case		[redacted]	

Preferred assumption	Section in EAG report	ICER £/QALY (Individual impact on company base case ICER)	Percentage change in ICER
EAG 01: Generalised gamma model for PFS extrapolation; CT only	2.2.1	[redacted]	[redacted]
EAG 02: Log-logistic model for PFS extrapolation; Pembrolizumab + CT	2.2.1	[redacted]	[redacted]
EAG 03: Resource utilisation to reflect EAG clinical experts' opinion PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+); Outpatient visits – 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08; Outpatient visits – 0.08	5.2	[redacted]	[redacted]
EAG Base Case (Applied all changes cumulatively)		[redacted]	[redacted]

Table 14: EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	LYG	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	5.01	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.10	[redacted]

Table 15: EAG probabilistic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	LYG	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	4.99	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.84	[redacted]

The results from the probabilistic sensitivity analysis are plotted in the cost-effectiveness acceptability curve and cost-effectiveness plane below (Figure 1 and Figure 2). At willingness-to-pay thresholds of £20,000 and £30,000, pembrolizumab + CT has a probability of being cost-effective compared to CT alone of [redacted] and [redacted] respectively.

Figure 1 Cost-effectiveness acceptability curve, EAG base case, dMMR

Figure 2 Cost-effectiveness plane, EAG base case, dMMR

8.1.1 EAG exploratory analyses dMMR

The exploratory analyses undertaken by the EAG for dMMR subgroup are presented in Table 16.

Table 16: EAG exploratory analyses, dMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
MSD base case (post clarifications)				[redacted]	2.12	[redacted]	[redacted]
Treatment waning in OS	No treatment waning assumed	**Scenario 1** 3 years after discontinuing pembrolizumab + CT	Precedent in previous NICE appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.88	[redacted]	[redacted]
		Scenario 2 4 years after discontinuing pembrolizumab + CT		[redacted]	1.92	[redacted]	[redacted]
HSU from McCarthy et al 2024	PFS: [redacted] PD: [redacted]	**PFS:** 0.72 **PD:** 0.67	Utilities were estimated based on progression status and tumour site data from KEYNOTE-158 using a UK value set.	[redacted]	2.11	[redacted]	[redacted]
Resource use frequency per week of blood tests and outpatient visits in the pembrolizumab + CT arm	PFS (on treatment): Blood tests - 0.17, outpatient visits - 0.17 PFS (off treatment) - Bood test – 0.17	**Scenario 1** PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+) Outpatient visits – 0.33 (up to	EAG Clinical experts most appropriate estimates.	[redacted]	2.12	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
	Outpatient visits – 0.06	cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08 Outpatient visits – 0.08					
		Scenario 2 PFS (on treatment): Blood test – 0.33 (up to cycle 18), 0.22 (cycle 19+) Outpatient visits – 0.30 (up to cycle 18), 0.13 (cycle 19+) PFS (off treatment):	Explore data from TA963 to assess uncertainty.	[redacted]	2.12	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		Blood tests – 0.17 (company's base case) Outpatient visits – 0.06 (company's base case)					

8.2 pMMR subgroup

The EAG's preferred assumptions for pMMR subgroup are presented in Table 17.

Table 17: EAG preferred model assumptions (pMMR cohort)

Preferred assumption	ICER (£/QALY)	Section in EAG report	Impact on company base case
Company base case ICER 20,107			
EAG 01: OS extrapolation for Pembrolizumab + CT: 1-knot normal	[redacted]	[redacted]	[redacted]
EAG 02: OS extrapolation for CT: 1 knot hazards	[redacted]	[redacted]	[redacted]
EAG 03: PFS extrapolation Pembrolizumab + CT: 1- knot hazards	[redacted]	[redacted]	[redacted]
EAG 04: PFS extrapolation CT: 2-knot hazards	[redacted]	[redacted]	[redacted]
EAG 05: Resource use PFS (on-treatment): Blood test - 0.33 (up to cycle 17), 0.17 (cycle 18+). Outpatients visit - 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off-treatment): Blood test- 0.08, outpatient visit – 0.08	[redacted]	[redacted]	[redacted]
EAG base case (All changes applied)	[redacted]		[redacted]

Table 18: Deterministic cost-effectiveness results, pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.61	[redacted]	[redacted]	[redacted]	0.83	[redacted]	[redacted]

Table 18 above shows the results of the deterministic cost-effectiveness analysis, based on EAG's preferred base case assumptions. The ICER increased from [redacted] (Company's base case) to [redacted] (EAG's base case). The main driver of the increased ICER was the OS extrapolation approach for pembrolizumab +CT.

Table 19:Probabilistic mean cost-effectiveness results, pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.67	[redacted]	[redacted]	[redacted]	0.81	[redacted]	[redacted]

Probabilistic sensitivity analysis was performed on the EAG base case using 1000 iterations drawn from parametric assumptions in the adapted economic model for the pMMR subgroup. Incremental costs were [redacted] and incremental QALYs 0.81 resulting in an ICER of [redacted] (Table 19). At a £30,000 WTP threshold pembrolizumab +CT return an iNMB of [redacted] and no iNHB. The cost-effectiveness scatterplot indicates that most iterations lie in the North-East quadrant i.e., Pembrolizumab+CT is both more costly and more effective than CT (Figure 3). While majority of the iterations were in the North-East quadrant, about 10% of the points were presented in the North-West quadrant depicting that for those cost and effect pairs, the intervention was more costly and less effective. The cost-effectiveness acceptability curve (CEAC) shows that the probability of pembrolizumab + CT being cost-effective compared to CT at £20,000 WTP threshold was [redacted] and increases to [redacted] at the £30,000 WTP threshold (Figure 4).

Figure 3: Cost effectiveness plane, pembrolizumab + CT versus CT: pMMR (EAG base case)

Figure 4: Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: pMMR (EAG base case)

8.2.1 EAG exploratory analyses pMMR subgroup

Table 20 shows the results of the EAG's exploratory analyses for the pMMR subgroup.

Table 20: EAG Exploratory Analyses, pMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
Company base case				[redacted]	1.18	[redacted]	[redacted]
Treatment waning in OS	No treatment waning assumed	**Scenario 1** 3 years after discontinuing pembrolizumab + CT	Precedent in previous NICE appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.04	[redacted]	[redacted]
		Scenario 2 4 years after discontinuing pembrolizumab + CT		[redacted]	1.06	[redacted]	[redacted]
HSU from McCarthy et al 2024	PFS: [redacted] PD: [redacted]	**PFS:** 0.72 **PD:** 0.67	Utilities were estimated based on progression status and tumour site data from KEYNOTE-158	[redacted]	1.15	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
			using a UK value set.				
Resource use frequency per week of blood tests and outpatient visits in the pembrolizumab + CT arm	PFS (on treatment): Blood tests - 0.17, outpatient visits - 0.17 PFS (off treatment) - Bood test – 0.17 Outpatient visits – 0.06	**Scenario 1** PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+) Outpatient visits – 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08 Outpatient visits – 0.08	EAG Clinical experts most appropriate estimates	[redacted]	1.18	[redacted]	[redacted]
		Scenario 2 PFS (on treatment):	Explore data from TA963 to assess uncertainty	[redacted]	1.18	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		Blood test – 0.33 (up to cycle 18), 0.22 (cycle 19+) Outpatient visits – 0.30 (up to cycle 18), 0.13 (cycle 19+) PFS (off treatment): Blood tests – 0.17 (company's base case) Outpatient visits – 0.06 (company's base case)					

9 Appendices

E] ˝┤ȸ →×¾Ɪπ̃ ĕȹ ĕ╧╗⁄╛ȹ τ ×ȹ╤╎ Ɪ⁄╛

×~ ~ • ȸ╩╕ ĕ╗ ╧╔

9 ±ȸɕ Ɪ♣ȹ [©□

[redacted]

Figure 5. Paramedic model fit over trial length (dMMR, CT only, PFS)

Figure 6. Parametric model fit over 20 years (dMMR, CT only, PFS)

Figure 7. Parametric model hazard functions plot (dMMR, CT only, PFS)

Figure 8. Spline model fit over trial length (dMMR, CT only, PFS)

Figure 9. Spline model hazard functions plot (dMMR, CT only, PFS)

Table 21. Statistical model fit (dMMR, CT only, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	555.9875	558.706		
Weibull	557.2919	562.7289		
Log-normal	536.4445	541.8815		
Log-logistic	538.6191	544.0561		
Gompertz	553.6009	559.0379		
Generalised Gamma	529.4607	537.6162		
Gamma	554.9992	560.4362		
Hazards k=1	**517.6222**	**525.7777**	**Similar**	**Best**
Hazards k=2	517.9625	528.8365	Similar	Similar
Hazards k=3	518.1894	531.7819	Similar	
Odds k=1	518.7822	526.9377	Similar	Similar
Odds k=2	516.7476	527.6216	Similar	Similar
Odds k=3	518.2708	531.8633	Similar	
Normal k=1	524.9321	533.0876		
Normal k=2	**516.4412**	**527.3152**	**Best**	Similar
Normal k=3	518.3485	531.941	Similar	

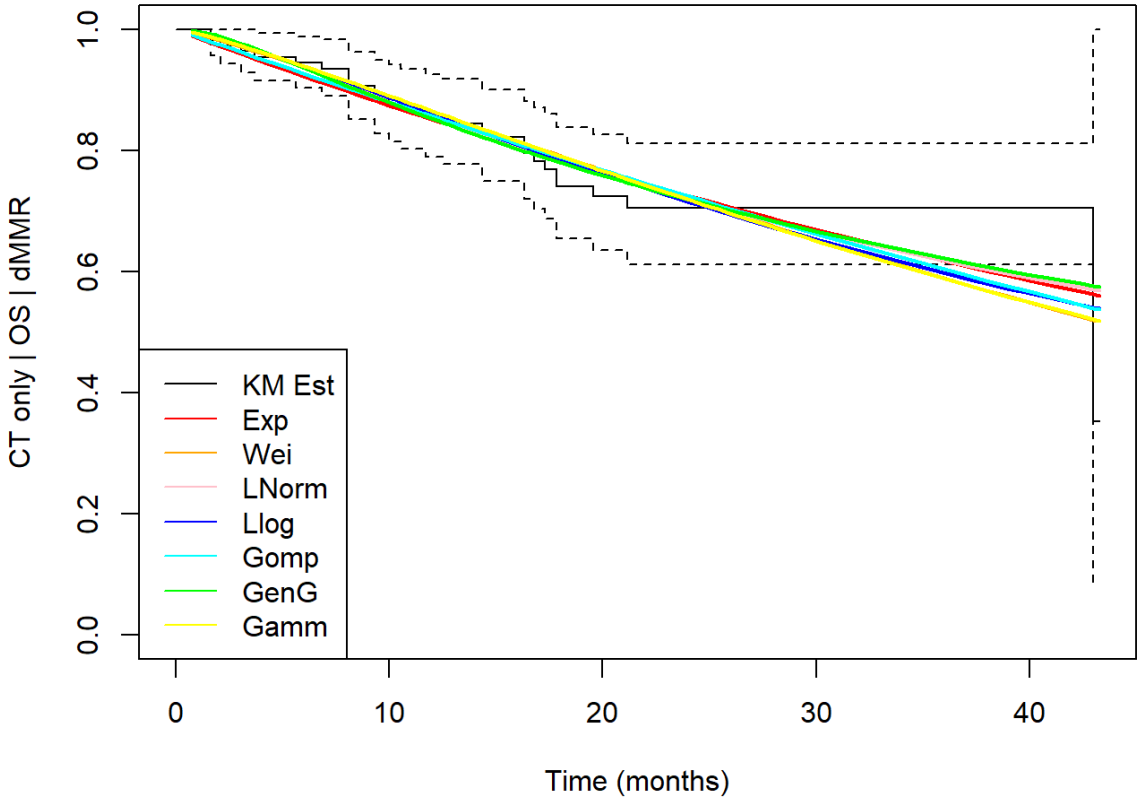


Figure 10. Parametric model fit over trial length (dMMR, CT only, OS)

ك

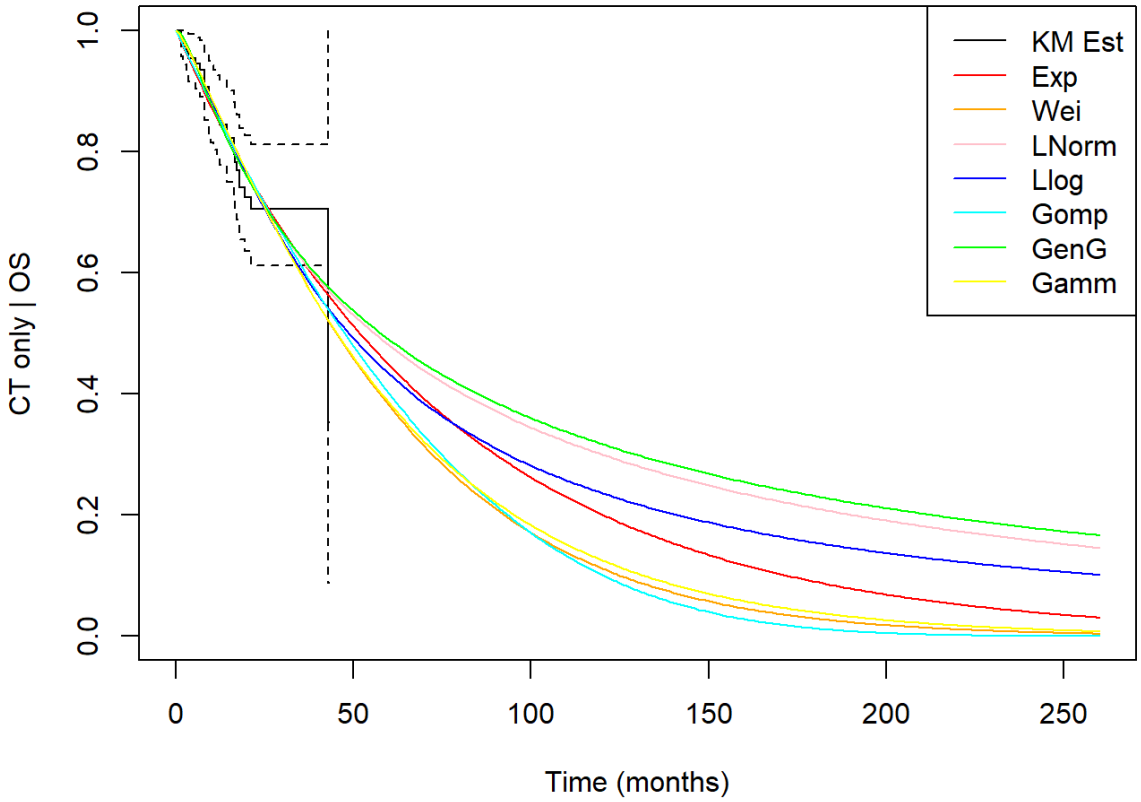


Figure 11. Parametric model fit over 20 years (dMMR, CT only, OS)

ك

Figure 12. Parametric model hazard functions plot (dMMR, CT only, OS)

ك

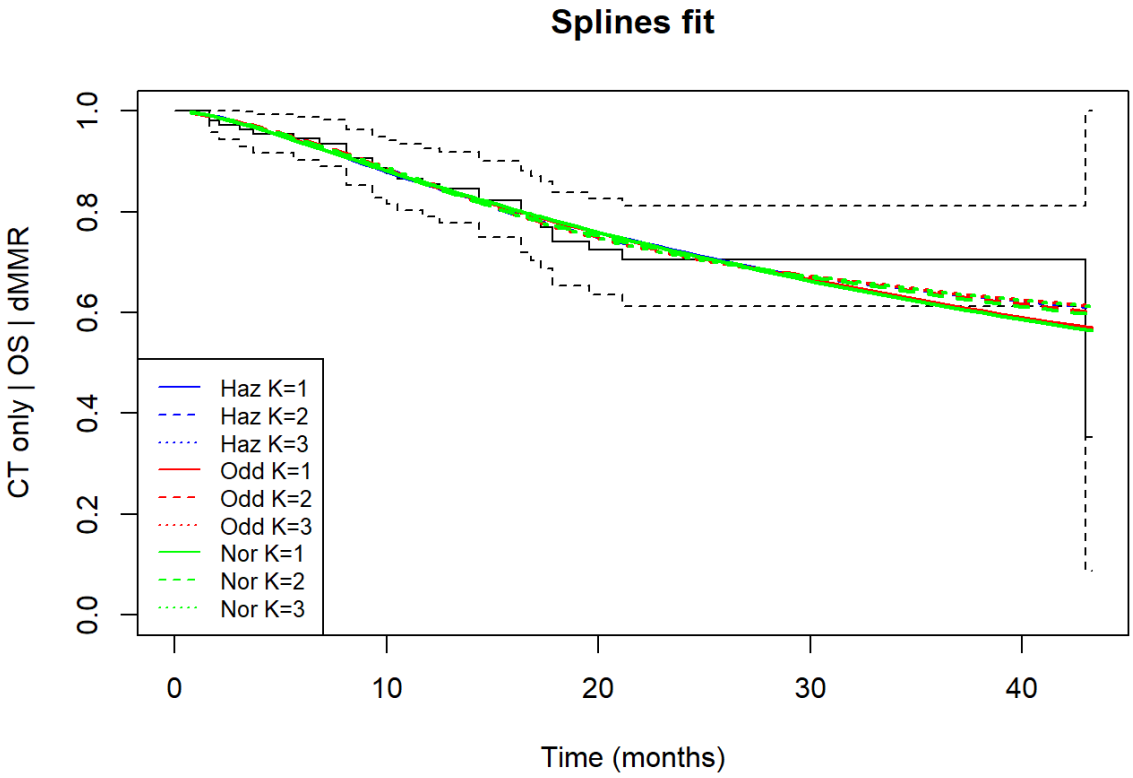


Figure 13. Spline model fit over trial length (dMMR, CT only, OS)

Figure 14. Spline model hazard functions plot (dMMR, CT only, OS)

Table 22. Statistical model fit (dMMR, CT only, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**288.9639**	**291.6824**	**Similar**	**Best**
Weibull	290.072	295.509	Similar	Similar
Log-normal	**288.7982**	**294.2352**	**Best**	**Similar**
Log-logistic	289.4804	294.9174	Similar	Similar
Gompertz	290.8655	296.3025	Similar	Similar
Generalised Gamma	290.7859	298.9414	Similar	
Gamma	289.8834	295.3204	Similar	Similar
Hazards k=1	291.1063	299.2617	Similar	
Hazards k=2	292.5084	303.3824	Similar	
Hazards k=3	294.3076	307.9001		
Odds k=1	291.0708	299.2263	Similar	
Odds k=2	292.592	303.466	Similar	
Odds k=3	294.3634	307.9559		
Normal k=1	290.7867	298.9422	Similar	
Normal k=2	292.3789	303.2529	Similar	
Normal k=3	294.0693	307.6618		

[redacted]

Figure 15. Parametric model fit over trial length (dMMR, Pembro + CT, PFS)

Figure 16. Parametric model fit over 20 years (dMMR, Pembro + CT, PFS)

Figure 17. Parametric model hazard functions plot (dMMR, Pembro + CT, PFS)

Figure 18. Spline model fit over trial length (dMMR, Pembro + CT, PFS)

Figure 19. Spline model hazard function plot (dMMR, Pembro + CT, PFS)

Table 23. Statistical model fit (dMMR, Pembro + CT, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**369.3953**	**372.0958**	**Similar**	**Best**
Weibull	370.8737	376.2746	Similar	Similar
Log-normal	368.7523	374.1533	Similar	Similar
Log-logistic	369.0505	374.4515	Similar	Similar
Gompertz	368.0403	373.4413	Similar	Similar
Generalised Gamma	370.7288	378.8302	Similar	
Gamma	371.106	376.507	Similar	Similar
Hazards k=1	370.3773	378.4787	Similar	
Hazards k=2	367.6256	378.4275	Similar	
Hazards k=3	369.5404	383.0428	Similar	

Odds k=1	370.0594	378.1609	Similar	
Odds k=2	367.6017	378.4036	Similar	
Odds k=3	369.5629	383.0653	Similar	
Normal k=1	370.6501	378.7515	Similar	
Normal k=2	**367.582**	**378.3839**	**Best**	
Normal k=3	369.58	383.0824	Similar	

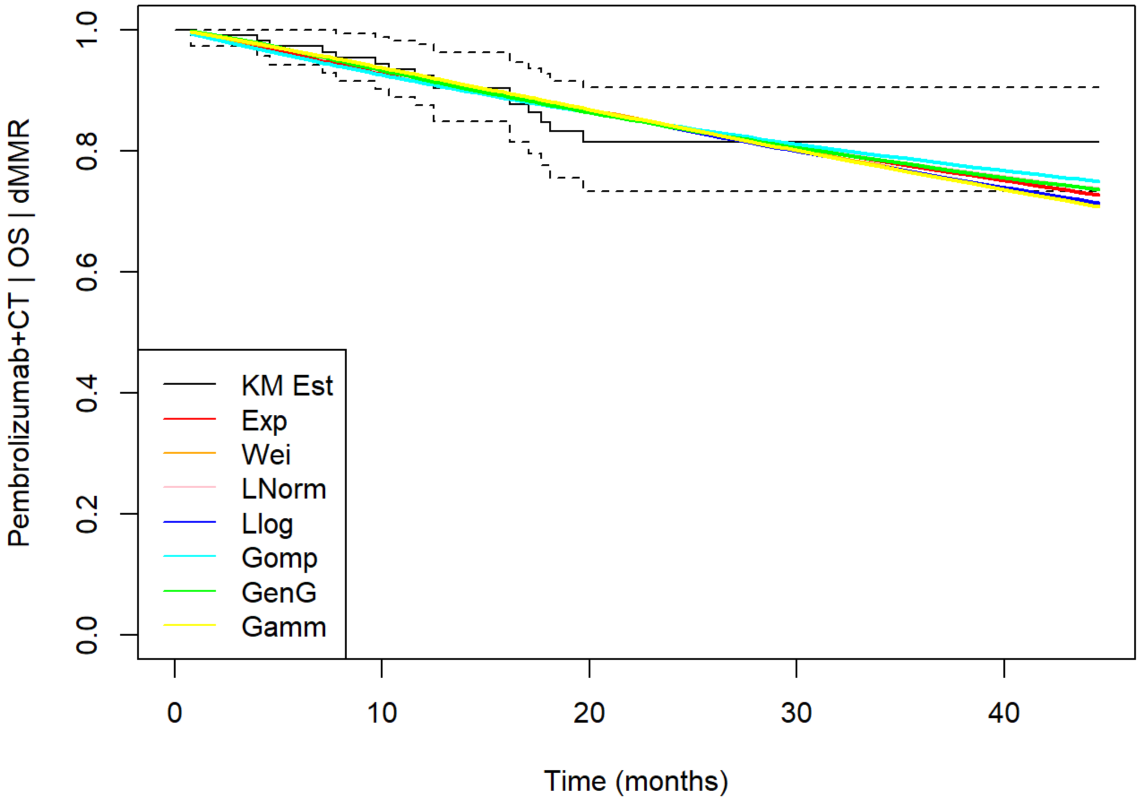


Figure 20. Parametric model fit over trial length (dMMR, Pembro + CT, OS)

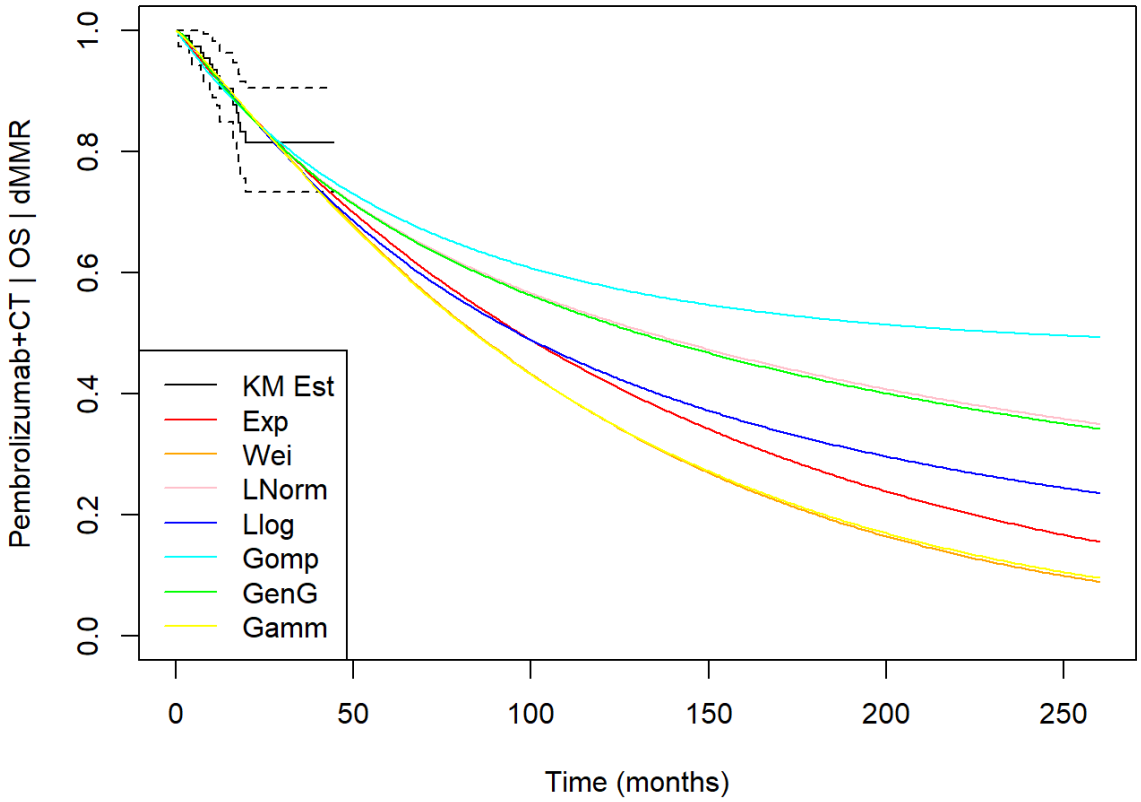


Figure 21. Parametric model fit over 20 years (dMMR, Pembro + CT, OS)

Figure 22. Parametric model hazard function plot (dMMR, Pembro + CT, OS)

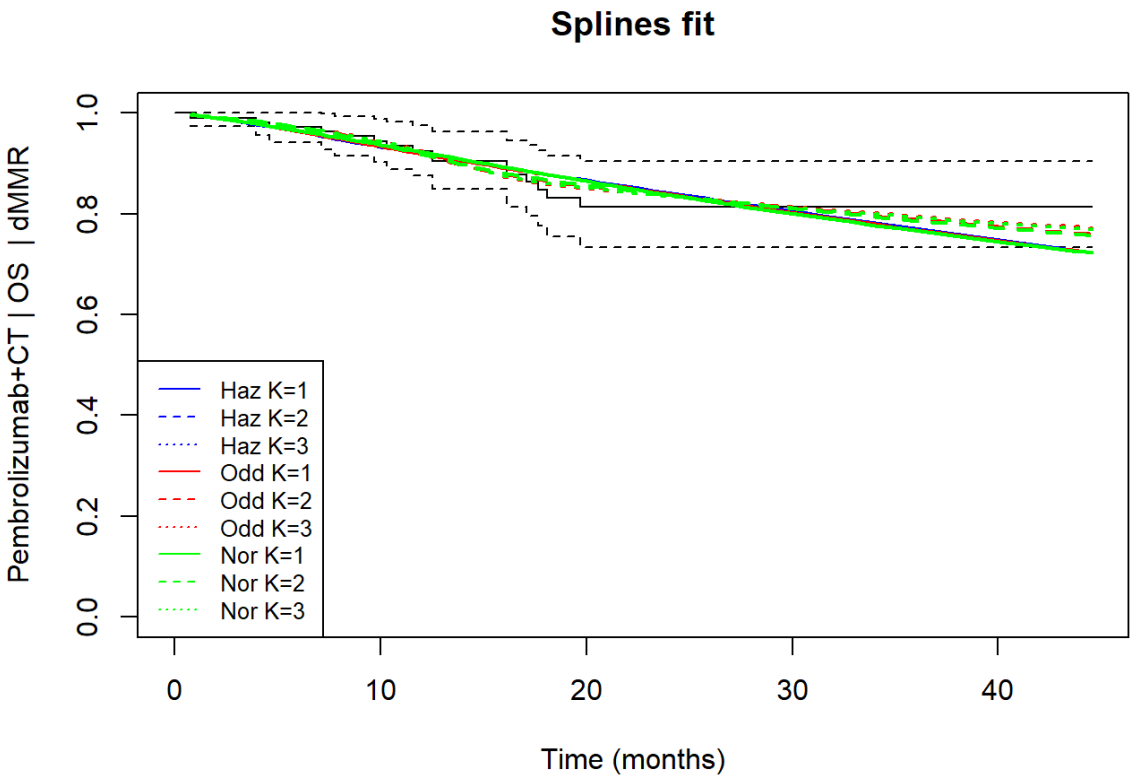


Figure 23. Spline model fit over trial length (dMMR, Pembro + CT, OS)

Figure 24. Spline model hazard function plot (dMMR, Pembro + CT, OS)

Table 24. Statistical model fit (dMMR, Pembro + CT, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**192.1025**	**194.8029**	**Best**	**Best**
Weibull	193.9073	199.3083	Similar	Similar
Log-normal	193.0927	198.4937	Similar	Similar
Log-logistic	193.4752	198.8762	Similar	Similar
Gompertz	193.9482	199.3492	Similar	Similar
Generalised Gamma	195.0917	203.1931	Similar	
Gamma	193.8267	199.2277	Similar	Similar
Hazards k=1	195.7026	203.8041	Similar	
Hazards k=2	NA	NA		
Hazards k=3	NA	NA		
Odds k=1	195.3957	203.4971	Similar	
Odds k=2	195.8219	206.6238	Similar	
Odds k=3	197.4079	210.9103		
Normal k=1	194.8541	202.9556	Similar	
Normal k=2	195.6898	206.4917	Similar	
Normal k=3	197.2784	210.7808		

[redacted]

Figure 25. Parametric model fit over trial length (pMMR, CT only, PFS)

ك

Figure 26. Parametric model fit over 20 years (pMMR, CT only, PFS)

ك

Figure 27. Parametric model hazard functions plot (pMMR, CT only, PFS)

ك

Figure 28. Spline model fit over trial length (pMMR, CT only, PFS)

Figure 29. Spline model hazard functions plot (pMMR, CT only, PFS)

Table 25. Statistical model fit (pMMR, CT only, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	1378.161	1381.862		
Weibull	1342.617	1350.017		
Log-normal	1305.333	1312.733		Similar
Log-logistic	1306.984	1314.385		Similar
Gompertz	1374.319	1381.72		
Generalised Gamma	1303.633	1314.735		Similar
Gamma	1327.624	1335.024		
Hazards k=1	**1299.93**	**1311.031**	**Similar**	**Best**
Hazards k=2	**1298.355**	**1313.157**	**Best**	Similar
Hazards k=3	1300.067	1318.569	Similar	
Odds k=1	1300.364	1311.465	Similar	Similar
Odds k=2	1299.294	1314.096	Similar	Similar
Odds k=3	1299.905	1318.407	Similar	

Normal k=1	1304.031	1315.133		Similar
Normal k=2	1298.635	1313.437	Similar	Similar
Normal k=3	1298.81	1317.313	Similar	

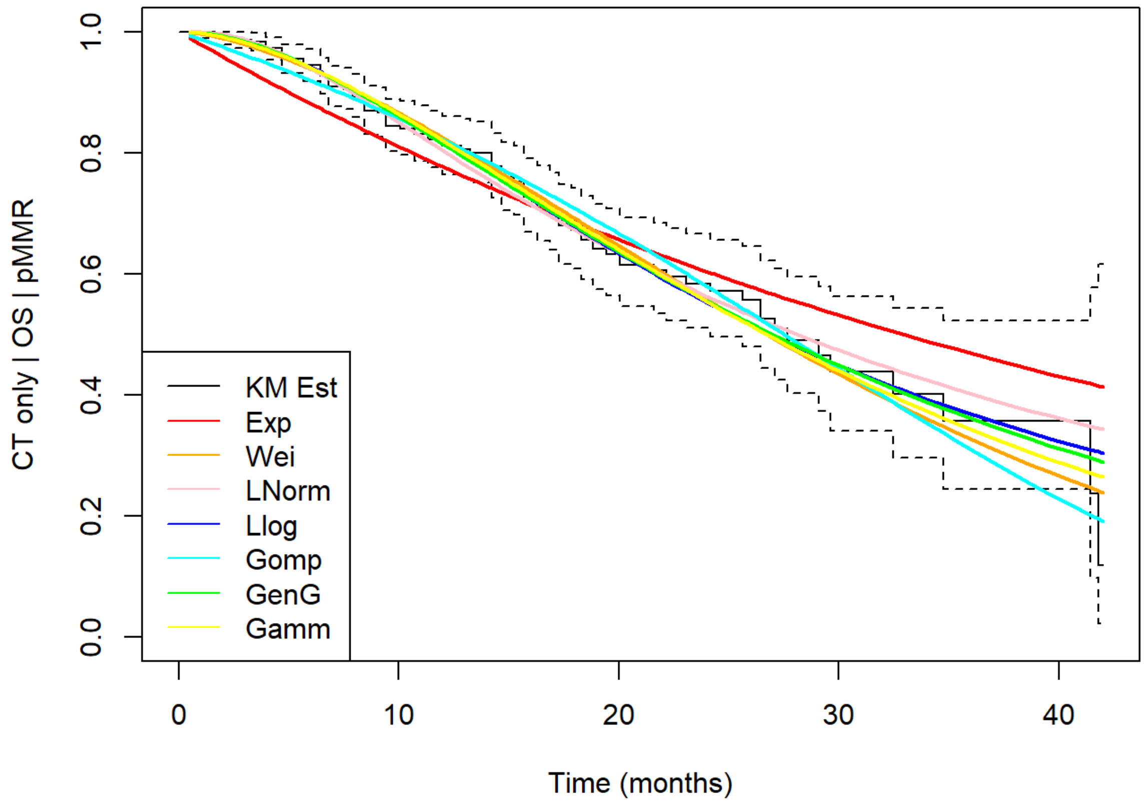


Figure 30. Parametric model fit over trial length (pMMR, CT only, OS)

ك

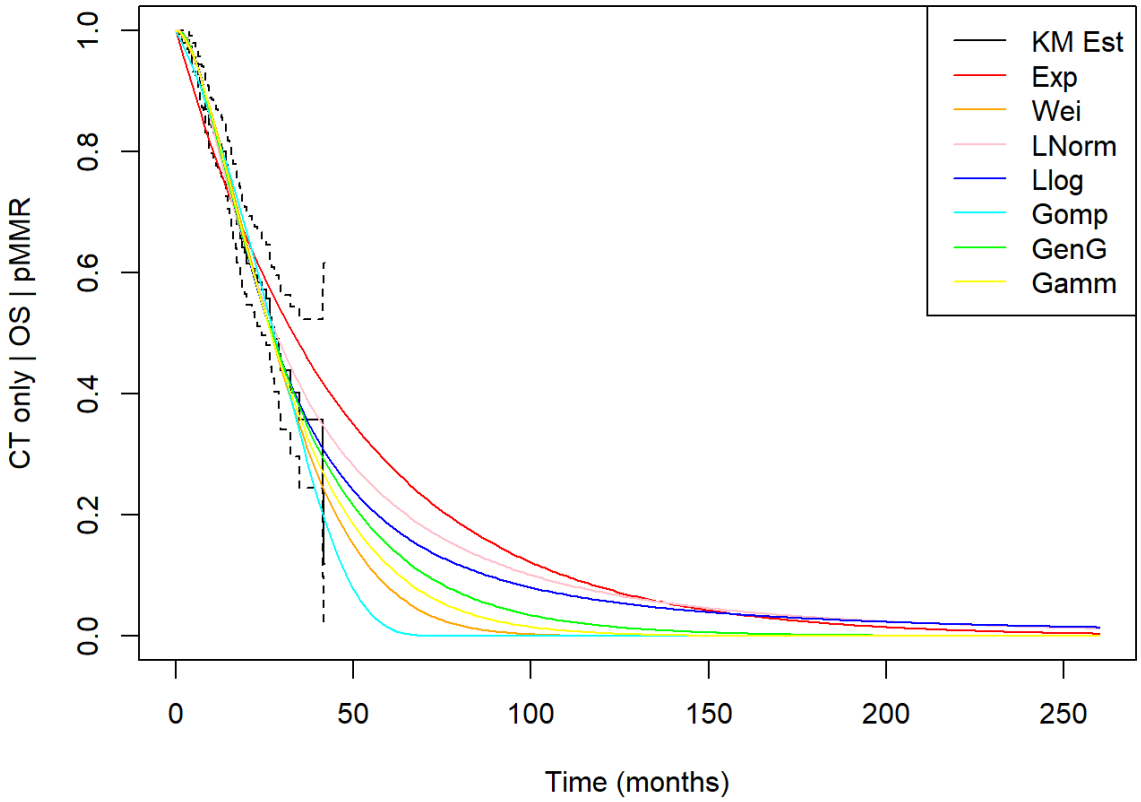


Figure 31. Parametric model fit over 20 years (pMMR, CT only, OS)

ك

Figure 32. Parametric model hazard functions plot (pMMR, CT only, OS)

ك

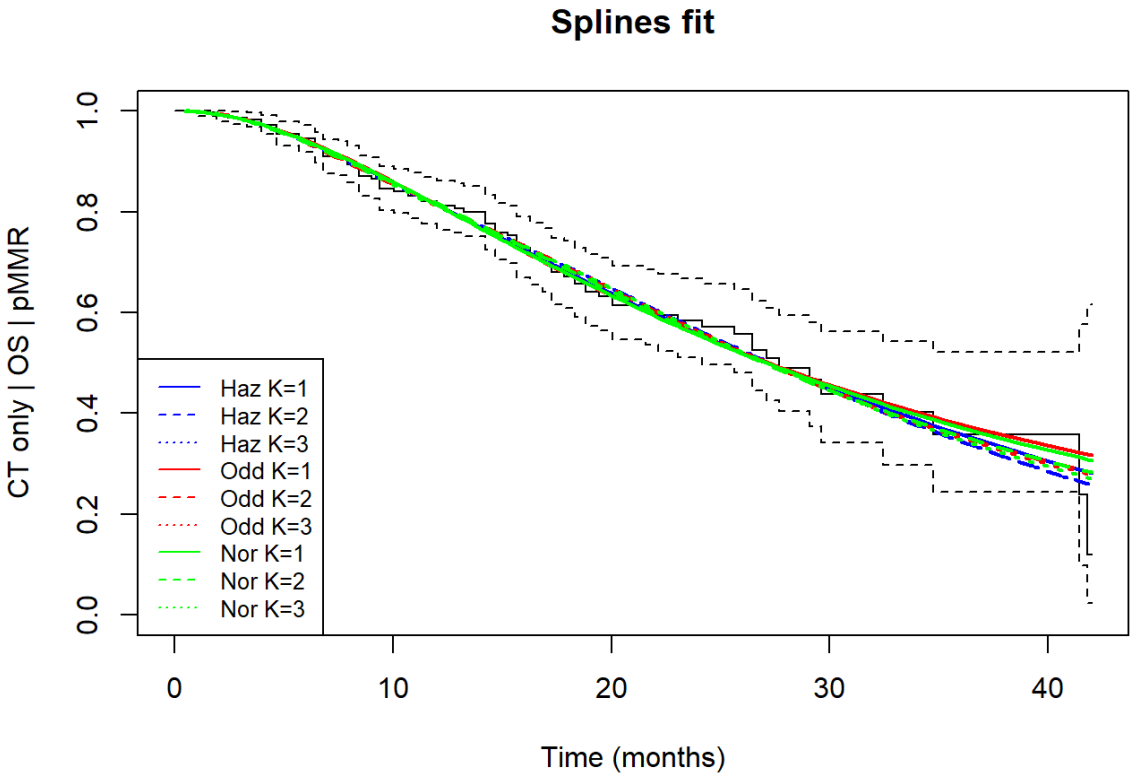


Figure 33. Spline model fit over trial length (pMMR, CT only, OS)

ك

Figure 34. Spline model hazard functions plot (pMMR, CT only, OS)

Table 26. Statistical model fit (pMMR, CT only, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	906.5028	910.2032		
Weibull	882.6766	890.0775	Similar	Similar
Log-normal	883.0764	890.4773	Similar	Similar
Log-logistic	882.3308	889.7316	Similar	Similar
Gompertz	891.1591	898.56		
Generalised Gamma	883.2572	894.3586	Similar	
Gamma	**881.5766**	**888.9775**	**Best**	**Best**
Hazards k=1	882.8736	893.975	Similar	Similar
Hazards k=2	884.1672	898.9689	Similar	
Hazards k=3	886.3696	904.8718	Similar	
Odds k=1	884.1634	895.2647	Similar	
Odds k=2	884.8031	899.6049	Similar	
Odds k=3	886.9745	905.4767		

Normal k=1	883.6905	894.7919	Similar	
Normal k=2	885.1027	899.9045	Similar	
Normal k=3	886.7418	905.2441		

[redacted]

Figure 35. Parametric model fit over trial length (pMMR, Pembro + CT, PFS)

ك

Figure 36. Parametric model fit over 20 years (pMMR, Pembro + CT, PFS)

ك

Figure 37. Parametric model hazard functions plot (pMMR, Pembro + CT, PFS)

Figure 38. Spline model fit over trial length (pMMR, Pembro + CT, PFS)

ك

Figure 39. Spline model hazard functions plot (pMMR, Pembro + CT, PFS)

Table 27. Statistical model fit (pMMR, Pembro + CT, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	1304.29	1307.987		
Weibull	1292.992	1300.386		
Log-normal	1268.061	1275.455		
Log-logistic	1268.868	1276.262		
Gompertz	1306.194	1313.589		
Generalised Gamma	1268.816	1279.907		
Gamma	1285.999	1293.393		
Hazards k=1	1263.741	1274.832		
Hazards k=2	**1248.968**	**1263.757**	**Best**	**Best**
Hazards k=3	1251.57	1270.056	Similar	
Odds k=1	1263.657	1274.748		
Odds k=2	1250.226	1265.014	Similar	Similar

Odds k=3	1251.84	1270.325	Similar	
Normal k=1	1269.282	1280.373		
Normal k=2	1250.884	1265.673	Similar	Similar
Normal k=3	1251.25	1269.735	Similar	

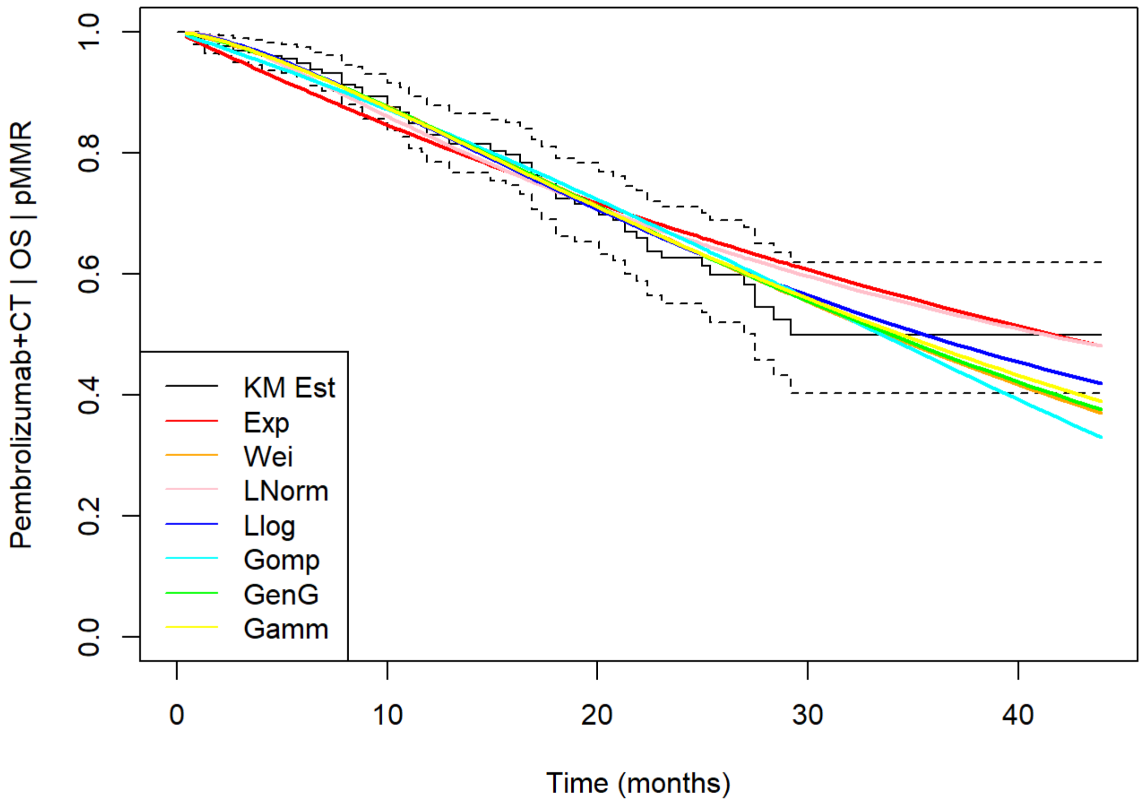


Figure 40. Parametric model fit over trial length (pMMR, Pembro + CT, OS)

ك

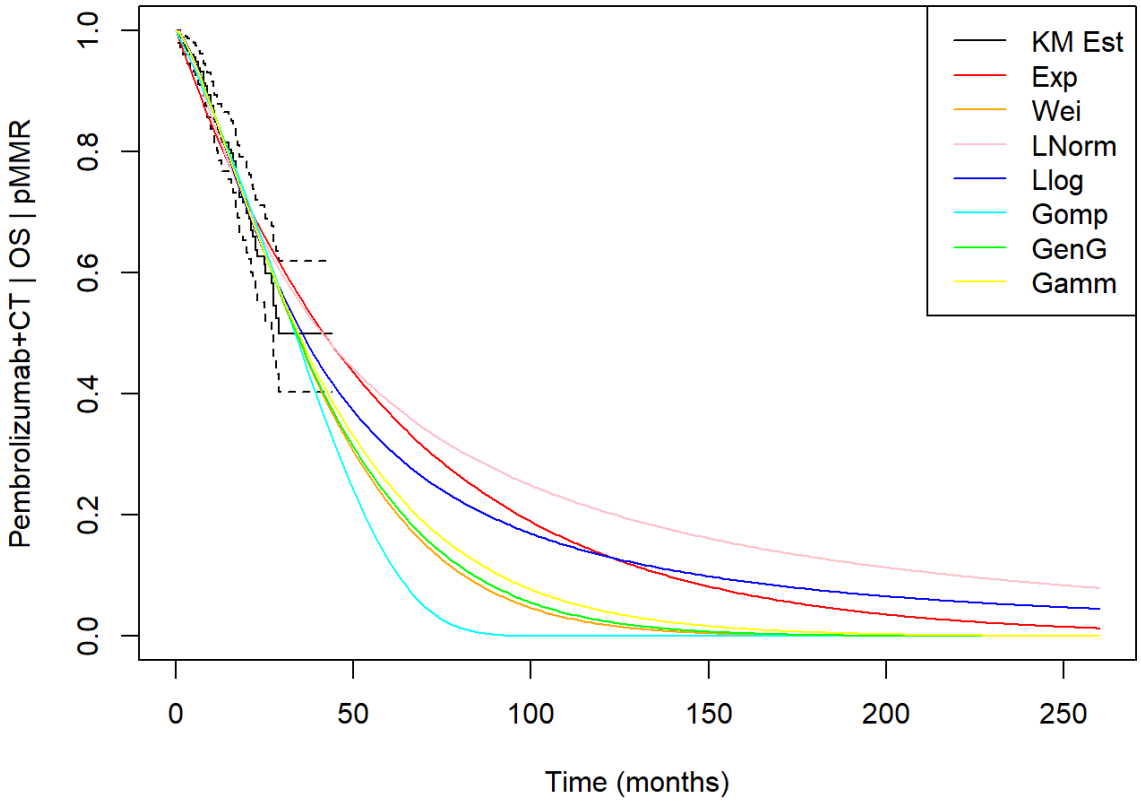


Figure 41. Parametric model fit over 20 years (pMMR, Pembro + CT, OS)

ك

Figure 42. Parametric model hazard functions plot (pMMR, Pembro + CT, OS)

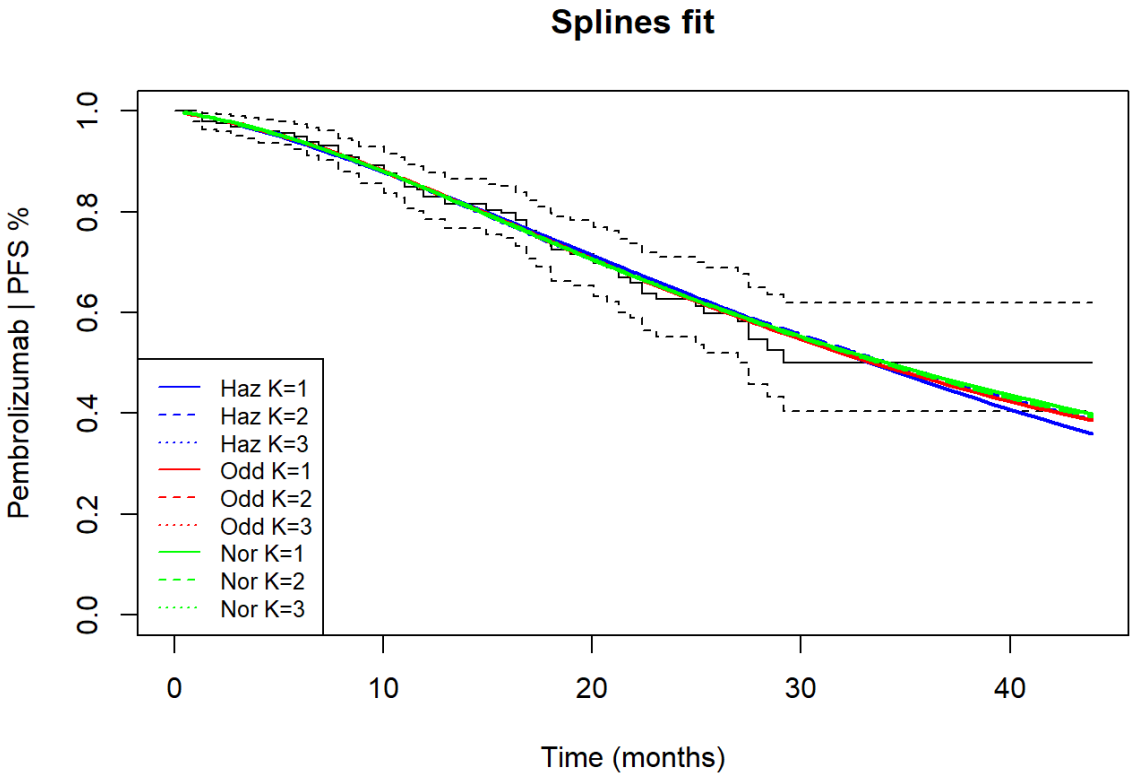


Figure 43. Spline model fit over trial length (pMMR, Pembro + CT, OS)

Figure 44. Spline model hazard functions plot (pMMR, Pembro + CT, OS)

Table 28. Statistical model fit (pMMR, Pembro + CT, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	786.8269	790.524		Similar
Weibull	779.5213	786.9155	Similar	Similar
Log-normal	785.1901	792.5843		
Log-logistic	779.5003	786.8945	**Best**	**Best**
Gompertz	782.8405	790.2347	Similar	Similar
Generalised Gamma	781.5019	792.5932	Similar	
Gamma	779.5904	786.9845	Similar	Similar
Hazards k=1	781.399	792.4903	Similar	
Hazards k=2	782.8147	797.603	Similar	
Hazards k=3	784.7755	803.261		
Odds k=1	780.2192	791.3104	Similar	Similar
Odds k=2	782.1489	796.9372	Similar	
Odds k=3	784.1311	802.6166	Similar	
Normal k=1	779.9208	791.0121	Similar	Similar
Normal k=2	781.8691	796.6575	Similar	
Normal k=3	783.8993	802.3848	Similar	

References

1. Hernández Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by Age and Sex for the UK*. 2022. URL: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d (Accessed June 2024).
2. NICE. *Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer*. National Institute for Health and Care Excellence 2023. URL: https://www.nice.org.uk/guidance/TA904 (Accessed 18 June 2024).
3. Di Dio C, Bogani G, Di Donato V, Cuccu I, Muzii L, Musacchio L*, et al.* The role of immunotherapy in advanced and recurrent MMR deficient and proficient endometrial carcinoma. *Gynecologic Oncology* 2023;**169**:27-33. http://dx.doi.org/10.1016/j.ygyno.2022.11.031
4. Ott PA, Bang YJ, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS*, et al.* Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1-Positive Endometrial Cancer: Results From the KEYNOTE-028 Study. *J Clin Oncol* 2017;**35**(22):2535-41. http://dx.doi.org/10.1200/jco.2017.72.5952
5. Antill Y, Kok PS, Robledo K, Yip S, Cummins M, Smith D*, et al.* Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. *J Immunother Cancer* 2021;**9**(6). http://dx.doi.org/10.1136/jitc-2020-002255
6. NICE. *Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency 2021*. National Institute for Health and Care Excellence 2022. URL: https://www.nice.org.uk/guidance/ta779 (Accessed 24 July 2024).
7. NICE. *Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma - TA661*. National Insitute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/TA661).
8. NICE. *Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy - TA655*. National Institute for Health and Care Excellence; 2020. URL: https://www.nice.org.uk/guidance/ta655).