NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from MSD

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Gynaecological Cancer Society
   b. Jo's Cervical Cancer Trust
   c. NCRI-ACP-RCP-RCR

4. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics - York

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

6. **Technical engagement response from company**
   a. Supportive analysis from other trials

7. **Technical engagement responses and statements from experts:**
   a. Dr Alexandra Taylor, Consultant in Clinical Oncology – clinical expert, nominated by MSD
   b. Dr Susan Lalondrelle, Consultant Clinical Oncologist, clinical expert, nominated by the Royal College of Physicians
   c. Ms Eluned Hughes, Head of Information and Engagement – patient expert, nominated by Jo's Cervical Cancer Trust (*see item 3b*)

8. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York
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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 chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Document B

Company evidence submission

March 2022

File name	Version	Contains confidential information	Date
ID3798_Pembrolizumab_NICE_STA_DocumentB_AIC_REDACTED	V2.0	Yes	23rd June 2022

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
APaT	All patients as treated
BGCS	British Gynaecological Cancer Society
BICR	Blinded independent central review
CDF	Cancer Drugs Fund
CI	Confidence interval
CPS	Combined positive score
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FAD	Final appraisal document
FIGO	International Federation of Gynaecology and Obstetrics
HPV	Human papillomavirus
HR	Hazard ratio
ITT	Intention-to-treat
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
QLQ-C30	Quality of life questionnaire – C30
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
SLR	Systemic literature review
SmPC	Summary of Product Characteristics
VAS	Visual analogue scale
WHO	World Health Organization

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

B.1.1. Decision problem

This submission covers the technology's anticipated full marketing authorization:

'KEYTRUDA (pembrolizumab), in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.'

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	Adults with untreated recurrent, persistent or metastatic cervical cancer	As per final scope	N/A
Intervention	Pembrolizumab in combination with paclitaxel and platinum-based chemotherapy (carboplatin or cisplatin) with or without bevacizumab	As per final scope	N/A
Comparator(s)	• Platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel or topotecan or etoposide • In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	• Platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel • In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	Etoposide has been excluded from the list of comparators. Etoposide is used in small cell cervical cancer, a histology which is not covered by the KEYNOTE-826 trial.[1, 2] Cervical cancer is not included as an indication in the etoposide SmPC. Although it is acknowledged that TA183 approved the use of topotecan in combination with cisplatin for women with recurrent or stage IVB cervical cancer if they have not previously received cisplatin, topotecan has been excluded from the list of comparators: • At the NICE scoping call held for this submission in December 2020, clinical experts in attendance did not report the use of topotecan in UK clinical practice. This was further confirmed at a recent advisory-board, in which clinicians confirmed that topotecan is not in use in the NHS in this indication[3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• Topotecan is not recommended by the BGCS guidelines for the treatment of advanced cervical cancer • Bevacizumab is currently the preferred option for first-line treatment of advanced or metastatic cervical cancer in conjunction with chemotherapy. Topotecan was also rarely indicated prior to bevacizumab becoming available; the NICE FAD for TA183 states that '90–95% of women within the licensed population will have previously received cisplatin'[4] Platinum-based monotherapy have also been excluded from the list of comparators to align with current treatment options recommended by the BGCS guidelines and clinician feedback.

	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: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life • Duration of response	Addition of the duration of response outcome to aid in capturing the most important health-related benefits of the Pembrolizumab in the patient population of interest.
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. The availability of any managed access arrangement for the	As per final scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	intervention will be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered based on: • Histology (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and poorly differentiated carcinoma) • Pelvic disease status (pelvic or locally recurrent cervical cancer and distant metastatic cervical cancer) • CPS of PD-L1 expression (< 10, ≥ 10 and all-comers) • Tumour mutational burden	This submission presents the subgroup analyses for the CPS ≥ 1 population	The subgroup analyses presented align with the licenced indication for pembrolizumab.
Key: BGCS, British Gynaecological Cancer Society; CPS, combined positive score; FAD, final appraisal document; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death-ligand 1; SmPC, Summary of Product Characteristics.			

B.1.2. Description of the technology being appraised

Pembrolizumab (KEYTRUDA®, MSD) is a humanized monoclonal anti-programmed cell death-1 antibody, which binds to the programmed death-ligand 1 (PD-L1) receptor, thereby blocking its interaction with ligands PD-L1 and programmed death-ligand 2 (PD-L2).[5] 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.

Table 2 presents a description of pembrolizumab in combination with chemotherapy. The draft Summary of Product Characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA)
Mechanism of action	Pembrolizumab is a monoclonal antibody, which binds to the PD-1 receptor, thereby potentiating an immune response to tumour cells.
Marketing authorisation status	The application for marketing authorization with the EMA is currently ongoing. Approval from the CHMP was granted in March 2022. EMA approval is expected in [redacted] followed by MHRA in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication under appraisal is: 'KEYTRUDA (pembrolizumab), in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1' 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

Method of administration and dosage	The recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. In KEYNOTE-826, patients received pembrolizumab 200 mg once every 3 weeks until disease progression, unacceptable toxicity, or patient withdrawal. Pembrolizumab could be administered for a maximum of 24 months, or up to a maximum of 35 cycles. The administration regimen for chemotherapy and bevacizumab are described in Section B.2.3.1.
Additional tests or investigations	Testing for PD-L1 tumour expression level, measured by the CPS which consists of the proportion of PD-L1–positive tumour cells and infiltrating immune cells relative to the total number of tumour cells.
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial and the total cost per administration is £5,260.
Patient access scheme (if applicable)	The price of pembrolizumab is subject to a Commercial Access Arrangement (CAA) with a simple discount of [redacted]%; therefore, administration of 200 mg pembrolizumab will cost £[redacted]. Due to the highly confidential nature of this figure MSD requests that documentation from the Evidence Assessment Group does not include the CAA price and instead references back to this table.
Key: CAA, Commercial Access Agreement; CHMP, Committee for Human Medicinal Products; CPS, combined positive score; EMA, European Medicines Agency; ICER, incremental cost-effectiveness ratio; MHRA, Medicines and Healthcare products Regulatory Agency; PD-L1, programmed cell death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; SmPC, Summary of Product Characteristics.	

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

Summary of key points:

- Patients with recurrent, persistent or metastatic cervical cancer have a median age of 51. Additionally, many patients are diagnosed with cervical cancer at a much earlier age, with nearly half of new cases occurring between the ages of 15 and 44 years. [6]
- The median overall survival (OS) with standard of care treatment is just 13-17 months[7]

- Minimal developments have been made in the management of recurrent, persistent or metastatic cervical cancer over the last decade, with the last NICE technology appraisal relating to pharmacological treatment of cervical cancer being published more than 12 years ago[8]
- The vast majority of patients with persistent, recurrent and metastatic cervical cancer seen in UK clinical practice are of working age, and many have families and dependents[3]
- The condition is relatively more prevalent in certain ethnic minorities and in lower socioeconomic groups[9, 10]
- There is a strong policy background in support of improving outcomes for these patients[11]

B.1.3.1 Disease background

Cervical cancer starts in the cells lining the cervix, the lower part of the uterus (womb). Between 70 and 80% of cervical cancers are squamous cell cancers, a cancer of the skin-like cells of the ectocervix.[12] Adenocarcinoma, which represents around 20% of cervical cancers, starts in the glandular cells of the endocervical canal. Less common histologies include adenosquamous (5-6%) and small cell cancer (3%). KEYNOTE-826 provides data for the squamous cell cancer, adenocarcinoma and adenosquamous carcinoma histologies; patients with small cell cancer are excluded.

An estimated 99.8% of cervical cancer cases are preventable, and, if the cancer is detected early and adequately treated, it is also curable.[11, 13] In 2020, the World Health Organization (WHO) announced a global initiative to eliminate cervical cancer within the next century, with the mandate that all countries must reach and maintain an incidence rate of < 4 per 100,000 women.[11] The WHO considers three strategies to be key in achieving the eradication of cervical cancer: vaccination, screening and treatment.

Persistent high-risk human papillomavirus (HPV) infection is the primary risk factor for developing cervical cancer, with over 90% of all cervical cancers estimated to be caused by HPV, particularly HPV Types 16 and 18.[14, 15] The risk of acquiring HPV

depends on several factors, including number of sexual partners, likelihood that the partner or partners were infected with HPV, and age of sexual debut.[16] Additional risk factors associated with developing advanced-stage cervical cancer include low-socioeconomic status, older age, black or Hispanic ethnicity, and lower education level.[10]

The HPV immunization programme introduced in England in 2008 invited girls aged 12–13 years to receive routine HPV vaccine. The success of the vaccination programme is evident from the observed substantial reduction in incidence of cervical cancer and of cervical intraepithelial neoplasia-3 (CIN3).[17] In addition to vaccination, the National Health Service Cervical Screening Programme aims to reduce the incidence of, and mortality from, cervical cancer through a population-based screening programme of all women aged 24.5–64 years.[18] In 2020/21, 4.59 million women in England were invited for screening, of whom 70.2% were adequately screened.[19] Cervical screening coverage varies across England, with lower rates of screening particularly evident in the youngest and oldest age groups invited, as well as in under-represented groups, such as those from lower socio-economic and ethnic minority communities. In the UK, women who are socioeconomically disadvantaged are less likely to attend cervical screening[20] and have a greater risk of developing cervical cancer.[9]

Cervical cancer is staged by the International Federation of Gynaecology and Obstetrics (FIGO) staging system, which is determined by physical examination and diagnostic tests, including palpation, inspection, colposcopy and endocervical curettage.[21, 22] A detailed description of FIGO staging of cervical cancer is provided in Appendix L. The staging of cervical cancer, including whether the cancer has metastasized, is one of the most important factors in evaluating treatment options. If the primary tumour does not respond to treatment or a second tumour develops despite the completion of treatment, the cancer is defined as persistent. Recurrent cancer is when the cancer returns months or years after achieving remission with the original treatment. Metastatic cancer is defined as the spreading of the cancer outside the original tumour site, to other areas of the body. If cervical cancer is recurrent, persistent or metastatic, there are limited treatment options other than platinum-based chemotherapies, with treatments usually aiming to alleviate

symptoms and improve quality of life (QoL), rather than being given with curative intent.

In the UK, the cervical cancer screening programme, together with the HPV immunization programme, has led to remarkable advances in the management of the condition. However, there are patients who do not receive an HPV vaccine, and do not attend screening. Thus, a proportion of patients remain at risk of developing persistent HPV infection and consequently cervical cancer. Moreover, patients who do not undergo screening are more likely to present at diagnosis with advanced-stage disease, and, for this group, current treatment options are limited and their prognosis is particularly poor. Minimal developments have been made in the management of recurrent, persistent or metastatic cervical cancer over the last decade, with the last NICE technology appraisal relating to pharmacological treatment of cervical cancer being published more than 12 years ago. The addition of pembrolizumab to the treatment landscape would be a step-change in the management of advanced cervical cancer.

B.1.3.2 Epidemiology

Globally, cervical cancer is estimated to account for 3.3% of all deaths due to cancer, and, among women, it is ranked ninth in mortality worldwide.[23] In England, the number of deaths from cervical cancer is much lower compared with many parts of the world, with the low number of deaths directly attributable to the success of the HPV vaccination programme in reducing number of cases of cervical cancer, and the screening programme in detecting cancer early. In 2020, there were 702 cervical cancer deaths (ICD10 code C53) in England.[24] By contrast, in 2018, nearly 90% of the global deaths attributed to cervical cancer occurred in low- and middle-income countries.[11]

Cervical cancer is listed as the 14th most common cancer in women in the UK.[13] In 2019, 2,735 new cervical cancer cases (ICD10 code C53) were registered in England, corresponding to an incidence rate of 9.8 per 100,000 population.[25] Nearly half of all cases (49.9%) were in people aged 15–44 years. Since the introduction of the HPV immunization programme, the incidence of new diagnoses of cervical cancer per 100,000 females has fallen from 12.0 in 1995 to 9.8 in 2019.[25] The overall

incidence in cervical cancer is expected to remain stable over the next few years, until the effect of the expanded immunisation programme is seen. Despite the success of immunization and screening in reducing the incidence of cervical cancer, and therefore number of deaths, there will always be a proportion of patients who present with advanced-stage cervical cancer and who require effective treatment options to manage their disease.

When stratified by stage at diagnosis, the English cancer registry reported that 30.1% of cervical cancer cases were diagnosed as Stage 1, 11.8% were Stage 2, 5.4% were Stage 3, 8.7% were Stage 4 and 43.9% were missing.[26] Furthermore, a retrospective study was conducted across six cancer centres in the North of England.[27] Of these patients, 47% were diagnosed as Stage 1, 18% as Stage 2, 13% as Stage 3, 11% as Stage 4; the stage was not documented in 11% of cases (staging as per FIGO 2018).

Survival rates have been estimated for women with Stage 1 and Stage 4 cervical cancer at diagnosis in England between 2014–2018 (Table 3).[28] As expected, patients diagnosed with Stage 4 cervical cancer have a much lower survival rate at 1, 2, 3 and 4 years following diagnosis, with only 17.9% of Stage 4 patients surviving to 4-years.

Table 3: Age-standardized net cancer survival rates for women (aged 15–99) diagnosed with Stage 1 and Stage 4 cervical cancer between 2014–2018

Age-standardized survival	Stage at initial diagnosis	
	Stage 1	Stage 4
1-year	97.8	49.6
2-year	93.1	29.8
3-year	90.6	22.3
4-year	90.6	17.9
Source: GOV.UK (National Cancer Survival Statistics).[28]		

B.1.3.3 Burden of disease

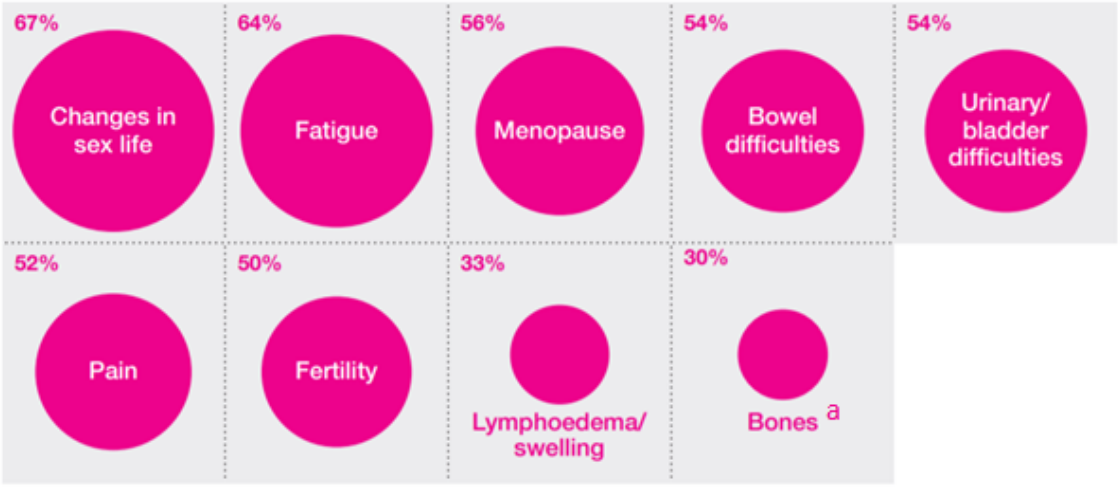
Women diagnosed with cervical cancer often experience substantial disruption to their QoL. Although early-stage cervical cancers and pre-cancerous cell changes are usually asymptomatic, some patients may experience symptoms including[29]:

- Irregular vaginal bleeding
- Changes in vaginal discharge
- Postcoital bleeding
- Pain in the lower back, pelvis or leg

These symptoms escalate in patients with advanced cervical cancer, and may progress to fatigue and feeling unwell, weight loss and loss of appetite, griping pain in abdomen, bloating, constipation, blood in the urine and excessive vomiting.[30, 31]

Jo's Cervical Cancer Trust conducted a survey of historical National Cancer Patient Survey participants in the UK between 2010–2013 and 2015, all of whom had their diagnosis of cervical cancer for at least 1 year.[32] Comorbidities are extremely common with cervical cancer. Of the 688 responses received, 88% of women had experienced at least one physical long-term consequence (defined as those that occur at least three to six months after treatment ending), and 24% experienced six or more long-term consequences of cervical cancer and its treatment. Examples of long-term consequences, and the percentage of women who experienced these consequences, are presented in Figure 1.

Figure 1: Percentage of women experiencing a long-term consequence of cervical cancer and its treatment



Source: Jo's Cervical Cancer Trust, 2017.[32]
Notes: [a], Some patients experience bone changes after pelvic radiotherapy for gynaecological cancer. Research suggests that over 1 in 10 (14%) will have tiny cracks in the bones, although these may not cause any symptoms.

Furthermore, a cervical cancer diagnosis has a long-term negative impact on women's mental health: 44% of women reported general anxiety, 44% reported a fear of recurrence, 37% reported a loss of confidence, and 33% experienced symptoms of depression.[32]

When asked about impact on their work life, nearly half (47%) of women reported a change since being diagnosed, with 60% of these women specifying the change was a consequence of their cervical cancer treatment.[32] This percentage increased in women who received more invasive treatment such as chemoradiation and exenteration surgery. As well as the financial implications associated with a change in employment status, women may also see returning to work as an important factor of rebuilding their life post-cancer.

In women diagnosed with more advanced cervical cancer, the combined financial burden of cancer-related costs, additional living arrangements and loss of income accrues to approximately £1,100 a month (April 2014 data).[33] Financial drivers for individuals include increased insurance premiums, specialist equipment and hiring of extra help such as childcare or cleaners.

There is also a wider societal financial implication with more than half of cervical cancer deaths in England and Wales occurring in women below the age of 65 years who may still be part of the labour force (2017 data).[34] The associated productivity loss was estimated to be £303.2 million.

Although recurrent, persistent and metastatic cervical cancer predominantly affects a younger population (median age of diagnosis: 51 years), their prognosis is poor. The median OS with standard of care treatment is just 13-17 months (further discussed in Section B.1.3.4.2).

B.1.3.4 Clinical care pathway and proposed positioning of the technology

B.1.3.4.1 Current clinical guidelines and relevant comparators for pembrolizumab

The typical clinical pathway of care for the treatment of cervical cancer in England is based on the 2020 British Gynaecological Cancer Society (BGCS) guidelines, as presented below.[2] Further guidelines include the National Institute for Health and

Care Excellence (NICE) cervical cancer pathway, the Royal College of Nursing guidance on HPV, cervical screening and cervical cancer, and the European Society for Medical Oncology recommendations for the treatment of cervical cancer. These guidelines are further presented in Appendix M.

The main treatment for early-stage cervical cancer (FIGO Stage IA-IB) is normally surgery, especially if the cancer is found early.[2] Surgical treatment options for cervical cancer include large loop excision of the transformation zone, cone biopsy or larger surgeries such as trachelectomy or hysterectomy, as well as potential surgery to remove lymph nodes. Surgery may be followed by radiotherapy and chemotherapy (chemoradiation) to aid in the treatment of cancer that has spread, or to reduce the risk of cervical cancer recurrence.

Treatment options for patients diagnosed with locally advanced cervical cancer (FIGO Stage IB3-IVA) normally includes chemoradiation.[2] Chemoradiation consists of external beam radiotherapy, intracavitary brachytherapy and concomitant chemotherapy with cisplatin. Additional radiation boosts to the involved lymph nodes may also be recommended for patients with unequivocally involved pelvic lymph nodes on imaging.

Systemic treatment is recommended for some patients diagnosed with recurrent, persistent or metastatic cervical cancer. The BGCS guidelines state all women with recurrent, persistent or metastatic cervical cancer with a World Health Organization (WHO) performance status of 0 or 1 should be considered for systemic treatment, whereas patients with a performance status of > 1 should be carefully assessed to determine their suitability and the likely benefit of treatment.[2] The measure of functionality status was first developed by the Eastern Cooperative Oncology Group (ECOG), and has since been adopted by the WHO.[35] The measure of functionality status is hereinafter referred to as the ECOG performance status, and is further defined in Appendix N.

The only first-line treatment recommended by BGCS is systemic chemotherapy (with cisplatin and paclitaxel, or carboplatin and paclitaxel) with or without bevacizumab depending on patient risk factors[2]; this has been the standard of care for some time for patients with recurrent, persistent, or metastatic cervical cancer. Cisplatin and

carboplatin, in combination with paclitaxel, have been shown to be of similar clinical effectiveness across various types of cancer, although the differing toxicity profiles between the platinum-based agents allow a tailored approach to treatment depending on patients' comorbidities.[2, 36]

Topotecan in combination with cisplatin was approved by NICE for the treatment of recurrent or metastatic cervical cancer in patients who have not previously received cisplatin (TA183; 2009).[8] Since the approval of topotecan, bevacizumab has become available for use in the UK via the CDF and is now, in combination with chemotherapy, the currently preferred option for first-line treatment of advanced or metastatic cervical cancer. Topotecan was also rarely indicated for management of cervical cancer before bevacizumab became available; the NICE final appraisal document (FAD) for TA183 states that '90–95% of women within the licensed population will have previously received cisplatin', and therefore are not eligible for treatment with topotecan.[4] Furthermore, topotecan is not recommended by the BGCS guidelines, and at a recent clinical advisory board, UK clinicians have confirmed that topotecan in not in use in the NHS for this indication.[3] Topotecan is therefore not a comparator of interest for this submission.

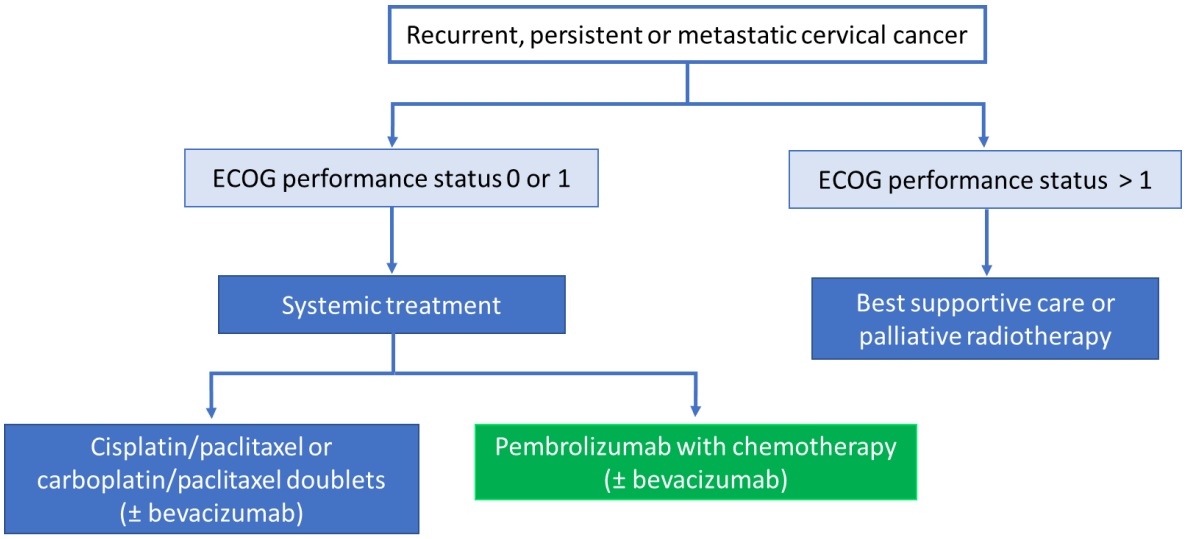
UK clinicians have confirmed that the proportion of patients receiving bevacizumab ranges by NHS trust from approximately 50–80%[3]; this proportion aligns with the 63% of patients receiving bevacizumab in the KEYNOTE-826 trial. The Blueteq approval criteria for bevacizumab states it must be given with chemotherapy and is not approved for use as a single agent maintenance therapy. The chemotherapy, paclitaxel with cisplatin or carboplatin, is usually given for six cycles. Although UK clinicians have confirmed that in practice, it may sometimes be administered for a longer duration. This happens on a case-by-case basis along with a reduced dose of chemotherapy to ensure the patient is still eligible. However, there is currently no evidence on the clinical effectiveness of continuing bevacizumab in the maintenance setting.

The administration of bevacizumab alongside chemotherapy should be dependent on any patient risk factors. For example, prior radiation is a risk factor for gastrointestinal and gall bladder perforation in patients treated for recurrent,

persistent or metastatic cervical cancer with bevacizumab. Treatment with bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.[37] This treatment option is available through the CDF with no plans to be evaluated by NICE.

Figure 2 presents the clinical pathway for patients with recurrent, persistent or metastatic cervical cancer, and the proposed positioning of pembrolizumab in the treatment pathway. In cases where patients present with an ECOG performance status of >1, patients may not be eligible for further systemic treatment; therefore, clinicians may recommend best supportive care or palliative radiotherapy. As pembrolizumab is intended as a new systemic treatment in patients with an ECOG performance status of 0 or 1, where systemic treatment is always preferred, best supportive care or palliative radiotherapy are not considered relevant comparators for this submission.

Figure 2: Clinical pathway of care for patients with recurrent, persistent or metastatic cervical cancer and the proposed placement of pembrolizumab



Key: BGCS, British Gynaecological Cancer Society; ECOG, Eastern Cooperative Oncology Group.
Source: Adapted from BGCS cervical cancer guidelines[2]

B.1.3.4.2 The unmet clinical need

Minimal developments have been made in the management of recurrent, persistent or metastatic cervical cancer over the last decade, with the most recent NICE appraisal for its treatment being published over 10 years ago.[8] As stated on the

scope consultation for this submission, Jo's Cervical Cancer Trust has expressed a need for increased treatment options for women with advanced cervical cancer[38]; the systemic treatment options available are very limited and unfortunately outcomes remain poor.

As discussed in Section B.1.3.4.1, current treatment options for recurrent, persistent or metastatic cervical cancer are limited to systemic chemotherapy with cisplatin and paclitaxel, or carboplatin and paclitaxel, with or without bevacizumab. A large randomised phase III trial (GOG-204) was conducted to compare four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine or vinorelbine[7]; the trial results were unable to demonstrate the superiority of any specific regimen, although paclitaxel and cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months) and was considered the preferred regimen based on the balance between efficacy and toxicity profile. Furthermore, the GOG-240 trial explored the addition of bevacizumab to the cisplatin and paclitaxel chemotherapy regimen over a 4 year follow-up.[39] GOG-240 demonstrated that addition of bevacizumab significantly prolonged median OS (16.8 versus 13.3 months; HR 0.765; P = 0.0068) compared to cisplatin and paclitaxel alone. Despite the improvement on the addition of bevacizumab, survival outcomes for this population are still limited, highlighting a need for alternative and more effective treatments.

B.1.3.4.3 Impact of COVID-19

Due to disruptions caused by the COVID-19 pandemic, there have been notable delays in the diagnosis and management of cervical cancer.[40] Attendance for screening was less than usual in 2020–2021; in women aged 25–49, screening uptake decreased from 70.2% in 2019–2020, to 68.7% in 2020-2021.[41, 42] One modelling study in the UK has evaluated the impact of COVID-19 on patient outcomes due to delays in the diagnosis of breast, colorectal and oesophageal cancer; it was demonstrated that there could be up to a 16% increase in cancer deaths in certain sites.[43] Furthermore, a 4-week delay in adjuvant/neoadjuvant treatment was shown to increase mortality for several cancers, including cervical cancer.[44]

B.1.4. Equality considerations

No equality considerations relating to the use of pembrolizumab have been identified or are anticipated except that the condition in question is relatively more prevalent in lower socioeconomic and ethnic minority groups. Improving outcomes for these groups is in line with NICE's "Principle 9. Aim to reduce health inequalities".[45]

B.2. Clinical effectiveness

Summary of key points:

Study identification

- A systematic literature review (SLR) identified one study (KEYNOTE-826) that provided direct efficacy and safety evidence for pembrolizumab and chemotherapy (± bevacizumab)
- KEYNOTE-826 is an ongoing Phase III, randomized controlled trial being conducted to assess the efficacy of pembrolizumab with chemotherapy (± bevacizumab) compared with placebo with chemotherapy (± bevacizumab) as a first-line therapy for recurrent, persistent or metastatic cervical cancer
- The first interim analysis has been published (Colombo et al. 2021[1]), with a data cut-off date of 3 May 2021

Efficacy

- The addition of pembrolizumab to chemotherapy, with or without bevacizumab, provides statistically significant OS and progression-free survival (PFS) improvements after a 22 month follow-up[1, 6]
  - In the CPS ≥ 1 population, median PFS was significantly longer in the pembrolizumab group (10.4 months; 95% confidence interval [CI] 9.7, 12.3) than the placebo group (8.2 months; 95% CI: 6.3, 8.5)
  - Median OS in the CPS ≥ 1 population was not reached in the pembrolizumab group (95% CI: 19.8, NE) and was 16.3 months (95% CI: 14.5, 19.4) in the placebo group
- The proportion of patients (CPS ≥ 1 population) who achieved a CR or PR was significantly greater in the pembrolizumab group than those treated with placebo (68.1% versus 50.2%, respectively; $p < 0.001$)
- Patients in the pembrolizumab group had a longer duration of response (DoR) compared to placebo (18.0 versus 10.4 months, respectively; CPS ≥ 1

population)

- Benefits were generally consistent across all protocol-specified subgroups, independent of whether the patient received bevacizumab

Safety

- The safety results of the first interim analyses of KEYNOTE-826 demonstrate that pembrolizumab offers a manageable and predictable AE profile[1, 6]
  - The overall incidence of AEs was generally similar between the pembrolizumab and placebo treatment groups and was largely consistent with the known safety profiles of pembrolizumab monotherapy, the chemotherapy administered (± bevacizumab), and the indication under study

HRQL

- Patients receiving pembrolizumab experienced no clinically meaningful drop in their health-related quality of life **(**HRQL), despite the addition of another targeted agent.[1]
  - When treated with pembrolizumab, the time to deterioration of HRQL was longer, and a higher proportion of patients had an improved or stable HRQL compared to placebo as assessed via the ED-5D-5L VAS score.

B.2.1. Identification and selection of relevant studies

A SLR was conducted to identify and select evidence on the efficacy and safety of first-line treatments for patients with recurrent, persistent or metastatic cervical cancer. This SLR covered a broad range of interventions used globally; the results of the SLR were then further refined to align with the decision problem presented within this submission. Of the 4,417 studies identified, 41 unique trials were considered to be relevant to the decision problem. KEYNOTE-826 (Colombo et al. 2021[1]) was the only study to provide direct evidence for pembrolizumab and standard of care in the treatment of recurrent, persistent or metastatic cervical cancer. Full details on the SLR are provided in Appendix D.1.

B.2.2. List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for pembrolizumab is presented in Table 4.

The pivotal regulatory evidence used to support pembrolizumab in combination with chemotherapy with or without bevacizumab (denoted ± bevacizumab hereafter) for the treatment of patients with recurrent, persistent or metastatic cervical cancer is the KEYNOTE-826 trial.[1, 6] This primary source of evidence provides information on 617 patients relevant to the decision problem, with a median follow-up of 17.2 months. Further details of KEYNOTE-826 are provided in Sections B.2.3 to B.2.6 of this submission.

Supportive evidence is provided by the earlier KEYNOTE-158 trial, a Phase II, single-arm basket trial of pembrolizumab monotherapy in patients with previously treated, advanced cancer in multiple advanced solid tumour types. For the subset of cervical cancer patients, KEYNOTE-158 served as a proof of concept trial to demonstrate efficacy of pembrolizumab monotherapy in patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy (i.e. second and later lines of treatment) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1) as determined by an FDA-approved test. Patients received pembrolizumab (200 mg) once every 3 weeks for 2 years, or until disease progression, unacceptable toxicity or patient withdrawal, and were followed-up for a median of 10.2 months. Efficacy and safety results of the cervical cancer subset of patients for the KEYNOTE-158 trial have been presented in Section B.2.6.3 and Section B.2.10.2, respectively. All other data for this trial, including methodology, are presented in Appendix O.2.

KEYNOTE-826 evaluates pembrolizumab in an earlier treatment setting than KEYNOTE-158 and served as the confirmatory study in the US setting for the accelerated approval granted by the FDA in June 2018 based on results from the KEYNOTE-158 trial. Full approval in the US based on the KEYNOTE-826 study occurred in October 2021.

Another key trial identified by the SLR is the GOG-240 trial, a Phase III randomized trial conducted to assess the efficacy of chemotherapy (cisplatin and paclitaxel or topotecan and paclitaxel) with or without bevacizumab in patients with recurrent, persistent or metastatic cervical cancer.[39] This trial has been used for validation of

the comparator/SoC arm of the KEYNOTE-826 trial. Further information on the GOG-240 trial is presented in Appendix Q.3.

Table 4: Clinical effectiveness evidence

Study	KEYNOTE-826
Study title	A Phase III, randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy versus chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826)
Trial number	NCT03635567
Study design	Phase III, randomized, double-blind, placebo-controlled trial
Population	Female participants of at least 18 years of age with recurrent, persistent or metastatic cervical cancer who were not eligible for treatment with curative intent (such as with surgery and/or radiation). Patients also must not have been previously treated with systemic chemotherapy, with the exception of chemotherapy used as a radio-sensitizing agent and completed at least 2 weeks before randomization with resolution of all-treatment-related toxicities were eligible for this study.
Intervention	Pembrolizumab + chemotherapy (paclitaxel + cisplatin or paclitaxel + carboplatin) ± bevacizumab
Comparator	Placebo + chemotherapy ± bevacizumab
Indicate if trial supports application for marketing authorisation	Yes
Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	Pivotal evidence for the use of pembrolizumab in combination with chemotherapy for the first-line treatment of recurrent, persistent or metastatic cervical cancer
Reported outcomes specified in the decision problem	• Overall survival • **Progression-free survival** • Response rates • **Adverse effects of treatment** • **Health-related quality of life** • Duration of response
All other reported outcomes	• **Time to progression** • **Post-progression survival** • **Duration of treatment**
Notes: Bolded outcomes represent those directly used in the economic model. **Source**: Colombo et al. 2021[1]; KEYNOTE-826 Clinical Study Report.[6]	

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

KEYNOTE-826 is the pivotal source of data for pembrolizumab in combination with chemotherapy ± bevacizumab in this submission. All clinical evidence presented in this submission is taken from the Colombo et al. 2021 publication, or corresponding KEYNOTE-826 clinical study report, for the 3 May 2021 data cut-off.[1, 6]

B.2.3.1 KEYNOTE-826

KEYNOTE-826 is an ongoing Phase III, randomized controlled trial being conducted to assess the efficacy of pembrolizumab with chemotherapy (± bevacizumab) compared with placebo with chemotherapy (± bevacizumab) as a first-line therapy for recurrent, persistent or metastatic cervical cancer.

Eligible patients were women (age ≥ 18 years) with a histologically confirmed diagnosis of recurrent, persistent or metastatic cervical cancer who were not suitable candidates for treatment with curative intent; and who were treatment-naïve to systemic chemotherapy, with the exception of chemotherapy used as a radio-sensitizing agent. The key inclusion and exclusion criteria applied at the time of screening are presented in Table 5.

Figure 3 presents the KEYNOTE-826 trial design schematic. Following screening, all eligible patients were stratified by the investigator's decision to use bevacizumab, PD-L1 status (i.e. CPS < 1 versus CPS 1 to < 10 versus CPS ≥ 10) and metastatic status at initial diagnosis (yes vs. no, FIGO 2009 Stage IVB). Of note, the FIGO staging system was revised in 2019 following the initiation of the KEYNOTE-826 trial.

PD-L1 expression was measured using the validated PD-L1 IHC 22C3 pharmaDx assay (Dako North America, Inc). The CPS determined by the number of PD-L1-stained cells (tumour cells, lymphocytes and macrophages) divided by the total number of viable tumour cells, multiplied by 100, and is expressed by the following formula:[46]

$$CPS = \frac{Number\ of\ PD\text{–}L1\ stained\ cells\ (i.e.\ tumour\ cells, lymphocytes\ and\ macrophages)}{Total\ number\ of\ viable\ tumour\ cells} \times 100$$

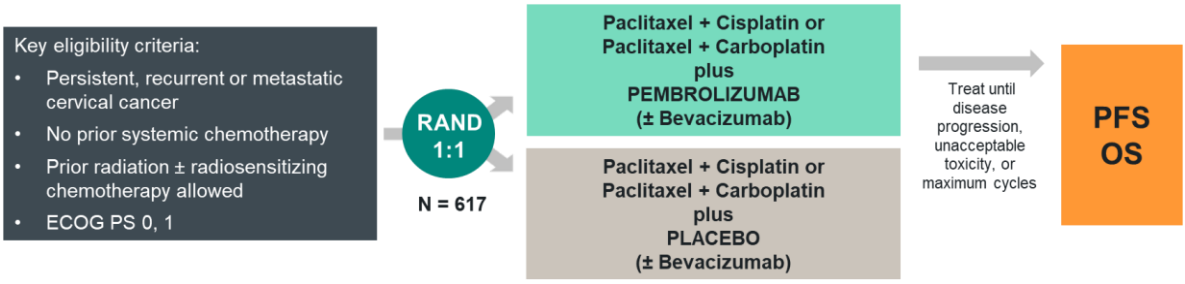
Patients were then randomly assigned at a 1:1 ratio to either:

- Treatment Group 1: pembrolizumab 200 mg every 3 weeks for up to 35 cycles
- Treatment Group 2: placebo every 3 weeks every 3 weeks for up to 35 cycles

All patients also received paclitaxel and the investigator's choice of cisplatin or carboplatin every 3 weeks. Protocol amendment 2 introduced a six-cycle limit of chemotherapy, although patients who continued to benefit from treatment without unacceptable adverse events (AEs) could continue beyond this limit. Bevacizumab was administered every 3 weeks at a dosage of 15 mg per kg of body weight at the investigator's discretion. The number of cycles of bevacizumab a patient could receive during the trial period was not limited. Tumour screening was scheduled every 9 weeks from baseline to Week 54, and every 12 weeks thereafter.

Treatment was continued until the patient experienced radiographic disease progression or unacceptable toxic effects, or until the maximum number of cycles for each component was reached. Treatment was also terminated if consent was withdrawn by the patient, or if a patient was treated with a prohibited therapy.

Figure 3: KEYNOTE-826 trial design schematic



Key: ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; RAND, randomized.
Source: KEYNOTE-826 ESMO 2021.[47]

Table 5 presents an overview of the methodology of the KEYNOTE-826 trial.

Table 5: Summary of KEYNOTE-826 trial methodology

Trial name	**KEYNOTE-826**
Location	This study was conducted at 151 centres in the following 19 countries: Argentina, Australia, Canada, Chile, Colombia, France, Germany, Israel, Italy, Japan, Mexico,

Trial name	**KEYNOTE-826**
	Peru, Russia, the Republic of Korea, Spain, Taiwan, Turkey, Ukraine, the US
Trial design	Phase III, multicentre, double-blind, placebo-controlled interventional study
Key eligibility criteria for patients	**Inclusion criteria:** 1. Had recurrent, persistent or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amenable to curative treatment (such as with surgery and/or radiation). 2. Had measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions. 3. Had provided archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated for prospective determination of PD-L1 status before randomization. 4. Had an ECOG PS of 0 to 1 within 14 days before randomization. **Exclusion criteria:** 1. Had a positive urine pregnancy test within 72 hours before randomization (WOCBP only). 2. Had known active CNS metastases and/or carcinomatous meningitis. 3. Had a known additional malignancy that was progressing or had required active treatment within the past 3 years. 4. Had a diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before randomization. 5. Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX 40, CD137). 6. Had received prior systemic chemotherapy for treatment of cervical cancer (chemotherapy used as a radio-sensitizing agent and completed at least 2 weeks before randomization was permitted).
Settings and locations where the data were collected	Each site had a treating investigator or qualified designee responsible for the treatment administered, and the recording of data The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by

Trial name	KEYNOTE-826
	physically or electronically signing the CRF
Trial drugs	**Intervention** • Pembrolizumab (200 mg) + chemotherapy ± bevacizumab **Comparator** • Placebo (normal saline or dextrose) + chemotherapy ± bevacizumab **Chemotherapy options** • Paclitaxel (175 mg/m^2) + cisplatin (50 mg/m^2) • Paclitaxel (175 mg/m^2) + carboplatin (AUC 5)
Permitted and disallowed concomitant medication	Patients were excluded from the trial if they: • Received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX40, CD137) • Received prior systemic chemotherapy for treatment of cervical cancer (chemotherapy used as a radio-sensitizing agent and completed at least 2 weeks before randomization is permitted) • Have not recovered adequately from toxicity and/or complications from surgery before randomization • Have received prior radiotherapy within 2 weeks before randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease • Have received a live vaccine within 30 days before randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed • Have severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients • Have a contraindication or hypersensitivity to any component of cisplatin, carboplatin, paclitaxel, or bevacizumab. NOTE: Investigators must use the local label for contraindications, prohibited medications, and precautions for use
Primary endpoints	• PFS per RECIST 1.1 as assessed by investigator, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

Trial name	KEYNOTE-826
	• OS, defined as the time from randomization to death due to any cause
Key secondary endpoints	• ORR per RECIST 1.1 assessed by investigator, defined as the percentage of patients with a best overall response of either confirmed CR or PR • DoR per RECIST 1.1 assessed by investigator, as defined as the time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first • Percentage of patients who were alive without disease progression at 12 months per RECIST 1.1, as assessed by BICR • PFS per RECIST 1.1, assessed by BICR, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first • Proportion of patients experiencing AEs, serious AEs, and immune-related AEs, and patients discontinuing treatment due to AEs • HRQL assessments using the global score of the EORTC QLQ-C30
Pre-planned subgroups	• Metastatic initial diagnosis (yes vs. no) • Bevacizumab use (yes vs. no) • PD-L1 status (CPS < 1 vs. CPS 1 to CPS < 10 vs. CPS ≥ 10) • Age (< 65 years vs. ≥ 65 years) • Race (white, non-white) • ECOG (1, 0)
Key: AE, adverse event; AUC, area under the curve; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; CRF, case report form; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; HRQL, health-related quality of life; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; PFS, progression-free survival; PR, partial response; QLQ-C30, Quality of Life questionnaire C30; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; WOCBP, women of childbearing potential. **Source:** KEYNOTE-826 clinical study report[6]; KEYNOTE-826 protocol.[48]	

The following analysis populations were pre-defined:

- **CPS ≥ 1 population (n = 548):** all patients with PD-L1 positive tumours
- **Intention-to-treat (ITT) population (n = 617):** all patients who were randomly assigned to a treatment arm, regardless of whether they received the study treatment

- **Safety analysis population (n = 616):** all patients who were randomly assigned to a treatment arm, and received at least one dose of the study treatment (all patients as treated [APaT])

This submission presents data for the first efficacy interim analysis, with a data cut-off date of 3 May 2021. In line with the anticipated licence for this submission, this submission presents efficacy data for the CPS ≥ 1 population. For completeness, the baseline characteristics and efficacy data for the ITT population are presented in Appendix O.1.2.

B.2.3.1.1 Patient baseline demographics and disease characteristics of patients in the KEYNOTE-826 study

Following the licenced indication for pembrolizumab with chemotherapy (± bevacizumab), the baseline demographics and disease characteristics for the KEYNOTE-826 trial CPS ≥ 1 (n = 548) patient population are presented in Table 6, and for the ITT population (n = 617) in Appendix O.1.2.1.

The baseline characteristics were generally well-balanced between the two treatment arms in both the CPS ≥ 1 and ITT patient populations. All patients were female and had an ECOG performance status of 0 or 1. The classification of patients by ECOG performance status is further detailed in Appendix N.

The mean age of the CPS ≥ 1 population was [redacted] (standard deviation [redacted]) years; the majority were white (59.3%), and non-Hispanic or Latino (61.1%). In the CPS ≥ 1 population, 63.1% of patients received bevacizumab, which is in line with the proportion of patients reportedly receiving bevacizumab in UK clinical practice (50–80%).[3] When assessing prior therapy for local disease, 39.2% of patients received prior chemoradiation only, 21.0% had no prior therapy, and 16.6% had prior chemoradiation and surgery.

Baseline characteristics for the European trial population are presented in Appendix E.1.1. In the CPS ≥ 1 population, the demographics and disease characteristics were generally well balanced between the overall trial population and the European trial population.

Patient disposition data for the KEYNOTE-826 trial is presented in Appendix D.2, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow.

Table 6: Patient baseline demographics and disease characteristics of the KEYNOTE-826 trial

	CPS ≥ 1 population		
	Pembrolizumab + chemotherapy (n = 273)	**Control (n = 275)**	**Total (n = 548)**
Female, n (%)	273 (100.0)	275 (100.0)	548 (100.0)
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	153 (56.0)	172 (62.5)	325 (59.3)
Asian	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Non-Hispanic or Latino	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
EU/EMEA	[redacted]	[redacted]	[redacted]
Latin America	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
0	160 (58.6)	148 (35.8)	308 (56.2)
1	111 (40.7)	127 (46.2)	238 (43.4)
2	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Stage at initial diagnosis, n (%)[a]			
I	55 (20.1)	48 (17.5)	103 (18.8)
II	76 (27.8)	85 (30.9)	161 (29.4)
III	5 (1.8)	7 (2.5)	12 (2.2)
IIIA	4 (1.5)	7 (2.5)	11 (2.0)
IIIB	41 (15.0)	37 (13.5)	78 (14.2)
IVA	6 (2.2)	3 (1.1)	9 (1.6)
IVB	86 (31.5)	88 (32.0)	174 (31.8)
Disease status at trial entry, n (%)			
Metastatic [b]	56 (20.5)	59 (21.5)	115 (21.0)
Persistent or recurrent with distant metastases at trial entry	170 (62.3)	156 (56.7)	326 (59.5)

	CPS ≥ 1 population		
	Pembrolizumab + chemotherapy (n = 273)	**Control (n = 275)**	**Total (n = 548)**
Persistent or recurrent without distant metastases at trial entry	47 (17.2)	60 (21.8)	107 (19.5)
Histology of subtype of cervical cancer, n (%)			
Adenocarcinoma	47 (17.2)	66 (24.0)	113 (20.6)
Adenosquamous/both – squamous and adenocarcinoma	13 (4.8)	12 (4.4)	25 (4.6)
Epidermoid carcinoma	[redacted]	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]	[redacted]
Squamous cell/squamous cell carcinoma	211 (77.3)	197 (71.6)	408 (74.5)
PD-L1 status, n (%)			
1 ≤ CPS < 10	115 (42.1)	116 (42.2)	231 (42.2)
CPS ≥ 10	158 (57.9)	159 (57.8)	317 (57.8)
Bevacizumab use, n (%)			
Yes	175 (64.1)	171 (62.2)	346 (63.1)
No	98 (35.9)	104 (37.8)	202 (36.9)
Prior therapy, n (%)			
Chemoradiotherapy and surgery	43 (15.8)	48 (17.5)	91 (16.6)
Radiation and surgery	18 (6.6)	21 (7.6)	39 (7.1)
Chemoradiotherapy only	112 (41.0)	103 (37.5)	215 (39.2)
Radiation only	28 (10.3)	21 (7.6)	49 (8.9)
Surgery only	16 (5.9)	23 (8.4)	39 (7.1)
None	56 (20.5)	59 (21.5)	115 (21.0)

Key: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynaecology and Obstetrics; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1.
Notes: [a] Stage at initial diagnosis determined using FIGO 2009/ NCCN 2017 criteria. [b] Patients with para-aortic lymph node involvement are included. Patients with metastatic disease received a diagnosis of Stage IVB disease and entered the trial without any previous treatment for cervical cancer.
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

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

A summary of statistical analyses conducted for the KEYNOTE-826 trial is presented in Table 7.

Approximately 600 patients were randomized in a 1:1 ratio to either Treatment Arm 1, pembrolizumab + chemotherapy ± bevacizumab, or Arm 2, placebo + chemotherapy ± bevacizumab.

This submission presents data from Interim Analysis 1; the database lock for Interim Analysis 1 was conducted on 3 May 2021. A final analysis is also planned for the KEYNOTE-826 study, which will be triggered when at least 184 overall survival (OS) events for CPS ≥ 10 group have been observed. It is anticipated this will occur in [redacted], approximately 44 months after the first patient was randomized. It is estimated that ~347 OS events for CPS ≥1 group and 420 OS events for all-comers will be observed by then.

Aligning with the licenced indication, the primary efficacy analyses presented in this submission focus on the CPS ≥ 1 population (Section B.2.6). The safety analyses focus on the APaT population, which consists of all randomized patients who received at least one dose of the study treatment (Section B.2.10.1.2). The ITT population, which includes all randomized patients enrolled in the trial is presented in Appendix O.1.2.

Table 7: Summary of statistical analyses (KEYNOTE-826 trial)

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-826	Primary Objective 1: • PFS based on RECIST 1.1 as assessed by the investigator Hypothesis 1: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to PFS per RECIST 1.1, as assessed by BICR for the CPS ≥ 1 group. Hypothesis 2: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to PFS per RECIST 1.1, as assessed by BICR for all-comers. Hypothesis 3: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to PFS per RECIST 1.1 as assessed by BICR for the CPS ≥ 10 group.	Efficacy analyses The primary hypotheses will be evaluated by comparing PFS and OS using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan–Meier method. Safety analyses The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% Cis provided for between group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages	The planned sample size is approximately 600 participants (510 participants for CPS ≥ 1 group; 270 participants for CPS ≥ 10 group) with 300 participants in each arm. The study is event-driven and completes after accumulation of sufficient events to determine efficacy for PFS and for OS. For all-comers (N = 600), with approximately 403 and 504 events between two arms at the planned PFS analyses, the study will have 92% power to detect a hazard ratio of 0.70 at the 0.005 significance level. With 273, 357, and 420 events between two arms at the planned OS interim and final analyses, the study will have 94% power to detect a hazard ratio of 0.7 at the 0.020 significance level.	If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits. When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirement.

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	Primary Objective 2: • OS Hypothesis 4: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to OS for the CPS ≥ 10 group Hypothesis 5: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to OS for the CPS ≥ 1 group Hypothesis 6: • The combination of pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to OS for all-comers	will be provided using the Miettinen and Nurminen method.		

Key: AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours Version 1.1.
Source: KEYNOTE-826 clinical study protocol.[48]

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

The KEYNOTE-826 trial conformed with the ethical principles originating from the Declaration of Helsinki, Good Clinical Practice requirements, and applicable country and/or local statutes and regulations regarding independent ethics committee review, informed consent and the protection of human participants in biomedical research.

The treatment assignment was masked to patients, all study personnel who prepared and/or dispensed the treatment, those involved in study treatment administration and/or who were involved in clinical evaluation of the patient.

The quality assessment of the KEYNOTE-826 trial has been conducted using Cochrane risk of bias, Version 2. The overall risk of bias was considered to be low – full results of this assessment are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 KEYNOTE-826: Summary of key efficacy outcomes

Table 8 presents a summary of the primary and secondary efficacy endpoints from Interim Analysis 1. At the data cut-off of 3 May 2021, the median duration of follow-up in the CPS ≥ 1 population was 18.3 months in the pembrolizumab group, and 16.3 months in the placebo group.[1, 6]

The KEYNOTE-826 trial met all primary and key secondary endpoints for all predefined populations (including CPS ≥ 1, ITT, and CPS ≥ 10). Compared with placebo, treatment with pembrolizumab resulted in a significantly longer PFS and OS. The median OS was not reached in the pembrolizumab group, whereas in the placebo group, the median OS was reported to be 16.3 months.

Table 8: Summary of key efficacy outcomes from KEYNOTE-826

	CPS ≥ 1 population (n = 548)	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Mean (SD) follow-up duration	17.2 (6.9)	15.0 (7.3)

Primary endpoints		
PFS by investigator assessment		
Median PFS, months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
PFS rate at Month 24 (95% CI)	33.1 (25.7, 40.7)	14.0 (7.7, 22.3)
OS		
Median OS, months (95% CI)	NR (19.8, NE)	16.3 (14.5, 19.4)
OS rate at Month 24 (95% CI)	53.0 (46.0, 59.4)	41.7 (34.9, 48.2)
Secondary endpoints		
ORR by investigator assessment		
Number of confirmed OR	186	138
ORR % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)
DoR by investigator assessment		
Median DoR, months (range)	18.0 (1.3, 24.2)	10.4 (1.5, 22.0)
PFS by BICR using RECIST 1.1		
Median PFS, months (95% CI)	12.8 (10.4, 20.6)	8.3 (7.7, 9.2)
PFS rate at Month 24 (95% CI)	39.3 (32.2, 46.4)	20.8 (14.8, 27.6)

Key: BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; DoR, duration of response; NE, not estimable; NR, not reached; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; SD, standard deviation.
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

B.2.6.1.1 Primary efficacy endpoint – progression-free survival per RESIST 1.1 by investigator assessment

Table 4 presents the results for PFS per RECIST 1.1 by investigator assessment for the CPS ≥ 1 population.

In the CPS ≥ 1 population, median PFS was significantly longer in the pembrolizumab group (10.4 months; 95% CI: 9.7, 12.3) than the placebo group (8.2 months; 95% CI: 6.3, 8.5).[1, 6] Patients treated with pembrolizumab resulted in a statistically significant reduction in the risk of disease progression or death in comparison to placebo (HR 0.62; 95% CI: 0.50, 0.77; p < 0.0001). The proportion of patients who were alive without disease progression at 12 months was also higher in the pembrolizumab group (45.5%; 95% CI: 39.2, 51.5) than in the placebo group (34.1%; 95% CI: 28.3, 40.0), as presented in Table 9.

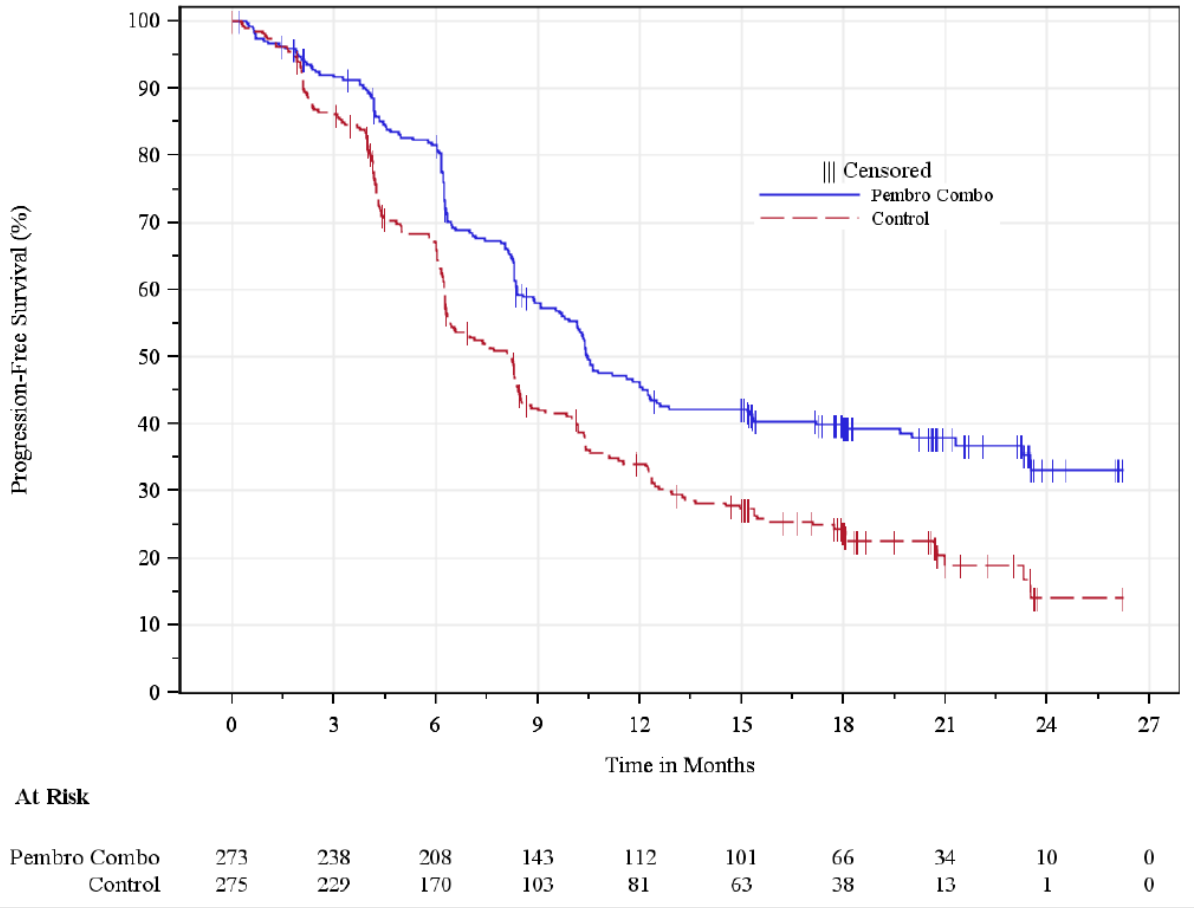
Table 9: Analysis of PFS in the KEYNOTE-826 trial (CPS ≥ 1 population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	Placebo + chemotherapy ± bevacizumab (n = 275)
Number of events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI, months) [a]	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
PFS HR (95% CI) [b]	0.62 (0.50, 0.77)	
p-value [c]	< 0.0001	
6-month PFS, % (95% CI)	[redacted]	[redacted]
12-month PFS, % (95% CI)	45.5 (39.2, 51.5)	34.1 (28.3, 40.0)
18-month PFS, % (95% CI)	[redacted]	[redacted]
24-month PFS, % (95% CI)	[redacted]	[redacted]

Key: CI, confidence interval; CPS, combined positive score; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; PD-L1, Programmed death-ligand 1; 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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10). [C] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10).
Source: Colombo et al. 2021[1] ; KEYNOTE-826 Clinical study report.[6]

As presented in Figure 4, the Kaplan–Meier (KM) curves for pembrolizumab and placebo separated by Month 2 and remained separated throughout the follow-up period.

Figure 4: Progression-free survival as assessed per RECIST 1.1 by investigator assessment (CPS ≥ 1 population)



Key: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; RECIST 1.1, Response Evaluation criteria in solid tumours version 1.1.
Source: KEYNOTE-826 Clinical study report.[6]

B.2.6.1.2 Primary efficacy endpoint – overall survival

Table 10 presents the results for OS for the CPS ≥ 1 population.

Overall survival was significantly longer in the pembrolizumab group compared with placebo.[1, 6] In the CPS ≥ 1 population, 53% (95% CI 46.0, 59.4) of patients were estimated to be alive at 24 months in the pembrolizumab group compared with 41.7% (95% CI 34.9, 48.2) of patients treated with placebo (hazard ratio [HR] 0.64; 95% CI: 0.50, 0.81; p < 0.001). Median OS in the CPS ≥ 1 population was not reached in the pembrolizumab group and was 16.3 months in the placebo group.

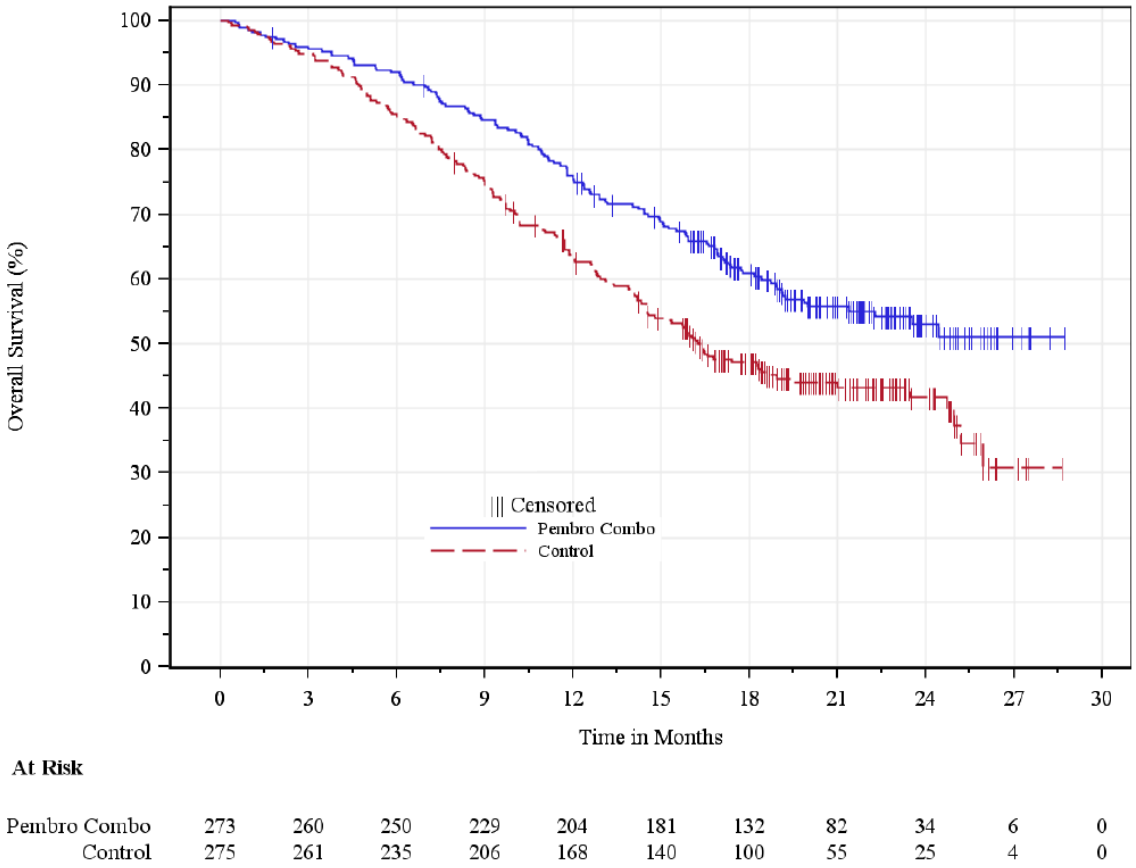
Table 10: Analysis of OS in the KEYNOTE-826 trial (CPS ≥ 1 population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	Placebo + chemotherapy ± bevacizumab (n = 275)
Number of events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI, months) [a]	NR ([redacted])	16.3 ([redacted])
OS HR (95% CI) [b]	0.64 (0.50, 0.81)	
p-value [c]	0.0001	
6-month OS, % (95% CI)	[redacted]	[redacted]
12-month OS, % (95% CI)	[redacted]	[redacted]
18-month OS, % (95% CI)	[redacted]	[redacted]
24-month OS, % (95% CI)	53.0 (46.0, 59.4)	41.7 (34.9, 48.2)

Key: CI, confidence interval; CPS, combined positive score; FIGO, International Federation of Gynaecology and Obstetrics; HR hazard ratio; NR, not reached; OS, overall survival; PD-L1, Programmed death-ligand 1.
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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10). [C] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10).
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

Figure 5 presents the KM curve for OS in the CPS ≥ 1 population. The curves for the pembrolizumab and placebo groups separated as early as 3 months, and remained separated throughout the trial evaluation period, in favour of patients treated with pembrolizumab.

Figure 5: Overall survival (CPS ≥ 1 population)



Key: CI, confidence interval; CPS, combined positive score; HR, hazard ratio.
Source: KEYNOTE-826 Clinical study report.[6]

B.2.6.1.3 Objective response rate per RECIST 1.1 by investigator assessment

Table 11 presents the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) by investigator assessment.

Pembrolizumab provides a significant improvement in the ORR compared to placebo. The proportion of patients in the CPS ≥ 1 group who achieved complete response (CR) or partial response (PR) was significantly greater in the pembrolizumab group than those treated with placebo (68.1% versus 50.2%, respectively; $p < 0.001$).[1, 6]

Table 11: Confirmed objective response based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)

	CPS ≥ 1 population (n = 548)	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Number of confirmed OR	[redacted]	[redacted]
ORR, % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)
CR, n (%)	62 (22.7)	36 (13.1)
PR, n (%)	124 (45.4)	102 (37.1)
SD, n (%)	58 (21.2)	88 (32.0)
PD, n (%)	9 (3.3)	29 (10.5)
Difference in percentage pembrolizumab group versus placebo group	[redacted]	
p-value	[redacted]	

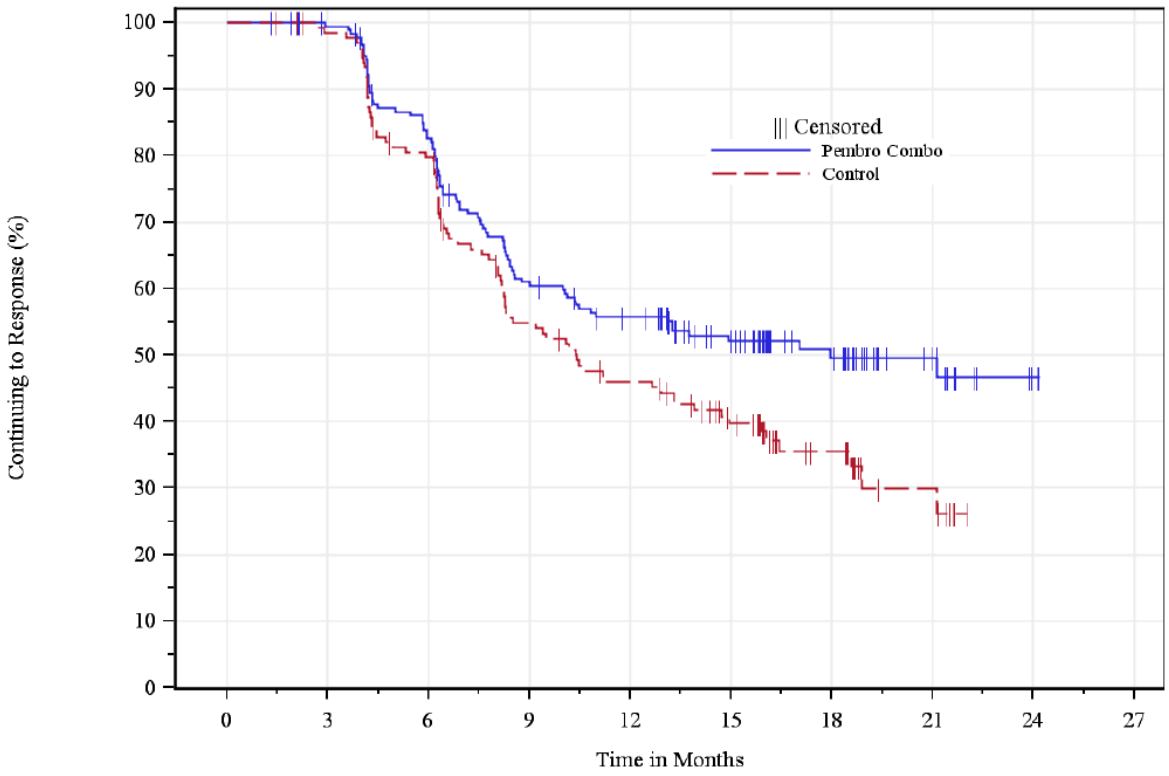
Key: CI, confidence interval; CPS, combined positive score; OR, objective response; ORR, objective response rate; RECIST 1.1, response evaluation criteria in solid tumours version 1.1.
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

B.2.6.1.4 Duration of response per RECIST 1.1 by investigator assessment

Figure 6 presents the KM curve for DoR, based on investigator assessment per RECIST 1.1.

In the CPS ≥ 1 population, patients in the pembrolizumab group experienced an improvement in DoR compared with placebo.[1, 6] The median duration of response was longer in the pembrolizumab group compared with placebo (18.0 versus 10.4 months, respectively). In the pembrolizumab group, a larger proportion of patients responding to treatment had extended responses compared with patients responding to placebo at ≥ 12 months ([redacted]% and [redacted]%) and at ≥ 18 months ([redacted]% and [redacted]%, respectively).

Figure 6: Duration of response based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)



Key: CPS, combined positive score; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1.
Source: KEYNOTE-826 Clinical study report.[6]

B.2.6.1.5 Exploratory efficacy outcomes

A summary of outcomes from the exploratory endpoints in the KEYNOTE-826 trial including ORR by blinded independent central review (BICR), DoR by BICR and PFS at 12 months by BICR are provided in Appendix O.1.1.1.

In order to better understand the OS and PFS outcomes, we examined the KM data by response category, as presented in Figure 7 and Figure 8, respectively. These KM curves demonstrate that a patient's response status is highly prognostic of both PFS and OS and accordingly, the OS and PFS results were better in complete responders (CR) than in partial responders (PR), patients with stable disease (SD) or patients with progressed disease (PD).

As presented in Figure 7, the OS events that occurred during the trial period are overrepresented in the PR and SD populations. The majority of patients who do not fully respond to treatment (i.e. partial responders or patients with stable disease) die within the trial period. It is therefore anticipated in the post-trial period, the vast majority of patients who have survived will be those that responded to treatment, resulting in a substantially decreased OS event rate.

It is noteworthy that OS at two years is [redacted]% and [redacted]% among complete responders in the pembrolizumab arm and placebo arm, and PFS is [redacted]% and [redacted]% respectively.[49]

Figure 7: OS KM curves, stratified by response category (CPS ≥ 1 population)

Key: CPS, combined positive score; CR, combined response; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.
Source: Data on file, 2022[50]

Figure 8: PFS KM curve, stratified by response category (CPS ≥ 1 population)

Key: CPS, combined positive score; CR, combined response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Source: Data on file, 2022[50]

B.2.6.2 KEYNOTE-826: Health-related quality of life outcomes

The EuroQol EQ-5D-5L VAS score in the CPS ≥ 1 population is presented below, and the ITT population is presented in Appendix O.1.2.3. Of note, the EQ-5D-5L VAS score for the CPS ≥ 1 patient population is utilized in the cost-effectiveness model for this submission.

A summary of results for the global health status/QoL European Organisation for the Research and Treatment of Cancer (EORTC) Quality of life questionnaire – C30 (QLQ-C30) from baseline for the CPS ≥ 1 population is reported in Appendix O.1.1.2.

Compared with patients in the placebo group, more patients treated with pembrolizumab reported improved and stable patient reported outcome scores[1, 6], demonstrating the treatment with pembrolizumab did not adversely impact the HRQL compared with current treatments available for patients with recurrent, persistent or metastatic cervical cancer.

Over a 30-week follow-up, [redacted]% of pembrolizumab patients in the CPS ≥ 1 population reported an improved and stable score compared with [redacted]% of CPS ≥ 1 patients treated with placebo (p = [redacted]).[6] The between group difference in least-squares mean change from baseline at Week 30 was [redacted] (95% CI: [redacted], [redacted]; p = [redacted]).

Empirical mean change from baseline and 95% CI for EQ-5D-5L VAS for the pembrolizumab and placebo groups are presented in Figure 9. A slightly larger decrease in mean change was seen in the placebo group compared with patients treated with pembrolizumab over time.

Figure 9: Empirical mean change from baseline for the EQ-5D-5L VAS score over time in KEYNOTE-826 (CPS ≥ 1 population)

Key: CI, confidence interval; CPS, combined positive score; EQ-5D-5L VAS, EuroQol-5 dimensions-5 levels visual analogue scales.
Source: KEYNOTE-826 Clinical study report[6].

The time to deterioration in the EQ-5D-5L VAS score was longer in patients treated with pembrolizumab than with placebo (HR [redacted], 95% CI [redacted]; p = [redacted]).[6] KM estimates for time to deterioration for EQ-5D-5L VAS score are presented in Figure 10.

Figure 10: Kaplan–Meier estimates of time to deterioration for EQ-5D-5L VAS score (CPS ≥ 1 population)

Key: CPS, combined positive score; EQ-5D-5L VAS, EuroQol-5 dimensions-5 levels visual analogue scales.
Source: KEYNOTE-826 Clinical study report.[6]

B.2.6.3 KEYNOTE-158

KEYNOTE-158 is a single-arm basket trial of pembrolizumab monotherapy in multiple advanced solid tumour types in a second line or later treatment setting. As KEYNOTE-158 evaluates pembrolizumab in a later treatment setting than KEYNOTE-826, KEYNOTE-158 does not fully align with the decision problem presented in this submission.

The results for the recurrent/metastatic cervical cancer subset of patients are presented in this section. These results are based on an interim analysis (data cut-

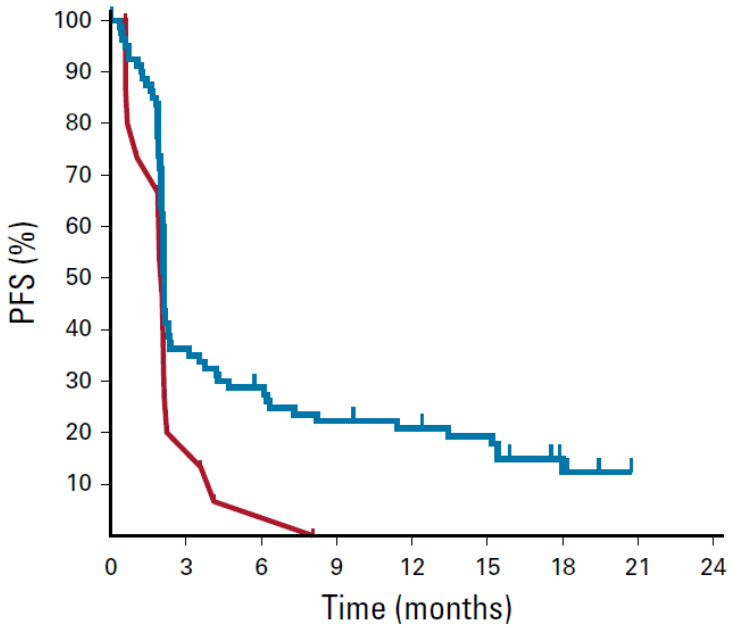
off 15 January 2018), with a median follow-up of 10.2 months (range: 0.6–22.7 months).[51] Patients continue to be observed for long-term outcomes.

Results are presented for the previously treated advanced cervical cancer population (i.e. 2L and above). PFS and OS results are presented in Section B.2.6.3.1 and B.2.6.3.2, respectively. Further outcomes, including ORR and DoR, are presented in Appendix O.2.2.

B.2.6.3.1 Progression-free survival

In the CPS ≥ 1 population (n = 82), the median PFS was 2.1 months (95% CI 2.1, 2.3 months).[51] A total of 53 patients in the CPS ≥ 1 population had died. Kaplan–Meier estimates of PFS for the CPS ≥ 1 population are presented in Figure 11.

Figure 11: Kaplan–Meier estimates of PFS in KEYNOTE-158, stratified by PD-L1 status

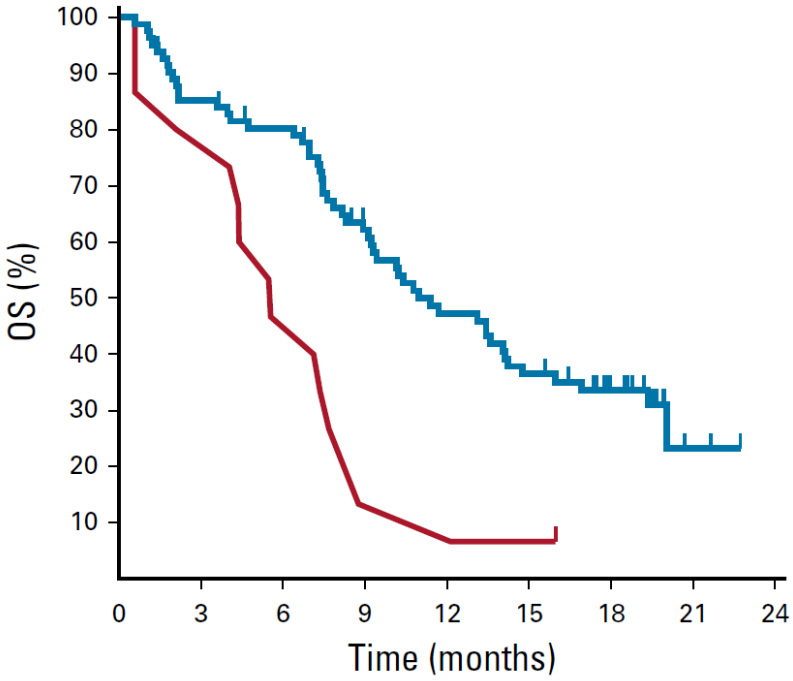


Key: CPS, combined positive score; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: PD-L1 positivity was defined as a CPS of 1 or greater.
Source: Chung et al. 2019.[51]

B.2.6.3.2 Overall survival

In the CPS ≥ 1 population, the median OS was 11 months (95% CI 9.1, 14.1 months).[51] The 6-month and 12-month estimates of OS in the CPS ≥ 1 population was 80.2% and 47.3%, respectively. Kaplan–Meier estimates of OS for the CPS ≥ 1 population are presented in Figure 12.

Figure 12: Kaplan–Meier estimates for OS in KEYNOTE-158, stratified by PD-L1+ and PD-L1- status



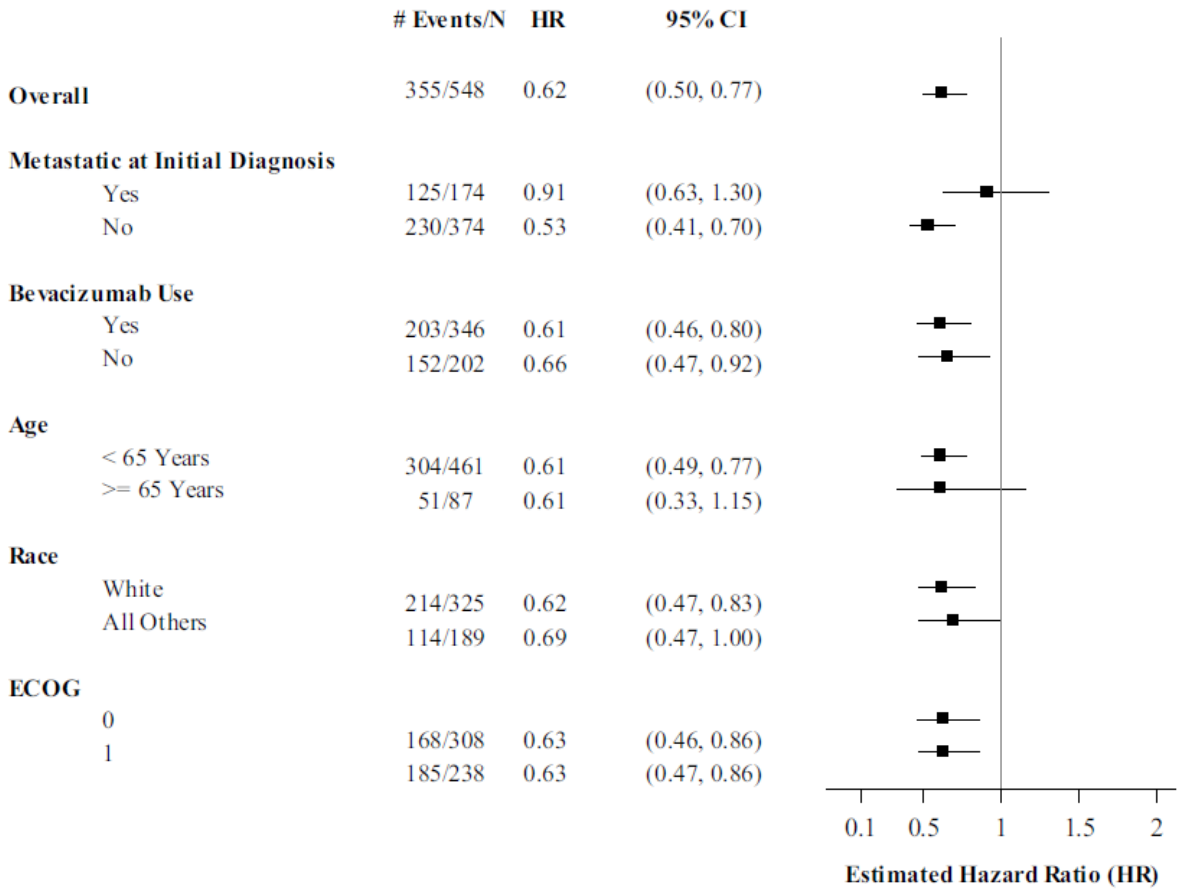
Key: CPS, combined positive score; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: PD-L1 positivity was defined as a CPS of 1 or greater.
Source: Chung et al. 2019.[51]

B.2.7. Subgroup analysis

The forest plots for PFS (based on investigator assessment per RECIST 1.1) and OS by subgroup factors for the CPS ≥ 1 population are presented in Figure 13 and Figure 14, respectively. The benefit of pembrolizumab was demonstrated across all patient subgroups for both primary efficacy endpoints (PFS per RECIST 1.1 as assessed by independent assessment and OS) when compared with placebo. The

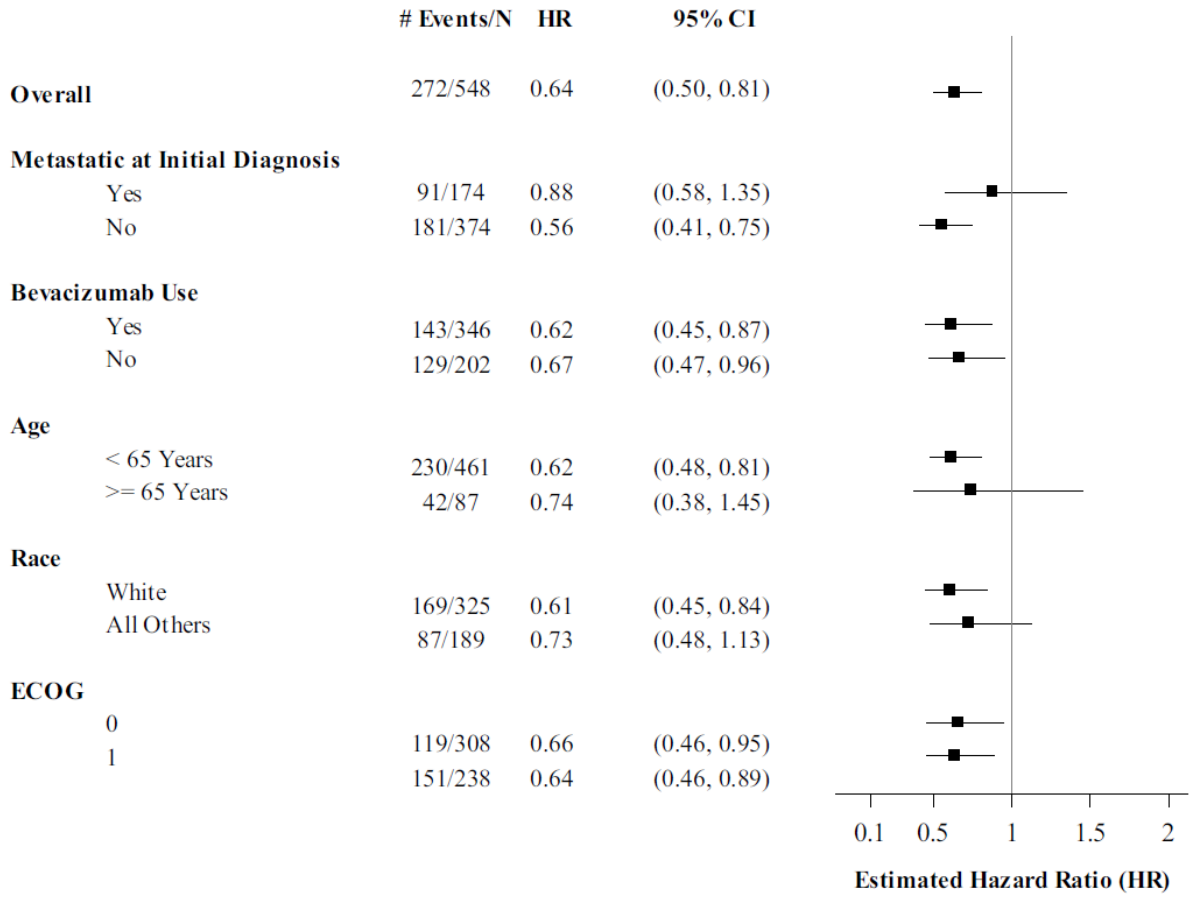
HRs in the pembrolizumab group were less than 1 in all pre-specified subgroups analysed within the CPS ≥ 1 population, and the 95% CIs for all subgroups overlapped with that of the overall population. The clinical benefit of pembrolizumab compared with placebo was also generally consistent across various pre-specified subgroups for the key secondary endpoint, ORR. Forest plots by subgroup factors for the ITT population are presented in Appendix E.1.3.

Figure 13: Forest plot of PFS hazard ratio by subgroup factors, based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)



Key: CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; RECIST, Response Evaluation Criteria in Solid Tumours, version 1.1.
Source: KEYNOTE-826 Clinical study report.[6]

Figure 14: Forest plot of OS hazard ratio by subgroup factors (CPS ≥ 1 population)



Key: CI, confidence interval; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
Source: KEYNOTE-826 Clinical study report.[6]

B.2.8. Meta-analysis

A meta-analysis is not required as a single trial (KEYNOTE-826, phase III RCT study) provides evidence for pembrolizumab in the indication being appraised. As discussed in Section B.2.2, KEYNOTE-158 provides evidence for the use of pembrolizumab, but in a later treatment setting than KEYNOTE-826, KEYNOTE-158 is therefore not appropriate evidence for a meta-analysis.

B.2.9. Indirect and mixed treatment comparisons

An SLR was conducted to identify relevant published clinical evidence of pharmacological treatments for recurrent, persistent or metastatic cervical cancer, in

line with the population investigated in KEYNOTE-826. Full details of the SLR search strategy, study selection process and results are presented in Appendix D.1.

KEYNOTE-826 provides robust head-to-head data for pembrolizumab and chemotherapy (± bevacizumab) versus chemotherapy (± bevacizumab), in which the chemotherapy administered was either paclitaxel and cisplatin or paclitaxel and carboplatin. As previously discussed in Section B.1.3.4.1, this chemotherapy regimen ± bevacizumab is the only first-line treatment currently available in the UK for recurrent, persistent, or metastatic cervical cancer. It is therefore believed that an ITC would not provide any additional information above what is presented in KEYNOTE-826.

A total of 56 publications of 41 unique trials were identified (including KEYNOTE-826). However, the majority of treatments evaluated were not of direct relevance to UK clinical practice. For the comparators of relevance, the evidence base was limited to 3 single-arm trials and 4 RCTs which could theoretically provide additional informative data to the KEYNOTE-826 trial.[7, 39, 52-56] Summaries of these studies are presented in Appendix D.1.4. Of note, the GOG-240 trial has been used later in this submission for validation of the economic model, and is further discussed in Appendix Q.3.[39]

Of these 7 trials, all evaluated the use of cisplatin and paclitaxel, and 1 also evaluated the use of carboplatin and paclitaxel. The only trial to report on the use of bevacizumab was the GOG-240 trial.[39] The median OS ranged from 9 to 18.3 months for trials reporting on cisplatin and paclitaxel, and was 17.5 months for carboplatin and paclitaxel. The median PFS ranged from 4.8 (cisplatin and paclitaxel) to 9.6 months (cisplatin, carboplatin and bevacizumab). The ORR ranged from 29.1% to 62.6%, although the ORR was not reported in the GOG-240 trial. In the GOG-240 trial, the addition of bevacizumab to cisplatin and paclitaxel increased the median OS and PFS compared with cisplatin and paclitaxel alone.[39]

AEs and patient-reported outcomes (PROs) were seldom reported across studies, leaving a gap in knowledge about the safety of the evaluated regimens and their impact on quality of life in these patients.

The majority of studies were of low quality. Researchers are often challenged with difficulties recruiting large sample populations, an incomplete understanding of natural history to best inform trial design, and limited access to resources in mounting high-quality RCTs. Compared to RCTs, single-arm trials are more likely to provide biased information about the differential effects of alternative health interventions; therefore, any comparative evaluations should be approached with caution. Another limitation is the minimal reporting of study and patient characteristics of interest. For example, information on histology, performance status, race/ethnicity, and prior treatment history were not reported for every included study. Therefore, outcomes should be interpreted within the context of available data.

Formal indirect treatment comparison using these data would be subject to a high degree of uncertainty, particularly compared with the high-quality comparative data available from the KEYNOTE-826. Naïve comparisons of outcomes for cisplatin and paclitaxel, and carboplatin and paclitaxel show reasonable alignment to the control arm of KEYNOTE-826.

B.2.10. Adverse reactions

B.2.10.1 KEYNOTE-826

The primary safety analyses, presented in this section, are based on the APaT population in all-comer participants, (n = 616), defined as patients who were randomly assigned to a treatment arm and received at least one dose of the study treatment. Safety outcomes assessed included evaluation of AEs, serious AEs (SAEs), drug-related AEs, immune-mediated AEs and infusion reactions.

B.2.10.1.1 Treatment exposure

Table 12 presents a summary of treatment exposure. The median duration of exposure was longer for the pembrolizumab group compared to placebo (10.0 months versus 7.7 months, respectively). This longer treatment exposure should therefore be taken into consideration when interpreting the safety analyses reported within this submission.

Table 12: Summary of treatment exposure (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)	**Placebo + chemotherapy ± bevacizumab (n = 309)**
Duration of therapy, months		
Mean (SD)	11.8 (8.1)	9.4 (6.8)
Median	10.0	7.7
Number of cycles of all trial drugs		
Mean (SD)	[redacted]	[redacted]
Median	14.0	11.0
Number of cycles of pembrolizumab/placebo		
Mean (SD)	[redacted]	[redacted]
Median	13.0	11.0
Number of cycles of chemotherapy		
Mean (SD)	[redacted]	[redacted]
Median	6.0	6.0
Number of cycles of bevacizumab		
Mean (SD)	[redacted]	[redacted]
Median	13.0	11.0

Key: APaT, all patients as treated; SD, standard deviation.
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

B.2.10.1.2 Adverse events

Table 13 presents the observed incidence of AEs, SAEs, drug-related AEs and deaths in the KEYNOTE-826 trial. The types, incidence, and severity of AEs in the pembrolizumab group were generally consistent with the known safety profiles of pembrolizumab monotherapy or the chemotherapy administered (± bevacizumab). Pembrolizumab + chemotherapy ± bevacizumab was generally tolerable, and the observed incidence of AEs was largely similar in the pembrolizumab and placebo treatment groups.

In total, 81.8% of patients in the pembrolizumab group, and 75.1% in the placebo group experienced one or more Grade 3–5 adverse events, and 49.8% of pembrolizumab patients and 42.4% of placebo patients reported one or more serious adverse events.

Table 13: Summary of adverse events (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)		**Placebo + chemotherapy ± bevacizumab (n = 309)**	
	Any Grade	**Grade 3–5**	**Any Grade**	**Grade 3–5**
No. of patients, n (%)				
≥ 1 AE	305 (99.3)	251 (81.8)	307 (99.4)	232 (75.1)
≥ 1 drug-related AE	298 (97.1)	210 (68.4)	300 (97.1)	198 (64.1)
SAEs	[redacted](49.8)	–	[redacted] (42.4)	–
Serious drug-related AEs	[redacted]	–	[redacted]	–
Death due to drug-related AEs	2 (0.7)	–	4 (1.3)	

Key: AE, adverse event; APaT, all patients as treated; SAE, serious adverse event.
Source: Colombo et al. 2021[1]; KEYNOTE-826 Clinical study report.[6]

Table 14 presents the most frequently reported AEs in the pembrolizumab and placebo groups. Anaemia, alopecia and nausea were the most frequently reported AEs in both arms of the trial, with a frequency of 61.2%, 56.4% and 39.7% in the pembrolizumab group, and 53.4%, 57.9% and 43.7% in the placebo group, respectively.

Table 14: Frequently reported adverse events, incidence of ≥ 20% in either group (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)	Placebo + chemotherapy ± bevacizumab (n = 309)
No. of patients, n (%)		
Anaemia	188 (61.2)	165 (53.4)
Alopecia	173 (56.4)	179 (57.9)
Nausea	122 (39.7)	135 (43.7)
Diarrhoea	109 (35.5)	92 (29.8)
Fatigue	88 (28.7)	84 (27.2)
Constipation	87 (28.3)	102 (33.0)
Arthralgia	82 (26.7)	80 (25.9)
Neuropathy peripheral	81 (26.4)	79 (25.6)
Vomiting	81 (26.4)	84 (27.2)
Hypertension	74 (24.1)	71 (23.0)
Urinary tract infection	73 (23.8)	80 (25.9)
Neutropenia	72 (23.5)	60 (19.4)
Peripheral sensory neuropathy	71 (23.1)	79 (25.6)
Asthenia	63 (20.5)	66 (21.4)
Thrombocytopenia	61 (19.9)	23 (7.5)

Key: APaT, all patients as treated.
Source: Colombo et al. 2021[1].

As presented in Table 15, the overall incidence of Grade 3–5 AEs was generally similar in both treatment groups. The most frequently reported Grade 3–5 AEs for the pembrolizumab and placebo groups were anaemia (30.3% and 26.9%), neutrophil count decrease (13.0% and 8.4%), neutropenia (12.4% and 9.7%) and hypertension (9.4% and 10.7%), respectively.

The median time from treatment initiation to onset of the first Grade 3–5 AE was similar in the pembrolizumab and placebo groups ([redacted] versus [redacted]).[6]

Table 15: Frequently reported Grade 3–5 adverse events, incidence of ≥ 5% in either group (APaT)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)	Placebo + chemotherapy ± bevacizumab (n = 309)
No. of patients, n (%)		
Anaemia	93 (30.3)	83 (26.9)
Neutrophil count decreased	40 (13.0)	26 (8.4)
Neutropenia	38 (12.4)	30 (9.7)
Hypertension	29 (9.4)	33 (10.7)
Urinary tract infection	27 (8.8)	25 (8.1)
Thrombocytopenia	23 (7.5)	14 (4.5)
Febrile neutropenia	22 (7.2)	14 (4.5)
Platelet count decreased	21 (6.8)	14 (4.5)
WBC count decreased	21 (6.8)	13 (4.2)
Key: APaT, all patients as treated. **Source:** Colombo et al. 2021[1].		

B.2.10.1.3 Drug-related adverse events

Table 16 presents the most frequently reported any Grade and Grade 3–5 drug-related AEs, as reported by investigator assessment. The most frequently reported any grade drug-related AEs were alopecia (55.7% and 55.7%), anaemia (48.5% and 42.7%) and nausea (33.9% and 38.8%) in the pembrolizumab and placebo groups, respectively. When assessing Grade 3–5 drug-related AEs, anaemia (24.8% and 21.0%), a decrease in neutrophil count (13.0% and 8.4%) and neutropenia (12.1% and 9.4%) were most frequently reported in the pembrolizumab and placebo groups, respectively.

Table 16: Any Grade drug-related AEs, incidence of ≥ 10% in either group (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)		Placebo + chemotherapy ± bevacizumab (n = 309)	
	Any Grade	**Grade 3–5**	**Any Grade**	**Grade 3–5**
No. of patients, n (%)				
Alopecia	171 (55.7)	0 (0.0)	172 (55.7)	0 (0.0)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)		Placebo + chemotherapy ± bevacizumab (n = 309)	
	Any Grade	**Grade 3–5**	**Any Grade**	**Grade 3–5**
Anaemia	149 (48.5)	76 (24.8)	132 (42.7)	65 (21.0)
Nausea	104 (33.9)	3 (1.0)	120 (38.8)	4 (1.3)
Diarrhoea	76 (24.8)	5 (1.6)	58 (18.8)	5 (1.6)
Neuropathy peripheral	75 (24.4)	8 (2.6)	76 (24.6)	9 (2.6)
Fatigue	70 (22.8)	8 (2.6)	77 (24.9)	13 (4.2)
Peripheral sensory neuropathy	69 (22.5)	3 (1.0)	78 (25.2)	6 (1.9)
Neutropenia	68 (22.1)	37 (12.1)	57 (18.4)	29 (9.4)
Vomiting	63 (20.5)	5 (1.6)	66 (21.4)	3 (1.0)
Neutrophil count decreased	56 (18.2)	40 (13.0)	47 (15.2)	26 (8.4)
Thrombocytopenia	55 (17.9)	21 (6.8)	58 (18.8)	12 (3.9)
Hypertension	54 (17.6)	20 (6.5)	55 (17.8)	23 (7.4)
Arthralgia	53 (17.3)	1 (0.3)	57 (18.4)	3 (1.0)
Myalgia	53 (17.3)	2 (0.7)	53 (17.2)	3 (1.0)
Hypothyroidism	52 (16.9)	3 (1.0)	25 (8.1)	1 (0.3)
Asthenia	51 (16.6)	5 (1.6)	56 (18.1)	4 (1.3)
Constipation	49 (16.0)	1 (0.3)	49 (15.9)	1 (0.3)
Platelet count decreased	49 (16.0)	21 (6.8)	40 (12.9)	14 (4.5)
Decreased appetite	45 (14.7)	4 (1.3)	33 (10.7)	1 (0.3)
Leukopenia	38 (12.4)	14 (4.6)	31 (10.0)	7 (2.3)
Proteinuria	38 (12.4)	6 (2.0)	22 (7.1)	3 (1.0)
White blood cell count Decreased	37 (12.1)	21 (6.8)	21 (6.8)	12 (3.9)
Rash	33 (10.7)	3 (1.0)	27 (8.7)	1 (0.3)
Alanine aminotransferase Increased	31 (10.1)	10 (3.3)	23 (7.4)	5 (1.6)
Epistaxis	26 (8.5)	1 (0.3)	36 (11.7)	1 (0.3)

Key: AEs, adverse events; APaT, all patients as treated.
Source: Colombo et al. 2021[1].

B.2.10.1.4 Adverse events of special interest

Table 17 presents a summary of the AEs of special interest (AESIs) observed in the pembrolizumab and placebo groups, including immune-mediated events and infusion-related reactions.

A large proportion of the AESIs were low in severity (Grade 1: [redacted]%; Grade 2: [redacted]%) and were recorded as resolved ([redacted]%) or resolving ([redacted]%).[6] The number of AESIs leading to discontinuation of the trial drug during the study follow-up was relatively low ([redacted]%), indicating that the treatment of AESIs was manageable through the administration of corticosteroids, supportive care and dose interruption.

Table 17: Patients with adverse events of special interest (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)	Placebo + chemotherapy ± bevacizumab (n = 309)
No. of patients, n (%)		
Hypothyroidism	56 (18.2)	27 (9.1)
Infusion reactions	41 (13.4)	39 (12.6)
Hyperthyroidism	23 (7.5)	9 (2.9)
Colitis	16 (5.2)	5 (1.6)
Severe skin reaction	14 (4.6)	1 (0.3)
Thyroiditis	11 (3.6)	1 (0.3)
Pneumonitis	6 (2.0)	1 (0.3)
Hepatitis	5 (1.6)	1 (0.3)
Adrenal insufficiency	4 (1.3)	0 (0.0)
Pancreatitis	3 (1.0)	1 (0.3)
Myositis	2 (0.7)	0 (0.0)
T1DM	2 (0.7)	0 (0.0)
Vasculitis	2 (0.7)	0 (0.0)
Hypophysitis	1 (0.3)	1 (0.3)
Encephalitis	1 (0.3)	0 (0.0)
Cholangitis sclerosing	1 (0.3)	0 (0.0)
Myocarditis	1 (0.3)	0 (0.0)
Nephritis	1 (0.3)	0 (0.0)

Key: APaT, all patients as treated.
Source: Colombo et al. 2021[1].

B.2.10.1.5 Deaths due to adverse events

Table 18 reports a summary of AEs resulting in death up to 90 days after the last administered dose. The overall incidence of AEs resulting in death was generally similar in the pembrolizumab and placebo groups, at 4.6% and 4.5%, respectively.

Table 18: Summary of AEs resulting in death up to 90 days after last dose (APaT population)

	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)	**Placebo + chemotherapy ± bevacizumab (n = 309)**
No. of patients, n (%)		
≥ 1 adverse events resulting in death	14 (4.6)	14 (4.5)
Infections and infestations	3 (1.0)	4 (1.3)
Cardiac disorders	2 (0.7)	1 (0.3)
Gastrointestinal disorders	1 (0.3)	2 (0.6)
General disorders and administration site conditions	2 (0.7)	1 (0.3)
Injury, poisoning and procedural Complications	1 (0.3)	0 (0.0)
Nervous system disorders	2 (0.7)	1 (0.3)
Reproductive system and breast disorders	1 (0.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)
Vascular disorders	2 (0.7)	1 (0.3)
Key: AEs, adverse events. **Source:** Colombo et al. 2021[1].		

B.2.10.1.6 Adverse events by bevacizumab use

The median exposure and AEs by bevacizumab use are reported for each treatment arm in Appendix F.1.1. Patients receiving bevacizumab reported a higher incidence of AEs in both treatment groups, although all reported AEs, with the exception of hypothyroidism, were AEs known to be associated with bevacizumab.

B.2.10.1.7 Safety overview

The safety results of the first interim analyses of KEYNOTE-826 demonstrate that pembrolizumab offers a manageable and predictable AE profile. The overall

incidence of AEs was generally similar between the pembrolizumab and placebo treatment groups and was largely consistent with the known safety profiles of pembrolizumab monotherapy, the chemotherapy administered (± bevacizumab), and the indication under study.

No new AESIs were identified during treatment with pembrolizumab and chemotherapy, with and without bevacizumab. The incidence of AESIs leading to discontinuation of any drug were low, suggesting the AESIs were manageable with corticosteroids, supportive care and dose interruption.

B.2.10.2 KEYNOTE-158

A summary of safety data from KEYNOTE-158 are provided in Appendix F.2. These data were consistent with those observed during the KEYNOTE-826 trial.

B.2.11. Ongoing trials

The KEYNOTE-826 trial is ongoing, with final analysis database lock estimated to occur in [redacted].

The KEYNOTE-158 (NCT0262867) is a Phase II basket trial of pembrolizumab monotherapy in multiple advanced solid tumour types that have progressed with standard of care systemic therapy (i.e. 2L and above within the Stage IV setting). Interim results were published in 2019 for the advanced cervical cancer subset of patients.[51] No further results for the KEYNOTE-158 cervical cohort are expected in the next year.

Further ongoing trials which are anticipated to provide additional evidence in the next 12 months are presented in Appendix P, of which only one (NCT03367871) fully aligns with the indication presented in the decision problem.

B.2.12. Innovation

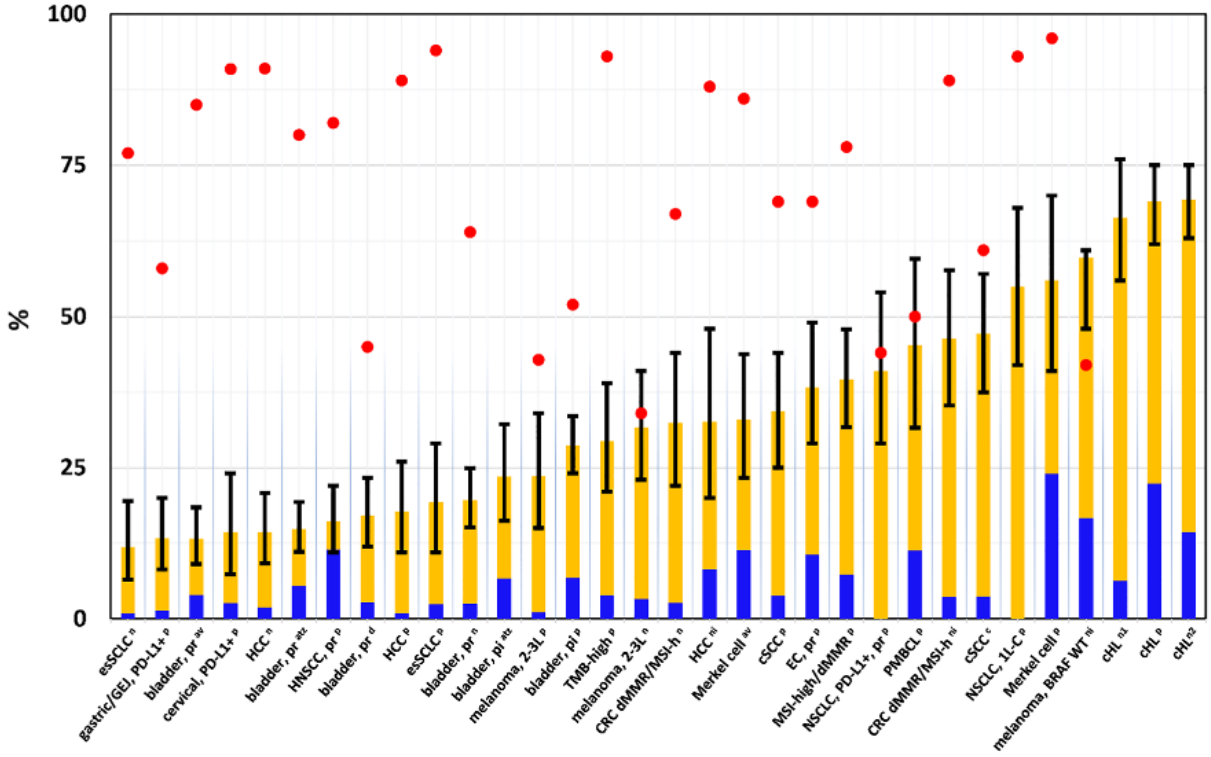
Minimal developments have been made in the management of recurrent, persistent or metastatic cervical cancer over the last decade, and there is a need for effective treatment options[38]. The systemic treatment options available are limited to systemic chemotherapy with cisplatin and paclitaxel, or carboplatin and paclitaxel, with or without bevacizumab. Unfortunately, outcomes remain poor. Furthermore, due to

disruptions caused by the COVD-19 pandemic, there have been notable delays in the diagnosis and management of cervical cancer.[40] Delays in diagnosis have been common. A 4-week delay in adjuvant/neoadjuvant treatment has been shown to increase mortality for several cancers, including cervical cancer.[44]

KEYNOTE-826 is the first randomised controlled Phase III trial to show positive results for immunotherapy in first-line recurrent, persistent or metastatic cervical cancer.[6] The last NICE technology appraisal relating to pharmacological treatment of cervical cancer was published more than 12 years ago.[8] Pembrolizumab offers a new systemic treatment as the first immunotherapy in this cohort of patients, and highlights the benefits in treatment prior to disease progression.

Immunotherapy has already been shown to provide benefit for patients in other cancer types. Pembrolizumab in particular has demonstrated antitumour activity in patients with advanced non-small cell lung cancer in 2014 via PD-L1 inhibition[57] and its effectiveness has been replicated in numerous other studies across a variety of cancer types. In the KEYNOTE-826 trial, the ORR was significantly greater in the pembrolizumab group than those treated with placebo and chemotherapy (68.1% versus 50.2%, respectively; $p < 0.001$).[6] The proportion of patients achieving a CR in the pembrolizumab group was 22.7% (95% CI: [redacted], [redacted]) compared to only 13.1% (95% CI [redacted], [redacted]) of patients treated with placebo and chemotherapy.[6] These are comparable to the highest ever recorded in immunotherapy trials to date (Figure 15).[58] High response rates were also seen in patients treated irrespective of concurrent bevacizumab usage. The two-year clinical data from the KN-826 trial strongly supports very good long-term outcomes for those patients showing evidence of complete response.[1]

Figure 15: Response rates and DoR of FDA approved PD-1 and PD-L1 blocking antibodies



Key: 1L-C, first line combination; 2L, second line; av, avelumab; at, atezolizumab; c, cemiplimab; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; d, durvalumab; dMMR/MSI-h, deficient mismatch repair/microsatellite instability high; EC, endometrial carcinoma; esSCLC, extensive-stage small cell lung cancer; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; ICI, immune-checkpoint inhibitor naive; n, nivolumab; ni, nivolumab-ipilimumab combination; NSCLC, non-small cell lung cancer; p, pembrolizumab; pi, cisplatin-ineligible; pl, pembrolizumab-lenvatinib combination; PMBCL, primary mediastinal B-cell lymphoma; pr, platinum-refractory; TMB, tumour mutation burden.
Notes: Red dots represent proportion of responders with ≥ 6-month DoR. Data were not available for 4 indications (red dot is missing). Orange bars represent partial responders, blue bars represent complete responders and black bars represent 95% CI.
Source: Chang, 2021[58]

The role that pembrolizumab can play in the treatment of cervical cancer is strongly supported by the scientific literature. The majority (90%) of advanced cervical cancer patients express PD-L1, making it an ideal biomarker for a treatment like pembrolizumab.[59] Sensitivity of HPV-related cancers to immunotherapy compared with SoC chemotherapy-based regimens has been demonstrated, which likely represents multiple distinct mechanisms promoting inflammation and immunogenicity.[60] Under normal immune response, T-cells are activated and attack tumour cells. Tumour cells evade the immune system by binding on T-cells using PD-L1 and PD-L2 ligands. Pembrolizumab is a highly-selective PD-1 IgG4 antibody

that binds to the PD-L1 receptor, thereby blocking PD-L1 and PD-L2 interaction and restores the immune response, resulting in high efficacy with no cytotoxic activity.[61]

If approved, pembrolizumab would help address the substantial unmet clinical need and provide a significant step change in the management of cervical cancer.

B.2.13. Interpretation of clinical effectiveness and safety evidence

As discussed in Section B.1.3.4.2, there is a clear unmet need for additional, novel treatment options with proven effectiveness for adults with recurrent, persistent or metastatic cervical cancer. The KEYNOTE-826 trial provides pivotal evidence to support the use of pembrolizumab and chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin [± bevacizumab]) in patients with recurrent, persistent or metastatic cervical cancer.[1] The addition of pembrolizumab to chemotherapy, with or without bevacizumab, provides statistically significant OS and PFS improvements after a 22 month follow-up. In the CPS ≥ 1 population, pembrolizumab reduced the risk of death by 36% (HR: 0.64, 95% CI: 0.50, 0.81, $p < 0.0003$). Despite a follow-up of 22 months, the median OS in the pembrolizumab group was not reached, whereas the OS was 16.3 months in the placebo group. The proportion of patients who achieved a CR or PR was significantly greater in the pembrolizumab group than those treated with placebo (68.1% versus 50.2%, respectively; $p < 0.001$), and patients in the pembrolizumab group had a longer duration of response compared to placebo (18.0 versus 10.4 months, respectively). These benefits were generally consistent across all protocol-specified subgroups, independent of whether the patient received bevacizumab. The two-year OS and PFS rates are particularly encouraging among those achieving a complete response to treatment with pembrolizumab and chemotherapy.

The KEYNOTE-158 trial also demonstrates good outcomes for pembrolizumab, even when used in a cohort of previously treated (i.e. second-line) advanced cervical cancer patients. In the CPS ≥ 1 population, patients treated with pembrolizumab had a PFS of 2.1 months, and an OS of 11 months, with an OS at 12-months of 47.3%.[51]

Safety results from KEYNOTE-826 showed that the pembrolizumab + chemotherapy (± bevacizumab) combination offered a manageable and predictable safety profile,

with most AEs resolved with the administration of corticosteroids and supportive care, along with dose interruption.[1, 51] The safety profiles were consistent with the known profiles of the individual trial agents. KEYNOTE-158 also provided supportive evidence for the safety of pembrolizumab, demonstrating safety outcomes consistent with the KEYNOTE-826 trial.

Importantly, patients receiving pembrolizumab experienced no clinically meaningful drop in their HRQL, despite the addition of another targeted agent.[1] When treated with pembrolizumab, the time to deterioration of HRQL was longer, and a higher proportion of patients had an improved or stable HRQL compared to placebo as assessed via the ED-5D-5L VAS score.

Pembrolizumab would provide women with the substantially improved outcomes related to long-term survival outcomes and HRQL. Additionally, as the vast majority of cervical cancer patients seen in UK clinical practice are of working age, and many have families and dependents, treatment can enable women to return to their daily lives, including work and their caring responsibilities.[3]

B.2.13.1 Strengths and limitations of the evidence base

KEYNOTE-826 presents the only combination regimen to demonstrate significant improvements in pre-specified analyses of OS, PFS, and ORR in the CPS ≥ 1 population in first-line treatment of patients with recurrent, persistent, or metastatic cervical cancer.[1]

The KEYNOTE-826 trial is a high-quality, randomized trial which adhered to a series of pre-defined steps in order to avoid any potential bias.[1] Patient randomization was performed using an interactive voice response system/integrated web response system. Double-blinding was conducted in-house, in which pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or other qualified site personnel. Patients were stratified according to metastatic status at initial diagnosis, the investigator decision to use bevacizumab, and PD-L1 status.

Expert clinicians at the clinical advisory board estimated that approximately 50–80% of first-line recurrent, persistent and metastatic cervical cancer patients receive

treatment with bevacizumab.[3] As there is a proportion of patients who cannot tolerate treatment with bevacizumab, treatment flexibility a key need.[2] KEYNOTE-826 provides evidence that demonstrates the benefits of pembrolizumab and chemotherapy with and without the addition of bevacizumab.

While it is positive that the median OS has not yet been reached in the pembrolizumab arm, from a statistical perspective the survival data are immature and extrapolation beyond the trial is required for economic analyses (Section B.3.3).

B.2.13.1.1 Study applicability to clinical practice

The population in KEYNOTE-826 aligned with the population outlined in the decision problem presented in this submission: adults with recurrent, persistent or metastatic cervical cancer.

The KEYNOTE-826 trial was conducted at 151 centres in 19 countries worldwide.[1] Despite this, no clear differences were identified when comparing the baseline patient demographics and disease characteristics of the overall trial population to a European subset of the trial. It has also been confirmed by UK clinicians that the KEYNOTE-826 trial population is representative of that seen within UK clinical practice.[3]

A broad range of patients were enrolled into the KEYNOTE-826 trial in terms of histology, prior therapies, disease status at trial entry and stage at initial diagnosis.[1] Baseline patient demographics and disease characteristics were generally well balanced between the two arms of the trial, with the exception of the proportion of patients with squamous cell carcinoma/adenocarcinoma. There was also a small difference in patients who received radiotherapy and the proportion of patients with distant metastases prior to trial enrolment, although this was not expected to significantly bias the results of the KEYNOTE-826 trial. UK clinicians have confirmed that patients enrolled in KEYNOTE-826 are generally representative of patients seen within UK clinical practice.[3]

Outcomes were generally similar across the various subgroups analysed. The median patient age in KEYNOTE-826 was 51 years, which is generally aligned with the median age of cervical cancer patients in England in 2019 (45–49 years).[62] The

chemotherapy control arm in the KEYNOTE-826 trial is representative of the standard of care currently used in the NHS. The proportion of patients in the trial receiving bevacizumab in combination with pembrolizumab and chemotherapy was also similar to that seen within UK clinical practice (63% versus an estimated 50–80%, respectively), as confirmed through clinical opinion.[3] It was noted that continuing bevacizumab beyond 6 cycles is not standard practice, although the decision on whether treatment is continued is based on clinician or/and patient choice. Expert clinicians confirmed that KEYNOTE-826 was generalisable to treatment of patients in UK clinical practice.[3]

The primary efficacy outcomes PFS and OS are well established trial endpoints which are of most relevance to patients, carers and healthcare professionals in UK clinical practice. HRQL endpoints also allow further assessment of the impact of recurrent, persistent or metastatic cervical cancer on patients, and allow formal utility analyses to support economic modelling.

B.2.13.2 End-of-life criteria

Pembrolizumab + chemotherapy (± bevacizumab) should be considered an end-of-life treatment, meeting the NICE criteria for such designation, as summarized in Table 19.

Table 19: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months.	Survival estimates for current care from KEYNOTE-826: Median survival = 16.3 months Survival estimates for current care from GOG 240: Median survival = 13.3 to 16.8 months	Section B.1.3 Page 14
	Survival estimates for current care from economic modelling: Median undiscounted survival = 17.2 months	Section B.2 Page 24

Criterion	Data available	Reference in submission (section and page number)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	Survival estimates for pembrolizumab + chemotherapy (± bevacizumab) from KEYNOTE-826: Median survival = Not reached	Section B.2.6.1 Page 40
	Survival estimates for pembrolizumab + chemotherapy (± bevacizumab) from KEYNOTE-158: Median survival = 11 months	Section B.2.6.3 Page 53
	Survival estimates for pembrolizumab + chemotherapy (± bevacizumab) from economic modelling: Median undiscounted survival = 24.4 months Median undiscounted LY gain versus current care = 7.2 months Mean undiscounted LY gain versus current care = 33.7 months	Section B.3.6 Page 137
Key: LY, life years.		

Patients on SoC in the UK can be considered to 'normally' survive for less than 24 months because:

- In KEYNOTE-826, 58.3% of patients in the SoC arm had died at 24 months
- Median OS for the SoC arm, which reflects the experience of 50% of patients, was 16.3 months
- The GOG-240 trial indicates that OS at 2 years is 28.3% in the chemo-only group and 35.3% in the chemo-bevacizumab group[39]
- The modelled mean OS on the SoC is 2.5 years (or 2.2 years with discounting) but, as the response-group analysis shows, this is likely to be heavily influenced by good OS outcomes in patients achieving CR, who constitute only 13% of patients in the SoC arm
- Expert opinion provided to MSD at an advisory board indicates that clinicians normally expect patients to survive for less than 24 months

- Median estimates from the pivotal trial, from the literature and expert testimony are commonly accepted by NICE committees as relevant data upon which to base the 'life expectancy criterion' decision[63]

Pembrolizumab meets the life extension of at least 3 months criterion because the median and mean modelled life extension is 8 months, and 2.8 years (1.8 including discounting), respectively.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

No studies relevant to the UK setting were identified in a systematic search for cost-effectiveness analyses for patients with persistent, recurrent, or metastatic cervical cancer (see details in Appendix G).

Only one NICE appraisal has been completed in cervical cancer, published in 2009.[8] TA183 recommends topotecan in combination with cisplatin for women with recurrent or stage IVB cervical cancer if they have not previously received cisplatin. Notably, the patient population for which topotecan is recommended constitutes a very small proportion of patients with persistent, recurrent or metastatic cervical cancer[8] (Section B.1.3.4.1). As TA183 is over a decade old and seems to use a simplistic modelling approach, it was deemed to provide limited information of relevance for this appraisal for pembrolizumab. A comparison of model features is provided in Table 20.

B.3.2. Economic analysis

There is a lack of treatment options for patients with advanced cervical cancer. With no new treatment options becoming available over the past decade, standard chemotherapies including paclitaxel and platinum-based agents (cisplatin, carboplatin) are the only treatment options, with an option for combination with bevacizumab through the Cancer Drugs Fund[64] (Section B.1.3). Outcomes remain poor for patients with persistent, recurrent, or metastatic cervical cancer (Section B.1.3.3). Pembrolizumab in combination with chemotherapy with or without bevacizumab represents a step-change improvement in the treatment pathway.

To assess the cost-effectiveness of pembrolizumab in combination with chemotherapy with or without bevacizumab (PEM+SoC) versus chemotherapy with or without bevacizumab (SoC) alone, a de novo economic model was required, as detailed below. The model inputs are based on the interim analysis of KEYNOTE-826 data, with a data cut-off date of 3rd May 2021.

A summary of key points is included below, with full details in the following sections.

Summary of key points:

- A de novo economic model was developed to evaluate the cost-effectiveness of pembrolizumab in combination with chemotherapy ± bevacizumab (PEM+SoC) versus SoC, in line with the final NICE scope, based on a UK National Health Service (NHS) and Personal Social Services (PSS) perspective over a lifetime time horizon.
- The model structure was determined after a comprehensive assessment of the disease context in cervical cancer, clinical trial data and feedback from UK clinical experts. A state transition model consisting of the health states 'progression-free', 'progressed disease' and 'death' was deemed most appropriate, compared with other model approaches.
- Clinical efficacy, health related quality of life and safety data were based on analysis of the patient-level data of the interim analysis from KEYNOTE-826.
  - The clinical trial data are the best source of evidence for PEM+SoC, as well as the SoC arm which reflects the real-world mix of treatments used in the UK.
  - TTP, PFS and PPS were the main efficacy inputs used to model health outcomes over patients' lifetime
- All relevant costs are included and sourced from appropriate UK databases, consistent with the NICE reference case.
- Cost categories included treatment acquisition and administration costs, AE management costs, health state resource use costs, the expected costs of PD-L1 testing, subsequent treatment costs and costs associated with end-of-life care
- The estimated ICER for PEM+SoC versus SoC is ~£34,000/QALY gained incorporating the Commercial Access Agreement (CAA) currently agreed for pembrolizumab, which show that PEM+SoC is highly likely to be cost-effective when the confidential discount is applied
- There is a high degree of unmet need for effective treatment options in advanced cervical cancer. PEM+SoC is an innovative, end-of-life technology that presents a step-change improvement for this patient population

B.3.2.1 Patient population

The modelled population is in line with the anticipated EMA and MHRA marketing authorisation for PEM+SoC: adults with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS≥1). This is the appropriate and relevant population for the decision problem in England, as discussed with NICE at the decision problem meeting on 9th February 2022.

The economic analysis addresses this patient population directly in line with the decision problem, and as such, focuses on the subgroup of patients in KEYNOTE-826 with CPS status greater or equal to 1 (Section B.2) accounting for approximately 89% of all patients enrolled to KEYNOTE-826 (548 patients; 273 in the pembrolizumab arm and 275 in the control arm). CPS status was a randomisation stratification factor in KEYNOTE-826.[65]

B.3.2.2 Model structure

An economic model was developed to assess the cost-effectiveness of PEM+SoC versus SoC. The analysis is conducted from the UK National Health Service (NHS) and Personal Social Services (PSS) perspective, in line with the NICE reference case. Consistent with best practice guidance on developing cost-effectiveness models, including NICE DSU TSD 13[66], 14[67] 19[68], and 21[69], the model structure was determined after considering each of the following factors and consultation with UK clinical experts[3] (further expanded upon in Section B.3.2.2.1):

i) The relative maturity of the KEYNOTE-826 PFS versus OS data, and the observed plateauing of PFS data in the pembrolizumab arm, which causes parametric survival models fitted to PFS and OS data to cross.
ii) The importance of the fuller and more explicit use of information on prognostic intermediate endpoints (i.e., progression) to inform mortality extrapolations, particularly when PFS is an appropriate surrogate for OS and mortality data are immature.
iii) The importance of being able to assess the clinical and biological plausibility of survival extrapolations by performing scenario analyses given the immaturity of the KEYNOTE-826 OS data.

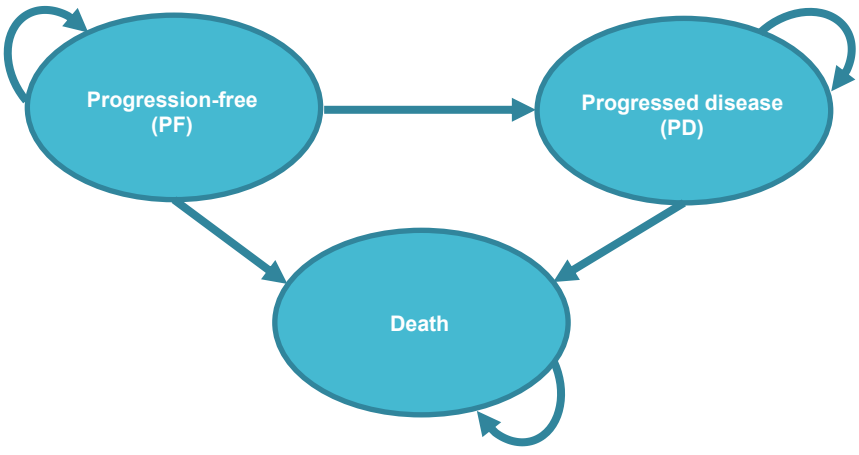
iv) Data analysis examining OS among response subgroups within the trial shows that most patients in the post-trial period will be complete or partial responders with low and declining event rates, particularly in the PEM+SoC arm.

This assessment showed that a state transition model consisting of the health states 'progression-free', 'progressed disease' and 'death' (Figure 16) is the most appropriate approach for assessing the cost-effectiveness of PEM+SoC.

In the model the following transitions are allowed:

- **Patients in the 'progression-free' health state can**:
  a) Remain in the 'progression-free' health state
  b) Move to the 'progressed disease' health state
  c) Move to the 'death' health state
- **Patients in the 'progressed disease' health state can**:
  d) Remain in the 'progressed disease' health state
  e) Move to the 'death' health state
- **Death is an absorbing health state**
  There are no transitions allowed out of this health state.

Figure 16: State transition model (three health-states)



The transitions described above are informed directly by KEYNOTE-826, using treatment arm-specific patient-level data for time-to-progression (TTP), PFS and PPS. Additionally, time on treatment (TOT) is directly based on the observed KM

data for each treatment from KEYNOTE-826 as the clinical trial covered the maximum duration of all treatment for all patients in England in both arms. This is the best source of data to assess the cost-effectiveness of PEM+SoC compared with SoC for use in the economic model.

In line with the NICE reference case[70], the modelled outcomes include all relevant costs associated with the intervention and comparator over patients' lifetimes (Section B.3.5), and health outcomes provided in life years (LYs) and quality-adjusted life years (QALYs), with results presented as total and incremental values (Section B.3.6). These outcomes adequately quantify the resource impact of treatment and the primary objectives of treating patients with cervical cancer: to improve quality of life, reduce the risk of disease progression, and extend long-term survival.

B.3.2.2.1 Justification for model structure

Following a comprehensive assessment of the evidence available to inform the economic analysis, a state transition model consisting of the health states 'progression-free', 'progressed disease' and 'death' was developed to assess the cost-effectiveness of PEM+SoC versus SoC. This was deemed the most robust approach for this appraisal based on the following four factors.

i) **The relative maturity of the KEYNOTE-826 PFS versus OS data, and the observed plateauing of PFS in the pembrolizumab arm, which causes parametric survival models fit to PFS and OS data to cross**

At the time of the interim analysis, PFS data for the CPS≥1 population were relatively mature. [redacted] out of 273 patients in the PEM+SoC arm ([redacted]) and [redacted] out of 275 patients in the comparator arm ([redacted]) had progressed (progression per RECIST 1.1 as assessed by the investigator) or died. At the end of follow-up, PFS KM estimates were [redacted] for PEM+SoC and [redacted] for the comparator arm.

As can be seen in Figure 4 of Section B.2.6.1.1, PEM+SoC is associated with a sustained, increasing benefit over chemotherapy in terms of PFS: the rate of progression plus death events over time decreases more in the PEM+SoC arm than in the SoC arm. It is also observed that the PFS curve for pembrolizumab plateaus

towards the end of the follow-up period. UK clinical experts validated these trends and explained that decreasing hazards are expected in the post-trial period in both arms because a minority of patients respond well to treatment and achieve durable PFS. Given the response data in KEYNOTE-826 and their clinical experience with immunotherapy treatments including pembrolizumab, where more patients respond well and responders respond more durably to treatment, they confirmed the plateauing effect would likely be greater in the pembrolizumab arm.

The OS data for the CPS≥1 population were substantially less mature than the PFS data. [redacted] out of 273 patients in the PEM+SoC arm ([redacted]) and [redacted] out of 275 patients in the SoC arm ([redacted]) had died. At the end of follow-up, OS KM estimates were [redacted] for PEM+SoC and [redacted] for SoC. As for PFS, PEM+SoC is associated with a sustained, increasing benefit over chemotherapy alone in terms of OS (Figure 5 of Section B.2.6.1.2). While the OS data are relatively immature, the rate of death events over time appears to decrease more in the PEM+SoC arm than in the SoC arm; however, longer follow-up is needed to confirm that OS in the PEM+SoC arm would plateau to the extent of the PEM+SoC PFS data. UK clinical experts consulted for this appraisal confirmed that the trends in hazards observed for PFS would be expected to become apparent for OS with longer-follow up.[3]

To estimate PFS and OS over a lifetime time horizon, survival analyses were conducted in accordance with best practice methods and guidance from NICE DSU TSD 14.[71] Six types of parametric survival models were fit to the PFS and OS data for PEM+SoC and the comparator arm from KEYNOTE-826.[67] For OS, models were fitted to all KM data available. For PFS, models were fitted to the KM data from 37 weeks onward, as models fitted to all KM data provided a poor fit to the data (for more information see Sections B.3.3.2 and B.3.3.3). Figure 17 and Figure 18 show an overlay of the KM data and parametric survival models for PFS and OS in the PEM+SoC and SoC arm, respectively. This analysis demonstrates two key issues:

1. In both arms, many of the parametric survival models for PFS and OS cross (particularly for pembrolizumab), which means many combinations of curves are implausible. This is highly problematic for partitioned survival models, which rely directly on these combinations of curves.

2. None of the OS extrapolations for PEM+SoC reflected clinical expectations around the prognostic impact of progression and durability of response observed for pembrolizumab in KEYNOTE-826 on OS (Section B.3.9.2).

The relationship between TTP and PPS in KEYNOTE-826 was also explored, to better understand the likely trajectory for OS. Analysis of the patient-level data demonstrated a positive correlation in both arms, further supporting the conclusions above (Appendix Q). The data from KEYNOTE-826 show that a model structure that is based on TTP and PPS, and not heavily reliant on the within-trial OS data, is more appropriate.

Figure 17: PFS and OS KM data and parametric extrapolations; PEM+SoC arm CPS≥1 population of KEYNOTE-826

Key: Exp, exponential; GenGam, generalised gamma; K-M, Kaplan–Meier; LogLog, log-logistic; LogNor, log-normal; OS, overall survival; PFS, progression-free survival; SoC, standard of care; Wei, Weibull

Figure 18: PFS and OS KM data and parametric extrapolations; SoC arm CPS≥1 population of KEYNOTE-826

Key: Exp, exponential; GenGam, generalised gamma; K-M, Kaplan–Meier; LogLog, log-logistic; LogNor, log-normal; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; SoC, standard of care; Wei, Weibull

ii) The importance of the fuller and more explicit use of information on prognostic intermediate endpoints (i.e., progression) to inform mortality extrapolations, particularly when PFS is an appropriate surrogate for OS and mortality data are immature

In oncology, progression is highly prognostic of death. UK clinical experts confirmed that PFS and OS should be positively related. In this case, any observed separation between PFS in the PEM+SoC and SoC arms would be expected to translate into a separation of OS with longer follow-up because improvements in PFS are not associated with a negative impact on post-progression survival (PPS).[3] Unlike for PFS, due to the relative immaturity of the OS data, the plateauing of OS data is not yet clearly observable.

In a state transition oncology model, progression and death are explicitly related with OS being a function of time to progression and pre- and post-progression survival. That is, information on progression is used to inform mortality extrapolations. In a standard three-health state partitioned survival oncology model, OS is modelled independently of PFS. OS extrapolations reflect within-trial trends in OS alone: information on progression is ignored.

The assumption of independence between OS and PFS is problematic for the partitioned survival model structure as progression *is* prognostic for death. The modelling of OS independent of PFS in partitioned survival models becomes more problematic when OS data are relatively immature, such as in KEYNOTE-826. In the within-trial period, all dependencies between OS and PFS are reflected in the data. However, in the post-trial period, (most of) this dependency is ignored with potentially important implications for extrapolation. As noted in NICE TSD 19[68], "extrapolating within-trial trends without considering the underlying disease process may not produce appropriate extrapolations." Hence, in cases where OS data are relatively immature, a state transition model is often more appropriate than a partitioned survival model as it does not only rely on OS data. Not considering the large reduction in the risk of progressing over time observed in KN-826 when extrapolating KN-826 OS data, will likely result in a substantial underestimation of long-term OS.

iii) The importance of being able to assess the clinical and biological plausibility of survival extrapolations by performing scenario analyses given the immaturity of the KEYNOTE-826 OS data

The lack of a structural relationship between PFS and OS in a partitioned survival model has additional important implications for the appropriateness of using this approach to inform decision-making. The NICE methods guidance recommends that the clinical and biological plausibility of extrapolations should be assessed and that alternative scenarios should be routinely considered for the extrapolation period.[67] When decision models are underpinned by a structure reflecting biological or clinical processes, it is possible to carefully consider the mechanisms underpinning extrapolations and to subject these to scrutiny and sensitivity analyses. For example, in a state transition model, the impact of assuming the same PPS for the intervention

and comparator can be assessed. This scenario analysis cannot be performed in a partitioned survival model.

The lack of structural relationship between endpoints also reduces the usefulness of probabilistic sensitivity analysis (PSA) results generated using partitioned survival models (in some PSA runs, PFS will be much shorter than in the base case analysis, while OS is much longer, which is clinically implausible).

iv) Data analysis examining OS among response subgroups within the trial shows that most patients in the post-trial period will be complete or partial responders with low and declining event rates, particularly in the PEM+SoC arm

Finally, analysis of OS data from KEYNOTE-826 demonstrates that response is highly prognostic of survival (Figure 19). As a result, OS cannot be reliably extrapolated beyond the trial period based on OS in the trial period alone. While the vast majority of patients who did not respond to PEM+SoC or SoC (i.e. with stable or progressed disease) had died at two years follow-up, only [redacted] and [redacted] of patients who had achieved complete or partial response on PEM+SoC had died, respectively (corresponding percentages for SoC: [redacted] and [redacted]), indicating that the composition of the patient cohorts changed fundamentally over the duration of follow-up. This has significant implications for expected outcomes beyond the trial period. Since the vast majority of patients alive at the end of the trial period achieved partial or complete response, the hazards of death will decline substantially over time. The more mature PFS data give an indication of the declining event rates that are expected to happen for OS in the post-trial period. This is another reason for using a model structure where OS beyond the trial is affected by progression rates, instead of being based purely on the immature OS data itself. In an advisory board conducted for this appraisal, UK clinical experts strongly supported the above conclusions and provided further insights, summarised below.[3]

Figure 19: OS KM data by response status categories for PEM+SoC and SoC for the CPS≥1 population of KEYNOTE-826

Summary of relevant feedback from UK clinical experts on the important factors for consideration during model development

MSD conducted an advisory board including seven UK clinical experts on 18th February 2022, with the objective of garnering insights regarding cervical cancer, their interpretations of the observed data from KEYNOTE-826, the generalisability of the KEYNOTE-826 trial to the UK setting, and the potential impact and positioning of pembrolizumab in the UK clinical pathway.

As mentioned above, feedback from clinical experts who participated in the UK advisory board strongly supported a state transition model structure:

- Durable PFS and OS for PEM+SoC are clinically plausible based on their experiences with immunotherapies in other advanced cancer indications, the positive outcomes for complete and partial responders in the PEM+SoC arm of KEYNOTE-826, and the relative youth and fitness of the patient cohort
- In cervical cancer PFS is a good proxy for OS. The trends in hazards observed for PFS would be expected to become apparent for OS with longer-follow up.
- PPS following treatment with PEM+SoC is expected to be more favourable than PPS with SoC alone; the opposite is clinically implausible.
- Given the response data in KEYNOTE-826 and their clinical experience with immunotherapy treatments including pembrolizumab, it is clinically plausible for a significant minority to respond very well and more durably to treatment, with a plateauing effect likely being greater in the pembrolizumab arm compared with SoC

In conclusion, based on the above assessment, the disease context in cervical cancer, clinical trial data and feedback from UK clinical experts, a state transition model consisting of the health states ‘progression-free’, ‘progressed disease’ and ‘death’ was considered to be appropriate. Any potential value of using another, more complex model structure was deemed to be outweighed by the added complexity of such an approach.

B.3.2.2.2 Key features of the analysis

Table 20 summarizes the key features of the base case cost-effectiveness analysis. As described in Section B.3.1, TA183 is over a decade old and seems to use a simplistic means-based modelling approach; therefore, it was deemed to provide information of limited use for this appraisal for pembrolizumab. In line with the NICE reference case, the model developed for this appraisal considers the relevant impact of PEM+SoC versus SoC alone over a lifetime time horizon (assumed to be 50 years). The model uses a weekly cycle length which allows for accurate estimation of the drug acquisition and drug administration costs according to their detailed dosing schedules.

Table 20: Features of the economic analysis

Feature	TA 183	Current appraisal	
	Values	**Chosen values**	**Justification**
Time horizon	36 months for the within trial analysis and 24 months for the indirect comparison.[72]	50 years	Lifetime time horizon based on mean age in KN-826 of [redacted] years (range, [redacted])[73]. After 50 years all patients in both the PEM+SOC and SOC arm have died within the economic model
Model structure	A within-trial analysis and a means-based model for the indirect comparison.[72]	Three health state transition model	Conceptually simple, and structurally reflects the impact of the disease on patients with advanced cervical cancer. Widely accepted by NICE and appropriately distinguishes costs and utilities according to different types of clinically meaningful events that impact patients' outcomes
Treatment waning effect	N/A	N/A	No evidence for treatment waning from KN-826 nor other pembrolizumab studies with longer follow up[57, 74, 75] The

Feature	TA 183	Current appraisal	
	Values	Chosen values	Justification
			impact of assuming equal PPS for PEM+SoC and SoC is assessed in a scenario analysis
Source of utilities	FACT-G data were mapped to utilities using an algorithm developed by researchers at the School of Public Health, University of Illinois at Chicago[76]	KN-826 EQ-5D-5L data were mapped to EQ-5D-3L and the UK tariff was used to obtain utilities.[65]	Most appropriate data and in line with recommendations in NICE methods guide and position statement on EQ-5D instruments[70, 77]
Source of costs	NHS reference costs and PSSRU	Resource use: Feedback from UK clinical experts[3] Unit costs: MIMS, eMIT, NHS reference costs, PSSRU	Standard cost databases that reflect the perspective of the NHS and PSS, in line with NICE reference case

Key: eMIT, electronic market information tool; FACT-G, Functional Assessment of Cancer Therapy – General; KN-826, KEYNOTE-826; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Service; PSSRU, Personal Social Services Research Unit.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Pembrolizumab combination treatment arm

In KEYNOTE-826, pembrolizumab was administered in combination with paclitaxel and cisplatin or carboplatin with or without bevacizumab. The latter treatments are reflective of SoC in current UK clinical practice (see Section B.3.2.3.2 and B.3.5.1 below for further details regarding the implementation of chemotherapy with and without bevacizumab in the economic model). Pembrolizumab treatment is implemented in the economic model per the dosing regimen used in KEYNOTE-826, the anticipated EMA and MHRA marketing authorisation and SmPC for the cervical cancer indication, and anticipated use in England:

- 200 mg every 3 weeks (Q3W), up to a maximum of 35 cycles (approximately 2 years) in combination with standard of care (SoC)

The impact of an alternative dosing regimen for pembrolizumab (400 mg every 6 weeks (Q6W)) is assessed in a scenario analysis.

B.3.2.3.2 Comparator arm

In current UK clinical practice, patients with recurrent, persistent, or metastatic cervical cancer may receive combinations of paclitaxel, carboplatin, cisplatin and bevacizumab (as an add-on to platinum-based chemotherapy under the CDF). These combinations are also the comparators included in the final NICE scope. Real-world decisions on which treatments are administered are based on clinician and patient choice, as is reflected in the administration of treatments in the comparator arm of KEYNOTE-826 (Table 21). The proportion receiving each treatment was confirmed to be broadly reflective of UK practice by clinical experts in England, Scotland and Wales.[3] In the economic model, the mixed basket of treatments that patients may receive in clinical practice is implemented per KEYNOTE-826, consisting of:

- Platinum chemotherapy (cisplatin or carboplatin) in combination with paclitaxel, with or without bevacizumab, up to a maximum of 6 treatment cycles
  - Carboplatin is administered at a dose of 750 mg, once every 3 weeks
  - Cisplatin is administered at a dose of 50 mg/m^2, once every 3 weeks
  - Paclitaxel is administered at a dose of 175 mg/m^2, once every 3 weeks
  - Bevacizumab may be administered in combination with chemotherapy as an option through the Cancer Drugs Fund (CDF) and is implemented in the model at a dose of 15 mg/kg, once every 3 weeks

The final NICE scope suggests that etoposide and topotecan should also be considered; however, as highlighted in comments to the draft scope, and explained in Section B.1.1 and B.1.3.4 with additional validation with UK clinical experts, they have been confirmed not to be relevant comparators for the UK.

Table 21: Treatments administered in the CPS≥1 population of KEYNOTE-826 (pembrolizumab, cisplatin, carboplatin, paclitaxel and bevacizumab)

Treatment	Pembrolizumab + SoC n (%), n total = 272	SoC only n (%), n total = 275
Pembrolizumab	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin + Carboplatin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Key: KN-826, KEYNOTE-826; SoC, standard of care		

B.3.3. Clinical parameters and variables

The clinical parameters incorporated into the economic model are based on the recent interim analysis of KEYNOTE-826[1] (data cut-off date of 3rd May 2021), where pembrolizumab met its dual-primary efficacy endpoints, demonstrating statistically significant comparative benefit for PFS per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator (PFS-INV) and OS in both the ITT population (n=617) and in patients with PD-L1 combined positive score (CPS) ≥1 (n=548). CPS status was a randomisation stratification factor in KEYNOTE-826. Full details of KEYNOTE-826[1] are provided in Section B.2. [redacted] all data presented in Section B.3 and used in the economic model are based on the CPS≥1 population of KEYNOTE-826. As the clinical trial provided a direct comparison of PEM+SoC with all relevant comparators in this indication, a within-trial analysis provides all the comparative evidence needed. The following clinical outcomes obtained from KEYNOTE-826 are used in the model:

- Time to progression (TTP)
- Progression-free survival (PFS)
- Post-progression survival (PPS)
- Health-related quality of life (HRQL)
- Adverse events (AEs)

- Time on treatment (ToT)

B.3.3.1 Estimation of transition probabilities

The median duration of follow-up at the interim analysis of KEYNOTE-826 in the CPS≥1 population was [redacted] months in the pembrolizumab arm, and [redacted] months in the SoC arm.[1, 73] In line with the NICE reference case, it was necessary to extrapolate the patient-level data beyond the trial period to assess the cost-effectiveness of PEM+SoC versus SoC alone over a lifetime time horizon.

Parametric survival modelling was conducted using R (software version 4.0.2 [2020-06-22]), and in accordance with best practice methods and guidance from NICE DSU TSD 14.[67] At each model cycle, transition probabilities and health state occupancy were determined based on data from the KEYNOTE-826 trial for TTP, PFS and PPS extrapolated over the model time horizon using parametric survival models.

B.3.3.1.1 Overview of transitions and data used to inform transition probabilities

Section B.3.2.2 and Figure 16 outline the state transition model structure.

Transition probabilities between the ‘progression free’ health state and the ‘progressed disease’ health state were informed by KEYNOTE-826 TTP data.

Transition probabilities between the ‘progression free’ health state and the ‘death’ health state were informed by the difference between KEYNOTE-826 PFS data and TTP data. As in PFS progressions and deaths are both considered events, and in TTP only progressions are considered events, the difference between PFS and TTP is equal to the deaths from the PFS health state.

Transition probabilities between the ‘progressed disease’ health state and the death health state were informed by KEYNOTE-826 PPS data. Tunnel states were used to ensure that patients in the ‘progressed disease’ health state were assigned the correct probabilities for transition to the ‘death’ health state based on the number of cycles since they entered the ‘progressed disease’ health state. Tunnel states were implemented using a Visual Basic® for Applications (VBA) macro. The VBA macro

implements the usual calculations for tunnel states but is computationally more efficient than programming these into the front-end of an Excel® model. The code was thoroughly validated following the process described in Section B.3.9.

B.3.3.1.2 Method of selection of appropriate parametric models

In line with TSD14 guidance[67], the following types of parametric survival models were fit to the survival data for each treatment arm:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalized gamma

Standard one-piece parametric models were fitted to the observed data from KEYNOTE-826. Two-piece models (KM data followed by parametric survival models fit from certain time points onward) were explored where necessary based on visual assessment of the fit of the parametric survival models to the KM data and the cumulative hazards over time for each treatment arm.

Suitability of parametric survival models for the base-case analysis and scenario analyses was assessed in accordance with NICE DSU TSD 21.[69] The following criteria were considered for the PEM+SoC arm and the SoC arm separately:

- Visual fit to the observed Kaplan–Meier (KM) data within the trial period for KEYNOTE-826.[73]
- Clinical plausibility of the long-term extrapolations
  - Validation was conducted against published OS, PFS and PPS data from the GOG 240 trial in advanced cervical cancer[78] (assuming bevacizumab as per KEYNOTE-826, which is in line with UK clinical practice); further details provided in Sections B.3.3.2, B.3.3.3 and B.3.3.4; and in Appendix Q. GOG 240 is an important trial for validation purposes because it provides long-term data for SoC OS, PFS and PPS (more than 4 years of follow-up) for a patient population that is comparable to KEYNOTE-826 (Appendix Q). At the final analysis, the authors

note that many patients continued to benefit from stable disease, and some were confirmed to be in long-term remission with no evidence of clinical and radiologic disease.[78]

  - TTP, PFS and OS at 50 years could not exceed 5%, to avoid the use of curves in which no events take place from a certain time onward.
- Assessment of the underlying hazard functions over time and clinical plausibility of hazard assumptions.
- Statistical goodness of fit to the observed data, as indicated by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values.

The most appropriate and clinically plausible models for TTP, PFS (the same type of model needed to be used for TTP and PFS to avoid clinically implausible pre-progression mortality estimates) and PPS were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses. An overview is provided in Section B.3.3.5. Although there are differences in the mechanism of action between pembrolizumab and the treatments comprising SoC, we worked on the assumption that, for each outcome, the same parametric survival model would need to be used for PEM+SoC and SoC.

B.3.3.2 Time to progression

The TTP KM data and cumulative hazard plots for PEM+SoC and SoC are presented in Figure 20 and Figure 21, respectively. At the time of the analysis, [redacted] out of 273 CPS≥1 patients treated with PEM+SoC ([redacted]) and [redacted] out of 275 CPS≥1 patients treated with SoC ([redacted]) had progressed. Median TTP was [redacted] (95% confidence interval (CI): [redacted]) in the PEM+SoC arm and [redacted] (95% CI: [redacted]) in the SoC arm. Final TTP KM estimates were [redacted] for PEM+SoC and [redacted] for SoC.

The observed data show that PEM+SoC is associated with a sustained, increasing benefit over SoC in terms of TTP, with the rate of progression events over time decreasing more in the PEM+SoC arm than in the comparator arm. There is a clear inflection point in the observed data between [redacted] weeks, after which TTP plateaus towards the end of the observed period. This is seen in the KM data and cumulative hazard plot and is particularly pronounced in the pembrolizumab arm. It is

also clear from Figure 20 that the TTP KM data for PEM+SoC and SoC are stepped. This is driven by the KEYNOTE-826 clinical trial protocol where tumour imaging assessments were performed every 9 weeks up to week 54 after randomization and every 12 weeks thereafter.

Figure 20: TTP KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

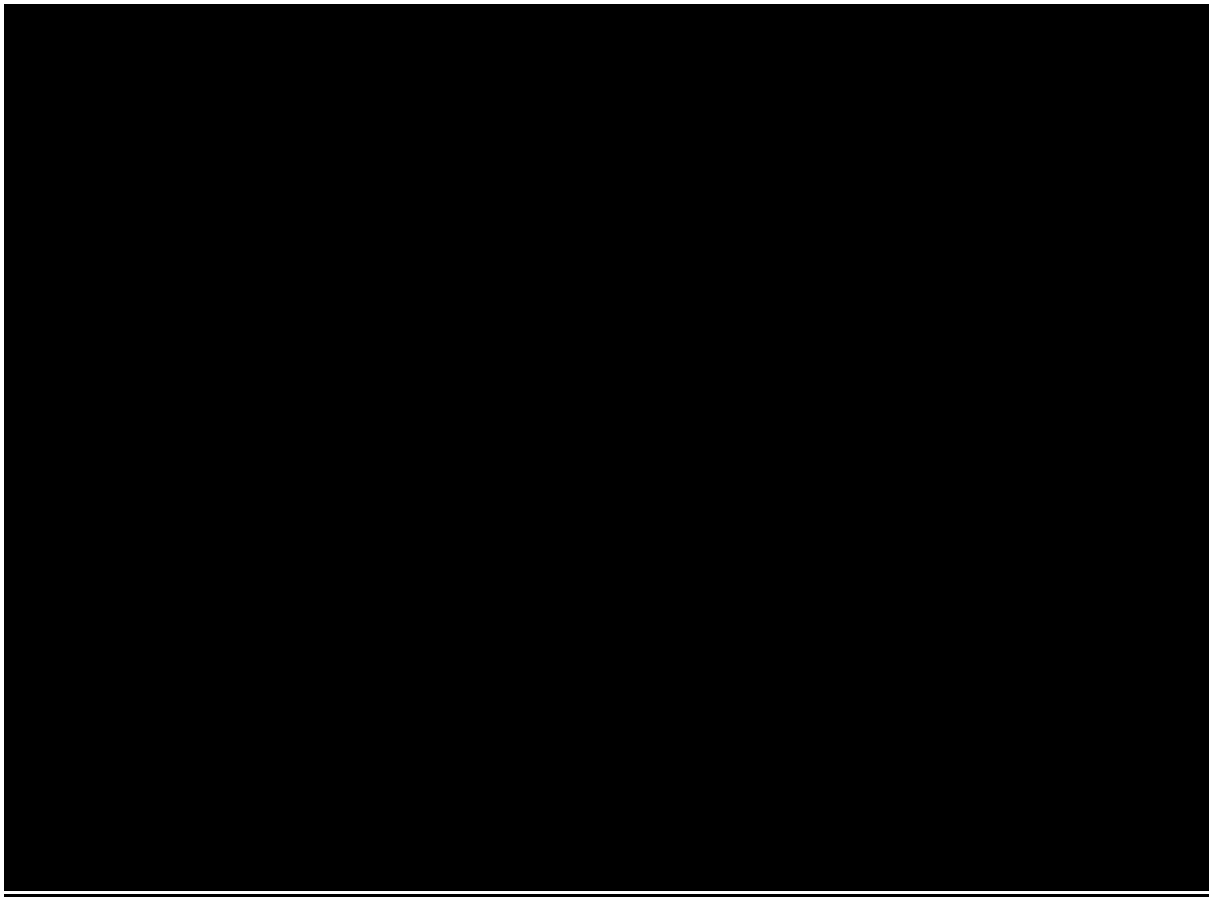
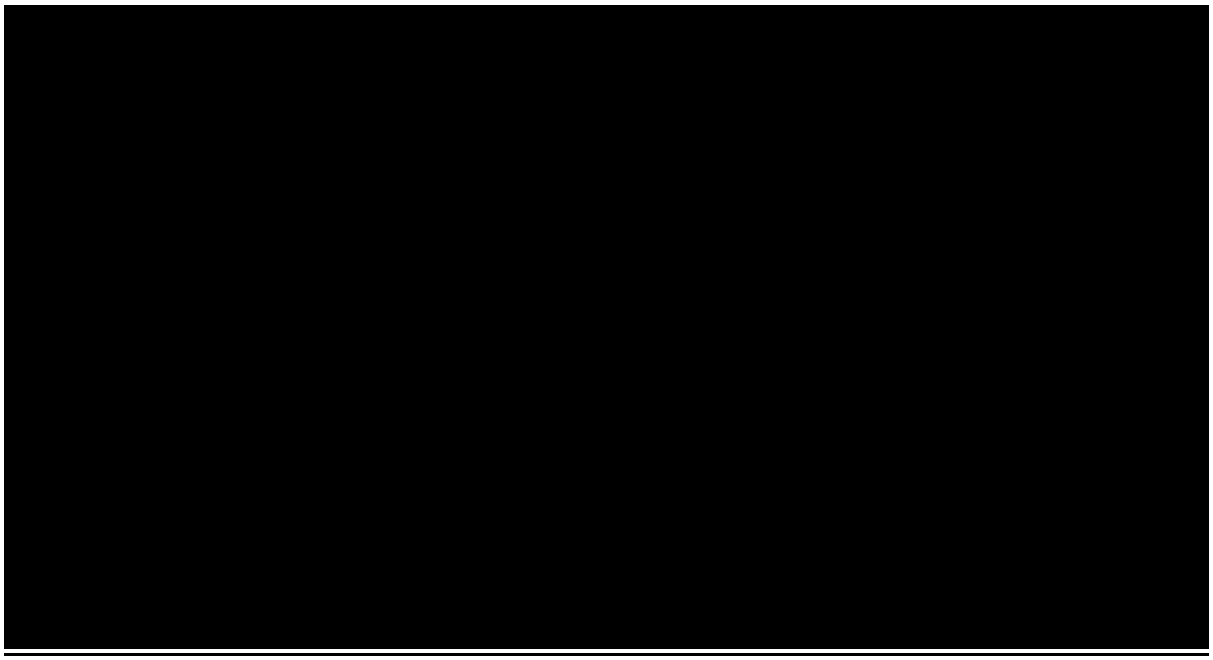


Figure 21: TTP cumulative hazards and log cumulative hazards over time for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826



In KEYNOTE-826, response status was highly prognostic of progression rates (Figure 22). As more patients on PEM+SoC achieve complete or partial response than on SoC alone, and as TTP in patients achieving complete or partial response on PEM+SoC is more favourable than on SoC alone, the difference in TTP will likely increase beyond the trial period. Also, as nearly all patients who did not progress before 90 weeks in the PEM+SoC arm achieved complete or partial response, and as the trends in TTP observed in these patients are favourable, TTP for PEM+SoC will likely keep plateauing beyond the trial period.

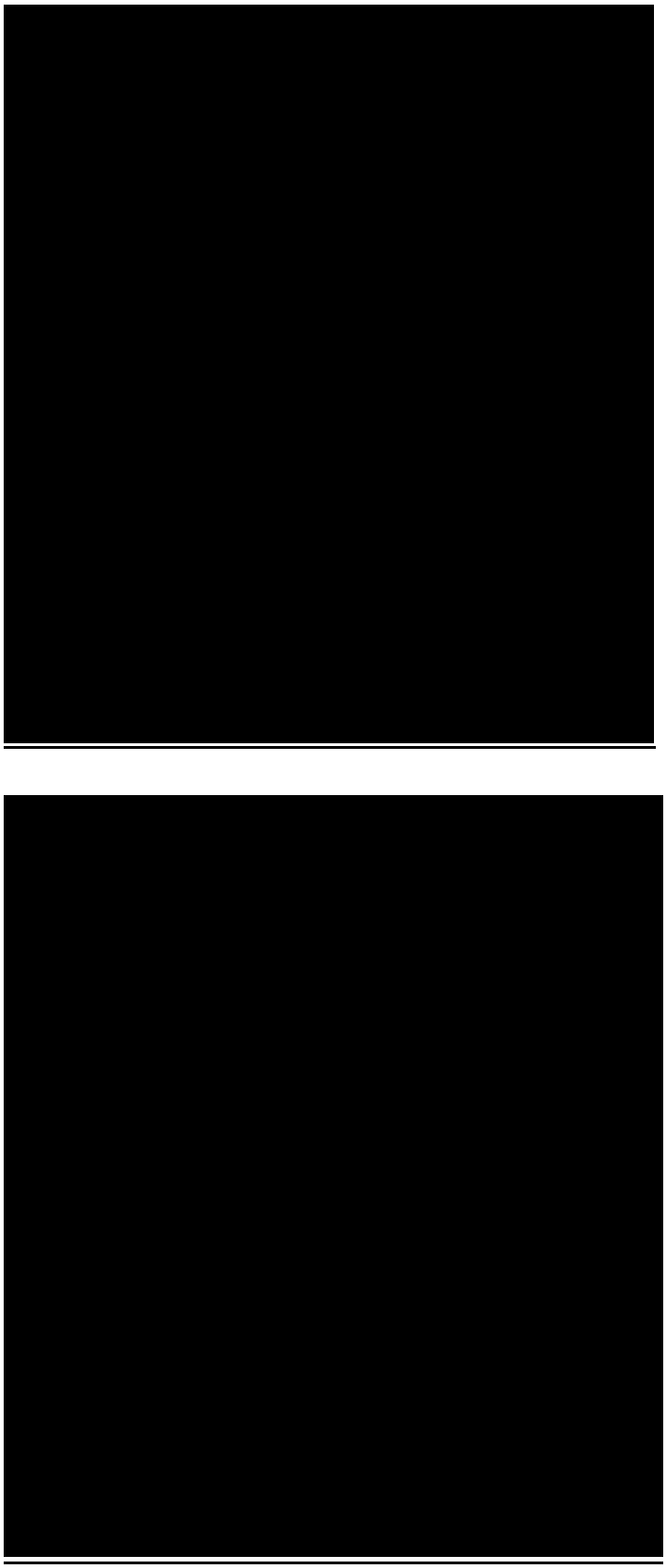
Figure 22: TTP KM data by response status categories for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

B.3.3.2.1 Parametric survival modelling

NICE TSD 14[67] guidance indicates that it is unnecessary to apply a proportional hazards modelling approach when patient-level data are available for both the intervention and comparator. Nonetheless, the proportional hazards assumption was tested for completeness. Visual inspection of the KM data and cumulative hazards and log-cumulative hazard plots over time demonstrated that the proportional hazards assumption does not hold (Appendix Q). Therefore, separate models were fitted to the individual arms of the KEYNOTE-826 trial.

Six standard parametric survival models were fit to the full KM dataset and assessed for suitability (Section B.3.3.1.2). As shown in Figure 23, these models provide a poor visual fit to the KM data for SoC, and an even worse fit for the PEM+SoC arm, where the point of inflection around [redacted] weeks is not reflected. These curves were therefore not considered appropriate, and an assessment of more flexible survival models was required.

Figure 23: Parametric survival models fit the TTP KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826



B.3.3.2.2 Two-piece parametric model selection

Given that the one-piece parametric curves fitted to all TTP KM data did not provide a good visual fit, and given there is a clear inflection point in the observed data and cumulative hazard plots, a number of flexible two-piece models (KM data followed by parametric survival models fit from certain time points onward) were explored:

- Visual assessment of the TTP KM data identified that after [redacted] the data are less stepped and more suitable for parametric survival modelling.
- The smooth spline model fitted to the data demonstrated that the TTP hazards in the PEM+SoC arm increase up to around 37 weeks and sharply decrease thereafter. In the SoC arm, hazards increase rapidly up to 37 weeks; beyond this time point, the hazards decrease and flatten in the longer-term. This suggests that two-piece parametric models are needed.
- For the two-piece models it was preferable to align time points with the completion of tumour imaging assessment schedules for an accurate reflection of TTP, which suggests 37 weeks, 46 weeks or 55 weeks as potentially useful cut-off points (after most patients' fourth, fifth and sixth assessment, respectively).
- Using a relatively late cut-off point was supported by the Chow test statistic, which peaks at 65 weeks for PEM+SoC and at 63 weeks for SoC (Appendix Q).

The number of patients at risk and number of remaining events after each cut-off point is presented in Table 22. Based on remaining event numbers, the 37-week models were considered for the base case analysis, the 46-week models were considered for scenario analyses, and the 55-week models were deemed inappropriate.

Table 22: Patients at risk, remaining events, and KM estimates for TTP for PEM+SoC and SoC at 0, 37, 46, and 60 weeks in the CPS≥1 population of KEYNOTE-826

Treatment arm	Time (weeks)	Patients at risk (n)	Events remaining (n)	KM estimate (%)
PEM+SoC	0	[redacted]	[redacted]	[redacted]
	37	[redacted]	[redacted]	[redacted]
	46	[redacted]	[redacted]	[redacted]
	55	[redacted]	[redacted]	[redacted]
SoC	0	[redacted]	[redacted]	[redacted]
	37	[redacted]	[redacted]	[redacted]
	46	[redacted]	[redacted]	[redacted]
	55	[redacted]	[redacted]	[redacted]
Note: Based on the data of the CPS≥1 population of KEYNOTE-826.				

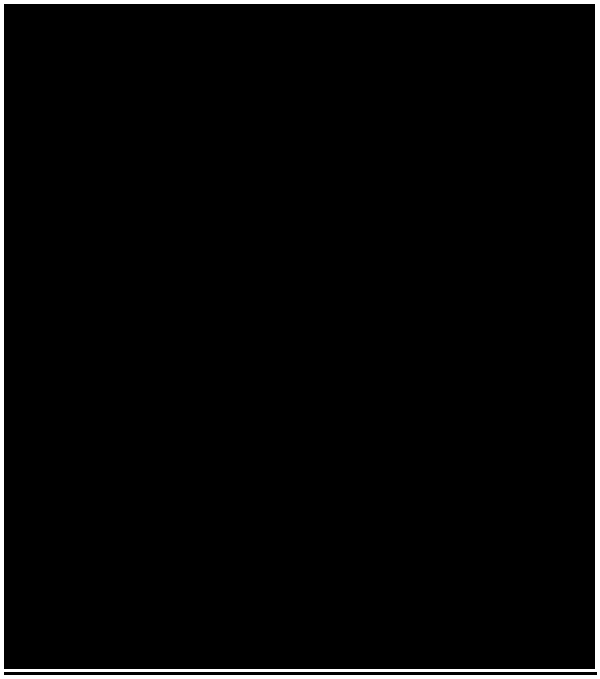
The parametric survival models fit to the KM data beyond 37 weeks are shown in Figure 24. The long-term extrapolations based on the 37-week models are displayed in Figure 25. Data on the statistical fit based on AIC/BIC values are provided in Table 23. The same data on the parametric survival models fit to the KM data beyond 46 weeks are given in Appendix Q.

As described in Section B.3.3.1.2, selection of the parametric distribution to be used in the base case analysis was based on visual fit to the KM data, the clinical plausibility of long-term extrapolations for PEM+SoC and SoC, the clinical plausibility of the hazard functions and the statistical fit to the observed data. The clinical plausibility of long-term extrapolations was assessed systematically against the following criteria:

- TTP curves were deemed inappropriate if, in combination with the base case analysis PPS curve (Section B.3.3.4), they caused modelled 4-year OS in the SoC arm to deviate more than an absolute 5% from expected 4-year OS for SoC based on the GOG 240 trial. Four-year OS based on the GOG 240 trial (assuming bevacizumab as per KEYNOTE-826, which is in line with UK clinical practice) was estimated to be approximately 15.1% (calculations performed to estimate this percentage are provided in Appendix Q).

- TTP curves were also deemed inappropriate if TTP at 50 years exceeded 5% in any of the arms, to avoid the use of curves in which no events take place from a certain time point onward.

Figure 24: TTP KM data and two-piece models (37 weeks), extrapolations to two-years; PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826



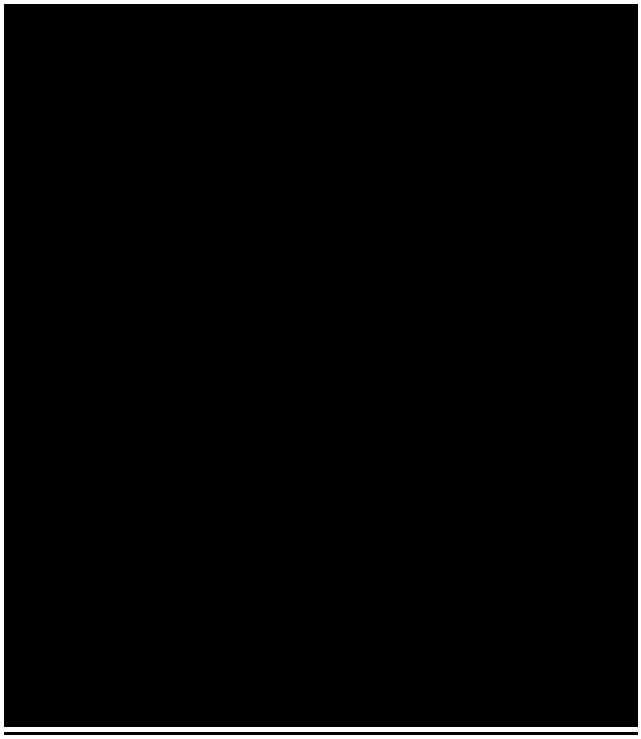
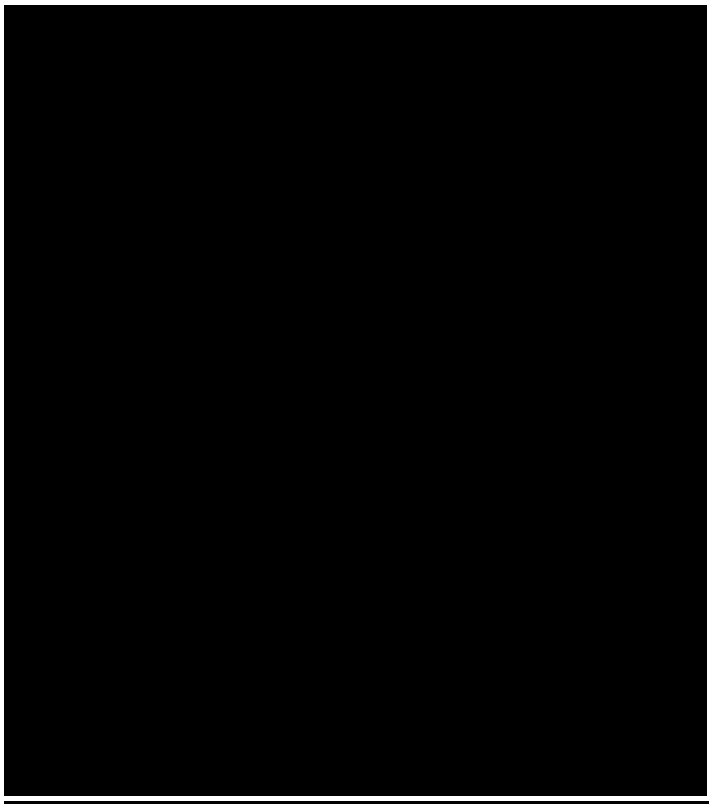


Figure 25: TTP KM data and two-piece models (37 weeks), long-term extrapolations; PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826



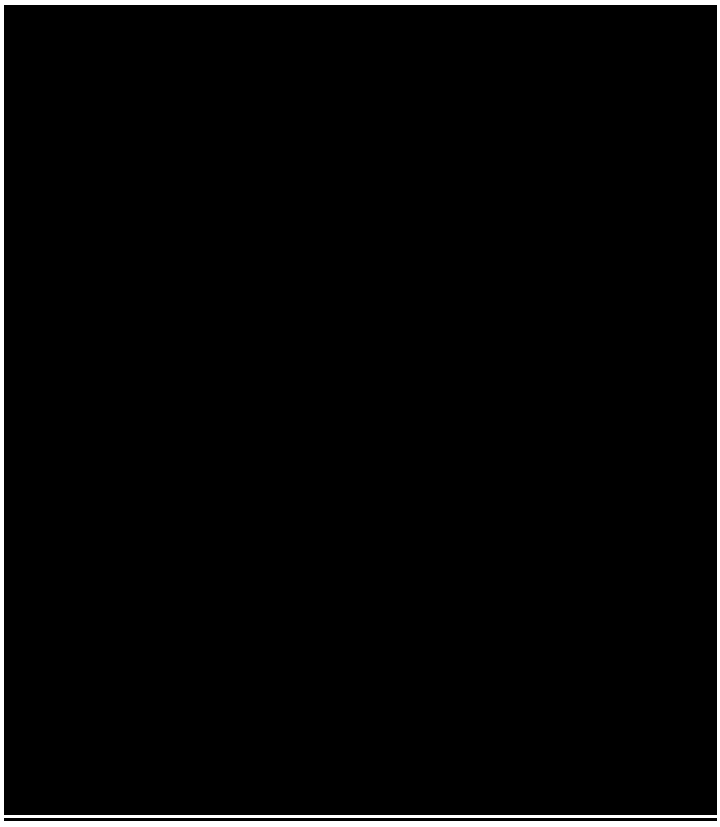


Table 23: Statistical fit of parametric survival models fit to the TTP KM data beyond 37 weeks for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

	PEM+SoC		SoC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Note: Curves were fit to the data of the CPS≥1 population of KEYNOTE-826.
*Best statistical fit based on AIC.

Table 24 summarizes the assessment of all selection criteria, with details provided below. **Considering this overview, the log-logistic models fit to the KM data beyond 37 weeks were used in the base case analysis for the PEM+SoC and SoC arms.** The impact of using the 37-week log-normal models is assessed in a scenario analysis. The impact of using the 46-week two-piece generalized gamma models was also tested in a scenario analysis (a summary of the assessment of all selection criteria for the 46-week models is provided in Appendix Q). TTP as used in the base case analysis is shown in Figure 28.

The visual fit to the KM data

The Gompertz and generalized gamma models provide the best visual fit to the KM data for the PEM+SoC arm (Figure 24). All other models underpredict the last section of the KM data for PEM+SoC and may underestimate the long-term TTP outcomes for patients treated with pembrolizumab. The exponential model provides a poor visual fit to the KM data for pembrolizumab and was therefore discarded. All parametric distributions provide a good visual fit to the KM data for the SoC arm of KEYNOTE-826.

Clinical plausibility of long-term extrapolations

It was possible to discard several distributions based on the PEM+SoC extrapolations. With the Gompertz or generalized gamma model, a substantial proportion of patients treated with PEM+SoC will never progress, which is deemed too optimistic. These distributions were therefore discarded. For SoC, the exponential and Weibull TTP distributions in combination with the base case PPS distribution resulted in an underestimation of four-year OS by more than 5% compared with the GOG 240 trial data. These distributions were therefore also discarded.

Plausibility of hazard assumptions

The plausibility of the implied hazard functions was assessed against smooth spline estimates of the observed hazards over time (Figure 26 and Figure 27). For PEM+SoC, the smooth spline hazards over time increase until around 37 weeks, followed by a sharp decline thereafter. The hazards associated with the generalized gamma model are most consistent with the smooth spline estimates. Additionally, feedback from UK clinical experts[3] indicated that decreasing hazards beyond the trial period are clinically plausible based on KEYNOTE-826 and experiences with immunotherapy in other advanced cancer indications. The exponential model is unrealistic because the hazard is constant over time. The remaining distributions decrease over time, which follows the direction of the observed hazards, but did not have a particularly good fit to the spline estimates. In the SoC arm, the smooth spline estimates increase until around 37 weeks. Beyond this time point, the hazards decrease and flatten in the longer-term. The hazards associated with the exponential and Weibull distributions are relatively constant over time, which is deemed to be most clinically plausible based on the above. The hazards associated with the other models were deemed to decrease too rapidly over time for most patients treated with SoC.

Figure 26: Hazards over time for the parametric survival models fit to the TTP KM data beyond 37 weeks for PEM+SoC versus smooth spline estimates for the CPS≥1 population of KEYNOTE-826

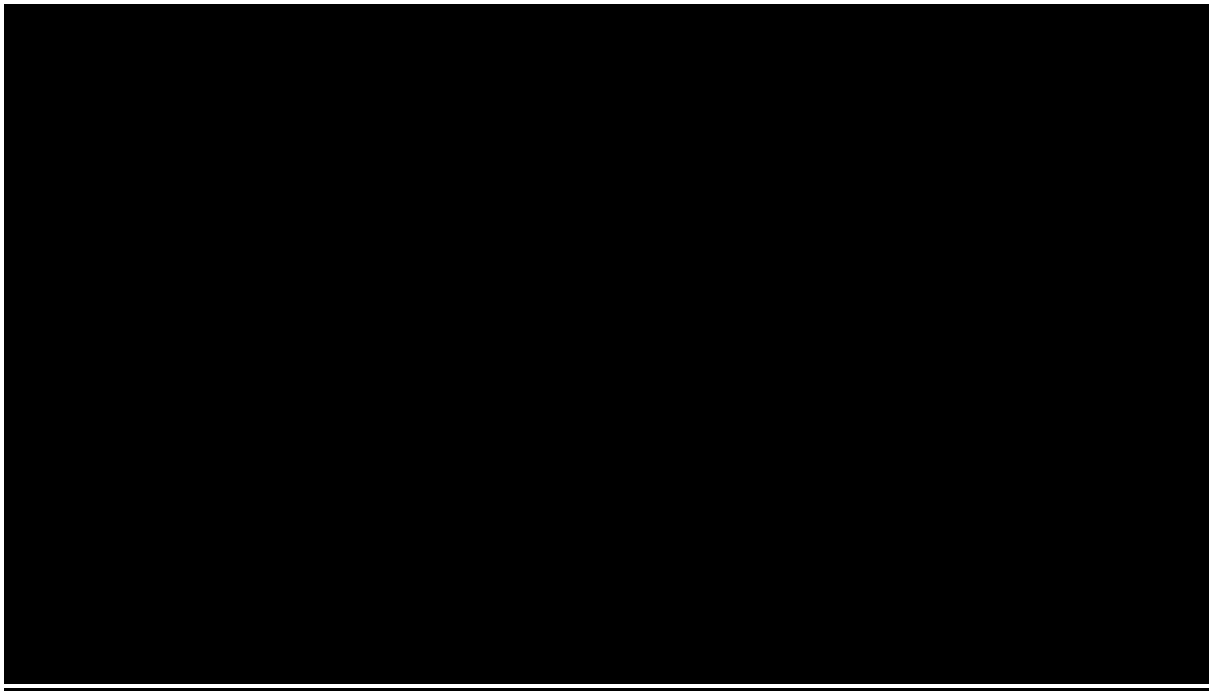


Figure 27: Hazards over time for the parametric survival models fit to the TTP KM data beyond 37 weeks for SoC versus smooth spline estimates for the CPS≥1 population of KEYNOTE-826

The statistical fit to the KM data

The AIC value for the exponential and Weibull models fit to the PEM+SoC data deviate more than 5 points from the AIC value for the Gompertz model, which provides the best statistical fit to the data. The AIC value for all models fit of the SoC data are within 5 points from the AIC value for the exponential model, which provides the best statistical fit to the SoC data.

Table 24: Assessment of parametric survival models fit to the TTP KM data beyond 37 weeks for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

PEM+SoC						
Parametric survival model	**Exponential**	**Weibull**	**Log-normal**	**Log-logistic**	**Gompertz**	**Generalized gamma**
Visual fit to KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term TTP extrapolations – TTP at 50yrs (5% allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Plausibility hazard assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statistical fit to the KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC						
Parametric survival model	**Exponential**	**Weibull**	**Log-normal**	**Log-logistic**	**Gompertz**	**Generalized gamma**
Visual fit to KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term extrapolations – 4-year OS (%) (deviation from 4-year GOG 240 OS (absolute %)) (5% deviation allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term TTP extrapolations – TTP at 50yrs (%) (5% allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Plausibility hazard assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statistical fit to the KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: KM, Kaplan-Meier; PEM+SoC, pembrolizumab combination treatment; SoC, standard of care; TTP, time to progression.

Figure 28: Modelled TTP (base case analysis) for PEM+SoC and SoC in the CPS≥1 population

B.3.3.3 Progression-free survival

The PFS KM data and cumulative hazard plots for PEM+SoC and SoC are presented in Figure 4 and Appendix Q. At the time of the interim analysis of KEYNOTE-826, [redacted] out of 273 CPS≥1 patients treated with PEM+SoC ([redacted]) and [redacted] out of 275 CPS≥1 patients treated with SoC ([redacted]) had progressed or died. Median PFS was [redacted] (95% CI: [redacted]) in the PEM+SoC arm and [redacted] (95% CI: [redacted]) in the SoC arm. Final PFS KM estimates were [redacted] for PEM+SoC and [redacted] for SoC.

As with TTP (Section B.3.3.2), the observed data for PFS show that PEM+SoC is associated with a sustained and increasing benefit over SoC. The rate of progression or death events over time decreases more in the PEM+SoC arm than in the comparator arm, and the KM data are stepped following the schedule for tumour imaging assessments.

B.3.3.3.1 Parametric survival modelling

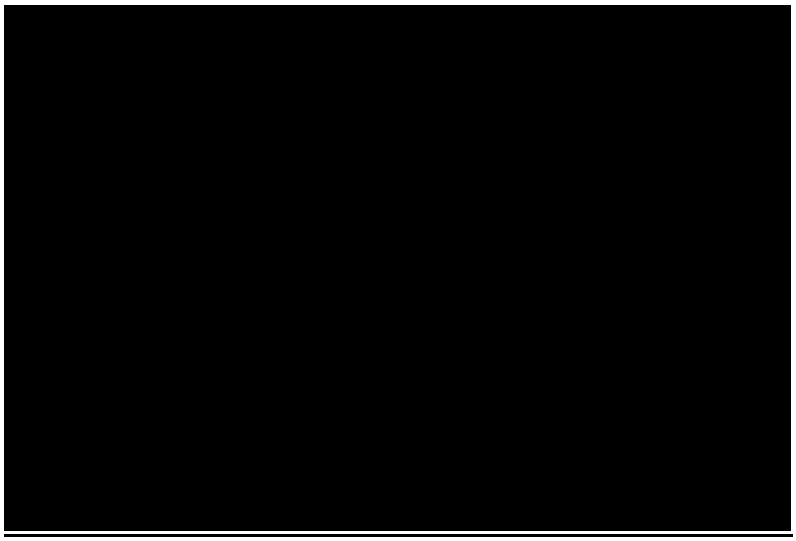
In the cost-effectiveness model, PFS is only used to estimate pre-progression mortality using the formula pre-progression mortality = PFS – TTP. To avoid clinically implausible pre-progression mortality estimates in the cost-effectiveness model, the same parametric survival models are used for PFS and TTP (i.e., using the same time point from which models are fit to the KM data and parametric distribution).

The parametric distributions fit to the observed data for PFS were assessed following the same process described in Section B.3.3.2.1 and Section B.3.3.2.2. Given the inherent similarities between PFS and TTP, similar results would be expected. Flexible survival models are required, outlined further below.

B.3.3.3.2 Two-piece parametric model selection

Appendix Q provides details of the assessment of two-piece parametric models for PFS, following the same process as outlined in Section B.3.3.2.2. The data show that **the log-logistic distribution fit to the PFS KM data beyond 37 weeks is a good option for the base case analysis**. The 37-week log-normal model might be slightly less appropriate as it underestimates PFS based on the GOG 240 trial in advanced cervical cancer by an absolute value of more than 3%, but it is tested in the scenario analysis along with the 46-week generalised gamma curve. PFS as used in the base case analysis is shown in Figure 29.

Figure 29: Modelled PFS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population



B.3.3.4 Post-progression survival

At the time of the first KEYNOTE-826 interim analysis, [redacted] out of the [redacted] patients who progressed on PEM+SoC ([redacted]) and [redacted] out of [redacted] patients who progressed on SoC ([redacted]) subsequently died. Median PPS was [redacted] (95% CI: [redacted]) in the PEM+SoC arm and [redacted] (95% CI: [redacted]) in the SoC arm. Final PPS KM estimates were [redacted] for PEM+SoC and [redacted] for SoC. The PPS KM plots for PEM+SoC and SoC are presented in Figure 30.

Figure 30: PPS KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

[redacted]

Unlike the TTP and PFS curves, the fundamental composition of patients that inform the PPS curves could be different between the PEM+SoC and SoC arms because only those patients who progressed within the duration of follow-up are included in the survival estimates. Analysis of the KEYNOTE-826 data demonstrated a positive association between TTP and PPS in both treatment arms: patient who remain progression-free for longer periods of time are also more likely to have longer post-

progression survival. As at the first interim analysis fewer patients progressed on PEM+SoC than on SoC only, using PPS data from the current interim analysis likely biases against PEM+SoC.

B.3.3.4.1 Parametric survival modelling

Although it is unnecessary to apply a proportional hazards modelling approach when patient-level data are available for both the intervention and comparator, the proportional hazards assumption was tested for completeness (Appendix Q). Based on visual inspection of the KM, statistical testing and cumulative hazards and log-cumulative hazard plots over time (Figure 31), the proportional hazards assumption was not deemed to hold, and it is appropriate to model PPS individually for each arm of the KEYNOTE-826 trial.

Figure 31: PPS cumulative hazards and log cumulative hazards over time for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

Based on the visual assessment of the KM data, cumulative and log-cumulative hazard plots there is not an obvious inflection point in the data for PPS, and the KM data are smooth. Therefore, the standard parametric survival models were deemed appropriate, and it was not necessary to explore other flexible types of models for PPS.

All parametric survival models fit to the KM data are shown in Figure 32 and Figure 33. Data on the statistical fit of the models are given in Table 25.

Figure 32: PPS KM data and parametric survival models for PEM+SoC in the CPS≥1 population of KEYNOTE-826

Figure 33: PPS KM data and parametric survival models for SoC in the CPS≥1 population of KEYNOTE-826

Table 25: Statistical fit of parametric survival models fit to the PPS KM data for PEM+SOC and SOC for the CPS≥1 population of KEYNOTE-826

	PEM+SOC		SOC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

*Best statistical fit based on AIC.
Note: Curves were fit to the data of the CPS≥1 population of KEYNOTE-826.

As with TTP, the parametric distribution used in the base case analysis was based on visual fit to KM data, clinical plausibility of long-term extrapolations for PEM+SoC and SoC, clinical plausibility of hazard functions and statistical fit to the observed data. Similar criteria for clinical plausibility were applied:

- PPS curves were deemed inappropriate if modelled PPS deviated more than an absolute value of 3% from 3-year PPS based on the GOG 240 trial, which was estimated to be 6.1% (assuming bevacizumab use before progression as per KEYNOTE-826) (calculations required to estimate this percentage are provided in Appendix Q).
- PPS curves were deemed inappropriate if PPS at 50 years exceeded 5% in any of the arms, to avoid the use of curves in which no events take place from a certain time point onward.

Table 26 summarizes the selection criteria for the PPS model distribution, with details of the assessment provided below. **The assessment supports the use of the generalised gamma distribution in the base case analysis.** The log-normal and log-logistic distributions as well as assuming equal PPS based on a generalised gamma distribution fitted to pooled PPS data for PEM+SoC and SoC from KEYNOTE-826 are tested in scenario analyses. PPS as used in the base case analysis is shown in Figure 36. As can be seen, PPS in the base case analysis is slightly more favourable for PEM+SoC than for SoC. This is supported by UK clinicians who confirmed that it is appropriate to expect that PPS following treatment

with pembrolizumab would be longer than with SoC alone; to suggest the opposite would be clinically implausible.[3]

The visual fit to the KM data

The only model that provides a poor visual fit to the KM data for PEM+SoC is the exponential model (Figure 32). All distributions provide a good visual fit to the KM data for SoC (Figure 33).

The clinical plausibility of long-term extrapolations

The exponential, Weibull and Gompertz models for SoC result in an underestimation of 3-year PPS based on the GOG 240 trial and were deemed to be inappropriate for the analysis.

The clinical plausibility of the hazard assumptions

For PEM+SoC, towards the end of follow up, the smooth spline estimates decline over time, as do the hazards associated with the log-logistic, log-normal and generalized gamma models (Figure 34). The hazard associated with the exponential model is constant. The hazards associated with the other models increase over time. For SoC, towards the end of follow up, the smooth spline estimates are constant over time, as is the hazard associated with the exponential model (Figure 35). The hazards associated with the generalized gamma model decline slightly. The hazards associated with the other models either decline or increase substantially.

Figure 34: Hazards over time for the parametric survival models fit to the PPS KM data beyond 37 weeks for PEM+SoC versus smooth spline estimates

Figure 35: Hazards over time for the parametric survival models fit to the PPS KM data beyond 37 weeks for SoC versus smooth spline estimates

The statistical fit to the KM data

The AIC values for the exponential, Weibull and Gompertz models fit to the PEM+SoC data deviate more than 5 points from the AIC value for the log-normal model, which provides the best statistical fit to the data. The AIC values for the exponential and Gompertz models fit to the SoC data deviate more than 5 points from the AIC value for the log-normal model, which provides the best statistical fit to the data.

Table 26: Assessment of parametric survival models fit to the PPS KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

PEM + SoC						
Parametric survival model	**Exponential**	**Weibull**	**Log-normal**	**Log-logistic**	**Gompertz**	**Generalized gamma**
Visual fit to KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term PPS – PPS at 50yrs (5% allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility hazard assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statistical fit to the KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC						
Parametric survival model	**Exponential**	**Weibull**	**Log-normal**	**Log-logistic**	**Gompertz**	**Generalized gamma**
Visual fit to KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term PPS extrapolations – 3-year PPS (%) (deviation from 3-year GOG 240 PPS (absolute %)) (3% deviation allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility long-term PPS – PPS at 50yrs (%) (5% allowed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical plausibility hazard assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statistical fit to the KM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: KM, Kaplan-Meier; PEM+SoC, pembrolizumab combination treatment; PPS, post-progression survival; SoC, standard of care.

Figure 36: Modelled PPS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population

B.3.3.5 Summary of base case modelling approach and scenario analysis

A comprehensive assessment of appropriate survival models for TTP, PFS and PPS was conducted (Section B.3.3.2, Section B.3.3.3 and Section B.3.3.4, 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. The most appropriate and clinically plausible models for TTP, PFS and PPS were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses. Additionally, we performed a 'pessimistic' scenario analysis in which the averages of the 37-week log-logistic and 37-week Weibull models were used to model TTP and PFS. Models used in the base case and scenarios are summarised in Table 27.

Table 27: Summary of TTP, PFS and PPS models selected for economic analysis (PEM+SoC and SoC)

	Treatment arm	TTP	PFS	PPS
Base case	PEM+SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Generalised gamma
	SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Generalised gamma
Efficacy Scenario 1	PEM+SoC	37-wk KM + Log-normal	37-wk KM + Log-normal	Generalised gamma
	SoC	37-wk KM + Log-normal	37-wk KM + Log-normal	Generalised gamma
Efficacy Scenario 2	PEM+SoC	46-wk KM + Generalised gamma	46-wk KM + Generalised gamma	Generalised gamma
	SoC	46-wk KM + Generalised gamma	46-wk KM + Generalised gamma	Generalised gamma
Efficacy Scenario 3	PEM+SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Log-normal
	SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Log-normal
Efficacy Scenario 4	PEM+SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Log-logistic
	SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Log-logistic
Efficacy Scenario 5	PEM+SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Generalised gamma (pooled data)
	SoC	37-wk KM + Log-logistic	37-wk KM + Log-logistic	Generalised gamma (pooled data)
Scenario 6	PEM+SoC	Average of 37-wk KM + Log-logistic and 37-wk Weibull	Average of 37-wk KM + Log-logistic and 37-wk Weibull	Generalised gamma
	SoC	Average of 37-wk KM + Log-logistic and 37-wk Weibull	Average of 37-wk KM + Log-logistic and 37-wk Weibull	Generalised gamma

Note: Curves were fit to the data of the CPS≥1 population of KEYNOTE-826.

Additionally, Table 28 provides an overview of modelled 5-year and 10-year OS for PEM+SoC and SoC for the base case analysis and the scenario analyses. As can be seen, 5-year OS for pembrolizumab ranges between [redacted] and 10-year OS ranges between [redacted]. Five-year OS for SoC ranges between [redacted] and 10-year OS ranges between [redacted]. The difference

between 5-year survival between PEM+SoC and SoC ranges between [redacted] and the difference in 10-year survival ranges between [redacted]. The differences between 5-year and 10-year survival between PEM+SoC in the base case analyses are [redacted], respectively, and are conservative compared with the differences in most other plausible scenarios. The only scenario that is substantially less favourable is the 'pessimistic' scenario.

Based on OS data for pembrolizumab stratified by response status categories at baseline (Figure 19), it appears that the 5-year and 10-year base case OS extrapolations, which are [redacted], are plausible. Many patients treated with PEM+SoC achieve complete or partial response ([redacted] of patients with CPS>1 where response data were available, respectively [Figure 19]). These patients follow the top two curves in the figure, which are associated with favourable OS over time, and which show evidence of plateauing. At 104 weeks, beyond which curves plateau, OS is [redacted] among complete and partial responders on PEM+SoC, respectively (Table 28). Of all patients alive at 104 weeks in the PEM+SoC arm, the vast majority ([redacted]) had complete or partial response ([redacted], respectively [calculated as product of % responding and % surviving in each response category]), so it is likely that OS for the whole CPS≥1 population will plateau beyond the follow-up duration of the trial. It is noteworthy that the complete response (CR) group in the pembrolizumab arm have an extremely slow OS event-rate. The better OS among CR patients in the pembrolizumab group is unsurprising, given the duration of response outcomes from the clinical trial and offers some supportive evidence that the good outcomes seen in the within-trial period might continue.

Table 28: Overall Survival KM Estimators by Response Category

Response Category	Survival % at 2yrs	Obs vs. Est based	Treatment
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Modelled 5-year and 10-year OS for all combinations of TTP and PPS models used in the base case analysis and scenario analyses (PEM+SoC and SoC)

Model used for TTP+PFS	Model used for PPS	5-year OS			10-year OS		
		Pembro	SoC	Difference	Pembro	SoC	Difference
37wk, log-logistic	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37wk, log-normal	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46wk, generalized gamma	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37wk, log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37wk, log-logistic	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37wk, log-logistic	Generalized gamma (pooled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average of 37-wk KM + Log-logistic and 37-wk Weibull	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Curves were fit to the data of the CPS≥1 population of KEYNOTE-826.

B.3.4. Measurement and valuation of health effects

The daily quality of life is severely impacted for women with persistent, recurrent, or metastatic cervical cancer (Section B.1.3.3). Common physical symptoms associated with aggressive disease and disease progression include pain, irregular vaginal bleeding, postcoital bleeding and changes in vaginal discharge; the negative psychological impact of cervical cancer on emotional and mental well-being is also a substantial contributor to the burden of illness. As such, there is a substantial unmet need for tolerable and effective treatment options for patients with advanced cervical cancer.

Pembrolizumab in combination with chemotherapy with or without bevacizumab is the first and only immune-oncology (IO) treatment option to demonstrate superior efficacy based on Phase III clinical trial evidence in patients with persistent, recurrent, or metastatic cervical cancer in the first-line setting. With no new treatment options becoming available over the past decade, outcomes remain poor for these patients (Section B.1.3). In line with the NICE reference case[70], and to incorporate the important impact on health-related quality of life (HRQL) described above, EuroQol-5 Dimension[79] (EQ-5D) data collected from the KEYNOTE-826 trial were analysed and used in the economic model.

As is common in previous NICE appraisals of pembrolizumab, a utility approach based on time-to-death (TTD) is applied in the economic model to incorporate the negative impact of disease progression on patients' HRQL over a lifetime time horizon. An alternative approach using HSUV is explored in a scenario analysis. Additionally, decrements to HRQL due to AEs and natural decline of age-related HRQL were considered in line with the NICE reference case.[70]

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

HRQL data were collected in the KEYNOTE-826 trial. EQ-5D-5L data were collected on Day 1 of Cycles 1 to 14, every other cycle thereafter, at end of treatment, and 30 days after the last treatment or before the initiation of a new anti-cancer treatment, whichever came first. The analyses of the EQ-5D-5L utilities were based on the Full Analysis Set (FAS) population. The total analysis population with a CPS≥1 consisted of [redacted] patients, resulting in a combined total of [redacted] EQ-5D measurements. The

population comprised of patients who were randomized (n = 548), received a study treatment (n=[redacted]), and completed at least one EQ-5D-5L questionnaire (n=[redacted]).

B.3.4.2 Mapping

Consistent with the position statement by the National Institute for Health and Care Excellence (NICE)[77] the EQ-5D-5L data from KEYNOTE-826 were mapped onto the 3L scale using the algorithm developed by van Hout et al. (2012)[80]

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

No studies relevant to the UK setting were identified in a systematic search for HRQL studies in patients with persistent, recurrent, or metastatic cervical cancer (see details in Appendix G). The KEYNOTE-826 trial remains the best source of evidence for use in the economic model.

B.3.4.4 Adverse reactions

The impact of AEs is incorporated into the economic model, consistent with the NICE reference case.[70] As a commonly accepted approach, Grade 3+ AEs that occurred in at least 5% of patients in either arm of KEYNOTE-826 were included. Adverse events were accounted for in the regression models that were developed to calculate health state utilities.

Frequencies of Grade 3+ AEs that occurred in at least 5% of patients, in either arm, are presented in Table 29. Frequencies are given in absolute numbers, proportions, and risks per week on treatment (which were derived by dividing the absolute numbers by the total time on treatment in the treatment arms). The average duration of each of these serious AEs is presented in Table 30.

Table 30: Included adverse event risks, based on data from CPS≥1 patients in KEYNOTE-826[73]

Adverse Event	PEM+SoC (n=273)		SoC n=275)	
	N (%)	Risk (n/week)	N (%)	Risk (n/week)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Key: KN-826, KEYNOTE-826; PEM+SoC, pembrolizumab combination treatment; SoC, standard of care.				

Table 31: Duration of adverse events, based on data from CPS≥1 patients in KEYNOTE-826[73]

Adverse Event	PEM+SoC *(duration in days)*	SoC *(duration in days)*
Anaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Key: KN-826, KEYNOTE-826; PEM+SoC, pembrolizumab combination treatment; SoC, standard of care; ToT, time on treatment. **Note:** Mean time on treatment for pembrolizumab is [redacted] days and [redacted] days for SoC.		

To calculate the total QALYs lost due to AEs, the disutility per AE is multiplied with the duration of the AE and the risk of the AE per week. This is then applied to the proportion of patients on treatment each cycle. The coefficient from the regression model that estimates the effect of grade 3+ AE is applied for each AE.

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

Regression models were fitted to utility values based on [redacted] EQ-5D-5L measurements collected in [redacted] patients enrolled in KEYNOTE-826, which were mapped to EQ-5D-3L using the van Hout et al. (2012)[80] algorithm to which the UK tariff was applied.

Historically, it has been common in health-economic models for oncological interventions to model utilities based on whether a patient has had a progression event or not. However, in immune-oncology, progression based methods may be less appropriate. Patients may experience a 'pseudo-progression' where the action of treatment is mistaken for disease, additionally, there may be delays between progression and experiencing symptoms, and different types of progression may affect HRQL differently.[81] To avoid some of these issues, and to capture the way in which advanced cervical cancer and pembrolizumab treatment impact patients' quality of life more appropriately, time-to-death utility values have been computed.

Therefore, in the base case, a regression model with time to death categories and grade 3+ AEs as independent variables is applied (Table 31). A regression model incorporating progression status and grade 3+ AEs as independent variables was tested in a scenario analysis (Table 32).

Table 32: Time-to-Death Utility Regression Model for patients with CPS≥1

Fixed effects parameter	Estimate	Standard Error	P-value
Intercept (TTD <30 days, No AEs)	[redacted]	[redacted]	[redacted]
Time to Death 30-90 days	[redacted]	[redacted]	[redacted]
Time to Death 90-180 days	[redacted]	[redacted]	[redacted]
Time to Death 180-360 days	[redacted]	[redacted]	[redacted]
Time to Death ≥ 360 days	[redacted]	[redacted]	[redacted]
Grade3+ AEs	[redacted]	[redacted]	[redacted]
Key: AEs, adverse events; TTD, time to death			

Table 33: Health State Utility Regression Model for patients with CPS≥1

Fixed effects parameter	Estimate	Standard Error	P-value
Intercept	[redacted]	[redacted]	[redacted]
Progression Status (PF vs PD)	[redacted]	[redacted]	[redacted]
Grade3+ AEs	[redacted]	[redacted]	[redacted]
Key: AEs, adverse events; PD, progressed disease; PF, progression-free			

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

A systematic search for published studies that reported cost and healthcare resource use data was conducted; as with the economic and HRQL searches, no studies relevant to the UK were identified (further details are provided in Appendix I).

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

- Drug acquisition costs
- Drug administration costs
- AE costs
- Monitoring costs (e.g. resource use and follow-up)
- Costs of testing
- Subsequent treatment costs
- End-of-life care costs

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Total drug acquisition costs are calculated for patients remaining on treatment in each arm of the model. These costs are calculated per component, based on the time on treatment for each component, dosing regimen, administration schedule, unit cost, and missed doses for each treatment, and accrued for the duration of treatment over the time horizon.

Pembrolizumab: As per the anticipated licence and the administration of pembrolizumab in KEYNOTE-826, the model uses a 200 mg fixed dose of pembrolizumab, administered as 30-minute intravenous infusion every 3 weeks (Q3W). The list price of a 100 mg vial of pembrolizumab is £2,630, resulting in a cost per administration of £5,260.[82]

Cisplatin, carboplatin, paclitaxel and bevacizumab: The dosing schedules are implemented for each treatment (cisplatin, carboplatin, paclitaxel and bevacizumab) as outlined in Table 33. All treatments that are dosed according to weight or body surface area are based on the average mean baseline characteristics obtained from KEYNOTE-826. An exception is made for bevacizumab. As the costs of bevacizumab are significantly higher than for the other agents, wastage of bevacizumab is considered (see below). In KEYNOTE-826, the mean body weight was [redacted] kgs (standard deviation: [redacted] kg) and the mean body surface area was [redacted] m^2 (standard deviation: [redacted] m^2).[73]

Table 34: Dosing schedules used in the analysis

Drug	Dosing per administration	Dosing frequency	Reference
Pembrolizumab	200 mg	Q3W	Keytruda SmPC[83]/ KN-826 Protocol[84]
Paclitaxel	175 mg/m^2	Q3W	Abraxane SmPC[85]/ KN-826 Protocol[84]
Cisplatin	50 mg/m^2	Q3W	KN-826 Protocol[84]
Carboplatin	750 mg	Q3W	KN-826 Protocol[84]
Bevacizumab	15 mg/kg	Q3W	National Cancer Drugs Fund[64]
Key: SmPC, summary of product characteristics; KN-826, KEYNOTE-826			

Cisplatin, 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)[86] where available. The list prices for pembrolizumab and bevacizumab are used based on the Monthly Index of Medical Specialities (MIMS)[82] database. With the recent loss-of-exclusivity of Avastin®, bevacizumab is currently available as various biosimilar entries. Although feedback from clinical experts at the UK advisory board[3] suggested that they would be rarely used, the impact of assuming the cheapest option per ml for bevacizumab (Alymsys®) instead of the

price for Avastin® was tested in a scenario analysis. Unit costs for each treatment included are presented in Table 34.

Table 35: Unit costs for each treatment included in the model

Treatment	Dose per unit	Units per pack	Cost per pack	Source
Pembrolizumab	25 mg/ml	4 ml	£2,630	MIMS 2020[82]
Paclitaxel	6 mg/ml	16.7 ml	£23.06	eMIT 2020[86]
	6 mg/ml	25 ml	£18.88	
	6 mg/ml	50 ml	£39.32	
	6 mg/ml	5 ml	£4.69	
Cisplatin	1 mg/ml	100 ml	£6.66	eMIT 2020[86]
	1 mg/ml	10 ml	£2.64	
	1 mg/ml	50 ml	£4.12	
Carboplatin	10 mg/ml	15 ml	£11.14	eMIT 2020[86]
	10 mg/ml	45 ml	£27.90	
	10 mg/ml	5 ml	£3.75	
	10 mg/ml	60 ml	£28.22	
Avastin (*originator*)	25 mg/ml	4 ml	£242.66	MIMS 2020[82]
	25 mg/ml	16 ml	£924.40	
Alymsys (*biosimilar*)	25 mg/ml	4 ml	£205.55	MIMS 2020[82]
	25 mg/ml	16 ml	£810.10	
Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities				

In the base case analysis, missed doses were considered using the proportion of administered versus expected doses as observed in KEYNOTE-826[87] (Table 35). These observed missed doses were applied to ensure that the costs modelled are explicitly related to the efficacy data used in the model. Also, doses are expected to be missed in clinical practice.

Table 36: Missed doses registered for each component under study[87]

Proportion of actual vs. expected number of cycles			
	Mean	**Standard Deviation**	**n**
PEM			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
PEM+SoC			
Paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]

To account for the wastage of medication occurring when tailoring the dosing of bevacizumab to the body weight of the patient, wastage calculations are implemented using the standard method of moments.[88] An overview of the dosing distribution for bevacizumab treatment is provided in Figure 37. The impact of not including wastage (vial sharing) is tested in a scenario analysis.

The total costs per administration of each treatment are summarized in Table 36. For combination regimens with platinum chemotherapy and bevacizumab, costs were weighted by the relevant proportions of patients receiving each treatment agent in KEYNOTE-826, as presented in Table 21.

Figure 37: Dosing distribution for treatment with bevacizumab

[redacted]

Table 37: Drug acquisition costs per treatment per administration in the model

Treatment arm	Drug	Total cost per administration	Administration Frequency
PEM+SoC	Pembrolizumab	[redacted]	Q3W
	Paclitaxel	[redacted]	
	Cisplatin	[redacted]	
	Carboplatin	[redacted]	
	Bevacizumab	[redacted]	
SoC	Paclitaxel	[redacted]	Q3W
	Cisplatin	[redacted]	
	Carboplatin	[redacted]	
	Bevacizumab	[redacted]	

Key: KN-826, KEYNOTE-826; N/A, not applicable; SoC, standard of care
Note: calculations are based on list price

B.3.5.1.2 Drug administration costs

Treatment administration costs are accrued for patients for the duration of treatment in each arm of the model. All treatments included are administered intravenously. It is assumed that costs are assigned only once for treatments requiring multiple IV administrations on the same day. As this assumption applies to both arms in the economic model, it is expected to have minimal impact on the results.

A unit cost of £329.75 is used when multiple treatments are administered (NHS reference costs SB13Z: 'deliver complex parenteral chemotherapy').[89] When only one treatment is administered that requires an hour or less, a unit cost of £295.92 is used (NHS reference costs SB12Z: 'deliver simple parenteral chemotherapy').

B.3.5.1.3 Treatment duration

Drug acquisition and drug administration costs are applied to the proportion of patients on treatment in each treatment cycle. The time on treatment (ToT) data from KEYNOTE-826 were sufficiently long to account for the maximum treatment duration of all considered treatments in England. As pembrolizumab has a stopping rule in place and SoC is given for a limited number of cycles (Table 37), the Kaplan–Meier data were sufficient to capture the proportion of patients on treatment each cycle. The ToT Kaplan–Meier data for pembrolizumab and SoC are presented in Figure 38.

A scenario is included where the duration of bevacizumab is not limited to 6 cycles but to 2 years. While patients in KEYNOTE-826 were permitted to continue bevacizumab monotherapy maintenance beyond completion of platinum-based chemotherapy, bevacizumab is only allowed in conjunction with chemotherapy in the UK. As this occurred to a similar extent in both arms of the trial (median [redacted] treatment cycles in the PEM+SoC arm and [redacted] treatment cycles in the SoC arm), the impact on the cost-effectiveness of PEM+SoC is likely to be small. In KEYNOTE-826, pembrolizumab combination treatment is effective versus SoC irrespective of the use of (any) bevacizumab.[1] UK clinical experts also confirmed that that there is no published data on the benefit of continuing bevacizumab in the maintenance setting.[3]

Table 38: Stopping rules in UK clinical practice

Drug	Maximum number of treatment cycles	Reference
Pembrolizumab	35 (~2 years)	Keytruda SmPC[83]
Paclitaxel	6	BGCS Guidelines[2]
Cisplatin	6	
Carboplatin	6	
Bevacizumab	6	Cancer Drugs Fund[64] BGCS Guidelines[2]
Key: BGCS, British Gynaecological Cancer Society; SmPC, summary of product characteristics		

Figure 38: Time on treatment Kaplan–Meier data for PEM+SoC and SoC in the CPS≥1 population from KN-826

[redacted]

B.3.5.2 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 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 2019/20[89]) and recent technology appraisals. A summary is presented in Table 38.

The costs associated with AEs per model cycle are calculated by multiplying the proportion of patients who receive at least one treatment that treatment cycle (Section B.3.5.1) by the risks for AEs per week on treatment (Table 29) and the unit costs per AE (Table 38).

Table 39: Adverse event costs applied in the *de novo* CE model

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
Anaemia	£2,700.00	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Neutrophil count decreased	£672.40	Assumed same as neutropenia	N/A
Neutropenia	£672.40	Weighted average of mean costs for HRG code WJ11Z: Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	NHS reference costs 2019/20[89]
Hypertension	£639.00	EB04Z, Hypertension, HRG	NHS reference costs 2019/20[89]
Thrombocytopenia	£782.31	TA600: Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small cell lung cancer (2018)	TA600: Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer
Febrile neutropenia	£7,045.00	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2017-2018 prices using the Hospital & community health services (HCHS) index	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Platelet count decreased	£672.40	Assumed same as neutropenia.	N/A

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
White blood cell count decreased	£1,515.42	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay	NHS reference costs 2019/20[89]
Key: HRG, Healthcare Resource Groups; SE, standard error.			

B.3.5.3 Monitoring costs

Costs associated with ongoing disease management, monitoring and patient follow-up are included in the economic model, in line with the NICE reference case.[70] Healthcare resources were specific to each health state (i.e. progression-free or progressed disease) which means that different costs are accrued in the 'progression free' and 'progressed disease' health states. Costs were applied to each resource and accrued according to the time spent in each health state. Relevant unit costs were sourced from the NHS reference cost[89] documentation and reflect 2019–2020 prices. It is assumed that disease monitoring is the same regardless of treatment arm. Table 39 summarizes the expected usage of each resource per month. Estimates are based on UK clinician input.[3] Resource use in the progression-free health state is differentiated based on time spent progression-free and resource use in the progressed disease health state is differentiated based on and being on/off subsequent treatment. Unit costs, which are presented in Table 40, were multiplied by the frequency of each resource to generate the total disease monitoring cost per month, which was then transformed to a cost per cycle (week) accrued over the model time horizon. Monitoring costs in the progressed disease health state are applied as a one-off cost upon progression, for the proportion of patients receiving a subsequent treatment ([redacted]).[3] Monitoring costs in progressed patients who do not receive subsequent treatment are expected to be covered by end-of-life care.

Table 40: Frequency of resource use applied in the *de novo* CE model

	Progression-free			Progressed disease	
Resource	**Year 1**	**Year 2**	**Year 3+**	**On Tx**	**Off Tx**
Consultant outpatient appointment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CT, computerized tomography; Off Tx, off treatment; On Tx, on treatment;

Table 41: Unit costs associated with resources applied in the *de novo* CE model

Resource	Unit cost	Description/Reference
Consultant outpatient appointment	£131.03	2019/20 NHS reference costs: outpatient attendance 503; gynaecological oncology non-admitted face-to-face outpatient attendance, weighted average consultant led and non-consultant led.[89]
CT scan	£107.34	2019/20 NHS reference costs: Weighted average of outpatient computerized tomography scans of one and two areas with and without contrast (RD20A, RD21A, RD22Z)[89]

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Cost of testing

PD-L1 testing is incorporated into the model as there are currently no treatments available in persistent, recurrent, or metastatic cervical cancer in routine commissioning in the UK which would require testing for PD-L1. The calculations of the diagnostic testing costs are informed by the estimated proportion of patients who have a CPS score greater than or equal to 1 (CPS≥1), the proportion of patients who receive PD-L1 testing in routine clinical practice, and the unit costs of the test (Table 41). This predicts the total average cost required to detect one patient eligible for treatment with PEM+SoC.

Table 42: Diagnostic testing costs applied in the *de novo* CE model

Input	Value	Reference
Proportion of patients being tested for PD-L1 in current clinical practice	0%	Assumption - No other targeted treatments available
Proportion of patients testing positive for PD-L1	89%	KN-826[73]
Cost of testing for PD-L1	£44.68	NHS reference costs 2019/2020, DAPS02 - Histopathology and histology[89]
Total testing cost per patient receiving treatment with Pembrolizumab	**£50.32**	

B.3.5.4.2 Subsequent treatment costs

The costs associated with subsequent treatments are included in the economic model, based on estimates of UK clinicians during an advisory board.[3] A one-off cost is calculated and applied at the point of progressing, based on the proportion of patients receiving subsequent therapies and the average observed duration of each treatment based on analysis of the patient-level data from KEYNOTE-826.

Clinicians estimated that approximately [redacted] of the patients would receive second-line treatment. Approximately [redacted] of patients would be treated with paclitaxel monotherapy and [redacted], [redacted] and [redacted] would receive doxorubicin, fluorouracil (5FU), or cisplatin + gemcitabine. This mix of treatments was different from what was seen in KEYNOTE-826, but clinicians did not expect this to affect outcomes as no subsequent treatment regimen is expected to be associated with a meaningful survival benefit. The proportions of patients receiving each subsequent treatment and the mean duration of the subsequent treatments are given in Table 42.

The dosing schedules and unit costs of therapies also used in KN-826 are the same as those previously described in Section B.3.5.1. Gemcitabine is administered as a 1000 mg/m² infusion, twice every three weeks; doxorubicin is administered as a 50 mg/ m² infusion, once every four weeks; and fluorouracil is administered as an infusion at 15 mg/kg once every week. The total drug acquisition cost per administration for subsequent therapies is detailed in Table 43.

Table 43: Subsequent treatments modelled

Subsequent treatment (KEYNOTE-826)	PEM + SoC		SoC	
	Proportion of patients	Mean treatment duration (days)	Proportion of patients	Mean treatment duration (days)
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Key: KN-826, KEYNOTE-826; NA, not applicable; SoC, standard of care. **Source:** Clinical advisory board (rates), KN-826 (duration). **Note:** when the standard error is not reported, 10% from the mean is assumed				

Table 44: Drug acquisition costs of subsequent treatments

Subsequent treatment	Acquisition cost
Paclitaxel	[redacted]
Doxorubicin	[redacted]
5FU	[redacted]
Cisplatin + Gemcitabine	[redacted]
Total one-off cost PEM + SoC	[redacted]
Total one-off cost SoC	[redacted]

B.3.5.4.3 Terminal care costs

The model includes the option to apply a one-off end-of-life cost to patients at the point of death to reflect terminal care costs. The end-of-life cost was calculated based on the average cost derived from the Round et al. (2015)[90] modelling study, which estimated the cost of cancer care during the final phases of life. The study presented the end-of-life costs related to health, social, charity, and informal care service for breast, colorectal, lung and prostate cancer individually in England and Wales. In the model, the mean health care costs across these different cancer types are used and inflated to 2019–2020 costs using indices from PSSRU[91], resulting in a cost of £4,611.54 per patient upon death.

B.3.5.5 Summary of base-case analysis inputs

A list of all model inputs and the measurement of uncertainty for ranges incorporated into the sensitivity analysis is provided in Appendix Q.5.

B.3.5.6 Assumptions

Topic	Assumption	Justification/Reason
Perspective and discounting	NHS and PSS payer perspective with costs and QALYs discounted by 3.5% annually.	In line with the NICE reference case[70].
Population	All patients with a CPS ≥ 1.	In line with the anticipated EMA/MHRA license.
Time horizon	Equal to 50 years.	50 years was deemed sufficiently long to reflect lifetime, as patients in the CPS≥1 population of KN-826 were on average [redacted] years old.[73]
Half-cycle correction	Not applied.	The model cycle is sufficiently short (one week) that half-cycle correction was not deemed necessary.
Model structure	State transition model	Full detail provided in Section B.3.2.2.
Definition of progression	Investigator assessed progression based on RECIST 1.1.	This is the primary outcome of KN-826 and most in line with expected UK clinical practice.[73]
Subsequent treatments	Based on expected UK clinical practice.	Subsequent treatments given in KN-826 are not fully reflective of the expected use in clinical practice in the UK.
Adverse events	Grade 3+ adverse events, affecting ≥5% of patients in either arm of KN-826 are included.	Commonly accepted approach in previous health technology appraisals.
Utilities	Time-to-death utilities applied based on KN-826 CPS≥1 population data. EQ-5D-5L mapped to 3L (UK tariff). Age adjustment applied based on UK population data. Adverse event disutilities applied based on findings in KN-826.	Full detail provided in section B.3.4.5.
Dosing and maximum treatment duration	Actual received dose as per KN-826. Pembrolizumab is given up to 35	Based on SmPCs, CDF guidance, and clinical guidelines.[64, 83, 92]

Topic	Assumption	Justification/Reason
	treatment cycles (~2 years) and other treatment options for a maximum of 6 treatment cycles.	
Bevacizumab costing	100% use of Avastin (originator)	Confirmed by clinical KOLs.[3]
Testing costs	Included	CPS≥1 testing is not included in current clinical practice as no other PD-L1 inhibitors are available for this population.

B.3.6. Base-case results

Table 44 presents the base-case results for PEM+SoC versus SoC. In patients with persistent, recurrent, or metastatic cervical cancer, treatment with pembrolizumab results in a mean increase in life years (LYs) of 2.80 and a mean increase in quality-adjusted life years (QALYs) of [redacted] when compared with SoC alone in England. The total QALYs accrued in the PEM+SoC arm is [redacted], while it is [redacted] for SoC. Similarly, the total LYs accrued in the PEM+SoC arm is 5.31 compared to 2.51 LYs for SoC. The base case ICER of PEM+SoC versus SoC is [redacted] per QALY gained, based on list prices. Section B.3.11 includes the ICERs incorporating the CAA currently agreed for pembrolizumab, which show that PEM+SoC is highly likely be cost-effective when the confidential discount is applied. Disaggregated results of the base case analysis are presented in Appendix J.

Table 45: Base-case results, PEM+SoC versus SoC – list prices

Treatment	Totals per treatment arm			Incremental results			ICER (£/QALY)
	LYs	QALYs	Costs	LYs	QALYs	Costs	
SoC	2.51	[redacted]	[redacted]	2.80	[redacted]	[redacted]	[redacted]
PEM+SoC	5.31	[redacted]	[redacted]				
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

B.3.7. Sensitivity analyses

B.3.7.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted where all inputs were varied simultaneously over 5,000 iterations, based on reported uncertainty values and appropriate distributional information. Where uncertainty parameters were not reported (i.e. standard errors, confidence intervals), a standard error of 10% around the mean value is assumed. To ensure that PSA runs for TTP and PFS, curves derived from essentially the same dataset, were plausible, we used the same random number for both. This assumption was relaxed in sensitivity analysis. Figure 39 and Figure 40 show the PSA results: the mean average outcomes of the probabilistic iterations result in an ICER of [redacted] per QALY, which is similar to the base case analysis.

Table 46: Mean PSA results, PEM+SoC versus SoC – list prices

	Totals per treatment arm			Incremental results			ICER (£/QALY)
Treatment	**LYs**	**QALYs**	**costs**	**LYs**	**QALYs**	**Costs**	
SoC	2.61	[redacted]	[redacted]	2.84	[redacted]	[redacted]	[redacted]
PEM+SoC	5.45	[redacted]	[redacted]				
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Figure 39: PSA scatterplot, PEM+SoC versus SoC – list prices, based on 5,000 iterations

Figure 40: Cost-effectiveness acceptability curve, PEM+SoC versus SoC – list prices, based on 5,000 iterations

B.3.7.2 Deterministic sensitivity analysis

A series of one-way sensitivity analyses (OWSAs) were performed to evaluate the sensitivity of the model to individual inputs, holding all else constant. In OWSA, the lower and upper bounds of a parameter were often set to ± 1.96 * SE of the base case value (or mean), where the SE was obtained from its source data. Alternatively, CIs were used when available. However, when such information was not available, the standard error was assumed to be within ± 10% of the base case value.

Results from the OWSA show us that the input parameter that affects the ICER most is the number of actual vs. expected cycles, followed by resource use estimators, and the mean treatment duration of paclitaxel in second line. (Figure 41). Other parameters have a notably smaller effect on the ICER.

Please note that survival and utility estimates were not included in the OWSA as these estimates depend on multiple, correlated inputs. Uncertainty in survival and utilities is included in the PSA results (Section B.3.7.1).

Figure 41: Tornado diagram (DSA results), PEM+SoC versus SoC

B.3.7.3 Scenario analysis

The results of all scenario analyses that were deemed plausible ranged between [redacted] and [redacted] per QALY gained (Table 46). The highest ICER is associated with the scenario analysis in which very pessimistic assumptions were made regarding survival inputs. Excluding this scenario results in a plausible range of ICERs between [redacted] and [redacted] per QALY gained (all treatments at list price).

Table 47: Results of scenario analyses for PEM+SoC vs. SoC

	Parameter	Justification	ICER	Percentage change
Base case				
1	Time horizon set to 40 years	Explore impact of alternative shorter time horizon in the model	[redacted]	[redacted]
2	Discount rate (costs and outcomes) set to 1.5%	Test impact of alternative time discounting assumptions	[redacted]	[redacted]
Treatment costs				
3	Pembrolizumab dosing: 400 mg Q6W	Alternative pembrolizumab dosing regimen	[redacted]	[redacted]
4	Assume biosimilar cost of bevacizumab	Alternative application of bevacizumab (cheaper than the cost of Avastin®)	[redacted]	[redacted]
Efficacy inputs (TTP, PFS, PPS)				
5	Use PFS-BICR	Test impact of alternative definition of PFS in the model	[redacted]	[redacted]
6	TTP and PFS: 37-wk KM + Log-normal	Test impact of alternative curves for TTP and PFS in the economic model	[redacted]	[redacted]
7	TTP and PFS: 37-wk KM + Log-logistic/Weibull		[redacted]	[redacted]
8	TTP and PFS: 46-wk KM + Generalised gamma		[redacted]	[redacted]
9	PPS: Log-normal	Test impact of next-best curved for PPS in the economic model	[redacted]	[redacted]
10	PPS: Log-logistic		[redacted]	[redacted]
11	Assume equivalent PPS across arms based on pooled estimates from KEYNOTE-826	Understand impact of alternative assumption around PPS between interventions	[redacted]	[redacted]
Duration of treatment				
12	Allow treatment for up to 2-years for chemotherapy & bevacizumab, modelled using the Kaplan-Meier curve.	Alternative structural assumptions surrounding TOT in the economic model	[redacted]	[redacted]
Utilities				
13	Alternative HSUV utility analysis		[redacted]	[redacted]

14	Remove age-adjustment for utilities	Understand the impact of using alternative assumptions for utility value inputs	[redacted]	[redacted]
15	Disutility AEs based on literature		[redacted]	[redacted]
Other costing assumptions				
16	AE costs excluded	Understand the impact of AE costs on the model results	[redacted]	[redacted]
17	Assume vial sharing (no wastage)	Assume that there is no drug wastage (unlikely to hold in clinical practice for drugs stored in vials)	[redacted]	[redacted]
18	Do not assume missed doses	Alternative cost assumptions relevant for PEM+SoC and SoC	[redacted]	[redacted]
19	End of Life costs not included		[redacted]	[redacted]
20	Subsequent treatment costs excluded		[redacted]	[redacted]
21	Alternative subsequent treatment distributions based on KN-826 data		[redacted]	[redacted]
22	Administration costs for subsequent treatments applied		[redacted]	[redacted]
23	Cost of testing excluded		[redacted]	[redacted]
24	TTP/PFS unrelated in PSA	Stress test assumption around relationship	[redacted]	[redacted]

B.3.7.4 Summary of sensitivity analyses results

The PSA, DSA and scenario analysis showed results to be robust to uncertainty around most input parameters. The inputs with the biggest impact on the ICER included alternate utility values, the discount rates for cost and health outcomes, classifying progression by BICR, the choice of survival curves for PFS/TTP and the assumption that doses would be missed along with what was observed in KEYNOTE-826. The PSA produced results that were similar to the deterministic analysis, with a high probability that PEM+SoC is cost-effective. While there is some uncertainty around the precise ICER of PEM+SoC versus SoC, care has been taken to provide an understanding of the potential impact of uncertainty by using the best data available, validating assumptions with external data and feedback from UK clinicians, and finally quantifying the potential impact in the sensitivity analyses where possible.

B.3.8. Subgroup analysis

None required.

B.3.9. Validation

B.3.9.1 Validation of cost-effectiveness analysis

The cost-effectiveness model was developed in line with the NICE reference case and guidance from the NICE DSU TSDs where appropriate, as referenced throughout Section B.3. The cost-effectiveness model was quality-assured by having health economists not involved in developing the cost-effectiveness model review the technical implementation of calculations/ coding for correctness and checking and testing inputs/ settings for logical inconsistencies. The validation process included identifying any errors and applying the necessary corrections for the final model used for the cost-effectiveness analysis.

This is the first economic evaluation assessing the cost-effectiveness of PEM+SoC for patients with recurrent, persistent or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥1). No study assessing the UK cost-effectiveness of PEM+SoC for the target population specified above was identified from the SLR;

therefore, it is not possible to compare the results of the economic model developed in this appraisal with any previous study.

B.3.9.2 Validation of clinical assumptions for cost-effectiveness analysis

To ensure that the cost-effectiveness analysis is consistent with clinical expectations and rationale, key model assumptions were validated by UK clinical experts where possible.

The survival models in the base case analysis considered the visual and statistical fit to the observed data from KEYNOTE-826, and clinical plausibility of long-term estimates based on supplementary evidence and UK clinical expert opinion (as described in Section B.3.3).

The cost-effectiveness model uses parametric survival models to extrapolate clinical data observed in KEYNOTE-826, which provides direct evidence for the efficacy and safety of PEM+SoC and SoC in the target population. However, as highlighted by the SLR results, there is a clear lack of data in the literature for cervical cancer and the potential effectiveness of SoC. GOG 240 is an important trial for validation purposes because it provides long-term data for OS, PFS and PPS in patients treated with SoC for a patient population that is comparable to KEYNOTE-826 (greater than 50 months, or 4 years, of maximal follow-up) (Section B.2.2, Appendix Q. At the final OS analysis, the authors note that many patients treated with SoC continued to benefit from stable disease, and some were confirmed to be in long-term remission, with no evidence of clinical and radiologic disease.[78] The published data from the GOG 240 trial in advanced cervical cancer was used to determine the most appropriate survival curves for the SoC in this analysis.

MSD conducted an advisory board including seven UK clinical experts on 18th February 2022, with the objective of garnering insights regarding cervical cancer, their interpretations of the observed data from KEYNOTE-826, generalisability of the KEYNOTE-826 trial to the UK setting, and the potential impact and positioning of pembrolizumab in the UK clinical pathway. The cost-effectiveness model settings and assumptions were justified; key statements are provided below:

- Durable PFS and OS for PEM+SoC are clinically plausible based on experiences of using immunotherapy in other advanced cancer indications, the positive outcomes for complete and partial responders in the PEM+SoC arm of KEYNOTE-826, and because of the relative youth and fitness of the patient cohort
- In cervical cancer PFS is a good proxy for OS. The trends in hazards observed for PFS would be expected to become apparent for OS with longer-follow up.
- PPS following treatment with PEM+SoC is expected to be more favourable than PPS with SoC alone; the opposite is clinically implausible.
- Given the response data in KEYNOTE-826 and their clinical experience with immunotherapy treatments including pembrolizumab, it is clinically plausible for a significant minority to respond very well and more durably to treatment, with a plateauing effect likely being greater in the pembrolizumab arm compared with SoC

B.3.10. Interpretation and conclusions of economic evidence

The key evidence presented in this submission is based directly on data from the KEYNOTE-826 trial; a phase III, randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy versus chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer. Importantly, PEM+SoC demonstrated superior efficacy to SoC alone, and is the first and only immunotherapy to do so in this setting.

Consistent with the NICE reference case and final NICE scope, a cost-effectiveness model was developed to compare PEM+SoC versus SoC, using patient-level data from KEYNOTE-826. The SoC arm is reflective of treatments administered for the target population in current UK practice (Section B.3.2.3.2). The model structure was determined after a comprehensive assessment of the disease context in cervical cancer, clinical trial data and feedback from UK clinical experts.

A range of parametric analyses based on time-to-event data for TTP, PFS and PPS were conducted according to best practice guidance to model health outcomes for PEM+SoC and SoC over a lifetime horizon. The survival models were assessed for robustness and appropriateness for use in the economic model based on NICE DSU TSD guidance. The base case analysis used the best-fitting and most clinically valid

survival models, with alternative plausible models tested in an extensive range of scenarios as summarised in Section B.3.3 and Section B.3.8.

With all treatments at list prices, the estimated ICER for PEM+SoC versus SoC alone is [redacted] per QALY gained. The results show that PEM+SoC is estimated to offer a substantial incremental health benefit compared with SoC, offering an additional 2.80 LYs and [redacted] QALYs per patient lifetime that is associated with an incremental cost of [redacted]. This supports the importance of PEM+SoC as a treatment for patients in this treatment setting who benefit from extended long-term survival stemming from the reduction in risk of progression and, hence, death; as demonstrated in KEYNOTE-826, this is particularly likely for patients who have responded well to treatment with PEM+SoC. The incremental costs are primarily driven by a longer duration of treatment for PEM+SoC coupled with the cost difference between treatments. Section B.3.11 presents the results incorporating the CAA currently agreed for pembrolizumab, which show that PEM+SoC is highly likely be cost-effective when the confidential discounts are applied. These ICERs should also be considered in the context of PEM+SoC being an innovative and highly beneficial technology that presents a step change for patients with persistent, recurrent, or metastatic cervical cancer. The results should also be considered in the context of end-of-life criteria based on the majority of patients who receive standard of care treatment having died by two years (see Table 19).

The sensitivity and scenario analysis confirm the robustness of the base case analysis, as there is a high degree of consistency between the results. Using the CAA price, the ICER is below the cost-effectiveness threshold, even in conservative analyses. The considerations outlined in Section B.3.3.2 and B.3.3.4 outline key areas where the model is thought not to have captured the full benefit associated with the intervention. Based on the mean PSA results, PEM+SoC is expected to offer an additional 2.84 LYs and [redacted] QALYs versus SoC at an additional cost of [redacted]. The probabilistic ICER was [redacted], close to the [redacted] recorded in the base case analysis.

It may be that the economic model has underestimated the benefit of pembrolizumab, given the prevalence of caregiving responsibilities among this

patient group and the potential for return to economic activity outlined in section B.1.3.3. It is also possible that utility measured in the trial period, which is used indefinitely in the model, would rise in the post-trial period, after which patients would no longer be on treatment and many would have been in complete or partial response for some time.

B.3.11. Cost-effectiveness analysis results incorporating the commercial access agreement [CAA] for pembrolizumab

B.3.11.1 Base case results (including confidential CAA for pembrolizumab)

The results presented in the submission are based on the list price for pembrolizumab (Document B, Section B.3.7). The estimated incremental cost-effectiveness ratio (ICER) for PEM+SoC versus SoC is £[redacted] per QALY gained, based on list price.

This appendix presents the corresponding results incorporating the CAA currently agreed for pembrolizumab. The results show that PEM+SoC is cost effective when the confidential discount is included, with an estimated ICER of £ 34,017 per QALY gained.

Table 48: Base-case results – including CAA for pembrolizumab

Technologies	Total costs (£)	Total LYG	Total QALYs	ΔCosts (£)	Δ LYG	ΔQALYs	ICER (£/QALY)
PEM+SoC	[redacted]	5.31	[redacted]	[redacted]	2.80	[redacted]	£34,017
SoC	[redacted]	2.51	[redacted]				

Key: Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM, pembrolizumab; QALYs, quality-adjusted life years; SoC, standard of care.

B.3.11.2 Disaggregated results of the base case incremental cost-effectiveness analysis (including confidential PAS for pembrolizumab)

The disaggregated results incorporating the CAA currently agreed for pembrolizumab are provided below.

Table 49: Disaggregated costs for PEM+SoC and SoC (pembrolizumab with CAA)

Category	SOC	PEM+SOC	Difference
Drug acquisition	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	£215	£207	-£8
Cisplatin	£5	£5	£0
Carboplatin	£165	£155	-£10
Bevacizumab	£6,591	£6,244	-£348
Administration	£1,758	£5,705	£3,947
Adverse events	£367	£1,426	£1,059
Diagnostic testing	£0	£50	£50
Subsequent treatment	£77	£72	-£6
Monitoring - preprogression	£1,049	£1,974	£925
Monitoring - post-progression	£227	£206	-£21
Terminal care	£4,265	£3,980	-£284
Total costs	[redacted]	[redacted]	[redacted]

B.3.11.3 Sensitivity analysis (including confidential CAA for pembrolizumab)

The probabilistic and one-way deterministic sensitivity analyses were re-run incorporating the CAA currently agreed for pembrolizumab. The results from 2,000 iterations are presented below.

B.3.11.3.1 Probabilistic sensitivity analysis

The PSA results including the CAA for pembrolizumab were fairly consistent with the base case results, although some differences in LYs/QALYs were observed. The probability that PEM+SoC was cost-effective at a threshold of £50,000/QALY was 85.9%.

Table 50: Mean probabilistic base case results, pairwise analysis (pembrolizumab with CAA)

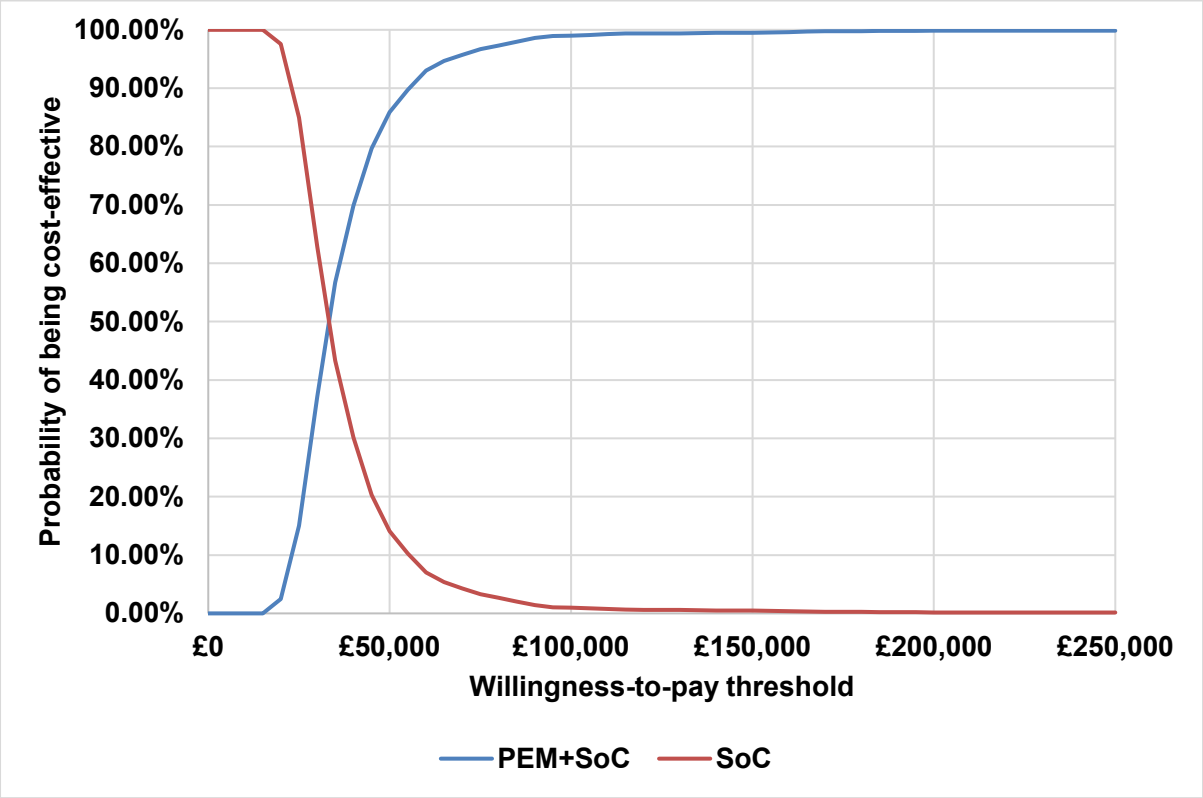
Technologies	Total costs (£)	Total LYG	Total QALYs	ΔCosts (£)	Δ LYG	ΔQALYs	ICER (£/QALY)
PEM+SoC	[redacted]	5.45	[redacted]	[redacted]	2.84	[redacted]	£32,977
SoC	[redacted]	2.61	[redacted]				

Key: Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM, pembrolizumab; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 41: PSA scatterplot, PEM+SoC versus SoC (pembrolizumab with CAA)

Key: ICER, incremental cost-effectiveness ratio; PEM, pembrolizumab; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care; WTP, willingness-to-pay.

Figure 42: Cost-effectiveness acceptability curve, PEM+SoC versus SoC (pembrolizumab with CAA)

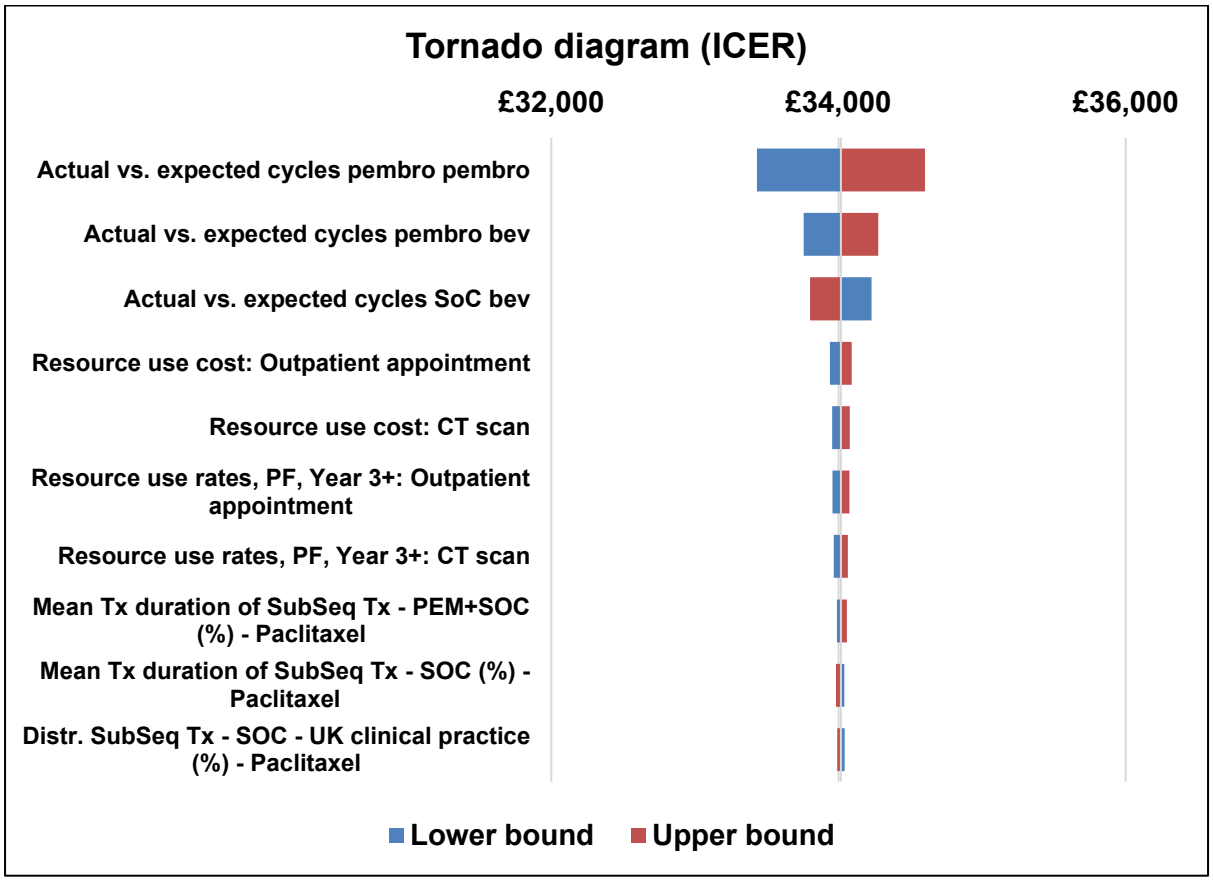


Key: ICER, incremental cost-effectiveness ratio; PEM, pembrolizumab; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care; WTP, willingness-to-pay.

B.3.11.3.2 Deterministic sensitivity analysis

The one-way DSA results including the CAA for pembrolizumab are presented below. Key drivers of the deterministic sensitivity analysis remain the same as those presented in Document B, Section 3.8.

Figure 43: Tornado diagram showing OWSA results, PEM+SoC versus SoC (pembrolizumab with CAA)



Key: ICER, incremental cost-effectiveness ratio; PEM, pembrolizumab; OS, overall survival; OWSA, one-way sensitivity analysis; sdlog, standard deviation log; ToT, time on treatment; tx, treatment; SoC, standard of care

B.3.11.3.3 Scenario analysis

The scenarios presented in Document B, Section 3.8.3 were re-run to include the CAA for pembrolizumab; these results demonstrate that PEM+SoC is highly likely to be cost effective when the confidential discounts are included, in all of the scenarios tested. Justification for the scenarios chosen is supplied in section B.3.7.3 of Document B. Here we include some additional notes on interpretation in the table.

Table 51: Scenario analysis – PEM+SoC versus SoC (pembrolizumab with CAA)

Scenario description	Notes	ICER	ICER: change from base case
Time horizon set to 40 years		£34,235	0.6%
Discount rate (costs and QALYs) set to 1.5%		£27,858	-18.1%
Pembrolizumab dosing: 400 mg Q6W	Popular in NHS practice as reduces need for visits	£33,225	-2.3%
Assume biosimilar cost of bevacizumab		£34,051	0.1%
Use Independent Review Committee data to determine progression	Plausible for progression to be classified in this way	£28,774	-15.4%
TTP and PFS: 37-wk KM + Log-normal	2nd choice curve	£33,892	-0.4%
TTP and PFS: 37-wk KM + Log-logistic/Weibull	Pessimistic scenario included for stress-testing purposes	£40,546	19.2%
TTP and PFS: 46-wk KM + Generalised gamma	First choice 46-week curve	£27,270	-19.8%
PPS: Log-normal	Alternate PPS curve 1	£33,029	-2.9%
PPS: Log-logistic	Alternate PPS curve 2	£36,271	6.6%
Assume equivalent PPS across arms based on pooled estimates from KEYNOTE-826	Pessimistic scenario based on clinical feedback	£36,707	7.9%
Allow treatment for up to 2-years for chemotherapy & bevacizumab, duration of treatment modelled based on 37-wk KM + log-logistic distribution (KEYNOTE-826, SoC arm)	Allow for continuation of bev outside CDF rules	£35,081	3.1%
Alternative HSUV utility analysis		£35,824	5.3%
Remove age-adjustment for utilities		£32,207	-5.3%
Disutility AEs based on literature		£33,924	-0.3%
AE costs excluded		£33,197	-2.4%
Assume vial sharing (no wastage)		£34,032	0.0%
Do not assume missed doses	Not preferred due to need to tie effectiveness data to actual doses of pembrolizumab received	£37,357	9.8%
EoL costs not included		£34,237	0.6%
Subsequent treatment costs excluded		£34,021	0.0%
Alternative subsequent treatment distributions		£34,131	0.3%

Administration costs for subsequent treatments applied		£33,936	-0.2%
Cost of testing excluded	Testing cost does not influence ICER much because of high CPS>1 prevalence	£33,978	-0.1%
PSA with TTP/PFS uncorrelated	TTP and PFS are derived from essentially the same dataset so this scenario is only presented for illustrative purposes	£35,610	4.7%

B.3.11.4 Conclusions

The sensitivity analyses show that the ICERs are generally robust to changes in the input values, indicating a relatively small impact of parameter uncertainty on the base-case results. The most impactful scenarios include those involving alternate utility values, low discount rates, 46-week break point for piecewise PFS/TTP and a set of pessimistic 37-week PFS/TTP survival curves.

Of the scenarios that meaningfully impact the ICER, the use of the 46-week piecewise survival curve break point appears to be the most relevant for decision-making. The selection of the 37-week break point over the 46-week break point for the base case was due to event numbers alone rather than any model fit or plausibility criteria. A set of “pessimistic” curves for PFS/TTP, which are simple averages between the base-case and the Weibull models are also supplied to stress test the results and PEM+SoC was still cost-effective.

The results presented in the base case and scenarios support the conclusion that, when confidential discount(s) are applied, pembrolizumab in combination with chemotherapy with or without bevacizumab is a cost-effective therapeutic option for patients with persistent, recurrent or metastatic cervical cancer. This treatment option offers a step change in clinical management of persistent, recurrent and metastatic cervical cancer patients. The difference in mean QALYs is driven primarily by increases in PFS, which are likely related to the good outcomes and high number of complete responders in the PEM+SoC arm of KN826.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: FIGO staging system

Appendix M: Current clinical guidelines for cervical cancer

Appendix N: ECOG performance status classification

Appendix O: Additional clinical effectiveness evidence for Section B.2

Appendix P: Ongoing trials

Appendix Q: Additional information for Section B.3 (cost-effectiveness analysis)

Appendix R: Cost-effectiveness analysis results incorporating the CAA for pembrolizumab

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Clarification questions

April 2022

File name	Version	Contains confidential information	Date
ID3798 Pembrolizumab clarification questions v0.4 to PM for company [NoACIC]		No	3rd May 2022

Section A: Clarification on effectiveness data

Decision Problem

A1. Please expand on the rationale for not providing the subgroup analyses requested in the NICE scope (other than CPS subgroup analyses, which are available in the CSR). Please report results for the subgroup analyses if the data are available.

MSD Response: At the scoping workshop, held in December 2020, MSD informed the group that there would be forest plots available of outcomes by certain patient characteristics but the trial was not powered to find differences between them. The investigation of tumour mutational burden is noted as a potential exploratory analysis but no data are available yet.

KEYNOTE-826 Trial

A2. Page 15 of the company submission (CS) states that patients with small cell cancer were excluded from the trial, but are these patients covered by the marketing authorisation?

MSD Response: The marketing authorisation was granted based upon the results from the KEYNOTE-826 trial, which did not include small cell cervical cancer patients.

A3. Priority question: Please report the proportion of patients receiving cisplatin & paclitaxel and the proportion of patients receiving carboplatin & paclitaxel in each trial arm.

MSD Response: Table 1 summarises the distribution of participants by administered treatment i.e. proportion of patients receiving cisplatin & paclitaxel and the proportion of patients receiving carboplatin & paclitaxel in each trial arm.

Table 1: Distribution of participants by administered treatment from cycle 1 to cycle 6. Participants with CPS ≥1 (APaT)

	Pembrolizumab + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)

Participants in population	272		275		547	
Randomized treatment (pembrolizumab/placebo)						
Randomised Treatment (Pembrolizumab/ Placebo)	272	(100.0)	275	(100.0)	547	(100.0)
Cisplatin and/or Carboplatin						
Cisplatin[a]	[redacted]		[redacted]		[redacted]	
Carboplatin[b]	[redacted]		[redacted]		[redacted]	
Cisplatin and Carboplatin[c]	[redacted]		[redacted]		[redacted]	
Missing	[redacted]		[redacted]		[redacted]	
Paclitaxel						
Paclitaxel	[redacted]		[redacted]		[redacted]	
Bevacizumab						
Bevacizumab	175	(64.3)	171	(62.2)	346	(63.3)
No Bevacizumab	97	(35.7)	104	(37.8)	201	(36.7)

Table reports participants who received at least one dose of the treatment during the considered period.
a: Participants who have received cisplatin and no carboplatin during the considered period.
b: Participants who have received carboplatin and no cisplatin during the considered period.
c: Participants who have received both cisplatin and carboplatin during the considered period.
Database Cutoff Date: 03MAY2021

As we have noted in Table 1 above, all subjects received Paclitaxel, so n(%) provided for Cisplatin and Carboplatin include use of paclitaxel.

A4. Priority question: How many trial patients have received a second course of pembrolizumab? (i.e. were re-treated as described in section 6.6.2 of the protocol). Was blinding maintained for these patients, in terms of investigator outcome assessments?

MSD Response: We can confirm that no patients received retreatment as described in Study Protocol section 6.6.2.

A5. Priority question: Please add the following pre-randomisation data to the CONSORT diagram (Appendix D, Figure 2):

- **Number of patients screened for eligibility**
- **Number ineligible/excluded, split by reasons**
- **Number of eligible patients who declined participation (split by reason for declining, if a significant number declined participation)**

MSD Response: Unfortunately, the figure was not updated. However, the requested data are available:-

- Number of patients screened for eligibility – 883

- Number ineligible/excluded, split by reasons – 266 [embedded below]: attached document provides a breakdown regarding ineligibility for inclusion or reason for exclusion
- Number of eligible patients who declined participation (split by reason for declining, if a significant number declined participation) – Not available

[redacted]

A6. Priority question: Please present the mean (SD) and median (IQR) PD-L1 CPS for each trial arm. Please also provide mean and median PD-L1 CPS data by best response category: i.e. for complete responders (CR), partial responders (PR), patients with stable disease (SD) and patients with progressed disease (PD).

MSD Response: Please see the requested information in Table 2– Table 10.

Table 2: Baseline PD-L1 CPS (ITT)

	Pembrolizumab + Chemotherapy N[a]=308	**Placebo + Chemotherapy** N[a]=309
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021		

Table 3: Baseline PD-L1 CPS - Participants with best response of complete response (as per investigator assessment) (ITT)

	Pembrolizumab + Chemotherapy N[a]=66	**Placebo + Chemotherapy** N[a]=40
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per Investigator Assessment is Complete Response		

Table 4: Baseline PD-L1 CPS - Participants with best response of partial response (as per investigator assessment) (ITT)

	Pembrolizumab + Chemotherapy N[a]=137	Placebo + Chemotherapy N[a]=117
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Complete Response		

Table 5: Baseline PD-L1 CPS - Participants with best response of stable disease as per investigator assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=69	Placebo + Chemotherapy N[a]=99
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per Investigator Assessment is Stable Disease		

Table 6: Baseline PD-L1 CPS - Participants with best response of progressive disease as per investigator assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=15	Placebo + Chemotherapy N[a]=33
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Progressive Disease		

Table 7: Baseline PD-L1 CPS - Participants with best response of complete response as per IRC assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=105	Placebo + Chemotherapy N[a]=64
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Complete Response		

Table 8: Baseline PD-L1 CPS - Participants with best response of partial response as per IRC assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=85	Placebo + Chemotherapy N[a]=102
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Partial Response		

Table 9: Baseline PD-L1 CPS - Participants with best response of stable disease as per IRC assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=77	Placebo + Chemotherapy N[a]=89
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Stable Disease		

Table 10: Baseline PD-L1 CPS - Participants with best response of progressive disease as per IRC assessment (ITT)

	Pembrolizumab + Chemotherapy N[a]=13	Placebo + Chemotherapy N[a]=30
Actual CPS Score at Baseline		
Mean (SD) Median (Q1; Q3) Min; Max	[redacted]	[redacted]
SD Standard deviation Database Cutoff Date: 03MAY2021 a: ITT participants whom Best Response as per IRC Assessment is Progressive Disease		

A7. Priority question: Please present CS Figures 4, 5 and 6 with 95% confidence intervals added to the curves.

MSD response: Please see the requested figures below. Apologies we are not able to provide relabelled figures; please note that TRT01PN=1 is “pembrolizumab + chemotherapy” and TRT01PN=2 is “placebo + chemotherapy”.

Figure 1: CS Figure 4 with 95% confidence intervals added to the curves

[redacted]

Figure 2: CS Figure 5 with 95% confidence intervals added to the curves

Figure 3: CS Figure 6 with 95% confidence intervals added to the curves

A8. Priority question: In Figure 13 of the CS please present the #Events/N for each trial arm separately for all subgroups. Please also run a test for interaction and present results for the 'metastatic at initial diagnosis' data.

MSD Response: Table 11 presents #Events/N separated by arm for all subgroups for the CS Figure 13.

Table 11: CS Figure 13 #Events/N for each trial arm separately for all subgroups

Subgroup	#Event / N Placebo+Chemotherapy	#Event / N Pembrolizumab+Chemotherapy
Overall	[redacted]275	[redacted]273
Metastatic at Initial Diagnosis		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted] 187
Bevacizumab Use		
Yes	[redacted] 171	[redacted] 175
No	[redacted] 104	[redacted] 98
Age		
<65 Years	[redacted] 229	[redacted] 232
>=65 Years	[redacted]46	[redacted] 41
Race		
White	[redacted] 172	[redacted]153
All Others	[redacted]	[redacted]
ECOG		
0	[redacted] 148	[redacted] 160
1	[redacted] 127	[redacted] 111

Interaction test for 'metastatic at initial diagnosis'

Results from the KN-826 clinical trial are extremely promising for women with a metastatic initial diagnosis. These results suggested a benefit with the addition of pembrolizumab despite the worsened prognosis for this patient subgroup. As requested, the test result for interaction is shown below (Table 12). Although this interaction test was significant for "treatment by MET-grouping", the result should be interpreted with caution. First, the clinical trial was not designed or powered to statistically test heterogeneity of treatment effect for the subgroup of participants who have metastatic disease at study entry. Thus, results of these post-hoc subgroup analyses are hypothesis-generating only and should not be overinterpreted. This is particularly true for small subgroups, where the observed results could be due to

random variation. Secondly, when testing multiple hypotheses simultaneously (five comparisons here: for “Met”, “Bev”, “Age”, “Race” and “Ecog”), correction for multiple hypothesis test should be considered as well.

Table 12: Interaction test log

c[redacted]

A9. Priority question: Please report the number of complete responders for each of the CPS 1-10 and CPS>10 subgroups, for each trial arm.

MSD Response: Please note that stratification for PD-L1 status in this study is: CPS <1 vs CPS 1 to <10 vs CPS ≥10, therefore we provided the requested number according to this and not to the questions above.

Table 13: Summary of complete response with confirmation based on investigator assessment per RECIST 1.1. Participants With CPS ≥1 and CPS <10 (ITT)

	Pembrolizumab + chemotherapy			Placebo + chemotherapy		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	115			116		
Complete Response (CR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Based on binomial exact confidence interval method. Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table. Database Cutoff Date: 03MAY2021						

Table 14: Summary of complete response with confirmation based on BICR assessment per RECIST 1.1. Participants With CPS ≥1 and CPS <10 (ITT)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	115			116		
Complete Response (CR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Based on binomial exact confidence interval method. BICR assessed responses per RECIST 1.1 (confirmed) are included in this table. Database Cutoff Date: 03MAY2021						

Table 15: Summary of complete response with confirmation based on investigator assessment per RECIST 1.1. Participants With CPS ≥10 (ITT)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	158			159		
Complete Response (CR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
a: Based on binomial exact confidence interval method. Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table. Database Cutoff Date: 03MAY2021						

Table 16: Summary of complete response with confirmation based on BICR assessment per RECIST 1.1. Participants With CPS ≥10 (ITT)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population Complete Response (CR)	158	[redacted]	[redacted]	159	[redacted]	[redacted]

a: Based on binomial exact confidence interval method.
BICR assessed responses per RECIST 1.1 (confirmed) are included in this table.
Database Cutoff Date: 03MAY2021

A10. Priority question: Please present figure 4 of the CS with the 'metastatic at initial diagnosis' patients omitted.

MSD Response: Please see the requested figures below. KEYNOTE-826 was not designed or powered to assess outcomes for the subgroup of participants with stage IVB disease at initial diagnosis separately. Despite the worsened prognosis for women with metastatic initial diagnosis, results for this subgroup were promising. Nonetheless, results of these subgroup analyses are hypothesis-generating only and should not be overinterpreted. This is particularly true for small subgroups, where the observed results could be due to random variation. While the magnitude of improvement varies to some degree from subgroup to subgroup, treatment effect in KEYNOTE-826 is positive across all subgroups.

Apologies we are not able to provide relabelled figures i.e. TRT01PN=1 is "pembrolizumab + chemotherapy" and TRT01PN=2 is "placebo + chemotherapy".

Table 17: Progression-free survival as assessed per RECIST 1.1 by investigator assessment (CPS ≥ 1 population, without 'metastatic at initial diagnosis')

[redacted]

A11. Priority question: The primary objective stated in the KEYNOTE-826 protocol is "To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (BICR)." This is reflected in the use of BICR-assessed PFS in Hypotheses 1-3. The SAP also reports the primary outcome as "The time from randomization to the first documented disease progression per RECIST1.1 as assessed by BICR or death due to any cause, whichever occurs first". However, Table 7 of the CS states the primary objective to be

"PFS based on RECIST 1.1 as assessed by the investigator", though hypotheses 1-3 still refer to BICR assessment. Please clarify this apparent inconsistency in stated primary objective measure between sources.

MSD response: The original study protocol was dated 13th June 2018, and on the 30th October 2020 a protocol amendment was issued. In this amendment the objectives including primary efficacy endpoints were modified. The primary PFS endpoint per RECIST 1.1 were outlined to be assessed by the investigator. The purpose of this amendment was to address discordance between BICR-confirmed progressive disease (PD) and investigator assessed PD that could affect the power of the trial.(1) The reason for this inconsistency was due to a protocol amendment which was implemented to allow for assessment of PD by the investigator in clinically stable participants. However, images were still submitted to BICR for both clinically stable and clinically unstable patients.

A12. Priority question: In the CSR, section *14.2.3.4 PFS using iRECIST by Investigator* is empty and refers to section 11, but it is not clear which data in section 11 relate to the iRECIST (as opposed to the RECIST 1.1 criteria). Please clarify where these data can be found.

MSD response: This was an error in the CSR. No result/text about PFS iRECIST was intended to have been provided in CSR. The study changed the primary endpoint from 'PFS by BICR' to 'PFS by Investigator PFS per RECIST 1.1' in protocol amendment 30th October 2020. Consequently, iRECIST was no longer applicable.

A13. Priority question: The trial protocol precluded crossover between treatment arms following progression: Did any participants cross over between trial arms prior to progression?

MSD response: We can confirm that no cross-over between trial arms prior to progression was observed as of the 3rd of May database cut-off.

A14. How many participants in each treatment arm switched from cisplatin to carboplatin?

MSD response: Eleven and six patients switched from cisplatin to carboplatin in pembro+chemo and placebo+chemo arms respectively.

A15. Priority question: Please provide the CSR appendices – these are not accessible from the pdf provided in the Reference Pack

MSD response: Unfortunately, MSD is not able to share appendix 16 due the document containing patient level data. Please specify a specific question and MSD can provide information as needed. The CSR in the reference papers includes Appendix 14 but MSD will reupload the document as part of the clarification question response.

Systematic literature review

A16. Appendix Table 3 lists the included studies. Not all the included studies are referenced (only the studies which also appear in Table 5). Please reference all the studies in Table 3 and provide the pdfs in a reference pack.

MSD response: Please see Table 18 with referenced all clinical SLR included studies.

Table 18: CS Appendix D Table 3 List of included studies

	Trial ID	Trial number	Principal publication	Publication type	Principal publication title	Associated publications
1	Alberts 1987(2)	--	Alberts 1987	Journal article	Phase II Randomized Trial of Cisplatin Chemotherapy Regimens in theTreatment of Recurrent or Metastatic Squamous Cell Cancer of the Cervix: A Southwest Oncology Group Study	--
2	Al-Saleh 1997(3)	--	Al-Saleh 1997	Journal article	Cisplatin/etoposide chemotherapy for recurrent or primarily advanced cervical carcinoma	--
3	Aoki 2018(4)	NCT00770874	Aoki 2018	Journal article	Phase iii study of cisplatin with or without s-1 in patients with stage ivb, recurrent, or persistent cervical cancer	NCT 2018(5)
4	Arseneau 1986(6)	--	Arseneau 1986	Journal article	A phase ii study of carboplatin in advanced squamous cell carcinoma of the cervix (a gynecologic oncology group study)	--
5	BGOG/ENGOT-CX1(7)	NCT02009579	Vergote 2021	Conference abstract	Randomised phase II BGOG/ENCOT-CX1 study of paclitaxel -carboplatin with or without nintedanib in first-line recurrent or advanced cervical cancer	--
6	Bonomi 1989(8)	--	Bonomi 1989	Journal article	A Phase II Evaluation of Cisplatin and 5Fluorouracil in Patients with Advanced Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study1e2	--
7	Burnett 2000(9)	--	Burnett 2000	Journal article	A phase ii study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix	--
8	Cadron 2005(10)	--	Cadron 2005	Journal article	Report of an Early Stopped Randomized Trial Comparing Cisplatin vs. Cisplatin/Ifosfamide/5-Fluorouracil in Recurrent Cervical Cancer	--
9	Coronel 2011(11)	--	Coronel 2011	Journal article	A double-blind, placebo-controlled, randomized phase III trial of chemotherapy plus epigenetic therapy with hydralazine valproate for advanced cervical cancer. Preliminary results	--
10	Coronel 2018(12)	--	Coronel 2018	Journal article	Carboplatin and low-dose paclitaxel. An effective regimen in older and comorbid patients with advanced cervical cancer. A phase II study	--
11	Daly 1996(13)	--	Daly 1996	Journal article	A short and intensive single-agent cisplatin regimen for recurrent carcinoma of the uterine cervix	--
12	Duenas-Gonzalez 2001(14)	--	Duenas-Gonzalez 2001	Journal article	Weekly Cisplatin/Low-Dose Gemcitabine Combination for Advanced and Recurrent Cervical Carcinoma	--

13	Fiorica 2002(15)	--	Fiorica 2002	Journal article	Phase II Trial of Topotecan and Cisplatin in Persistent or Recurrent Squamous and Nonsquamous Carcinomas of the Cervix	--
14	Gebbia 2002(16)	--	Gebbia 2002	Journal article	Vinorelbine and Cisplatin for the Treatment of Recurrent and/or Metastatic Carcinoma of the Uterine Cervix	--
15	Ghaemmaghami 2003(17)	--	Ghaemmaghami 2003	Journal article	First-line chemotherapy with 5-FU and platinum for advanced and recurrent cancer of the cervix: a Phase II study	--
16	Goedhals 2005(18)	--	Goedhals 2005	Journal article	Vinorelbine and Cisplatin in Advanced Squamous Cell Carcinoma of the Cervix: The South African Experience	--
17	GOG 179(19)	--	Long 2006	Journal article	Clinical results and quality of life analysis for the MVAC combination (methotrexate, vinblastine, doxorubicin, and cisplatin) in carcinoma of the uterine cervix: A Gynecologic Oncology Group study	Monk 2005(20); Long 2005(21)
18	GOG 204(22)	NCT00064077	Monk 2009	Journal article	Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study	NCT 2018(23); Cella 2010(24)
19	GOG 240(25)	NCT00803062	Tewari 2017	Journal article	Final Overall Survival of the Phase III Randomised Trial of Chemotherapy with and without Bevacizumab for Advanced Cervical Cancer: An NRG Oncology/Gynecologic Oncology Group Study	Penson 2013(26); Tewari 2014(27); NCT 2019(28)
20	HCOG study(29)	--	Dimopoulos 2002	Journal article	Combination of Ifosfamide, Paclitaxel, and Cisplatin for the Treatment of Metastatic and Recurrent Carcinoma of the Uterine Cervix: A Phase II Study of the Hellenic Cooperative Oncology Group	--
21	JCOG0505(30)	NCT00295789	Kitagawa 2015	Journal article	Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505	Kitagawa 2012(31, 32)
22	JCOG1311(33)	jRCTs031180007	Ishikawa 2021	Journal article	A randomized phase II/III trial of conventional paclitaxel and carboplatin with or without bevacizumab versus dose-dense paclitaxel and carboplatin with or without bevacizumab, in stage IVB, recurrent, or persistent cervical carcinoma (JCOG1311): Primary analysis	--
23	JO29569(34)	--	Sugiyama 2017	Journal article	A single-arm study evaluating bevacizumab, cisplatin, and paclitaxel followed by single-agent bevacizumab in Japanese patients with advanced cervical cancer	--

24	KEYNOTE-826(35)	NCT03635567	Colombo 2021	Journal article	Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer	Colombo 2021(35); Clinical Study Report(1)
25	Kudelka 1997(36)	--	Kudelka 1997	Journal article	An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix	Kudelka 1996(37); Kudelka 1997(36)
26	Lukic 2000(38)	--	Lukic 2000	Journal article	Single-drug cisplatin chemotherapy for metastatic cancer of the uterine cervix revisited	--
27	Matulonis 2006(39)	--	Matulonis 2006	Journal article	Phase I/II dose finding study of combination cisplatin and gemcitabine in patients with recurrent cervix cancer	--
28	McGuire 1989(40)	--	McGuire 1989	Journal article	A Randomized Comparative Trial of Carboplatin and Iproplatin in Advanced Squamous Carcinoma of the Uterine Cervix: A Gynecologic Oncology Group Study	--
29	McGuire 1996(41)	--	McGuire 1996	Journal article	Paclitaxel Has Moderate Activity in Squamous Cervix Cancer: A Gynecologic Oncology Group Study	--
30	Moore 2004(42)	--	Moore 2004	Journal article	Phase III Study of Cisplatin With or Without Paclitaxel in Stage IVB, Recurrent, or Persistent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study	McQuellon 2006(43)
31	Morris 2004(44)	--	Morris 2004	Journal article	Phase II Study of Cisplatin and Vinorelbine in Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study	--
32	Omura 1997(45)	--	Omura 1997	Journal article	Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: A gynecologic oncology group study	--
33	Papadimitriou 1999(46)	--	Papadimitriou 1999	Journal article	Phase II Trial of Paclitaxel and Cisplatin in Metastatic and Recurrent Carcinoma of the Uterine Cervix	--
34	Pignata 1999(47)	--	Pignata 1999	Journal article	Phase II Study of Cisplatin and Vinorelbine as First-Line Chemotherapy in Patients With Carcinoma of the Uterine Cervix	--
35	Rose 1999(48)	--	Rose 1999	Journal article	Paclitaxel and Cisplatin as First-Line Therapy in Recurrent or Advanced Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study	--
36	SWOG 8321(49)	--	Weiss 1990	Journal article	A Phase II Trial of Carboplatin for Recurrent or Metastatic Squamous Carcinoma of the Uterine Cervix: A Southwest Oncology Group Study	Weiss 1989
37	Symonds 2015(50)	--	Symonds 2015	Journal article	Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer	--

					(CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial	
38	Tebbutt 1998(51)	--	Tebbutt 1998	Journal article	A Phase II Trial of Carboplatin and Etoposide for Relapsed or Metastatic Carcinoma of the Cervix	--
39	Thigpen 1981(52)	--	Thigpen 1981	Journal article	Cis-Platinum in Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix:	--
40	Vermorken 2001(53)	--	Vermorken 2001	Journal article	Randomized phase III trial of bleomycin, vindesine, mitomycin-C, and cisplatin (BEMP) versus cisplatin (P) in disseminated squamous-cell carcinoma of the uterine cervix: An EORTC Gynecological Cancer Cooperative Group study	--
41	Zanetta 1999(54)	--	Zanetta 1999	Journal article	Paclitaxel, ifosfamide and cisplatin (TIP) chemotherapy for recurrent or persistent squamous-cell cervical cancer	--

A17. For the risk of bias assessments (Appendix D3 p32), please provide the details which justify the judgements made, if available.

MSD response: Please see Table 19 for risk of bias assessments of RCTs based on the Cochrane Collaboration's Tool for Assessing Risk of Bias 2.(55)

Table 19: Summary of assessment of risk of bias for RCTs included in the systematic literature review

	Randomisation			Deviations from intended interventions							Missing outcome data				Outcome assessment					Selection of reported result		
Trial ID	**1.1**	**1.2**	**1.3**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**3.1**	**3.2**	**3.3**	**3.4**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**5.1**	**5.2**	**5.3**
Alberts et al. 1987(2)	Y	NI	NI	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	PN	PN	NI	PN	NA	PY	PN	PN
Aoki et al. 2018(4)	Y	Y	PN	Y	Y	PN	NA	NA	PY	NA	PY	NA	NA	NA	PN	N	Y	PN	NA	Y	PN	PN
BGOG/ENGOT-CX1(7)	Y	NI	PN	N	N	NA	NA	NA	PY	NA	PY	NA	NA	NA	PN	PN	N	NA	NA	NI	PN	PN
Cadron et al. 2005(10)	Y	NI	PN	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	PN	PN	NI	PN	NA	NI	PN	PN
Coronel et al. 2011(11)	Y	NI	PN	N	N	NA	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	N	NA	NA	PY	PN	PN
GOG 179(19)	Y	NI	PN	NI	NI	N	NA	NA	PY	NA	PY	NA	NA	NA	PN	PN	NI	PN	NA	Y	PN	PN
GOG 204(22)	Y	NI	PN	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	NI	PN	NI	PN	NA	PY	PN	PN
GOG 240(25)	Y	PY	PN	Y	Y	N	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	Y	PN	NA	Y	PN	PN
JCOG0505(30)	Y	NI	PN	Y	Y	PN	NA	NA	PY	NA	Y	NA	NA	NA	PN	PN	Y	PN	NA	Y	PN	PN
JCOG1311(33)	Y	PY	N	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	PN	PN	NI	PN	NA	Y	N	N
KEYNOTE-826(35)	Y	Y	PN	N	N	NA	NA	NA	Y	NA	Y	NA	NA	NA	N	N	N	NA	NA	Y	N	N
McGuire et al. 1989(40)	Y	NI	N	NI	NI	PN	NA	NA	PY	NA	PY	NA	NA	NA	PN	N	NI	PN	NA	Y	PN	N
Moore et al. 2004(42)	Y	PY	N	NI	NI	PN	NA	NA	PY	NA	PY	NA	NA	NA	PN	N	NI	PN	NA	PY	PN	PN
Omura et al. 1997(45)	Y	PY	PN	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	NI	NI	NI	PN	NA	PY	PN	PN
SWOG 8321(49)	Y	NI	NI	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	PN	N	NI	PN	NA	NI	PN	PN
Symonds et al. 2015(50)	Y	Y	PN	N	N	NA	NA	NA	PY	NA	Y	NA	NA	NA	N	N	N	NA	NA	PY	N	N
Vermorken et al. 2001(53)	Y	NI	PN	NI	NI	PN	NA	NA	PY	NA	Y	NA	NA	NA	NI	PN	NI	PN	NA	PY	PN	PN
Key: N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Y, Yes.																						

Section B: Clarification on cost-effectiveness data

Treatment effectiveness

B1. Priority question: Please provide standard parametric extrapolations of OS data from KEYNOTE 826 including AIC and BIC fits.

a) **Please comment on the clinical plausibility of OS predictions with specific reference to the plausibility of OS for SoC patients.**

MSD response: see below

b) **Please provide an overview of the predictions made by the model and those predicted by the extrapolated OS data commenting specifically on any inconsistencies.**

MSD response: The standard parametric extrapolations of the OS data for PEM+SoC and SoC for the CPS>=1 population from KEYNOTE 826 are provided in Figure 17 and Figure 18 of the company submission, and the corresponding AIC and BIC fits are provided here in Table 20.

Table 20: Statistical fit of parametric survival models fit to the OS KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

	PEM+SoC		SoC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Note: Curves were fit to the data of the CPS≥1 population of KEYNOTE-826.
*Best statistical fit based on AIC.

The Weibull and Gompertz parametric extrapolations substantially underestimate 4-year SoC OS based on the GOG 240 trial, which is estimated to be 15.1% [see Appendix Q of the company submission], by an absolute -7.2% and -10.2% respectively. The exponential, log-normal, log-logistic and generalized gamma parametric extrapolations are more in line with 4-year SoC OS based on the GOG

240 trial, with absolute deviations of +0.7%, +4.1%, +1.3% and -2.8%, respectively), but even these standard parametric extrapolations of the OS data are inappropriate for use in economic modelling because:

1) all standard parametric extrapolations of OS data have a poor visual fit to the KM data for PEM+SoC observed in KEYNOTE 826 (and most standard parametric extrapolations have a poor visual fit to the KM data for SoC).

   Figure 4 shows that none of the standard parametric extrapolations of PEM+SoC OS data reflects the inflection point in the OS KM data that can be seen around 60 weeks (also seen in smooth spline hazards in Figure 5), which was expected given pembrolizumab's mechanism of action.

Figure 4: Parametric survival models fit to the OS KM data for PEM+SoC and SoC in the CPS≥1 population of KEYNOTE-826

2) none of the standard parametric extrapolations of OS data reflects the sharp decline in OS hazard rates towards the end of follow-up for PEM+SoC observed in KEYNOTE 826.

Figure 5 shows that the sharp decline in OS hazard rates towards the end of follow-up for PEM+SoC observed in KEYNOTE 826 is not reflected by any of the one-piece parametric extrapolations of OS data: for most of the extrapolations, the hazards remain relatively constant or even increase towards the end of follow-up for PEM+SoC, which is not expected given pembrolizumab's mechanism of action and data from previous immunotherapy studies.

Figure 5: Hazards over time for the parametric survival models fit to the OS KM data for PEM+SoC versus smooth spline estimates for the CPS≥1 population of KEYNOTE-826

3) the parametric extrapolations of OS data cross with extrapolations of PFS data (with more extensive crossing observed for PEM+SoC than for SoC)

As can be seen in Figure 17 and Figure 18 of the CS, the one-piece parametric extrapolations of OS data cross with extrapolations of PFS data. This means the standard parametric extrapolations of OS data are clinically implausible: As explained in the company submission, the crossing of curves is caused by the clear plateauing observed in the PFS data not yet being observed to the same extent in the OS data, because the OS data are substantially less mature than the PFS data. UK clinical experts consulted for this appraisal confirmed that the trends in hazards observed for PFS would be expected to become apparent for OS with longer-follow up.

4) none of the parametric extrapolations of OS data reflects clinical expectations around the prognostic impact of progression and durability of response observed for

pembrolizumab in KEYNOTE-826 on OS. As detailed in other responses to the ERG's clarification questions, the clinical expectation is that there will be a 'long tail' of durable responders, particularly in the pembrolizumab arm.

B2. The direct application of the TTP KM curve to estimate progression is likely to overestimate real TTP and thus survival and utility, given the infrequency of assessment in KEYNOTE 826. Please fit conventional spline models to TTP data and implement these in the economic model.

MSD response: MSD understand the ERG's point that, because of its 'bumpy' nature, the application of the TTP KM curve for the first 37 weeks of the model could cause some overestimation of TTP. We feel this limitation is minor for several reasons; firstly, the absolute effect will be very small with TTP only overestimated by a few weeks at most (assessments were every 9 weeks in the trial), secondly, any overestimation applies equally to both arms meaning the net effect will be even smaller, thirdly, it is unlikely that patients would experience an instantaneous change in utility upon radiographic progression and those with symptomatic progression would already be accounted for as they would have presented between the routine follow-up times and fourthly, this only applies to a small section (the first 37 weeks) of the economic model's time horizon. Overall, we considered it highly unlikely that this issue meaningfully affects the ICER and therefore did not feel that the extra complexity introduced by spline modelling would advantage decision-making.

B3. Priority question: The two-piece models used in the base-case estimate a significant number of patients achieving very long survival on both pembrolizumab and SoC, amounting to cure-like benefits in many patients.

MSD response: We will preface our responses to this question by stating that, while such data and advice as are available support the model's estimates, we believe it is difficult for anyone to be confident about the proportion of patients in this indication remaining alive in the long term:

- Bevacizumab has only been available for a few years and the longest published follow-up data are at 4 years, which we have used to select and validate survival curves for this model.(56)

- There is no/little clinical experience of using pembrolizumab in this population outside of the KEYNOTE-826 clinical trial, especially in the UK.

- Pembrolizumab itself has only been available in any indication for a few years; a long tail of patients who respond very well to treatment is common across immunotherapy studies and commonly observed in clinical practice.(57-62)

- The KEYNOTE-826 population is relatively uncommon, with perhaps 300 incident cases per year in England. Assuming an incidence rate of <10 cases per year for a typical consultant oncologist, there would be very limited data for individual clinical advisors to estimate long term survivorship, even if the relevant drugs had been available for 10+ years.

Given the points above, we would ask NICE and the ERG to carefully consider whether they believe it is possible for a clinical adviser to accurately estimate OS at time points beyond 10 years, particularly in the pembrolizumab arm of the model.

a) Please comment on the plausibility of the survival estimates generated by the model with reference to direct clinical advice supporting the model predictions on SoC in current practice.

MSD response: the longest published data for SoC OS comes from the GOG 240 trial.(25) The economic model producing a good fit to the four-year OS from this study was used as an explicit curve selection criterion for TTP curves. TTP curves were deemed inappropriate if, in combination with the base case analysis PPS curve, they caused modelled 4-year OS in the SoC arm to deviate more than an absolute 5% from expected 4-year OS for SoC based on the GOG 240 trial, which was estimated to be 15.1%. 4-year SoC OS in the base case analysis presented in the company submission was 12.7%. To quote the discussion section of the paper "At greater than 50 months of maximal follow-up, many patients continue to benefit from stable disease, and some have been cured with no evidence of clinical and radiologic disease."

Data on the longer term predictions were shown to clinicians at the UK advisory board. As noted above, the clinicians highlighted that bevacizumab has not been

around for very long, that pembrolizumab has not been available in the UK in this indication and that incident cases of metastatic cervical cancer in their clinics are relatively rare. Their level of confidence in being able to validate long term survival predictions, or select between competing curves was therefore quite low. Clinicians confirmed that 11% OS at 5-years is plausible, that long term outcomes are poor and that 20-year OS is likely to be below 5%; perhaps 1%. The model predicts OS is 3% at 10-years and 1.3% at 20 years for the SoC. The clinicians confirmed that cases of long-term complete response are rare but do exist. Although rare, these cases should be considered in the context of relatively low numbers treated by individual consultants per year. One clinician outside the advisory board confirmed to MSD that they have one patient at five years and another approaching seven years, both still have complete response following treatment with bevacizumab.

Taken together, we believe this empirical evidence and clinical advice, along with the robust set of curve selection criteria detailed in Document B of the submission support the OS estimates for SoC produced by the model.

b) Previous appraisals of immunotherapies have applied a waning effect on treatment benefits beyond the point of treatment cessation. Please justify the permanent treatment effect modelled on pembrolizumab, and provide direct clinical comment on the plausibility of the claimed benefits in this population on pembrolizumab.

MSD response: Clinicians at the UK advisory board were unable to comment on the length of treatment effect *per se* but commented that there is always a long tail among patients treated with immunotherapy and that the long-term projections for pembrolizumab do not look unreasonable. KEYNOTE-826 has some of the highest complete response (no evidence of clinical or radiologic disease) of any immunotherapy trial conducted, which clinicians consider to be prognostic of a long tail in OS.

We would point out that there is no UK clinical experience using pembrolizumab in this population, none globally in this indication outside the 2 years of this clinical trial, none globally in any indication for more than a few years and the

only empirical evidence for longer term follow up on pembrolizumab in other disease areas shows little or no waning effect.(57-62) If the long-term OS projections are considered by clinicians to be plausible, this also provides some validation of a long term treatment effect by implication.

Treatment waning assumptions have been inconsistently applied in NICE appraisals of immunotherapy in the past, for example, a recent review of nivolumab appraisals found that in only about half of decisions did the committee's base case assumptions include a waning effect (63) and there was no mention of treatment waning in pembrolizumab appraisals TA772,(64) TA709,(65) TA540,(66) TA366 (67) or TA357 (68). We would stress that these assumptions, where they have been applied, are not based on any empirical evidence. In all the longer term follow up trials of pembrolizumab a long tail can be seen,(58, 60, 62) even when complete response rates are much lower than in KEYNOTE-826.

To implement treatment waning relies on an implicit assumption that at some point in the model's time horizon, remaining patients become 'the same' between the arms. The only empirical evidence we have from KEYNOTE-826 indicates that patients in Complete Response, who will presumably constitute the majority of progression free patients in the downstream part of the model, have more durable response in the pembrolizumab arm. The fact that even within response categories patients cannot be considered the same between arms is one reason why the hazards of progression appear to be diverging rather than converging in the within trial period. In the context of diverging hazards, a "permanent treatment effect" might even be seen as conservative.

In short, we believe there is some empirical evidence and clinical advice to substantiate a long-term treatment effect and that there is none to substantiate an assumption of treatment waning.

c) **Please provide scenario analyses in which a waning of the treatment effect is applied. Aligning with previous committee preferences please include scenarios for 3 years and 5 years post discontinuation of treatment.**

MSD response: We have provided the requested scenario analyses in the separately provided model but, for the reasons highlighted in the response above, we do not believe that there is any strong evidence that these should be considered base case assumptions.

d) **If the company maintains the plausibility of a proportion of patients achieving cure or cure-like benefits, please substantiate this statistically through the use of mixture cure modelling, and include these models in the economic model.**

MSD response: We have not been able to provide a "mixture-cure" model due to a lack of data to substantiate the relevant assumptions. To provide some data by way of independent statistical substantiation of the model's predictions we have, however, undertaken a survival analysis for OS weighted by response group (CR, PR, SD, PD) and supplied a separate report detailing this analysis. There are two scenarios; one where OS is modelled using exponential survival models for all groups and another where the best fitting model, selected by the average of AIC and BIC is used.

The weighted survival analysis shows the expected trend that patients who were in CR after treatment gradually make up an increasing proportion of survivors. The long-term OS predicted for the pembrolizumab and placebo arms is similar to that predicted by the economic model and, perhaps more crucially, provides some evidence that it is not unreasonable to expect a small proportion of patients to achieve very long survival. Given the available data and evidence, MSD believes this is the best available method for statistically substantiating the long-term predictions of the economic model. **Error! Reference source not found.** shows an example output from the analysis, which is supplied separately and should be treated as AIC.

Figure 6: Example output from the Weighted Survival Analysis report

B4. Priority question: Modelled patients appear to experience mortality rates lower than those experienced by the general population as they age. Please update the model to ensure the mortality cap in the model is applied correctly across all patients regardless of progression status. Capping the PFS and PPS curves as done in the executable model does not achieve this.

MSD response: We agree that capping of PPS curves as was done in the model, did not prevent patients in the progressed disease health state from having a lower mortality probability than observed in the general population at their age in some model cycles. Thanks for pointing this out. We have corrected this error in the provided model: as it occurred in very few model cycles and affected very few patients, effects on the ICER were negligible (-£2). Technical comments on the methods used are provided in the overview sheet of the provided model.

B5. Priority question: The ERG considers there to be two sub-populations based on a patients' eligibility to receive bevacizumab.

a) **Please justify the pooling of these two patient groups in the base-case analysis.**

MSD response: MSD have submitted for the CPS≥>1 population for several reasons:

- The population in the submission is exactly in line with the KEYNOTE-826 marketing authorisation, which is also reflective of the population and mix of treatments seen in UK clinical practice

- MSD consider that “patients treated with bevacizumab” (“bev”) and “patients not treated with bevacizumab” (“no bev”) are not distinct subpopulations in the way that a subpopulation specified by a biomarker, histology or cancer stage might be considered distinct. The decision about initiating bevacizumab is reached following a discussion between the clinician and the patient based on an overall benefit/risk assessment which incorporates a number of factors. In other words, if the balance of risks/benefits were to change through the differential introduction of pembrolizumab, it is possible the constitution of the groups would also change.

- The trial was not powered to formally assess efficacy and safety in the “bev” and “no bev” sub-populations. Rather, KEYNOTE-826 was designed to assess the value of pembrolizumab when added to standard care, which may or may not include bevacizumab.

- Splitting up the population in this way would substantially reduce the number of events available to produce robust cost-effectiveness analyses.

- The point estimates for primary outcome treatment effects are not meaningfully different between the “bev” and “no bev” groups in the CPS≥1 population (OS HR 0.588 vs. 0.668 and PFS HR 0.603 vs. 0.645, respectively), are statistically significant in both and confidence intervals significantly overlap.

MSD considers that it is possible to specify subgroups that have a poorer prognosis by stage, histology and clinical history in any advanced cancer trial but that NICE committees do not routinely do this where the treatment works well across the subgroups, where incremental costs do not substantially differ and where the treatment is cost-effective in the whole population. The implication of examining different cost-effectiveness analyses in the “bev” and “no bev” groups is that, despite evidence of broadly equivalent clinical effectiveness, a different decision might be

reached based on cost-effectiveness alone i.e. to recommend pembrolizumab in the “bev” group and not in the “no bev” group, simply because they have a poorer prognosis due to a higher disease burden. We consider that such a decision would represent an equalities issue; it would mean that a treatment that is effective in both populations and cost-effective in the overall population would be denied to those patients with the greatest unmet need.

MSD is also concerned that to reach a differential decision for the “no bev” group might create a perverse incentive within the healthcare system; if pembrolizumab were only available for patients having bevacizumab, clinicians will be incentivised to prescribe bevacizumab, and patients incentivised to request it in order to access the benefits of pembrolizumab. This could expose patients to a greater than necessary risk/benefit profile. Something similar to this already occurs in practice. At present, the CDF rules dictate that bevacizumab is only able to be continued post 6 cycles if chemotherapy is continued. Clinicians have indicated to us that it is not uncommon for patients to continue low-dose chemotherapy unnecessarily in order to continue to access bevacizumab. Clinical advice received by MSD indicates that the proportion deemed fit for bevacizumab is highly variable across the country (50-80% across centres represented at the UK advisory board). We are concerned that differential recommendations for the subpopulations would introduce even greater variation in practice.

Finally, we are concerned that to reach a different decision for the groups would restrict choices for patients who are fit enough for bevacizumab as well as patients who are not. A patient who is fit enough for bevacizumab and therefore has a better prognosis but does not wish to take it is covered by the KEYNOTE-826 marketing authorisation and should be able to access pembrolizumab in combination with chemotherapy. “Pembrolizumab + bevacizumab” is not a combination treatment and therefore it makes little sense to recommend the two together as a combination, especially when the use of bevacizumab does not appear to meaningfully alter the treatment effect of pembrolizumab.

b) **Please provide cost-effectiveness results stratified by whether patients receive bevacizumab.**

MSD response: We have been unable to provide this within the time available but also consider, for all the reasons listed in the response to part a) that considering the subgroups separately from a cost-effectiveness point of view is not appropriate. Although we have not been able to do the analyses requested, we would note that the company's base case ICER for the whole population is quite far below the threshold. It is also important to note that CR and PR rates are still high at 17% and 42% in the "no bev" group receiving pembrolizumab (vs. 4% and 33% on chemotherapy alone) and HRs for OS and PFS are similar. Taking this evidence together with the other decision-relevant considerations discussed in our response to B5 part a), we consider the risk that pembrolizumab represents a cost-ineffective use of NHS resources in the "no bev" population to be small.

c) **Please provide OS data extrapolations stratified by whether patients receive bevacizumab as per question B1.**

MSD response: Below are the relevant graphics. OS appears to be lower in the "no bev" group but, based on the CR and PR data quoted in the response above and the shape of the curve it is still reasonable to expect a 'long tail' of OS to emerge as the data mature.

Figure 7: OS Extrapolations for the group with bevacizumab

Figure 8: OS extrapolations for the group without bevacizumab

B6. The economic analysis currently accounts only for grade 3 and 4 AEs occurring in >5% of patients. This approach fails to account for notable differences in some grade 1 and 2 AEs of special interest.

a) Please justify the current approach to modelling AEs and the omission of AEs of special interest.

MSD Response: We did not consider Grade 3+ AEs occurring in fewer than 5% of patients in both treatment arms, nor Grade 1 and 2 AEs of special interest (AEOSIs) occurring in >5% of patients in either treatment arm in the economic model as we expected that the impact on model results would be negligible (we expected that the added value of doing so would be outweighed by the added model complexity).

b) Please modify the economic analysis to account for all AEs of special interest occurring in more than 5% of patients.

MSD Response: We performed a scenario analysis in which we also considered the QALYs lost and costs associated with all Grade 1 and Grade 2 AEs of special interest occurring in >5% of patients in either treatment arm. The AEs that needed to be added to the model were: hyperthyroidism (grade 1 and 2), infusion reactions (grade 2), and hypothyroidism (grade 1). Effects on model outcomes were minimal, even when 100% of the disutilities and costs for Grade 3+ AEs were assumed for these lower-grade AEs.

B7. Priority question: The KEYNOTE 826 trial protocol indicates that retreatment with pembrolizumab was permitted (see question A4). Please provide details of any retreatment with pembrolizumab, including the proportion of patients who are retreated and the duration of any retreatment.

a) **Please comment on how and if retreatment with pembrolizumab has been accounted for in the model.**

MSD response: At the time of the interim analysis, “re-treatment” with pembrolizumab, as defined in the protocol, has not been observed for any patient.

In case the ERG’s intent was to explore 2L+ treatment with pembrolizumab after progression, a small number of progressing patients received this in each arm. In our response to question B8, we have provided mean treatment durations and accounted for these costs in a scenario analysis in the economic model.

Resource Use

B8. Priority question: Please provide further information on the subsequent treatments received in the KEYNOTE 826 trial including the following: i) the proportion of patients receiving subsequent treatment by treatment arm, ii) the distribution of all treatments received by treatment arm, iii) the duration of subsequent treatment.

a) **Please provide a scenario analysis in which the modelled subsequent treatments are based on all subsequent treatments received by patients in the KEYNOTE 826 trial (the ERG recognises that this scenario may not be consistent with UK practice).**

MSD response: Please find **Error! Reference source not found.** and Table 22 below which include data on the proportion of progressing patients in KEYNOTE-826 who received the most common subsequent treatments and the mean duration by arm. There are a small number of additional patients in each trial arm who received a range of less common treatments (typically a single patient per treatment) but, in the interests of time, we excluded all treatments with <3% in at least one of the arms and were unfortunately unable to source cost and dosing schedules for these within the timeframe. As the model is not sensitive to subsequent treatment costs, this limitation is minor.

In addition to providing this information, we have implemented the extra subsequent treatment options of interest into the model. Instead of only exploring subsequent received in second-line (2L) we have expanded the inclusion to all subsequent treatment lines. In addition, we have modelled the use of pembrolizumab in later treatment lines.

In the process of incorporating these extra subsequent treatment options, we noticed that we could base subsequent treatment percentage on two denominators:

1. The proportion of patients who progressed (as was done in the base case)
2. The proportion of patients who completed/discontinued (new scenario)

The proportions included in the base case were scaled to match the number of progressing patients, however, the information in **Error! Reference source not found.** are based on the proportion of patients who progressed. Therefore, an extra option is included to explore results with the latter denominator selected. All of these scenarios have a small impact on the cost-effectiveness results.

Table 21: Proportion of progressors receiving subsequent treatments

	Observed in KN-826			
	PEM+SoC		**SoC**	
Second line treatment	**Parametrised**	**Input**	**Parametrised**	**Input**
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
	% of progressed			

	PEM+SoC		SoC	
Additional lines treatment	**Parametrised**	**Input**	**Parametrised**	**Input**
Gemcitabine Hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]	[redacted]	[redacted]

Table 22: Mean duration of subsequent treatments

Mean treatment duration (days)						
Second line treatment	**Parametrised PEM+SoC**	**PEM+SoC Mean**	**PEM+SoC SE**	**Parametrised SoC**	**SoC Mean**	**SoC SE**
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All lines treatment	**Parametrised PEM+SoC**	**PEM+SoC Mean**	**PEM+SoC SE**	**Parametrised SoC**	**SoC Mean**	**SoC SE**
Gemcitabine Hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B9. Priority question: Please provide data on the proportion of patients that receive bevacizumab maintenance treatment (i.e. following discontinuation of platinum-based chemotherapy and paclitaxel).

MSD response: As made visible in Figure 38 of the CS, when treatment with platinum-based chemotherapy and paclitaxel are finished, 67.9% and 60.1% of patients are continued bevacizumab treatment for at least one cycle post chemotherapy in the Pem + SoC and SoC arms, respectively.

We have implemented a scenario where the costs of bevacizumab maintenance treatment are accounted for the economic model and this has a small effect on the

ICER, making Pem + SoC marginally more cost-effective. This is because the difference in drug acquisition costs is offset by the difference in administration costs.

B10. Priority question: The modelled pre-progression health state costs appear to exclude several cost elements typically included in advanced cancer models. Namely, GP visits, nurse/nurse specialist visits, and blood-counts.

a) **Please justify the current approach to modelling pre-progression health state costs and the omission of these cost elements.**

MSD response: At the UK advisory board, we showed clinicians the PFS and PPS health state resource uses from NICE TA620 (olaparib for ovarian cancer). We selected this as a starting point because it was a relatively recent gynaecological cancer appraisal that used a three-state model. The clinicians disagreed that the resource uses that had been used in this appraisal were appropriate for the KEYNOTE-826 population and provided the estimates that we used in the model instead.

b) **Please provide scenario analysis including these cost elements.**

MSD response: We have programmed a scenario including GP visits, nurse (specialist) visits, blood-counts, and thyroid function tests into the model version that has been made available. Frequency was kept consistent with the costs already included in the model and costing was based on the NHS reference costs 2019-2020 and PSSRU (2021). Including these additional resource costs has a marginal effect on the results of the cost-effectiveness model.

B11. Clinical advice to the ERG stated that thyroid function tests would typically be undertaken in patients undergoing immunotherapy.

a) Please comment on whether you agree that this is standard practice in patients undergoing immunotherapy.

b) Please provide a scenario analysis where the additional costs of thyroid function tests are accounted for.

MSD response: This has been included in our response to question B10 part b).

B12. In Table 38 of the CS, the adverse event cost of febrile neutropenia is inflated to 2017-2018 prices. Please justify why this cost was not inflated to a 2019-2020 price.

a) Please provide a scenario analysis in which the cost of febrile neutropenia is inflated to a 2019-2020 price

MSD response: Because this cost was sourced in the preliminary stages of the project, it was inflated to the wrong cost year. We have now corrected this and added it to the extra sheet in the new model version. This has a marginal effect on the cost-effectiveness results.

Health-related quality of life

B13. Priority question: The description of the quality of life data collected as part of KEYNOTE 826 appears to indicate that only visual analogue scale (VAS) data was collected. Please confirm the quality of life data collected as part of the KEYNOTE 826 trial and whether this was collected using the full EQ-5D-5L tool or just collected on a VAS.

a) If only VAS data was collected please comment on how this was mapped to EQ-5D-3L as the necessity for mapping in these circumstances is not clear to the ERG.

MSD response: We can confirm that EQ-5D-5L tool was used to collect of the quality of life data.

b) The company submission outlines that the Van Hout algorithm was used to map utility values to EQ-5D-3L. Please justify the use of the Van Hout algorithm and explain why the Hernández-Alava algorithm (recommended by the updated methods guide) was not used. We note that Hernández-Alava algorithm was recommended to the company at the decision problem meeting.

MSD response: Please note that this submission is following the old NICE methods guide (69) and, consistent with the position statement by NICE (70), the base case utilities were derived using EQ-5D-5L data from KEYNOTE-826 mapped onto the 3L scale using the algorithm developed by van Hout et al.(71).

We have run the analysis using the Hernández-Alava algorithm (72). The utility values are very similar and consequently, when implemented in the model, there is a minimal impact on the ICER. Please find the alternative results below:-

Table 23: Cost-effectiveness of PEM+SoC versus SoC using the Hernández-Alava utility mapping algorithm – list prices

Treatment	Totals per treatment arm			Incremental results			ICER (£/QALY)
	LYs	QALYs	Costs	LYs	QALYs	Costs	
SoC	2.51	[redacted]	[redacted]	2.80	[redacted]	[redacted]	£33,924
PEM+SoC	5.31	[redacted]	[redacted]				
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

B14. Priority question: The ERG does not consider the use of VAS scores to estimate utilities appropriate. Please justify why collected EORTC-C30 data from KEYNOTE 826 was not used to generate the utility values used in the model.

a) **Please present a scenario analysis using the EORTC-C30 data collected from KEYNOTE 826. These values should be mapped to EQ-5D-3L using an appropriate mapping algorithm in line with the NICE methods guide.**

MSD response: HRQoL as an exploratory endpoint was assessed using the EORTC QLQ-C30 (scores other than global score), EORTC QLQ CX24, and EuroQoL EQ-5D-5L and VAS. However, the utilities were assessed using just EQ-5D-5L tool. Based on the NICE hierarchy of preferred health-related quality-of-life methods EQ-5D tool used in the KN826 is appropriate and no further mapping exercises from the other tools like EORTC-C30 should be required.

B15. Priority question: Please provide the mean (and 95% CI) baseline utility, as measured by EQ-5D and EORTC-C30, in each treatment arm in KEYNOTE 826.

MSD response: Please see the response to B16 for data on baseline EQ-5D utility values.

Mean (and SD) baseline utilities for the EORTC-C30 for pembrolizumab + chemotherapy and placebo + chemotherapy were 62.97 (22.72) and 66.21(22.03) respectively (CSR Table 14.2-63).

B16. Priority question: Please estimate the mean utility value at baseline in each treatment arm in the model, with the TTD utility method and compare this to the mean baseline utility values in KEYNOTE 826. Please implement for both the base-case model and any scenario presented as part of the response to question B13.

MSD response: The mean utility value for patients at baseline was 0.683 and 0.704 for pembrolizumab + SoC and SoC treatment arms respectively, irrespective of any statistical or economic modelling.

Further, Table 24 provides the utility value from the economic model in each treatment arm for cycle one of the economic model (week one) under alternate statistical models of health utility (by TTD or by health state) and crosswalks (van Hout (71) or Hernandez-Alava (72)).

Table 24: Utility values from KN-826 and the cost-effectiveness model

	Pembrolizumab + chemotherapy	Placebo + chemotherapy
Mean utility at trial baseline, van Hout crosswalk	[redacted]	[redacted]
Mean utility at trial baseline, Hernandez-Alava crosswalk	[redacted]	[redacted]
Utility in cycle 1 of the model, with utilities modelled by TTD, van Hout crosswalk	[redacted]	[redacted]
Utility in cycle 1 of the model, with utilities modelled by health state, van Hout crosswalk	[redacted]	[redacted]
Utility in cycle 1 of the model, with utilities modelled by TTD, Hernandez-Alava crosswalk	[redacted]	[redacted]
Utility in cycle 1 of the model, with utilities modelled by health state, Hernandez-Alava crosswalk	[redacted]	[redacted]
Key: NA, not available		

It is not clear to us what concern the ERG hopes to address with this question but we have provided an interpretation of these data below:

The trial utilities being lower at baseline than the average TTD (and PFS) based utility is not surprising given that patients have not had the opportunity to benefit from treatment yet. It is reasonable to expect trial utilities to more closely resemble the TTD-based approximations used in the model as patients began to benefit from treatment. The same phenomenon would be observed with progression-based

utilities; a patient that has had CR or PR in response to treatment and is progression-free can be expected to have a higher utility than a patient who was in the PFS state at baseline yet they would be assigned the same utility in the economic model.

The slight discrepancy in model-based utility values between the arms at baseline is also not a cause for concern. This derives from the TTD approach and although perhaps a little unintuitive for the first few model cycles, any potential bias would quickly disappear as treatment effect began to be the dominant influence on utility between the arms.

There are also limitations with the intuition behind the progression-based approach that are outlined in the relevant section of the CS. Overall we feel that, while both approaches necessitate some level of simplification of the patient experience, the TTD approach is likely to be the more accurate.

It is not clear what is meant by “Please implement for both the base-case model”. Our apologies for not clarifying this with the ERG at the relevant time.

B17. Priority question: Please clarify whether the EQ-5D and EORTC-C30 questionnaires were administered in KEYNOTE 826 after patients discontinued their primary treatment or after disease progression.

MSD response: All questionaries were administered at both the time of discontinuation and at the 30-day safety follow up visit. This is standard practice for the KEYNOTE series of trials.

B18. Priority question: For each time point that the EQ-5D and EORTC-C30 questionnaire was administered in KEYNOTE 826, please provide the total patients available and the number of completed questionnaires, for

a) **All patients in each treatment arm.**

b) **All patients in each treatment arm, for each progression status (pre-progression and post-progression).**

c) **All patients in each treatment arm, in each TTD category.**

MSD response: Please see two embedded files for the EQ-5D (for CPS≥1) and other health related quality of life for ITT population tools (EORTC QLQ-C30, QLQ-CX24 Symptom Scores, and of EQ-5D VAS) that provide the total patients available and the number of completed questionnaires for each tool, results by progression status and by TTD category. Unfortunately, at this time we are not able to provide, for EQ-5D and EORTC QLQ-C30, the total patients available and the number of completed questionnaires by progression status and TTD disaggregated by visit.

[redacted]

[redacted]***Question 18.b - All patients in each treatment arm, for each progression status (pre-progression and post-progression).***

Table 25: EQ-5D Health Utility Scores (Progression-Free status based on Investigator Assessment) - UK Utility Value Crosswalk Mapping Participants With CPS ≥1 (All-Comer Full Analysis Set)

	Pembro Combo (N=256)		Control (N=264)		Total (N=520)	
	n†	m‡	n†	m‡	n†	m‡
Progression-free	[redacted]					
On Treatment						
Off Treatment						
Progressive						
On Treatment						
Off Treatment						

Database Cutoff Date: 03MAY2021
n† = Number of patients with non-missing EQ-5D score.
m‡ = Number of records with non-missing EQ-5D score.
EQ-5D score during baseline is not included.

Question 18.c - All patients in each treatment arm, in each TTD category.

Table 26: Number of patients and observations for the TTD regression analysis shows the total number of patients and observations in each TTD category in the regression analysis. The data disaggregated by visit was unable to be produced in time for the clarification question response deadline. If still required by the ERG we can supply at the technical engagement stage.

Table 26: Number of patients and observations for the TTD regression analysis

	[redacted]					
-						

[redacted]

B19. Priority question: Please provide further information on how the disutility associated with AEs was calculated as the provided explanation is unclear.

MSD response: This question refers to the mixed effects regression model of EQ-5D health utility, which was summarised in section B.3.4.5 and Tables 17 and 18. Briefly, patient-level EQ-5D-5L data was first calculated using the van Hout (71) crosswalk to a UK 3L value set. Only patients with PD-L1 CPS≥1 at baseline were included in the analysis set.

Descriptive analyses and conventional linear regressions are limited in that the assumption of independence between observations is not realistic in this context – observations may be more correlated if they are from the same patient than if they are from different patients. Linear mixed effects regressions account appropriately for this potential within-patient correlation. Since one patient could have multiple utility measures within the same health state or time-to-death category, mixed linear effects models with random subject intercept were used for this analysis to account for within-subject correlation. We used the *lmer* command in the *lme4* package with R statistical software version 4.02.(73)

The general formulation is as follows in general for a linear combination of k_1 time-independent and k_2 time-dependent covariates, where *i* denotes individual, and *j* denotes observation time when the EQ-5D measures was taken.

$$Utility_{i,j} = \beta_{0,i} + \Sigma_{k=1}^{k_1}\beta_k \cdot x_{i,k} + \Sigma_{k=k_1+1}^{k_1+k_2}\beta_k \cdot x_{i,j,k} + e_{i,j}$$

$$e_{i,j} \sim Normal(0, \sigma^2)$$

A series of statistical models was considered with the aim to find the most parsimonious model that could be incorporated into the cost-effectiveness model. The best fitting model was identified by considering Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) model fit statistics. Since mixed effects models are fitted by Restricted Maximum Likelihood rather than full likelihood, the statistical significance of additional parameters is not estimated.

The final model considered most parsimonious contained the covariates listed in Table 17, defined more specifically in Table 27 below.

Table 27: Further information on the statistical model of EQ-5D utility by time to death (base case)

k	Covariate name	Definition of $x_{i,k}$	β_k
0	Intercept	NA	0.431
1	Time to death 30-90 days	Equals 1 if time of death is observed and is within 30 to 89 days inclusive of the observation date; otherwise equals zero.	0.077
2	Time to death 90-180 days	Equals 1 if time of death is observed and is within 90 to 179 days inclusive of the observation date; otherwise equals zero.	0.209
3	Time to death 180-360 days	Equals 1 if time of death is observed and is within 180 to 359 days inclusive of the observation date; otherwise equals zero.	0.275
4	Time to death ≥ 360 days	Equals 1 if time of death may not be observed but is known to be at least 360 days from the observation date; otherwise equals zero.	0.329
5	Grade 3+ AEs	Equals 1 if a grade 3 or more AE (all-cause) became onset on or before the observation date and was resolved on or after the observations date; otherwise equals zero.	-0.033

Consequently, the regression coefficient for grade 3+ all-cause AEs (β_5 = -0.033) provides a disutility whilst experiencing grade 3+ AEs of 0.033.

Section C: Textual clarification and additional points

C1. Priority question: Please provide the following reference from CS Document B:

#3: Merck Sharp & Dohme Corp. Advisory Board held on 18 February 2022-Data on File. 2022.

MSD response: Please see advisory board report in separate file uploaded with the clarification question responses, which summarises the key topics discussed.

C2. Priority question: In Table 6 of the CS the EU/EMEA row numbers do not add up to make the total. Please clarify what the correct numbers are.

MSD response: This was a pasting error in Doc B. According to CSR, this should have been:

- Pembro: 91 (33.3)
- Control: 98 (35.6)
- Total: 189 (34.5)

C3. In Table 36 of the CS the missed doses registered for each component under study are presented. Should the headings be PEM + SoC and SoC rather than PEM and PEM+SoC?

MSD response: Yes, thank you for identifying this. The headers should indeed be PEM+SoC and SoC.

Literature Searches

C4. Priority question: Inaccessible Data: For the clinical searches, the embedded systematic literature review (SLR) report on page 4 of Appendix D was included in the original company submission but could not be reviewed as it would not open. Please provide this report.

MSD response: Please see SLR report as a separate in the reference pack uploaded with this response.

C5. Priority question: Missing Search Strategies: For the clinical searches, in the original submission there is insufficient information on the searches of the clinical trials registries and conference proceedings (listed in Appendix D, D.1.1, pp. 4-5). For both economics searches, there is mention of searches on the NICE website on page 19 of the embedded document on page 50 of Appendix G, but these are not documented. Please provide these data if available.

MSD response:

i) For the clinical search:

Regarding the clinical trial registries, ClinicalTrials.gov was searched with the following restrictions: cervical cancer as “condition or disease”; recruitment status as “recruiting”, “active, not recruiting”, or “completed”; and study results as “with results”. This resulted in 320 hits, of which three met the inclusion criteria and were included in the SLR. The EU Clinical Trials Register was searched with the following restriction: advanced cervical cancer as “condition or disease”. This resulted in 154 hits, none of which met the inclusion criteria.

Regarding conference proceedings, the Northern Lights database was searched using the following search strategy for the American Society of Clinical Oncology Annual Meeting (ASCO, 2020-2021), European Society for Medical Oncology Congress (ESMO; 2019-2021), and European Society of Gynaecological Oncology (ESGO; 2019-2021): exp Uterine Cervical Neoplasms/ or (cervi* adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab. This resulted in 137 hits for ASCO, 60 hits for ESMO, and no hits for ESGO. One abstract from ESMO and one abstract from ESGO met the inclusion criteria and were included in the SLR. Because the Society for Gynecologic Oncology’s Annual Meeting is not indexed in Northern Lights, proceedings from 2019-2021 were hand-searched. However, no abstracts met the inclusion criteria.

ii) For the economics search:

Search strings for the economic systematic literature review are available embedded in the Appendix G. The manual hand-searching of NICE website using *cervical cancer, cervix cancer, cervical and cervix* resulted in the retrieval of one technology assessment.

C6. Missed Condition Terms: For the clinical searches, the following terms would be missed: carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma, uterine cervix adenocarcinoma.

For both the economics searches and the health-related quality of life searches, the following terms would be missed on Medline, Embase, and PubMed: carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. For the health-related quality of life searches, this also applies to the searches of Cochrane CENTRAL and CDSR.

The search strategy for the economics searches using the CRD databases NHS EED, HTA, and DARE uses no MeSH terms. The MeSH term Uterine Cervical Neoplasms will bring back 541 hits. Moreover, a search for 'cervical cancer' is quite limited.

Please justify the exclusion of these condition terms.

MSD response:

i) Clinical searches:

Database subject headings were selected and employed in the search strategies to increase the sensitivity of the search. Specifically, for the Embase search, the Emtree term "uterine cervix carcinoma" was exploded, meaning that all records with the narrower Emtree term "uterine cervix adenocarcinoma" were retrieved. For the MEDLINE search, the only relevant MeSH term "uterine cervix neoplasms" was employed.

To determine whether the absence of the keywords "carcinoma colli uteri", "endocervical carcinoma", "endocervix carcinoma", or "uterine cervix adenocarcinoma" in the title or abstract fields may have served to miss relevant studies, we reran the search strategies with the inclusion of these keywords. An Embase search with the inclusion of these terms retrieved two studies that were not retrieved by the original search strategy; one was irrelevant due to wrong study design, and one duplicated a record retrieved by the original MEDLINE search (which was ultimately excluded due to intervention not of interest). Similarly, a MEDLINE search with the inclusion of these terms retrieved two studies that were not retrieved by the original search strategy; one was irrelevant due to wrong study design, and one duplicated a record retrieved by the original Embase search (which was ultimately excluded due to intervention not of interest).

Therefore, the combination of database subject headings and keywords employed in the original search strategies appears to be sufficiently broad so as to capture all relevant studies.

ii) Economic searches:

The searches employed two methods to capture all relevant population keywords:

- Method 1:

- If we refer to the Emtree in embase.com, carcinoma colli uteri, endocervical carcinoma, and endocervix carcinoma are already indexed as synonyms of “uterine cervix carcinoma”
- “Uterine cervix carcinoma” is further indexed under the “uterine cervix cancer,” which itself is the broadest cervix-related relevant terminology in embase.com
- Our search strategies utilized the “uterine cervix cancer” terminology, resulting in 128962 search hits. This covers the “uterine cervix carcinoma” as well as the three additional keywords (listed as its synonyms)
- If to create a separate search string using the three keywords highlighted by the ERG, it would be just a duplication of search numbers. These are already covered within the provided screening/evidence pack

- Method 2
  - Another way of identifying the publications associated with the highlighted keywords is through search string no—3 in the disease facets (Table 1 in section 2.1 of the economic SLR report). Since we have used an asterisk* functionality on cervi, we are able to identify words like endocervical and endocervix. In addition, there is a NEAR/5 proximity operator in search string no. 3, and it will identify the “carcinoma” keyword within the specified number of words (n=5) from cervi*.

Table 28: Extraction from Economic SLR – *Table 1: Summary of search hits retrieved from Embase® and MEDLINE® searched via embase.com (From Database inception to 31st October 2021) – Economic review*

No	Search strings	Hits
#1	'uterine cervix cancer'/syn	128962
#2	'cervical tumor' OR 'cervical neoplasm'	1705
#3	cervi* NEAR/5 (cancer* OR oncolog* OR neoplas* OR carcinom* OR malignan* OR tumor* OR tumour* OR mass* OR growth* OR cyst* OR adenocarcinom* OR squamous)	176614

Regarding the CRD York database, the “cervical cancer” terminology was utilized, which is a broad, relevant, and specific keyword resulting in 447 search hits (not limited). This covers all the relevant publications. Also, it should be noted that this database was last updated ~7 years ago; the majority of the evidence in this database is not aligned with the latest published literature; it is already indexed in other up-to-date databases; HTAD (one of the listed components in CRD) was also manually searched (NICE and SMC websites). Apart from the systematic searching on different biomedical databases, also an extensive grey literature search was conducted using focused cervical-related keywords (multiple variations, e.g., cervix, cervical, uterus, uterine) on different platforms (e.g., databases, google search engine) to ensure that the final evidence pack is complete from every perspective.

C7. For the clinical searches, the PRISMA diagram does not list the number of records from ‘European Union Clinical Trials Registry’ (EU CTR) even though this source is listed as one of the sources searched in Appendix D, D.1.1, page 4. Please provide this if available.

MSD response: As none of the search results from the EU Clinical Trials Register met the inclusion criteria, no records identified from this source were included in the SLR.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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

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

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

Information on completing this submission

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

About you	
1. Your name	[redacted]
2. Name of organisation	**BGCS**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Gynaecological Cancer Society** Funded by member subscription fees
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**Yes** MSD/AZ Alliance sponsored both the May Virtual Annual Society Meeting and the Cheltenham Autumn Meeting on 29/10. Total amount of sponsorship £35,000.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms, maintain quality of life and increase PFS (slow progression)and OS (prolong survival)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	The significant improvement in survival seen with the addition of pembrolizumab to platinum-based chemotherapy (overall survival at 24 months increased by >10% and a reduced risk of death of >30% with pembrolizumab compared with placebo) is clinically meaningful.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Treatment options for women with locally recurrent, unresectable cervix cancer and metastatic cancer are very limited after 1st line and so for many 2nd line treatment and beyond needs to be in the context of a clinical trial and this is also an unmet need (very few cervix cancer trials in UK)
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Carboplatin and paclitaxel q21 days x 6 (+/- bevacizumab via the Cancer Drug Fund)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Reed N, Balega J, Barwick T et al. British Gynaecological Cancer Society (BGCS) Cervical Cancer Guidelines: Recommendations for Practice (2020) ESMO https://www.annalsofoncology.org/article/S0923-7534(19)42148-0/pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes. Minimal variation as little funded treatment available in the UK for women with cervix cancer

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Would bring UK closer in line with other developed countries whose outcomes are significantly better in Gynae cancers in the UK
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
• How does healthcare resource use differ between the technology and current care?	Patients would currently attend for 6 cycles of carboplatin and paclitaxel but this would mean some patients, responding well, may continue on iv treatment with pembrolizumab as maintenance for up to 35 cycles
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None specific, the treatment would be taken up by NHS Cancer centres

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as per N Engl J Med 2021; 385:1856-1867
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Benefit seen in all-comers (intention-to-treat) population – efficacy may be more pronounced in those with a higher PDL-1 expression level
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Capacity for the delivery of the continued treatment beyond standard 6 cycles of chemotherapy but all units will now have considerable experience with this drug in other tumour sites
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment to be continued to a maximum of 35 cycles as long as acceptable toxicity and disease control. This would be assessed by standard cross-sectional imaging, usually CT, as per standrd
15. Do you consider that the use of the technology will result in any substantial health-	no

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes as above

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The more severe adverse events seen more commonly with the addition of pembrolizumab were anaemia and neutropenia which can be managed and occur only a little more frequently than with placebo
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the control arm is the current standard of care in the UK as described above
• 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?	PFS and OS balanced against acceptable toxicity yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	N Engl J Med 2021; 385:1856-1867
21. How do data on real-world experience compare with the trial data?	unknown
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

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

- There are very few options of treatment for women with recurrent and metastatic cervical cancer
- The outcomes are currently very poor and the rates of survival in UK are worse than in other European countries
- This cancer most commonly affects young women who can contribute to society if they are well and live longer
- This is a relatively rare cancer
- Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer can make a big difference for those women and significantly improve their outcomes

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Jo's Cervical Cancer Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Jo's Cervical Cancer Trust is the UK's leading cervical cancer charity. We are here for everyone who needs us, for as long as they need us, and we won't stop until the day that cervical cancer is no more. Cervical cancer can be devastating but we're here to reduce the impact. We provide trustworthy information, campaign for change and provide support at every step.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	£15,000 from MSD in September 2021.

If so, please state the name of manufacturer, 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?	Through our online Forum, emails with supporters and members of our community and previous research around access to different treatments and drugs.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	There are around 3,200 new cervical cancer cases in the UK every year, that's nearly 9 every day (2016-2018)[i]. If caught early, cervical cancer can be very treatable, however many treatments bring long term and often life-changing consequences including bowel/bladder damage, mental health impact, infertility and lymphoedema[ii]. For those with an incurable diagnosis, there are few palliative treatments. This means opportunities to extend life are limited.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For people with recurrent, persistent or metastatic cervical cancer the aim of treatment is to relieve symptoms and improve quality of life. There are currently limited treatments for those with such diagnoses. Avastin (bevacizumab) is currently the only targeted medication used to help treat advanced and late-stage cervical cancers in the UK. It has a proven overall survival benefit when added to chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer, extending life by many months in some cases. However, some contraindications to bevacizumab are common complications of recurrent or metastatic cervical cancer, including active bleeding, most commonly vaginal bleeding; a common complication from their disease, meaning not all patients are eligible for it. Despite its benefits, only 14.5% of metastatic/recurrent cervical cancer patients treated over a 10-year period were eligible to receive bevacizumab. Identifying new therapies for metastatic/recurrent cervical cancer patients with improved safety profiles that would allow for their use in this challenging population is critical[iii]. The introduction of pembrolizumab is extremely positive as it extends the opportunities to extend, and improve quality of, life. At the moment, pembrolizumab is not available on the NHS and the cost of private treatment is extremely high meaning there is a significant inequality in access to a drug that can give life. Currently, if patients are even told about pembrolizumab at all, their only option is to pay exorbitant prices (anecdotally £10,000 per treatment), with families resorting to crowdfunding to pay these bills at an already difficult time. It is not available for cervical cancer patients through the Cancer Drugs Fund either. Pembrolizumab is currently offered to cervical cancer patients in other countries (e.g. USA). This makes it more disappointing for patients in the UK that they do not have access to it.

	At Jo's Cervical Cancer Trust we believe there is an urgent need to introduce this drug so that a greater number of women have the opportunity to access life-saving and life-extending medication.
8. Is there an unmet need for patients with this condition?	For women who receive a late-stage diagnosis of cervical cancer, the prognosis can often be poor. There are currently very few treatment options for those with recurrent, persistent or metastatic cervical cancer. If these treatment options prove to be unsuccessful, patients are left with no alternatives. Patients are also left with little control or decision making-power over the treatment they receive, because of the limited options. Currently bevacizumab is the only targeted therapy treatment used to treat cervical cancer. Jo's Cervical Cancer Trust believes it is crucial that as many effective treatments as possible are made available to cervical cancer patients. This is supported by clinicians including Dr. Antonio González-Martín, Cancer Centre Director, Clínica Universidad de Navarra, who described pembrolizumab for treating recurrent, persistent or metastatic cervical cancer as "a practice-changing study", adding "The data are so solid in terms of increment in overall survival that this combination should be considered the new standard of care for women with persistent, recurrent or metastatic cervical cancer.[iv]" There has been a need for some time for innovation and development for treating cervical cancer patients, and we are pleased that this technology may provide that.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The research to support the use of pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer has found that: • Progression-free and overall survival were significantly longer with pembrolizumab than with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab. • Adding pembrolizumab alongside chemotherapy treatment can reduce the risk of death by 33%

	and lower the likelihood of disease progression or death by 35%. • For patients who cannot receive bevacizumab, adding pembrolizumab to chemotherapy alone still has clinically meaningful benefit[v]. • Pembrolizumab plus chemotherapy with or without bevacizumab demonstrated a statistically significant improvement in overall survival and progression-free survival compared to chemotherapy with or without bevacizumab in this patient population. Additionally, more patients responded to the pembrolizumab regimen, with an objective response rate of 68% versus 50%, respectively. • "After many years of limited progress in developing new treatment options for persistent, recurrent or metastatic cervical cancer, we saw notable improvements in overall survival in KEYNOTE-826, with a 36% reduction in the risk of death. With today's approval, healthcare providers in the EU will be able to offer certain patients with advanced cervical cancer a long-awaited immunotherapy option that has shown significant improvement in overall survival.[vi]" • Women diagnosed with persistent, recurrent or metastatic cervical cancer often have a low survival rate. The pembrolizumab regimen for women with persistent, recurrent or metastatic cervical cancer is the first of its kind for an immunotherapy regimen in Europe. At Jo's Cervical Cancer Trust we are encouraged by these findings, and believe they provide a strong argument for the introduction of this treatment type to the NHS. This treatment appears to offer better outcomes than existing treatment types, and has the potential for significant rates of progression-free and overall survival. The addition of a new treatment option also affords patients the opportunity to make choices about their treatment pathway, and may provide more opportunities to find a type of treatment that works for them. Pembrolizumab, in some cases, can prolong life by several months. Extra time at the end of life cannot be understated. The impact of Avastin (bevacizumab) - currently the only targeted medication used to help treat advanced and late-stage cervical cancers in the UK - has been significant on the women it is used to treat. The below quotes demonstrate the impact of treatment for advanced stage cancers. We anticipate

	Pembrolizumab being able to offer further benefits to the quality of life and well-being of women with recurrent, persistent or metastatic cervical cancer – in particular, longer progression-free and overall survival, and significant reduction in the risk of death[vii]. *"My daughter had Avastin. The consultant made a special case for her. It didn't save her life, but it did give enough time for her and her brother to make up. They hadn't spoken for nearly a year and she got to see her beloved niece and nephew once more."* *"Avastin, in particular, I believe has had a huge part to play. My consultant explained that Avastin will add a number of months onto my life expectancy and that it is proven to improve treatment of chemotherapy alone. I have now exceeded my prognosis. I feel incredible that I was given the chance to receive this, although I do feel upset that not everyone is given the option to receive this miracle drug."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments this drug can bring side effects, including anaemia, low concentration of white blood cell, fistula, infection, or haemorrhage, and some patients have had to stop treatment because of them. Common side effects included fatigue, pain, nausea and vomiting, and difficulty breathing (dyspnea). A significant number of patients had side effects that required treatment with corticosteroids[viii]. For many women these side-effects will be acceptable, if the treatment offers the opportunity for recovery, progression-free survival, or an extended lifespan. Any treatment plan should include full discussion of the risks and benefits.

Commented [KS1]: Is there something more scientific to back this up?

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.	For patients who cannot receive bevacizumab, adding pembrolizumab to chemotherapy alone still has clinically meaningful benefit. This means that for patients who cannot receive Avastin - currently the only targeted medication used to help treat advanced and late-stage cervical cancers in the UK – there will now be another option. For patients with recurrent cervical cancer, previous treatment options may have been exhausted, so the additional option of pembrolizumab as a treatment type offers them further opportunity for recovery, progression-free survival, or an extended lifespan[ix]. At Jo's Cervical Cancer Trust we believe it is essential that as many patients as possible have the opportunity to access effective treatments.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Pembrolizumab is offered to other people already on the NHS such as non-small cell lung cancer patients and patients with incurable secondary triple negative breast cancer[x]. While cervical cancer is a rarer cancer, it is an inequality that it is not offered to cervical cancer patients.

Commented [KS2]: Reference? Maybe expand this line too? You're basically saying those who can't have avastin can get this so it's positive?

Other issues	
13. Are there any other issues that you would like the committee to consider?	The position from Jo's Cervical Cancer Trust is: "For patients in one of the most difficult situations, living with advanced cervical cancer, there are precious few treatment options. Pembrolizumab presents an amazing option which can literally give life and we needed to see it available on the NHS yesterday. The reality is that without pembrolizumab available on the NHS, we are seeing women with advanced cervical cancer lose out on precious time with their family and loved ones for no good reason. We know that pembrolizumab is a brilliantly effective drug which affords many people with other types of advanced cancers more time. We must see the same extended to those with cervical cancer across the UK. These women have no time to wait and we urge NICE and approval bodies throughout the UK to act fast."

Key messages

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

- There are currently very few drugs for recurrent, persistent or metastatic cervical cancer
- The evidence suggests that use of pembrolizumab can lead to a significant improvement in overall survival and progression-free survival, compared to chemotherapy with or without bevacizumab
- Pembrolizumab is already offered to other people already on the NHS such as non-small cell lung cancer patients. We believe this should be extended to cervical cancer patients
- This opportunity to extend lives – and improve their quality – must not be missed.

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[i] https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer#:~:text=There%20are%20around%203%2C200%20new,year%20(2016%2D2018).

[ii] https://www.jostrust.org.uk/about-us/our-research-and-policy-work/our-research/long-term-consequences-cervical-cancer

[iii] https://journals.sagepub.com/doi/full/10.1177/1179554918779587

[iv] https://www.esmo.org/newsroom/press-office/immunotherapy-prolongs-survival-in-recurrent-persistent-or-metastatic-cervical-cancer

[v] https://www.esmo.org/newsroom/press-office/immunotherapy-prolongs-survival-in-recurrent-persistent-or-metastatic-cervical-cancer

[vi] https://www.merck.com/news/european-commission-approves-mercks-keytruda-pembrolizumab-plus-chemotherapy-with-or-without-bevacizumab-for-patients-with-persistent-recurrent-or-metastatic-cervical-cancer-whose/

[vii] https://www.nejm.org/doi/10.1056/NEJMoa2112435

[viii] https://www.rxlist.com/consumer_pembrolizumab_keytruda/drugs-condition.htm#what_are_side_effects_associated_with_using_pembrolizumab

[ix] https://www.esmo.org/newsroom/press-office/immunotherapy-prolongs-survival-in-recurrent-persistent-or-metastatic-cervical-cancer

[x] https://www.england.nhs.uk/2018/06/nhs-england-strikes-deal-on-new-nice-recommended-lung-cancer-immunotherapy-drug/

NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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

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

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

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

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

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of this treatment is in terms of reducing symptoms from metastatic cervical cancer and improve quality of life and to slow the progression (worsening) of cancer thereby prolonging progression free survival (PFS) and overall survival (OS).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Women with recurrent/ persistent advanced cervical cancer have limited effective treatment options. In this setting the benefit seen with the addition of pembrolizumab to platinum-based chemotherapy is a significant advance for patients as overall survival at 24 months increased by >10% and there was an associated reduction in the risk of death of >30% with pembrolizumab compared with placebo. This outcome has a significant and meaningful impact to patients and their families in terms of survival, but also improved quality of survival by management of symptoms.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Treatment options for women with locally recurrent, unresectable cervix cancer and metastatic cancer are very limited after 1st line and so for many 2nd line treatment and beyond needs to be in the context of a clinical trial and this is also an unmet need (very few cervix cancer trials in UK)
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Carboplatin/cisplatin and paclitaxel q21 days x 6 (+/- bevacizumab via the Cancer Drug Fund), in recurrent disease there is the option of topotecan and cisplatin, however there is significant toxicity associated with this regimen and so alternative efficacious and less toxic options are urgently needed.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The main guidelines are below: ESMO https://www.annalsofoncology.org/article/S0923-7534(19)42148-0/pdf Reed N, Balega J, Barwick T et al. British Gynaecological Cancer Society (BGCS) Cervical Cancer Guidelines: Recommendations for Practice (2020)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	The pathway of care is well defined in the UK and there is consensus that for women who are fit enough to receive treatment that the preferred options is cisplatin/ carboplatin and taxol and bevacizimab is added via the Cancer Drugs Fund. There is minimal variation due to the limited number of options for treatment in this setting.

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The availability of pembrolizmab would add a much needed new effective (symptom control and extension of survival) and less toxic treatment option for women, who up until now have had a poor overall outlook. It is important that women in the UK have access to the best treatment options to ensure that our outcomes remain in line with that of other similar countries.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in line with current care in the UK.
• How does healthcare resource use differ between the technology and current care?	Currently women attend 3 weekly for intravenous chemotherapy for 6 cycles and the group receiving pembrolizumab would then continue with intravenous treatment post chemotherapy (maintenance) for up to 35 cycles
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment will be in tertiary care within specialist oncology clinics. Treatment will be initiated and supervised by clinicians who have specialist experience in the treatment of cervical cancer.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Immunotherapies, such as pembrolizumab, are already routinely used in the treatment of a number of different cancers and all cancer centres/ units in the UK have experience/ SOPs in place so no additional facilities/training will be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes we expect pembrolizumab to provide clinically meaningful benefit. (ref: N Engl J Med 2021; 385:1856-1867) A recent trial demonstrated that in 548 patients with a PD-L1 combined positive score of 1 or more, median progression-free survival was 10.4 months in the pembrolizumab group and 8.2 months in the placebo group (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.50 to 0.77; P<0.001). In the overall trial population of 617 women it demonstrated a significant improvement in progression-free survival of 10.4 months in the pembrolizumab group compared to 8.2 months in the placebo group an (hazard ratio, 0.65; 95% CI, 0.53 to 0.79; P<0.001). In 317 patients with a PD-L1 combined positive score of 10 or more, progression-free survival was 10.4 months and 8.1 months, respectively (hazard ratio, 0.58; 95% CI, 0.44 to 0.77; P<0.001). Importantly there was also an improvement in overall survival at 24 months and a reduction in the risk of death: Overall survival at 24 months was 53.0% in the pembrolizumab group and 41.7% in the placebo group (hazard ratio for death, 0.64; 95% CI, 0.50 to 0.81; P<0.001), 50.4% and 40.4% (hazard ratio, 0.67; 95% CI, 0.54 to 0.84; P<0.001), and 54.4% and 44.6% (hazard ratio, 0.61; 95% CI, 0.44 to 0.84; P=0.001), for the above groups respectively. Treatment was generally well tolerated.

• Do you expect the technology to increase length of life more than current care?	As section 11 part 1 above.
• Do you expect the technology to increase health-related quality of life more than current care?	The trial above demonstrated improved control of symptoms, and this will have a positive impact on a patient's overall wellbeing and quality of life in routine use.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Within the trial (ref: N Engl J Med 2021; 385:1856-1867) a benefit was seen in all women treated with pembrolizumab compared to placebo regardless of PDL1 status and this would be the preferred use of this technology.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	There will be additional visits associated with administration of intravenous pembolizimab. However immunotherapies such has pembrolizumab are already routinely used in the treatment of a number of different cancers and all cancer centres/ units in the UK have experience/ SOPs in place so no additional

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.)	facilities/training will be required. No specific additional concerns are expected with the use of this agent in women with cervical cancer/ patient acceptability.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would be expected to be continued to a maximum of 35 cycles providing there is disease control (assessed clinically and via standard cross-sectional imaging, usually CT, as required) and toxicity is acceptable.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None known.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, as per previous responses.
• Is the technology a 'step-change' in the management of the condition?	Yes, as per previous responses.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as per previous responses.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side effects seen with the addition of pembrolizumab were haematological - anaemia and neutropenia, these can be satisfactorily managed and within the trial only occurred slightly more frequently than with placebo (The most common grade 3 to 5 adverse events were anaemia (30.3% in the pembrolizumab group and 26.9% in the placebo group) and neutropenia (12.4% and 9.7%, respectively). (ref: N Engl J Med 2021; 385:1856-1867)

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the control arm used in the trial referenced below is the current standard of care in the UK. (ref: N Engl J Med 2021; 385:1856-1867)
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trial demonstrated improved outcomes for women with difficult to treat cervical cancer – with improved progression free and overall survival in the group receiving pembrolizumab. Importantly there was limited additional toxicity associated with this treatment. The combination of improved activity and tolerability for this group of women are important outcomes and offer a new treatment option where there are currently only limited toxic alternatives.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	N Engl J Med 2021; 385:1856-1867
21. How do data on real-world experience compare with the trial data?	Unknown
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	NA
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • New effective and tolerable treatment option for women with recurrent/persistent metastatic cervical cancer • Addresses area of unmet clinical need where there are limited therapeutic options. • Impressive reduction in risk of death/ overall survival.	

Thank you for your time.

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Evidence Review Group's Report
Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Date completed 30/05/2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135578.

Declared competing interests of the authors

None

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:

Rodgers M, Walton M, Corbett M, Answer S, Njoroge M, Fulbright H, Naik R, Powell M, Eastwood A, Hodgson R. Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2022.

Contributions of authors

Mark Rodgers, Mark Corbett and Sumayya Anwer performed the critique of clinical evidence and co-authored sections 1, 2 and 3 of the report. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections. Helen Fulbright wrote the sections on the search strategies. Matthew Walton, Martin Njoroge, Sumayya Anwer and Robert Hodgson critiqued the company's model, and co-authored Sections 1, 4, 5 and 6 of report. Robert Hodgson took overall responsibility for the cost effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike's information criterion
APaT	All patients as treated
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BGCS	British Gynaecological Cancer Society
BNF	British National Formulary
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPS	Combined positive score
CR	Complete response
CS	Company submission
CSR	Clinical study report
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EoL	End-of-life
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
ERG	Evidence Review Group
FAD	Final appraisal determination
FDA	U.S. Food and Drug Administration
HRG	Healthcare resource group
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan-Meier
LS(M)	Least square (means)
MHRA	Medicines & Healthcare Products Regulatory Agency
NA	Not Applicable
N/A	Not Applicable

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	No response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PfC	Point for clarification
PFS	Progression-free survival
PICOS	Population, Intervention, Comparison, Outcomes, and Study design
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SD	Standard deviation
SD	Stable Disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
STA	Single technology appraisal
STM	State transition model
ToT	Time on treatment
TTD	Time to death
TTP	Time to progression
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1.	Applicability of the KEYNOTE-826 trial to the NHS population	2.2.1 and 3.2.2.1
2.	Immature overall survival data	3.2.3.1
3.	Uncertain relationship between progression-free survival and overall survival	3.2.1.3 and 4.2.2.1
4.	Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	3.2.3.1
5.	Application of two-year stopping rule	2.3 and 4.2.6.1
6.	Appropriateness of state transition model	4.2.2.1
7.	Extrapolation of PFS	4.2.6.1
8.	Extrapolation of PPS	4.2.6.2
9.	Treatment waning effect for pembrolizumab	4.2.6.1
10.	Health state utilities	4.2.7.1
11.	Resource use	4.2.8
12.	Relevance of bevacizumab and availability of bevacizumab biosimilar	4.2.4
13.	End-of-life criteria	7

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The company's preferred extrapolation of PFS is based on a two-piece approach, the ERG prefers to use a single piece
- The company prefers to assume a differential PPS across treatment arms, the ERG prefers to assume a common (pooled) duration of PPS across treatment arms
- A lifetime treatment benefit is assumed by the company, whereas the ERG prefers the assumption of a 3-year treatment benefit to align with previous appraisals
- Time-to-death utilities are preferred by the company, yet the ERG considers there to be more conceptual validity to using progression-based utilities

- Time on treatment with pembrolizumab is capped at 24 months in the company's economic model, though the ERG prefers to use a 35-cycle cap in line with the KEYNOTE-826 trial
- The company model does not account for GP/nurse visits, blood-counts, and thyroid function tests costs, whereas the ERG prefers to include these costs
- The company model costs disutilities associated with Grade >3 events occurring in >5% of patients, the ERG model also includes Grade 1 and 2 AE's of special interest occurring in >5% of patients

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 progression-free survival
- Increasing overall survival

Overall, the technology is modelled to affect costs by:

- Its higher acquisition costs
- Its higher administration costs

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit for pembrolizumab (extrapolation of progression free survival)
- The size of the post-progression survival benefit for pembrolizumab (extrapolation of post-progression survival)
- Treatment waning
- Utility values applied in the model (time to death vs progression based)

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Applicability of the KEYNOTE-826 trial to the NHS population

Report section	2.2.1 and 3.2.2.1
Description of issue and why the ERG has identified it as important	Patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 were excluded from the KEYNOTE-826 trial. However, the ERG's advisors estimated that 20-30% of ECOG PS 2 patients would be eligible for systemic treatments in the NHS. Conversely, patients with ECOG PS 0 were over-represented in KEYNOTE-826 (56% of patients) compared with the ERG advisers' estimate for the relevant NHS population (10-15%). In the NHS, bevacizumab would not be continued for as many cycles as were observed in KEYNOTE-826 (where the number of cycles was unlimited). In KEYNOTE-826, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could have affected results to slightly favour pembrolizumab. Collectively, these issues mean that pembrolizumab may be less efficacious when used in an NHS setting, i.e. the KEYNOTE-826 results may be somewhat over-optimistic.
What alternative approach has the ERG suggested?	Not applicable.
What is the expected effect on the cost-effectiveness estimates?	The limited evidence adds uncertainty to the cost-effectiveness estimates. The ERG does not consider it appropriate to extrapolate results of the presented economic analysis to an ECOG 2 population.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the proportion of ECOG 2 patients who receive systemic treatment. Evidence on the effectiveness of pembrolizumab in an ECOG 2 population; the ERG is unaware of any appropriate data sources.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Immature overall survival data

Report section	3.2.3.1
Description of issue and why the ERG has identified it as important	Overall survival (OS) data from KEYNOTE-826 are immature, with the median OS not being reached in the pembrolizumab group. This means that appropriate methods must be used for extrapolating and estimating longer-term OS data (see Issues 3 and 6).
What alternative approach has the ERG suggested?	Not applicable due to data immaturity.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The KEYNOTE-826 final trial analysis is anticipated in [redacted].

Issue 3 Uncertain relationship between progression-free survival and overall survival

Report section	3.2.1.3 and 4.2.2.1
Description of issue and why the ERG has identified it as important	In the company submission (CS), progression-free survival (PFS) is considered to be an appropriate surrogate for OS. However, it is unclear to what extent this is true; the CS does not robustly demonstrate that such an association exists, providing limited evidence based on clinical opinion and an analysis of KEYNOTE-826 . The ERG's clinical advisors do not believe that PFS is necessarily a reliable surrogate for OS in this population, noting that treatment can delay progression without extending survival. Extrapolation estimates of OS beyond the available trial data and into the longer-term are therefore highly uncertain.

What alternative approach has the ERG suggested?	The surrogate relationship between PFS and OS is a key assumption of the economic analysis, see issue 6.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The KEYNOTE-826 final trial analysis is anticipated in [redacted]. This may help validate whether observed improvements in PFS translate into OS benefits.

Issue 4 Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis

Report section	3.2.3.1
Description of issue and why the ERG has identified it as important	The subgroup of patients with metastases at initial diagnosis had statistically significantly worse PFS outcomes than patients without metastases at initial diagnosis. OS results were also notably different. This apparent lack of effect for PFS (in particular) and for OS was similar (in terms of hazard ratios) to that seen in the PD-L1 CPS <1 subgroup, which was excluded from the EMA's marketing authorisation.
What alternative approach has the ERG suggested?	Appropriate analysis of the metastatic subgroup in the economic model.
What is the expected effect on the cost-effectiveness estimates?	Unclear; apparent lack of efficacy in the metastatic population is likely to imply a higher ICER in this subgroup.
What additional evidence or analyses might help to resolve this key issue?	Appropriate analysis of the metastatic subgroup in the economic model. Clinical and/or expert opinion on the biological plausibility of a differential treatment effect.

Issue 5 Application of two-year stopping rule.

Report section	2.3 and 4.2.6.1
Description of issue and why the ERG has identified it as important	In KEYNOTE-826 a stopping rule was imposed limiting the maximum treatment duration to 35 cycles (about two years). It is unclear whether a stopping rule would be considered appropriate in clinical practice. The ERG, however, note a stopping rule has been applied in nearly all previous appraisals of pembrolizumab.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical validation of the appropriateness of a stopping rule.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6 Appropriateness of state transition model

Report section	4.2.2.1
Description of issue and why the ERG has identified it as important	The company's economic analysis uses a state transition model (STM). A key assumption of this approach is that is implies a surrogate relationship between PFS and OS. As discussed in Issue 3, there is limited evidence provided to support this assumption and uncertainty regarding the reliability of PFS as a surrogate. The ERG also notes that the model generates predictions that do not always align with the observed data and demonstrates a bias in favour of pembrolizumab. The ERG also has substantive concerns regarding the company's justification for the STM approach. The company's justification is founded on the extrapolations of time to progression (TTP) and PFS data, and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations.

	However, as discussed in Issue 7, it is unclear whether the TTP (PFS) extrapolations preferred by the company are clinically plausible. Alternative, more conservative, approaches to extrapolating TTP (PFS) do not result in TTP (PFS) crossing.
What alternative approach has the ERG suggested?	The ERG does not inherently object to a STM approach but is concerned about the clinical plausibility of model predictions. A partition survival model may be more appropriate if more mature OS data become available.
What is the expected effect on the cost-effectiveness estimates?	Using a partition survival approach (the alternative to a STM) would likely increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	The final cut analysis from KEYNOTE-826 (expected [redacted]) may resolve some of the uncertainty regarding the appropriateness of TTP (PFS) extrapolation and will help validate model predictions.

Issue 7 Extrapolation of PFS

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	The company's approach to extrapolating TTP and PFS uses a two-piece extrapolation approach which is justified on the basis of an observed inflection point in the TTP/PFS curve for pembrolizumab. The company considers this inflection point evidence of an emerging plateau and that observed hazards in the tail of the KM are indicative of an ongoing sustained decline in the risk of progression. This approach implies a very long tail to the survival function and result in the model predicting very substantial OS benefits. The ERG considers that this approach is potentially inappropriate given the immaturity of the data supporting the purported 'inflection point' in the TTP/PFS curve for pembrolizumab, and notes that this approach leads to substantive numbers of patients surviving beyond 5 years. While immunotherapies have historically been associated with durable response rates, the ERG considers there to be little evidence to support a paradigm shift in outcomes as modelled by the company.
What alternative approach has the ERG suggested?	The ERG considers a single-piece approach to be more reasonable given the limited OS evidence available.
What is the expected effect on the cost-effectiveness estimates?	Using a single-piece log-logistic model preferred by the ERG increases the ICER from £34,017 per QALY in the company's base-case to £71,907 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival estimates would help to determine the most appropriate approach to modelling TTP/ PFS. The final cut analysis from KEYNOTE-826 (expected [redacted]) may also help to resolve some of this uncertainty.

Issue 8 Extrapolation of PPS

Report section	4.2.6.2
Description of issue and why the ERG has identified it as important	The company's base-case model uses a single-piece generalised gamma model to predict post-progression survival (PPS). The ERG is concerned that this model results in overly optimistic estimates of survival with an overly long-tail. Treatment options in the second-line setting are extremely limited and it is unlikely that any patients would be alive beyond 3 years post progression. The company approach to modelling PPS also assumes a differential survival benefit across treatment arms with patients progressing on pembrolizumab assumed to have longer PPS. The available KM data, however, shows limited evidence to support this, assumption.
What alternative approach has the ERG suggested?	The ERG prefers to use a pooled PPS curve for both treatment arms and considers that more conservative parametric functions, such as the Weibull, provide more plausible predictions.
What is the expected effect on the cost-effectiveness estimates?	Pooling the PPS curves results in an increase in the ICER from £34,017 per QALY in the company base-case to £36,231 per QALY. Using the Weibull model in place of generalised gamma (assuming pooled PPS) results in an increase in the company base-case ICER to £34,832 per QALY.

What additional evidence or analyses might help to resolve this key issue?	Further exploration of the clinical plausibility of the company's base case assumptions would be useful. More mature data on PPS would also be useful to inform the most appropriate parametric model.

Issue 9 Including treatment waning effect for pembrolizumab

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	The company assumes a lifetime duration of the treatment effect associated with pembrolizumab. Evidence provided by the company to support this assumption is limited given the relatively short follow- up in KEYNOTE-826. The ERG considers that the application of a life-time treatment effect is highly uncertain and that insufficient evidence is available to substantiate this assumption. The ERG notes that previous appraisals of immunotherapies have applied a waning effect, in which mortality rates gradually return to those of the comparator therapy over a number of years following the discontinuation of treatment.
What alternative approach has the ERG suggested?	A benefit of treatment limited to between three and five years after discontinuation is preferred by the ERG. This aligns with committee preferences in several appraisals of immunotherapies.
What is the expected effect on the cost-effectiveness estimates?	When the duration of survival benefit is limited to three years (post treatment discontinuation), the ICER increases from £34,017 per QALY to £42,919 per QALY. When a five years limit is implemented the ICER increases to £38,823 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Uncertainties regarding long-term survival of patients receiving pembrolizumab may be resolved through additional follow-up in KEYNOTE-826. However, it is unlikely that data would be sufficiently mature following the expected [redacted] data cut to support a five-year survival benefit duration. More detailed analyses of long-term data from Phase III trials of other immunotherapies may provide supporting evidence for a durable treatment benefit.

Issue 10 Health state utilities

Report section	4.2.7.1
Description of issue and why the ERG has identified it as important	The approach taken by the company was to predict HRQoL by time to death (TTD). The ERG has conceptual issues with this approach as it relies on future death events to predict current HRQoL status. The ERG is also concerned that the TTD approach severs the link between progression and violates the accepted norm that progression status is major driver of HRQoL. Moreover, the TTD approach favours pembrolizumab and results in a treatment related utility benefit which has not been evidenced.
What alternative approach has the ERG suggested?	The ERG prefers the use of progression-based health state utilities estimated from KEYNOTE-826.
What is the expected effect on the cost-effectiveness estimates?	Using progression-based utilities increases the company base-case ICER from £34,017 in per QALY to £36,591 per QALY.
What additional evidence or analyses might help to resolve this key issue?	A comparison of the fit of the progression-based and TTD-based models would aid in determining which is statistically the most appropriate. Discussion and evidence on clinical plausibility of each approach would be useful. The company may also wish to amend their model structure to allow the mean utility for the cohort to be estimated on a per-cycle basis, to allow for the validation of predicted utility values over time.

Issue 11 Resource use

Report section	4.2.8
Description of issue and why the ERG has identified it as important	The ERG identified several issues relating to resource use. The most important related to the application of the stopping rule and the subsequent treatments modelled. The economic model applies a strict 24 month stopping rule. This does not fully align with KEYNOTE-826 where a 35-cycle limit was applied. This reduces the acquisition cost associated with pembrolizumab and severs the link between treatment costs and health effects. The ERG does not consider this reflective of

	practice and notes that previous NHS England policy permits patients to receive a full allocation of doses even when these fall outside the 24-month window. Modelled subsequent treatments do not utilise the distribution of therapies used in KEYNOTE-826, as the company consider that the treatments received by patients were not reflective of UK practice. The company's submission, however, provided only limited information on subsequent treatments received in KEYNOTE-826 and did not fully respond to clarification response on this point. Given the limited information provided, it is unclear if the company's base-case assumptions are appropriate. The ERG is also concerned about the subsequent treatments modelled. The ERG's clinical advisor raised concerns about the use of doxorubicin in this population and considered that paclitaxel would be used less frequently than assumed in the base-case.
What alternative approach has the ERG suggested?	Modelled time on treatment should align with KEYNOTE-826 and remove the 24-month cap imposed in the economic analysis. The ERG's preference would be to base the proportions of subsequent therapies received on the full data for each treatment arm from KEYNOTE-826.
What is the expected effect on the cost-effectiveness estimates?	Removing the time on treatment cap results in an increase in the ICER from £34,071 per QALY in the company base-case to £34,952 per QALY. The impact of alternative assumptions regarding subsequent treatment use is unknown.
What additional evidence or analyses might help to resolve this key issue?	Confirmation of the commissioning policy for pembrolizumab and the appropriateness of a 24-month vs 35-cycle time on treatment cap. Further information on the subsequent treatments received by patients in KENOTE-826 is necessary to inform the ERG preferred approach. It may also be appropriate to elicit additional UK clinical opinion on the composition of subsequent treatments used in NHS practice.

1.6 Other key issues: summary of the ERG's view

Issue 12 Relevance of bevacizumab and availability of bevacizumab biosimilar

Report section	4.2.4
Description of issue and why the ERG has identified it as important	NHS commissioning of bevacizumab did not follow the normal NICE process but instead was commissioned directly by NHS England. The cost-effectiveness of bevacizumab is therefore unknown. The ERG considers this commissioning route problematic as the cost-effectiveness of pembrolizumab may be influence by the cost-effectiveness of bevacizumab. The ERG also notes the availability of bevacizumab biosimilars. It is uncertain to what extent these are used in practice. The ERG, however, considers it realistic that a proportion of patients initiated on bevacizumab may be given a biosimilar product.
What alternative approach has the ERG suggested?	This ideally would be addressed by fully incremental analysis considering each of the four alternatives (doublet chemotherapy, doublet chemotherapy plus bevacizumab, doublet chemotherapy plus pembrolizumab, doublet chemotherapy plus bevacizumab and pembrolizumab). Reflect market share of biosimilars in the base-case analysis.
What is the expected effect on the cost-effectiveness estimates?	The impact of including bevacizumab as a comparator is difficult to quantify due to pembrolizumab's positioning as a combination therapy. Scenario analysis using biosimilar prices resulted in a small increase in the ICER from £34,017 to £34,056. This analysis is exclusive of commercial arrangements for comparator treatments.
What additional evidence or analyses might help to resolve this key issue?	Evidence to support appropriate comparisons is not available to resolve this issue. Resolution of this uncertainty may be partially addressed by considering subgroup analysis of KEYNOTE-826 stratifying by the investigator's decision to use bevacizumab.

	Further evidence of biosimilars in UK practice will help inform the appropriate base-case assumptions.

Issue 13 End-of-life criteria

Report section	7
Description of issue and why the ERG has identified it as important	The company considered the End of Life (EoL) criteria noting median survival is less than 24 months. The ERG notes that the EoL criteria are typically interpreted with respect to mean or average life-expectancy. This is in line with actuarial methods which use mean life-expectancy. It is also in line with decision making for cost-effectiveness, which is based on mean costs and QALYs. Mean OS predicted for the standard of care arm is 2.5 years using the company preferred assumptions and 2.08 using the ERG's preferred assumptions. These suggest that the EoL criteria are not met.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Determines maximum willingness to pay threshold.
What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival is required to determine whether EoL criteria are met.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the ERG are described in Section 5.4. For further details of the exploratory and sensitivity analyses done by the ERG, see Section **Error! Reference source not found.**. The results of the ERG's exploratory analyses including the ERG's preferred base case are presented in Table 1 with probabilistic results for the ERG's preferred based case presented in Table 2

Table 1 ERG exploratory scenarios

Scenario	Technology	Incremental			ΔICER vs corrected BC
		Costs	QALYs	ICER	
ERG-corrected company base-case	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,021	-
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	SoC				
	Pembrolizumab	[redacted]	[redacted]	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	SoC				
	Pembrolizumab	[redacted]	[redacted]	£36,231	£2,209
2. b) Pooled survival curve for PPS using Weibull curve.	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,832	£811
3. a) Treatment waning for pembrolizumab between 3 and 5 years	SoC				
	Pembrolizumab	[redacted]	[redacted]	£42,919	£8,897
	SoC				

3. b) Treatment waning for pembrolizumab between 5 and 7 years	Pembrolizumab	[redacted]	[redacted]	£38,823	£4,802
4. Progression based utilities	SoC				
	Pembrolizumab	[redacted]	[redacted]	£36,591	£2,569
5. Subsequent therapy distribution from KEYNOTE-826	SoC				
	Pembrolizumab	[redacted]	[redacted]	£33,472	-£549
6. Full Pembro ToT KM curve used to calculate costs	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,952	£930
7. All patients receive biosimilar bevacizumab	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,056	£34
8. Bevacizumab maintenance treatment allowed	SoC				
	Pembrolizumab	[redacted]	[redacted]	£32,885	-£1,136
9. GP/nurse visits, blood-counts, and thyroid function tests costs	SoC				
	Pembrolizumab	[redacted]	[redacted]	£35,072	£1,051
10. All AEs of special interest occurring in more than 5% of patients modelled	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,220	£198
ERG preferred base-case (Scenarios 1, 2 (a), 3 (a), 4, 6, 9 & 10)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£95,529	£61,508

Table 2 ERG's alternative base-case analysis results (probabilistic)

Scenario	Technology	Total			Incremental		
		Costs	LYs	QALYs	Costs	QALYs	ICER
ERG-corrected company base-case (probabilistic)	SoC	[redacted]	2.11	[redacted]			
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£93,159

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report, the ERG has reviewed the clinical and cost-effectiveness evidence in the Company Submission (CS) in support of pembrolizumab (KEYTRUDA) with chemotherapy for treating recurrent, persistent or metastatic cervical cancer. The application for marketing authorization with the EMA in this indication is currently ongoing. EMA approval was received in March 2022[1] and MHRA approval was granted in May 2022.

In this section, the ERG critiques the company's proposed treatment pathway, positioning of pembrolizumab, and its definition of the decision problem when compared with the NICE scope.

2.2 Background

Pembrolizumab is a humanised monoclonal anti-PD-L1 antibody, which binds to the PD-1 receptor expressed by tumour cells and thus allows the patient's immune system to target and destroy these cells.

Section B.1.3 of the CS provides a brief and accurate overview of recurrent, persistent or metastatic cervical cancer, its aetiology, epidemiology, and prognosis.

2.2.1 Treatment pathway

The treatment pathway indicates that patients with an ECOG status of 0 or 1 receive systemic treatment and patients with a ECOG performance status (PS) >1 receive best supportive care or palliative radiotherapy. However, the British Gynaecological Cancer Society (BGCS) guidelines suggest that a proportion of women with ECOG PS 2 may also be considered for systemic treatment.[2] Clinical advice to the ERG suggests that 20-30% of patients undergoing systemic chemotherapy for recurrent, persistent or metastatic cervical cancer have ECOG PS 2 (see Section 3.2.2.1).

The systemic therapies in the proposed pathway (cisplatin or carboplatin with paclitaxel, with or without bevacizumab depending on patient risk factors) reflect clinical practice for a majority of UK patients. However, clinical advice to the ERG indicated that treatment choice is strongly guided by patient preference. This means that topotecan may be used occasionally, and platinum-based monotherapy may be used in some patients (~10%) who want to avoid paclitaxel-associated toxicity effects, such as hair loss.

Clinical advice to the ERG also suggested that the aim of treatment in this population is 'disease free' survival. Therefore, doublet therapy may not be initiated immediately in very fit patients, due to the burden of inconvenience and toxicity outweighing the limited potential for symptomatic or survival benefits. These patients may choose to start treatment only once their symptoms have worsened.

The ERG's clinical advisors agreed that over 50% of patients eligible for systemic chemotherapy would receive concomitant bevacizumab. Patients are considered eligible for bevacizumab on the basis of having better performance status, no significant comorbidities (e.g. hypertension), and low risk of bowel fistula formation.

The treatment pathway in the CS includes only first-line systemic therapy. BGCS guidelines state: "Second line treatment and beyond is dependent on the interval of progression since first line treatment in those patients with a good partial response with first line treatment and are more than 6 months out, rechallenging with platinum/paclitaxel could be considered. Mitomycin/5FU, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity but there is no standard of care. Response rates are universally poor and entry into clinical trials where possible to assess novel and immunotherapeutic agents should be strongly considered depending on patient's fitness and desires."[2] The ERG's clinical advisors suggested that fewer than half of patients with recurrent, persistent or metastatic disease would receive second-line treatment, and the choice of treatment in this group would be driven by clinician judgment alongside the BCGS recommendations.

2.2.2 Company's proposed positioning

The ERG agrees with the company's proposed positioning of pembrolizumab as first-line systemic therapy, in combination with chemotherapy (cisplatin or carboplatin plus paclitaxel) with or without bevacizumab. This is in line with BGCS guideline recommendations and the KEYNOTE-826 trial.

2.3 Critique of company's definition of decision problem

Table 3 summarises the decision problem as defined in the NICE scope and the CS.

The CS appropriately presents the results for the CPS (combined positive score) ≥1 trial subpopulation. This reflects the anticipated licence for pembrolizumab and constitutes 89% of the trial intention-to-treat (ITT) population.

The company seeks a recommendation for pembrolizumab in adults with untreated recurrent, persistent or metastatic cervical cancer, unrestricted by performance status. This matches the NICE scope and the granted licence indication. However, as noted in section 2.2.1, the KEYNOTE-826 trial that informs the CS included only patients with an ECOG PS of 0 or 1, whereas in practice around 20-30% of patients considered eligible for systemic therapy would have ECOG PS 2. In addition, the

proportion of patients with an ECOG PS 0 is substantially greater in the trial than seen in UK practice (see Section 3.2.2.1). Therefore (a) the trial population is likely to be fitter on average than the eligible UK treatment population and (b) the CS does not provide any evidence on the effects of pembrolizumab in eligible ECOG PS 2 patients.

KEYNOTE-826 permitted up to 35 cycles (approximately 2 years) of pembrolizumab (though participants who stopped treatment on achieving stable disease but subsequently experienced radiographic disease progression could receive up to 17 additional cycles (approximately 1 year)). However,

[redacted]

It states that

[redacted][3] The ERG's clinical advisors considered two years to be a reasonable treatment duration for pembrolizumab in this indication, given the absence of evidence on longer-term effects of immunotherapeutic agents. See Section 4.2 for further discussion of stopping rules.

The company's decision problem is restricted to platinum-based chemotherapy in combination with paclitaxel, with or without bevacizumab. The ERG's clinical advisors agreed this is the treatment most commonly used in practice. However, variations in disease presentation and patient preference mean that a small proportion of patients may receive topotecan or platinum-based monotherapy, as treatment options are limited.

The ERG's clinical advisors agreed that etoposide should be excluded as a comparator.

The ERG's clinical advisors noted that, if available, pembrolizumab might be preferred as an alternative to bevacizumab in patients with poorer performance status or risk factors for adverse outcomes. They added that the relative effects of adding pembrolizumab instead of bevacizumab to chemotherapy in patients eligible for either monoclonal antibody would also be of interest. However, KEYNOTE-826 was not designed to provide a randomised head-to-head comparison of chemotherapy plus pembrolizumab versus chemotherapy plus bevacizumab.

Outcomes in the company's decision problem match those in the NICE scope, with the addition of duration of response (DOR). The ERG agrees that these outcomes are all important for evaluating the effects of pembrolizumab in this indication. The ERG's clinical advisors noted that patients particularly value time without symptomatic disease. This preference, in combination with the limited survival benefits of currently available treatment for many patients, means that management often focuses on improving quality of life.

While overall survival (OS) was included as an outcome in the decision problem, it should be noted that OS data in the KEYNOTE-826 trial were immature, meaning that KEYNOTE-826 cannot currently provide a direct estimate of the effect of pembrolizumab on longer-term survival. In their justification for the economic model structure (CS p.81), the company states that "*UK clinical experts consulted for this appraisal confirmed that the trends in hazards observed for progression free survival (PFS) would be expected to become apparent for OS with longer-follow up*." Therefore, to estimate the effects of pembrolizumab on OS in the economic model, information on progression was used to inform mortality extrapolations (see Section 4.2.6 of the ERG report). However, the ERG's clinical advisors do not believe that progression-free survival (PFS) is necessarily a reliable surrogate for OS in this population: they noted that treatment can delay progression without extending survival.

Of the four subgroups in the NICE scope (histology, pelvic disease status, CPS of PD-L1 expression, tumour mutational burden), only CPS was considered in the KEYNOTE-826 trial. Randomisation was stratified by CPS, with the CPS≥1 population presented as the effectiveness analysis population in the CS, on the basis that this aligns with the licence for pembrolizumab (n.b. CPS≥10 and all-comer analysis sets from KEYNOTE-826 are available in figures 5 and 6 of the CS appendix). In response to a query from the ERG, the company stated that investigation of tumour mutational burden is a potential exploratory analysis for which no data are yet available (PfC A1). The KEYNOTE-826 clinical study report concluded "The treatment benefit of pembrolizumab plus chemotherapy with or without bevacizumab…was consistent across all the major subgroups tested in participants with persistent, recurrent, or metastatic cervical cancer *including by histology*". However, the ERG could not find any subgroup analysis based on histology, and none was provided in the CS or the company's response to points for clarification.

Subgroup analyses conducted in KEYNOTE-826 (and presented in the CS for the CPS≥1 population) were: metastatic disease at initial diagnosis, bevacizumab use, age (<65 or ≥65 years), race (white, all others), ECOG status (0 or 1). See Section 3.2.3.1 for further details.

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	ERG comment
Population	Adults with untreated recurrent, persistent or metastatic cervical cancer	The population was restricted to adults with untreated recurrent, persistent or metastatic cervical cancer and a CPS of PD-L1 expression score ≥1	Restriction by CPS is consistent with the licence.	KEYNOTE-826 included only patients with an ECOG status ≤1. Compared with the NHS setting, the trial population consequently overrepresented ECOG 0 status patients (56% vs 10-15%) and underrepresented ECOG 2 status patients (0% vs 20-30%). The trial population is therefore likely to be fitter on average than the eligible UK treatment population and provides no evidence on the effects of pembrolizumab in ECOG 2 status patients.
Intervention	Pembrolizumab in combination with paclitaxel and platinum-based chemotherapy (carboplatin or cisplatin) with or without bevacizumab	As per final scope	N/A	The intervention is consistent with the NICE scope. KEYNOTE-826 permitted up to 35 cycles (approximately 2 years) of pembrolizumab, though [redacted].
Comparator(s)	Platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel or topotecan or etoposide In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	Platinum chemotherapy (cisplatin or carboplatin) in combination with paclitaxel In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	Etoposide has been excluded from the list of comparators. Etoposide is used in small cell cervical cancer, a histology which is not covered by the KEYNOTE-826 trial. Cervical cancer is not included as an indication in the etoposide SmPC. Although it is acknowledged that TA183 approved the use of topotecan in combination with cisplatin for women with recurrent or stage IVB cervical cancer if they have not previously	The company's decision problem is restricted to platinum-based chemotherapy in combination with paclitaxel, with or without bevacizumab. The ERG's clinical advisors agreed this is the treatment most commonly used in practice. However, variations in disease presentation and patient preference mean that a small proportion of patients may receive

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			received cisplatin, topotecan has been excluded from the list of comparators: At the NICE scoping call held for this submission in December 2020, clinical experts in attendance did not report the use of topotecan in UK clinical practice. This was further confirmed at a recent advisory-board, in which clinicians confirmed that topotecan is not in use in the NHS in this indication Topotecan is not recommended by the BGCS guidelines for the treatment of advanced cervical cancer Bevacizumab is currently the preferred option for first-line treatment of advanced or metastatic cervical cancer in conjunction with chemotherapy. Topotecan was also rarely indicated prior to bevacizumab becoming available; the NICE FAD for TA183 states that '90–95% of women within the licensed population will have previously received cisplatin' Platinum-based monotherapy have also been excluded from the list of comparators to align with current treatment options recommended by the BGCS guidelines and clinician feedback.	topotecan or platinum-based monotherapy. The ERG's clinical advisors agreed that etoposide should be excluded as a comparator. The ERG's clinical advisors noted that the effects of adding pembrolizumab instead of bevacizumab to chemotherapy would be of interest. However, the KEYNOTE-826 trial does not include this as a randomised comparison. n.b. In table 1 of the CS, the "Decision problem addressed in the company submission" column incorrectly identifies "Platinum chemotherapy (cisplatin or carboplatin) alone" as a comparator included in the CS.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life Duration of response	Addition of the duration of response outcome to aid in capturing the most important health-related benefits of the Pembrolizumab in the patient population of interest.	Overall survival data were immature in the KEYNOTE-826 trial. The ERG's clinical advisors do not consider PFS to be a reliable surrogate for OS

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
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. The availability of any managed access arrangement for the intervention will be taken into account.	As per final scope	N/A	The economic analysis is line with the reference case. See Table 11 for details. Confidential commercial arrangements for comparator treatments have not been accounted for in the company's analysis. The ERG presents analyses inclusive of these commercial arrangements in a confidential appendix to this report.
Subgroups to be considered	If the evidence allows the following subgroups will be considered based on: Histology (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and poorly differentiated carcinoma) Pelvic disease status (pelvic or locally recurrent cervical cancer and distant metastatic cervical cancer) CPS of PD-L1 expression (< 10, ≥ 10 and all-comers) Tumour mutational burden	This submission presents the subgroup analyses for the CPS ≥ 1 population	The company clarified that analyses of tumour mutational burden are not yet available. The absence of histology and pelvic disease status subgroups was not explicitly addressed.	CPS≥10 and all-comer analysis from KEYNOTE-826 were reported in the CS appendices. Subgroup analyses conducted in KEYNOTE-826 and presented in the CS were: metastatic disease at initial diagnosis, bevacizumab use, age (<65 or ≥65 years), race (white, all others), ECOG status (0 or 1). Though the KEYNOTE-826 mentioned the observed treatment effects being "…consistent across all the major subgroups tested in participants with persistent,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				recurrent, or metastatic cervical cancer *including by histology*", no histology subgroup data could be found among the provided materials.
Special considerations including issues related to equity or equality				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify all relevant evidence regarding the clinical efficacy and safety of first-line treatments for patients with recurrent, persistent or metastatic cervical cancer. Details of the review are reported in Appendix D of the CS. No network meta-analysis or indirect comparison was conducted – see Section 3.3.

3.1.1 Searches

The CS included searches to identify evidence on the efficacy and safety of first-line treatments for patients with recurrent, persistent or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix D.1.1 of the CS.

In response to the ERG's PfCs (C4-C7), the company provided additional search strategies and related information.

An appraisal of the literature searches is presented in Appendix 9.1

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review were presented in Table 2 of the CS Appendix document. The ERG considers these criteria to be appropriate to the decision problem. Two independent reviewers evaluated all titles and abstracts, and full-texts, which will have minimised the possibility of reviewer errors or bias affecting the selection process.

3.1.3 Critique of data extraction

The CS appendix stated that data were extracted "by two reviewers and reconciled by the third reviewer" so it appears likely that the process used will have limited the possibility of errors or bias affecting data extraction.

3.1.4 Quality assessment

Studies included in the systematic review were evaluated for risk of bias by two reviewers, using version 2 of the Cochrane risk of bias tool. The results were reported in Appendix D3 (p31); these were limited to judgements only, so the ERG asked the company (clarification question A17) to provide the details to justify the judgements made. The company responded with a table of very brief answers (e.g. yes, no, probably yes, etc) to signalling questions, which was insufficient to clarify this reporting issue. The ERG therefore looked for any risk of bias issues in the two trials used in the economic modelling: KEYNOTE-826 and GOG-240.[4] The ERG considered KEYNOTE-826 to be at

low overall risk of bias. The randomisation methods (interactive voice response system/integrated web response system) were robust. Blinding of patients, caregivers and outcome assessors appeared to be adequate, although few specific details were provided on how blinding was achieved (e.g. no details were presented on the similarity of appearance of pembrolizumab and placebo). In terms of patient attrition from the trial, nineteen patients withdrew consent in the placebo group compared with 13 in the pembrolizumab group; it was unclear how many of these patients were successfully followed up, but where survival data were missing the stated approach was to censor at the last known alive date. Although the risk of bias was low, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could have affected results to slightly favour pembrolizumab; the ERG's clinical advisor stated that patients with adenocarcinoma have poorer outcomes than patients with squamous cell carcinoma.

There is more uncertainty over the risk of bias in the GOG-240 trial.[4] Block randomisation was used and the methods of allocation concealment were not reported. Nevertheless, key baseline characteristics such as histology, performance status and age were well-balanced across groups. However, GOG-240[4] was an open-label trial with patients and caregivers not blinded to study treatments. It is unclear whether or not outcome assessors were blinded and to what extent the lack of blinding in this study may have biased the trial's results.

A discussion of the KEYNOTE-826 trial's applicability to the NHS was presented in Section B.2.13.1.1 of the CS (p71). The ERG's clinical advisor considered the trial population was broadly representative of NHS patients. The exception was that in KEYNOTE-826 patients with ECOG 2 performance status were excluded; the ERG's clinical advisor estimated that in the NHS around 20-30% of patients receiving a systemic therapy would have an ECOG status of 2.

3.1.5 Evidence synthesis

No evidence synthesis was conducted since only one eligible randomised trial of pembrolizumab (KEYNOTE-826) was identified in the systematic review and the company considered that the comparator evidence identified in other studies would not usefully add to the evidence provided in KEYNOTE-826 (see Section 3.3).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Trial design and methods

3.2.1.1 KEYNOTE-826

Section B.2.3 of the CS (p.28) summarises the design and methodology of the KEYNOTE-826 trial. Briefly, this was a randomised, double-blind, placebo-controlled, multinational trial comparing pembrolizumab plus chemotherapy (paclitaxel + cisplatin/carboplatin) with or without bevacizumab versus placebo plus chemotherapy with or without bevacizumab in adults with recurrent, persistent or metastatic cervical cancer.

Eligible patients were stratified by investigator's decision to use bevacizumab, PD-L1 status, and metastatic status at initial diagnosis, and randomised to receive either 200mg pembrolizumab or placebo every 3 weeks for up to 35 cycles.

Both treatment arms received paclitaxel and the investigator's choice of cisplatin or carboplatin every 3 weeks, with some participants receiving bevacizumab (15 mg per kg of body weight) at the investigator's discretion. Chemotherapy was limited to six-cycles, though patients who continued to benefit without unacceptable adverse events (AEs) could continue beyond this limit. There was no limit on the number of cycles of bevacizumab a patient could receive.

Treatment was planned to continue until radiographic disease progression, experience of unacceptable toxic effects, or the maximum number of cycles for each treatment component (see Section 3.2.1.3 for further details on treatment duration).

Primary endpoints were progression-free survival (PFS) based on RECIST 1.1 as assessed by investigator (see PfCs A11 and A12), and overall survival (OS). Secondary endpoints were objective response rate (ORR), duration of response (DOR), PFS rate at 12 months, patient-reported quality of life, safety and tolerability.

3.2.1.2 KEYNOTE-158

Section B.2.6.3 and Appendix F.2 of the CS briefly present results from KEYNOTE-158: a single-arm basket trial of pembrolizumab monotherapy in multiple advanced solid tumour types in a second line or later treatment setting. As this trial includes a very different treatment population (e.g. PFS 2.1 months vs 10.4 months in KEYNOTE-826) and does not align with the decision problem for this evaluation, it is not discussed further in the ERG report.

3.2.1.3 Points for critique

Use of interim analyses

The KEYNOTE-826 trial is ongoing. The CS presents data from the first planned interim analysis, with the CPS≥1 population followed up for a median of [redacted] The final trial analysis is anticipated [redacted].

The short follow-up period for the interim analysis means that a substantial proportion of data for some time-to-event outcomes were censored, with overall survival data in particular being immature. Section B.3.2.2 of the CS describes how the company's model uses the relatively more mature progression data to inform overall survival extrapolations. However, the ERG's clinical advisors did not entirely agree with the assertion that PFS is an appropriate surrogate for OS, noting that a proportion of patients in this population can experience delayed progression without an overall survival benefit (see Section 4.2.6.1).

Treatment duration

KEYNOTE-826 permitted a maximum of 35 treatment cycles of pembrolizumab (equivalent to around 24 months treatment duration) in the absence of disease progression or prohibitive toxicity. This was implemented as stopping rule in the model (see Section 4.2).

However, it should be noted that the current SmPC for pembrolizumab states "Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication)". While the maximum treatment duration in most pembrolizumab KEYNOTE trials was 35 cycles or 24 months, the SmPC does not explicitly mandate a stopping rule for cervical cancer.[5] The United States Prescribing Information (USPI) recommends treatment "until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months".[6]

In previous appraisals, pembrolizumab has mostly been recommended with a stopping rule (n=14/15), either explicitly in the recommendations (n=13) or in the marketing authorisation (n=1).[7-20]

Reported clinical effectiveness outcomes

The main body of the CS reports most primary and secondary endpoints specified in the KEYNOTE-826 protocol, with exploratory outcomes presented in the appendices (see Table 4). However, health related quality of life was an exception – the main body of the CS reports an exploratory measure (EuroQoL EQ-5D-5L) rather than the principal measure (EORTC QLQ-C30 global score) specified in the protocol. Section 3.2.3.1 of this ERG report therefore summarises the EORTC QLQ-C30 global score results.

Table 4 Reporting of pre-specified endpoints in the company submission

Outcome	Assessment method (where relevant)	Endpoint specified in protocol / clinical study report	Reported in CS?
OS	-	Primary	Yes
PFS	BICR	Secondary	Yes
	Investigator	Primary	Yes
ORR	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
DOR	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
PFS rate at 12 months	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
EORTC QLQ-C30 global score	-	Secondary	Appendix only
EuroQoL EQ-5D-5L	-	Exploratory	Yes
EORTC QLQ-C30 (scores other than global score)	-	Exploratory	No
EORTC QLQ-CX24	-	Exploratory	No

CONSORT flowchart, discontinuation and treatment switching

Appendix D.2 of the CS reported CONSORT diagrams to illustrate patient flow though the KEYNOTE -826 trial for the CPS≥1 (n=548) and ITT populations (n=617). Discontinuations were broadly similar between treatment arms, except for the noticeably higher rate of discontinuation due to radiographic progression in the placebo arm.

The ERG requested clarifications regarding the 266 participants screened but excluded from the trial (PfC A5). This information is summarised in Table 5. 10.2% of patients were specifically excluded for having an ECOG PS >1, though it is not clear whether further patients with ECOG PS >1 scores were excluded for other reasons. Table 5 Participants screened and excluded prior to randomisation

Table 5 Participants screened and excluded prior to randomisation

Reason for exclusion	Number of participants excluded (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Response to PfC A5

Despite the trial protocol permitting a second course of treatment with pembrolizumab under certain circumstances, the company clarified that no participants in KEYNOTE-826 actually received retreatment (see PfC A4).

No patients switched between the KEYNOTE-826 treatment arms (PfC A13), and a small number switched from cisplatin to carboplatin within the treatment arms (pembrolizumab arm n=11, placebo arm n=6; PfC A14). Consequently, there are no important concerns about trial results being influenced by treatment switching in KEYNOTE-826.

Bevacizumab treatment rules

KEYNOTE-826 did not limit the number of cycles of bevacizumab a patient could receive, and on average patients received more cycles of bevacizumab (median 12) than they did chemotherapy (median 6). This compares with a median of 7 cycles of bevacizumab (range 0-36) in the GOG-240 trial.[4] The BGCS guidelines recommend the addition of bevacizumab to chemotherapy, depending on patient risk factors,[2] and the National Cancer Drugs Fund (CDF) list states that bevacizumab is *only* approved for use in combination with combination chemotherapy and is not approved for use as a single agent maintenance therapy.[21] Therefore patients in KEYNOTE-826 are likely to have been treated with bevacizumab for longer than patients in UK clinical practice.

The company's advisory board (PfC C1) noted [redacted].[22]

The company's base case cost effectiveness analysis includes a six cycle stopping rule for bevacizumab, with a scenario analysis to reflect the longer treatment duration observed in the trial (see 4.2.4).

3.2.1.4 Risk of bias

See section 3.1.4

3.2.2 Population

Section B.2.3.1.1 of the CS (p.34) summarises the population of the KEYNOTE-826 trial.

3.2.2.1 Points for critique

Applicability of the trial population to UK practice

The KEYNOTE-826 excluded patients with an ECOG performance status greater than 1 (i.e. those with lower fitness). However, the anticipated licence for pembrolizumab does not restrict patient eligibility on the basis of performance status, and the ERG's clinical advisors suggest that 20-30% of patients currently receiving systemic therapy have an ECOG performance status of 2 (Table 6). This value may be slightly higher among patients with metastatic disease (30-35%). In addition, the proportion of patients in KEYNOTE-826 with a ECOG performance status of 0 (56.2%) is greater than would be expected in practice (10-15%). Therefore, on average, patients in KEYNOTE-826 are likely to have been fitter than those in the UK treatment population.

Table 6 Proportion of participants by ECOG performance status: KEYNOTE-826 vs UK practice

ECOG performance status	KEYNOTE-826 (CPS≥1 population)	Current recipients of systemic therapy in UK clinical practice (ERG clinical advisor estimates)
0	56.2%	10-15%
1	43.4%	50-60%
2	[redacted]*	20-30%

*Patients with ECOG 2 PS were ineligible for KEYNOTE-826

Despite being an international multicentre trial, KEYNOTE-826 did not include any UK sites. The ERG's clinical advisors noted that the proportion of patients of white ethnicity in the trial (59.3%; Table 6 of the CS) was notably lower than would be seen in UK practice (approximately 85%), but that this is unlikely to cause major generalisability concerns.

Baseline comparability of treatment arms

Table 6 of the CS (p.35) summarises key baseline participant characteristics from KEYNOTE-826. Most characteristics were balanced between arms, except for a greater proportion of patients with adenocarcinoma in the placebo arm (24% placebo vs 17% pembrolizumab). As prognosis for

adenocarcinoma is poorer than for squamous cell disease, this could have affected results to slightly favour pembrolizumab (see risk of bias section 3.1.4)

The ERG requested the proportion of patients receiving cisplatin and paclitaxel and the proportion of patients receiving carboplatin and paclitaxel in each trial arm (PfC A3). These data are reported in Table 7 below and values appear balanced between the trial arms. [redacted] reflects UK practice, where carboplatin/paclitaxel is often preferred due to clinician familiarity with this combination, and toxicity concerns (particularly nephrotoxicity) relating to cisplatin in this population.

Table 7: Distribution of participants by administered treatment from cycle 1 to cycle 6. Participants with CPS ≥1 (APaT)

	Pembrolizumab + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	272		275		547	
Randomized treatment (pembrolizumab/placebo)						
Randomised Treatment (Pembrolizumab/ Placebo)	272	(100.0)	275	(100.0)	547	(100.0)
Cisplatin and/or Carboplatin						
Cisplatin[a]	[redacted]					
Carboplatin[b]						
Cisplatin and Carboplatin[c]						
Missing						
Paclitaxel						
Paclitaxel	[redacted]					
Bevacizumab						
Bevacizumab	175	(64.3)	171	(62.2)	346	(63.3)
No Bevacizumab	97	(35.7)	104	(37.8)	201	(36.7)

Table reports participants who received at least one dose of the treatment during the considered period.
a: Participants who have received cisplatin and no carboplatin during the considered period.
b: Participants who have received carboplatin and no cisplatin during the considered period.
c: Participants who have received both cisplatin and carboplatin during the considered period.
Database Cutoff Date: 03MAY2021

Source: Response to PfC A3, Table 1

3.2.3 Effectiveness

Section B.2.6. of the CS presents the clinical effectiveness results of KEYNOTE-826, with further outcome data reported in Appendix O.

3.2.3.1 Points for critique

Progression-free survival per RECIST 1.1 by investigator assessment (CPS≥1 population)

Table 9 and Figure 4 of the CS (p.42-3) present the results for PFS per RECIST 1.1 by investigator assessment, which show a statistically significant reduction in the risk of disease progression or death in patients treated with pembrolizumab compared with placebo. In response to a request from the ERG (PfCs A7, A10), the company provided the PFS Kaplan-Meier plots with added 95% confidence intervals for the CPS≥1 population, both including and excluding the 'metastatic at initial diagnosis' subgroup (see Figure 1 and Figure 2 below). There is a [redacted] between the curves in Figure 2, [redacted]. This is consistent with the data from the subgroup analysis that showed [redacted] (see section 3.2.3.1).

Figure 1: Progression-free survival per RECIST 1.1 by investigator assessment (CPS≥1 population) with 95% confidence intervals added to the curves

[redacted]

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A7)

Figure 2 Progression-free survival as assessed per RECIST 1.1 by investigator assessment (CPS ≥ 1 population, without 'metastatic at initial diagnosis')

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A10)

Overall survival (CPS≥1 population)

Table 10 and Figure 5 of the CS (p.44-5) present the results for OS, which suggests significantly longer survival in the pembrolizumab group compared with the placebo group. As acknowledged in the CS, the OS data are immature, with median OS yet to have been reached for the pembrolizumab arm in the presented interim analysis. This has implications for the cost-effectiveness modelling, which relied on progression data to inform longer-term mortality extrapolations (see Section 4.2.6.1).

The OS Kaplan-Meier plot with added 95% confidence intervals requested by the ERG is presented in Figure 3 below.

Figure 3: Overall survival (CPS≥1 population) with 95% confidence intervals added to the curves

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A7)

Objective response rate (ORR) per RECIST 1.1 by investigator assessment (CPS≥1 population)

Section B.2.6.1.3 of the CS (p.45) reports ORR from KEYNOTE-826. This significantly favours pembrolizumab over placebo, due to the greater percentage of patients achieving complete response (22.7% vs 13.1%) or partial response (45.4% vs 37.1%).

As shown in section B.2.6.1.5 of the CS, a patient's response status is highly prognostic of both OS (figure 7, p.49) and PFS (figure 8, p.50), with poorer outcomes observed for each decrease in response category. It appears from these figures that pembrolizumab-related gains in PFS and OS observed in KEYNOTE-826 are largely driven by responders. For patients with stable disease status, there appears to be little or no difference between pembrolizumab and placebo arms in terms of PFS (median ~26 weeks in each arm) or OS (median ~52 weeks in each arm). However, the ERG's clinical advisors noted that even achieving stable disease could be considered a good result in this population, particularly among younger patients with young children.

Duration of response per RECIST 1.1 by investigator assessment (CPS≥1 population)

Section B.2.6.1.4 of the CS (p.46) briefly summarises the duration of response data from KEYNOTE-826. The Kaplan-Meier plot with added 95% confidence intervals requested by the ERG is presented in Figure 4 below. Despite the numerically longer median duration of response among pembrolizumab-treated patients, the confidence intervals for the two treatment arms substantially overlap for much of the available follow-up period.

Figure 4: Duration of response (CPS≥1 population) with 95% confidence intervals added to the curves

[redacted]

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: response to PfC A7)

Health related quality of life

Section B.2.6.2 of the CS reported health related quality of life (HRQoL) outcomes from KEYNOTE-826. The main body of the document presented results of the EuroQol EQ-5D-5L VAS score for the CPS≥1 population. While the proportion of patients with an improved or stable score over a 30-week follow-up slightly favoured pembrolizumab over placebo [redacted]), the between group differences in least-squares mean change from baseline over the same period did not ([redacted]). Time to deterioration on this score was longer among pembrolizumab- than placebo-treated patients, [redacted]).

The principal pre-specified HRQoL measure for the trial was the EORTC QLQ-C30 global score (results reported in CS Appendix O.1.1.2). Briefly, [redacted] difference between treatment arms was observed for this measure, either in terms of difference in least-squares mean change from baseline to week 30 ([redacted]) or time to deterioration ([redacted]).

Based on these results, the observed delays in progression among pembrolizumab-treated CPS≥1 patients in KEYNOTE-826 does not appear to translate into substantial HRQoL benefits.

Subgroup analyses

The company estimated treatment effects, as HRs and corresponding 95% CIs for PFS and OS for the following subgroups in order to determine whether treatment effects were consistent across the subgroups:

1) Metastatic at initial diagnosis (yes/no)
2) Bevacizumab use (yes/no)
3) PD-L1 status (CPS < 1/ 1≤ CPS <10/ CPS ≥ 10)
4) Age (< 65 years/ ≥ 65 years)
5) Race (white/ non-white)
6) ECOG performance status (0/1)

The estimated HRs and 95% CIs were presented graphically as forest plots for the CPS ≥ 1 population (Figures 13 and 14 in CS Document B), and for the ITT population (Figures 5 and 6 in CS Appendix E). The company was confident that the benefit of pembrolizumab compared to placebo was demonstrated for all subgroups for primary and secondary endpoints, as the HRs comparing pembrolizumab to placebo were less than 1 in all subgroups, and were consistent with the overall HR. However, the 95% CI for patients who were metastatic at initial diagnosis, aged ≥65 years, or were not white intersected the line of "null effect" for both PFS and OS, indicating that the HRs for these subgroups were not statistically significant. In their initial submission document, the company did not test for interactions for any of the subgroups.

Although the HRs estimated for patient subgroups are consistent with HRs for the CPS ≥ 1 population from KEYNOTE-826, the results presented in Figures 13 and 14 in CS Document B cannot be considered formal comparisons.

Age

The forest plots in Figures 13 and 14 show that while the benefit of pembrolizumab for patients under 65 years was statistically significant for both OS and PFS, this benefit was not statistically significant in patients aged 65 years or older. The patient age subgroup could become more important over time

especially with the continued uptake of the HPV vaccine; with more vaccinated younger women, over time the population of patients with cervical cancer would be older.

Metastatic at initial diagnosis

Patients who were metastatic at initial diagnosis had statistically significant worse outcomes for PFS and OS compared to patients who were not. The apparent lack of effect was similar in terms of HRs to those seen in the subgroup of patients who had a PD-L1 status of CPS <1, which was excluded from the EMA's marketing authorisation.

In their response to PfCs, the company provided results for a test of interaction for the 'metastatic at initial diagnosis' subgroup (PfC A8). The analysis of deviance for the interaction of patients being metastatic at initial diagnosis and treatment group was shown to be statistically significant [redacted]. However, the company cautioned against over-interpreting results of post-hoc analyses as KEYNOTE-826 was not designed or powered to allow for formal testing of the heterogeneity in subgroups.

Patients diagnosed with Stage IV (or metastatic) cervical cancer have a much lower survival rate comparatively. According to Table 3 in CS Document B, only 17.9% of patients who were diagnosed as stage IV survived beyond 4 years compared to 90.6% of patients who were diagnosed with stage I cervical cancer. In their response to PfC A9, the company reiterated that patients who are metastatic have a poorer prognosis compared to patients who are not. The ERG's clinical advisors considered it plausible that patients who were metastatic at initial diagnosis could respond differently to treatment compared to patients who were not.

PD-L1 Status

The company stratified PD-L1 status into three categories according to the patient's CPS. Patients who had a CPS < 1 were excluded from any clinical- and cost-effectiveness analyses as they were not relevant to the marketing authorisation. The remaining patients were separated into 1 ≤ CPS <10 and CPS ≥ 10. PD-L1 status has been regarded as an important biomarker for predicting treatment effect in previous appraisals (TA 737), and by the company's clinical advisors.[22] Figures 5 and 6 (CS Appendix E.1.2) show that the higher-CPS subgroups have larger point-estimates for PFS and OS, though for the licenced subgroups of interest (i.e. 1≤CPS<10 and CPS≥ 10), the difference is small and both subgroup estimates fall within each other's CI.

In response to a query from the ERG, the company provided mean PD-L1 CPS data by best response category from KEYNOTE-826 (see Table 8). This indicates some evidence of a relationship between CPS and response among pembrolizumab treated patients that is not apparent in placebo treated patients.

Table 8 Mean (SD) PD-L1-CPS by best response category observed in KEYNOTE-826

	Mean (SD) PD-L1 CPS	
Response	**Pembrolizumab + Chemotherapy**	**Placebo + Chemotherapy**
CR as per investigator assessment	[redacted]	[redacted]
CR as per IRC assessment	[redacted]	[redacted]
PR as per investigator assessment	[redacted]	[redacted]
PR as per IRC assessment	[redacted]	[redacted]
SD as per investigator assessment	[redacted]	[redacted]
SD as per IRC assessment	[redacted]	[redacted]
PD as per investigator assessment	[redacted]	[redacted]
PD as per IRC assessment	[redacted]	[redacted]

Source: Response to PfC A6

Bevacizumab use

The ERG considers the subgroup of patients who are eligible for and receive bevacizumab to be a distinct population from patients who are contraindicated and cannot receive it. According to the ERG's clinical advisors a patient's eligibility for bevacizumab depends on their fitness and whether they have comorbidities. Patients who have cardiac symptoms, risks of hypertension and risks for fistulas are generally not eligible for bevacizumab.

In their response to PfC B5, the company disagrees with the ERG as they believe bevacizumab eligibility is not an objective quantity in the way a biomarker, histology or cancer stage would be. The decision to receive bevacizumab is made after discussion between a patient and their clinician following a benefit/risk assessment. The ERG appreciates that it might be difficult to differentiate between the two subpopulations as receiving bevacizumab greatly depends on clinician judgement. However, the ERG considers the two subgroups to differ in terms of prognosis and treatment effect such that they could be considered distinct populations.

As the trial was not powered to formally assess the difference in efficacy in the bevacizumab and non-bevacizumab population, it is difficult to determine whether there was a difference in the two subpopulations in terms of treatment effect. In their response to PfC B5, the company point out that splitting the population into these subgroups would reduce the number of events that would be used to produce robust cost-effectiveness analyses, which the ERG also appreciates.

The company also detailed what they considered negative implications of differentiating between patients based on bevacizumab eligibility. The company believed that different recommendations based on whether patients received bevacizumab could lead to equality concerns, could incentivise clinicians to prescribe bevacizumab in order to allow patients to receive pembrolizumab, or could restrict treatment options for patients.

The ERG does not think patient eligibility for bevacizumab raises any concerns about equality as treatment eligibility is not influenced by any protected characteristics.

3.2.4 Adverse events

Adverse event (AE) data were reported on pages 60-67 of the CS. AEs were assessed in the safety analysis population which comprised 616 patients who had received at least one dose of trial treatment in KEYNOTE-826. Results were presented as tables of frequencies and percentages. Table 13 of the CS presents a summary of AEs. Although [redacted] no tests of statistical significance were presented.

The activation of the immune system by immune checkpoint inhibitors, such as pembrolizumab, can enhance the immune response against cancer cells. However, this activation can also induce the development of immune-related AEs, which may affect multiple organ systems. In the CS, a section on 'Adverse events of special interest' (AESIs, CS p65) collectively included immune-mediated events (associated with pembrolizumab's mechanism of action) and infusion-related reactions. In KEYNOTE-826, rates of the following AESIs were all higher in the pembrolizumab group than in the placebo group: hypothyroidism, hyperthyroidism, thyroiditis, colitis, severe skin reactions, pneumonitis and hepatitis (see CS, Table 17). There was no meaningful difference between groups in the incidence of infusion reactions. The published paper for KEYNOTE-826 also reported that 34% of pembrolizumab patients had potentially immune-mediated AEs compared with 15% in the placebo group, including in 11% and 3%, respectively, who had grade 3 to 5 events.[23] No statistical comparisons for these outcomes were made, partly because immune- or potentially immune-mediated adverse events "*have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation*."[24]

The *Special warnings and precautions for use* section of the SmPC for pembrolizumab lists numerous immune-related adverse reactions and advises that patients should be monitored for such events.[5] This section of the SmPC also advises that pembrolizumab in combination with chemotherapy should be used with caution in patients ≥75 years after careful consideration of the potential benefit/risk on an individual basis. Considering that pembrolizumab has been approved for use in many other types of cancer for several years, the ERG sought to identify broader evidence on the incidence of AESIs. An Information Specialist (HF) designed a search strategy to identify systematic reviews of immune-mediated AEs of pembrolizumab and PD-1 inhibitors. Ovid Embase was the only database used, due to time constraints and because of its extensive coverage of drugs and pharmacology. The strategy used relevant subject headings and search syntax for the database and was limited to English language

papers from 2015 to the present. Eligible reviews had to report a meta-analysis of RCT data comparing immune-mediated AE rates in the pembrolizumab and/or PD-1 inhibitors arms with the placebo/standard care arms. Results had to be reported as odds ratios or relative risks with 95% confidence (or credible) intervals. To maximise sample sizes, eligible reviews had to evaluate more than one type of cancer population.

Fourteen eligible reviews with meta-analyses were identified, which were published between 2017 and 2022 (Table 9). As a class, PD-1 inhibitors significantly increase the risk of patients developing pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders. In the colitis meta-analysis, reported in Wang et al 2020,[25] six of the seven trials of PD-1 inhibitors were of pembrolizumab, whereas in Wang et al's 2020 pruritus meta-analysis only one study was of pembrolizumab. Some of the reviews also reported meta-analyses for only pembrolizumab trials (for some outcomes); these showed pembrolizumab to be significantly associated with increases in the risk of developing pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders.

The evidence of the incidence of rashes was somewhat uncertain. There was no evidence of associations between PD-1 inhibitors and pneumonia and no evidence of associations with cardiovascular AEs.

ERG summary

The main CS document does not clearly state that pembrolizumab is significantly associated with numerous immune-related AEs, which patients need monitoring for (although this is stated in the SmPC). The RCT evidence for pembrolizumab studied in a broad range of cancer populations shows significant associations with pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders. For PD-1 inhibitors as a class, the RCT evidence shows significant associations with pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders.

Table 9 Published recent meta-analyses of PD-1 inhibitor immune-related adverse events

Study, funding	No. of studies, No. of patients	Intervention	AESI outcomes	Results (95% CI), Heterogeneity (I^2 value)
Fujiwara et al 2021,[26] None	8, 5190	PD-1 inhibitors	Pneumonitis grades 1-5 Pneumonitis grades 3-5	OR 2.43 (1.54 to 3.85), I^2=4% OR 2.15 (1.05 to 4.43), I^2=0%
Hu et al 2021,[27] Government (China)	7, NR on forest plot	PD-1 inhibitors	Arrhythmology grades 1–5 Cardiac failure grades 1–5 Coronary artery disease grades 1–5 Pericardial disease grades 1–5 Cardiac arrest grades 1–5	OR 0.77 (0.23 to 2.63), I^2=50% OR 0.96 (0.36 to 2.58), I^2=0% OR 1.17 (0.34 to 4.00), I^2=26% OR 0.88 (0.27 to 2.93), I^2=0% OR 0.79 (0.25 to 2.92), I^2=0%
Huang et al 2019,[28] Government (China)	7, NR on forest plot	Pembrolizumab	Pneumonitis	OR 5.40 (2.39-12.17), NR
Huang et al 2019,[29] NR (no conflict of interests declared)	3, 1286	PD-1 inhibitors	Immune-related AEs grades 3-5	OR 2.27 (1.61 to 4.58), I^2=0%
Rahouma et al 2019,[30] NR (no conflict of interests declared)	13, 6118 (AG) 11, 6118 (HG)	PD-1 inhibitors	All grade pneumonitis (AG) High grade pneumonitis (HG)	OR 4.11 (1.50 to 11.22) I^2=80% OR 2.32 (1.19 to 4.51) I^2=15%
Su et al 2018,[*31] None	9, 4289 (PD1) 4, 2346 (P)	PD-1 inhibitors (PD1) Pembrolizumab PD-1 inhibitors Pembrolizumab (P) PD-1 inhibitors Pembrolizumab	Endocrine disorders grades 1-5 Endocrine disorders grades 1-5 Hyperthyroidism grades 1-5 Hyperthyroidism grades 1-5 Hypothyroidism grades 1-5 Hypothyroidism grades 1-5	OR 10.75 (6.62 to 17.45), I^2=0% OR 9.85 (5.65 to 17.17) I^2=0% OR 4.87 (2.50 to 9.49) I^2=0% OR 5.09 (2.36 to 10.97) I^2=0% OR 8.34 (4.64 to 15.00) I^2=0% OR 7.73 (3.86 to 15.49) I^2=0%
Su et al 2019,[32] NR (no conflict of interests declared)	9, 4767 (PD1) 4, 2824 (P)	PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P)	Pneumonitis grades 1-5 Pneumonitis grades 1-5 Pneumonitis grades 3-5 Pneumonitis grades 3-5 Pneumonia grades 1-5 Pneumonia grades 1-5 Pneumonia grades 3-5 Pneumonia grades 3-5	OR 5.17 (2.82 to 9.47) I^2=0% OR 5.35 (2.61 to 10.96) I^2=0% OR 4.14 (1.82 to 9.42) I^2=0% OR 5.64 (1.94 to 16.38) I^2=0% OR 0.88 (0.34 to 2.30) I^2=28% OR 0.90 (0.37 to 2.19) I^2=0% OR 0.70 (0.42 to 1.17) I^2=6% OR 0.62 (0.36 to 1.05) I^2=0%
Tian et al 2021,[33] Government (China)	15, 8371 11, 6285	PD-1 inhibitors	Hypothyroidism Hyperthyroidism	OR 8.34 (5.24 to 13.28) I^2=37% OR 5.59 (3.46 to 9.04) I^2=0%

Study, funding	No. of studies, No. of patients	Intervention	AESI outcomes	Results (95% CI), Heterogeneity (I^2 value)
Wang et al 2017,[34] Government (China)	5, 2745	PD-1 inhibitors	All-type all-grade hepatotoxicity All-type high-grade hepatotoxicity	OR 1.94 (1.28 to 2.94) I^2=0% OR 1.58 (0.66 to 3.78) I^2=0%
Wang et al 2020,[25] None	18, 9318 (PD1) 6, 4223 (P) 10, 5840 (PD1) 6, 4223 (P) 7, 4714 (PD1) 5, 3223 (PD1) 8, 5125 (PD1) 6, 4223 (P) 7, 4714 (PD1) 3, 2139 (PD1) 8, 4193 (PD1) 12, 10193 (PD1) 3, 2791 (P)	PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors Pembrolizumab PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors Pembrolizumab PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors Pembrolizumab	Any immune-related AE Any immune-related AE Pneumonitis Pneumonitis Colitis Hypophysitis Hypothyroidism Hypothyroidism Hyperthyroidism Hepatitis Pruritus Rash Rash	RR 2.65 (1.84 to 3.83) I^2=90% RR 3.56 (2.49 to 5.10) I^2=81% RR 2.10 (0.85 to 5.18), I^2=82% RR 2.92 (1.92 to 4.44), I^2=0% RR 2.96 (1.62 to 5.38) I^2=0% RR 4.79 (1.54 to 14.89) I^2=0% RR 7.78 (5.36 to 11.57) I^2=0% RR 8.15 (5.44 to 12.20) I^2=30% RR 7.03 (4.35 to 11.34) I^2=0% RR 9.31 (2.18 to 39.85) I^2=0% RR 2.28 (1.38 to 3.76) I^2=77% RR 1.58 (0.98 to 2.54) I^2=86% RR 1.42 (0.76 to 2.68 I^2=85%
Wei et al 2020,[35] NR (no conflict of interests declared)	9, NR on forest plot 7 NR on forest plot	PD-1 inhibitors PD-1 inhibitors	Grade 1-5 Colitis Grade 3-5 Colitis	OR 3.64 (1.87 to 7.06) I^2=0% OR 4.56 (1.68 to 12.36) I^2=0%
Xavier et al 2022,[36] Hospital (Brazil)	5, 2575	PD-1 inhibitors	All grade cardiovascular AEs Grade 3–5 cardiovascular AEs	RR 0.96 (0.77 to 1.20) I^2=0% RR 1.28 (0.77 to 2.12) I^2=0%
Yang et al 2019,[37] NR	11, 6001	PD-1 inhibitors	Rash Pruritus	RR 2.11 (1.63 to 2.74) I^2=41% RR 4.49 (3.04 to 6.65) I^2=53%
Yang et al 2021,[38] None	17, NR on forest plot 16, NR on forest plot 8, NR on forest plot	PD-1 inhibitors	Hypothyroidism Hyperthyroidsim Thyroiditis	RR 8.78 (5.07 to 15.22) I^2=52% RR 7.94 (5.17 to 12.19) I^2=0% RR 5.93 (2.30 to 15.31) I^2=0%

*Reports using risk ratios in the methods section and odds ratios in the forest plots. Key: AEs Adverse events, AESI Adverse events of special interest, AG All grade, CI Confidence interval, HG High grade, NR Not reported, OR Odds ratio, P Pembrolizumab,PD1 PD-1 inhibitors, RR Relative risk

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an SLR to identify relevant clinical evidence on pharmacological treatments for recurrent, persistent, or metastatic cervical cancer. Of the 56 publications (41 trials) that were identified, only 7 trials (3 single-arm and 4 RCTs) investigated comparators that were considered clinically relevant to UK practice by the company Table 10.The ERG's clinical advisors agreed that the comparators chosen were reasonable, although topotecan is used in clinical practice in a minority of patients (circa 10%).

All trials evaluated the use of cisplatin and paclitaxel; one trial[39] compared carboplatin and paclitaxel to cisplatin and paclitaxel. Two trials[4, 40] compared treatment with cisplatin and paclitaxel to other treatments such as topotecan, vinorelbine, and gemcitabine, but these treatment arms were ignored by the company as they were not relevant comparators. GOG-240[4] was the only trial that provided evidence on the use of bevacizumab and was used by the company to validate the economic model (see Section 4.2.6.1)

Table 10. Summary of relevant comparators identified in the SLR

Study	Trial Type/ Phase	Location	ECOG Performance Status	Cancer Stage	Treatment	Age, Median (Range)	Cycles, Median (Range)	N	Median Follow-up (months)	Median OS, months (95% CI)	Median PFS, months (95% CI)	ORR, n(%)
Coronel 2018[41]	Single arm/ Phase II	Mexico	1-3	Recurrent or persistent to primary treatment, or untreated Stage IVB	Cisplatin + Paclitaxel	54 (26-91)	5 (1-6)	30	12.5 (Range:1-37)	7.7	14.3	CR: 3 (10) PR: 9 (30)
Papadimitriou 1994[42]	Single arm/ Phase II	Greece	0-3	Primary stage IV, or recurrent	Cisplatin + Paclitaxel	51 (24-77)	6 (1-6)	34	NR	9 (Range: 0.5-22.5+)	NR	CR: 5 (14.7) PR: 11 (32.4)
Rose 1999[43]	Single arm/ Phase II	US	0-2	NR	Cisplatin + Paclitaxel	47 (24-67)	6 (1-10)	41	NR	10.0+ (Range: 0.9-22.2)	5.4+ (Range: 0.3-22.0+)	CR: 5 (12.2) PR: 14 (34.1)
Monk 2008 (GOG-204)[40]	RCT/ Phase III	NR	0-1	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	50 (29-81)	6	103	NR	12.87 (10.02, 16.76)	5.82 (4.53, 7.59)	CR: 3 (2.9) PR: 27 (26.2)
					Cisplatin + Vinorelbine	49 (24-76)	5	108			3.98 (3.19, 5.16)	CR: 8 (7.4) PR: 20 (18.5)
					Cisplatin + Gemcitabine	45 (20-89)	4	112			4.70 (3.58, 5.59)	CR: 1 (0.9) PR: 24 (21.4)
					Cisplatin + Topotecan	48 (25-75)	5	111			4.57 (3.71, 5.75)	CR: 2 (0.9) PR: 24 (21.6)

Tewari 2017 (GOG-240)[4]	RCT/ Phase III	US, Canada, and Spain	0-1	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	46.5 (SD:12.1)	6 (1-6)	114	NR	15.0	6.7 (5.7, 8.1)†	CR: 11 (9.6) PR: 41 (36.0)
					Cisplatin + Paclitaxel + Bevacizumab			115		17.5	9.6 (7.2, 12.7)†	CR: 18 (15.7) PR: 40 (34.8)
					Topotecan + Paclitaxel	48.9 (SD:11.7)		111		16.2	NR	CR: 13 (11.7) PR: 41 (36.9)
					Topotecan + Paclitaxel + Bevacizumab			112		12.0	NR	CR: 13 (12) PR: 41 (37)
Kitagawa 2015 (JCOG0505)[39]	RCT/ Phase III	Japan	0-2	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	53 (29-74)	NR	123	17.6	18.3 (16.1, 22.9)	6.9 (5.7, 7.9)	NR
					Carboplatin + Paclitaxel	53 (22-72)		121		17.5 (14.2, 20.3)	6.2 (5.5, 7.2)	NR
Moore 2004[44]	RCT/ Phase III	NR	0-2	IVB, recurrent, or persistent	Cisplatin	46.0 (22-84)	Unclear, in absence of disease, toxicity patients supposed to receive 6 cycles	134	NR	8.8	2.8	CR: 8 (6.0) PR: 18 (13.4)
					Cisplatin + Paclitaxel	48.5 (21-77)		130		9.7	4.8	CR: 20 (15.4) PR: 27 (20.8)

Unless specified differently for a particular study, the uncertainty for each estimate is indicated in brackets after the estimate.

† While these values do not appear in the peer-reviewed publications, they are available from the ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/results/NCT00803062) and Table 5 in Appendix D of the CS.

Abbreviations: CI: confidence interval, CR: complete responders, NR: not reported, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PR: partial responders, SD: standard deviation.

The company did not conduct an ITC, as they did not believe that it would add to the evidence provided in KEYNOTE-826. The ERG agrees with the company that the evidence available would not provide useful comparisons between treatments. However, evidence from the other studies should probably not be disregarded completely as these studies may provide longer-term survival data for comparator treatments, which were not available for KEYNOTE-826 using the current data cut-off. While most studies[40-44] identified in the SLR did not present KM plots for OS and PFS for longer than 3 years, two studies Tewari 2017[4] and Kitagawa[39] reported KM plots for 4 and 5 years, respectively.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect treatment comparison; the reasons are discussed in Section 3.3.

3.5 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence for pembrolizumab plus chemotherapy versus placebo plus chemotherapy is based on single trial (KEYNOTE-826). The study appears to be at low risk of bias for most domains, although some aspects of the trial design and the availability of only an interim analysis create areas of uncertainty.

KEYNOTE-826 shows that pembrolizumab is associated with improved PFS in the CPS≥1 population, a difference that appears to be driven largely by PFS gains among patients who achieve complete response. A similar pattern of improvement can be seen for OS, although the available data are immature and the effect is uncertain.

The company model uses PFS as surrogate for unavailable longer-term OS, though the ERG's clinical advisors were not confident that this was appropriate in the population under consideration. Extrapolation estimates of OS beyond the available trial data and into the longer-term are therefore highly uncertain.

Where reported, HRQoL differences between the treatment arms of KEYNOTE-826 are relatively small and mostly statistically non-significant.

The safety and adverse event evidence from KEYNOTE-826 is broadly in line with wider RCT evidence for pembrolizumab used in a range of cancer populations which shows significant associations with pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders. For PD-1 inhibitors as a class, the RCT evidence shows significant associations with pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders.

The subgroup of patients in KEYNOTE-826 with metastases at initial diagnosis had statistically significantly worse PFS outcomes than patients without metastases at initial diagnosis. OS results were also notably different. This apparent lack of effect for PFS (in particular) and for OS was similar (in terms of hazard ratios) to that seen in the PD-L1 CPS <1 subgroup, which was excluded from the EMA's marketing authorisation.

Three issues suggest that pembrolizumab may be less efficacious when used in an NHS setting than was observed in KEYNOTE-826:

Firstly, KEYNOTE-826 excluded patients with an ECOG 2 performance status. However, the ERG's advisors estimated that 20-30% of ECOG 2 patients would be eligible for systemic treatments in the NHS. Conversely, patients with an ECOG 0 status were over-represented in KEYNOTE-826 (56% of patients) compared with the ERG advisors' estimate for the relevant NHS population (10-15%).

Secondly, in the NHS, bevacizumab would not be continued for as many cycles as was used in KEYNOTE-826 (where the number of permitted cycles was unlimited).

Finally, in KEYNOTE-826, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could potentially have affected results to slightly favour pembrolizumab.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company undertook two systematic literature reviews (SLRs) to identify relevant economic evaluations and studies reporting on the health-related quality of life (HRQoL) of patients with high risk, locally advanced, and persistent, recurrent, or metastatic cervical cancer in the first-line setting.

4.1.1 Searches

The original company submission included searches to identify cost-effectiveness evidence, cost and healthcare resource use measurement and valuation, and health-related quality of life studies for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies was included in CS Appendix G (Pages 43-50) and Pages 9-21 of an embedded economic SLR report on Page 50 of Appendix G.

In response to the ERG's PFCs, a further document was provided by the company, which included clarifications on issues raised by the ERG. The ERG was largely satisfied that the conduct of the cost-effectiveness searches was methodologically sound. The ERG raised a couple of minor reservations with regards to ambiguous reporting of several aspects of the cost-effectiveness and resource use searches. A detailed appraisal of evidence identification methods is provided in Appendix 9.1.1 to 9.1.4 to the ERG Report.

4.1.2 Eligibility criteria used for study selection

Study eligibility criteria applied by the company were described in CS Appendix G for the review of economic evaluations, and CS Appendix H for the quality-of-life studies. There was no date or language limit applied. The population of interest in both cases was to include patients of broadly similar characteristics to those in KEYNOTE-826. Two reviewers independently assessed studies based on title and abstracts, with discrepancies reconciled by a third reviewer. Full text screening and data extraction was again performed by two reviewers, with any discrepancies resolved by a third reviewer.

The ERG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate.

4.1.3 Studies included in the cost-effectiveness review

A total of 30 unique studies met the inclusion criteria, of which 18 were cost-effectiveness analyses, with one budget impact model, and one NICE health technology appraisal (TA183). The company considered only the NICE appraisal relevant to the UK setting, which was published in 2009. Due to

the age of the study, the company considered it of limited relevance for the present appraisal, but did provide a comparison of their *de novo* economic analysis with TA183 in Table 20 of the CS.

The second review of HRQoL studies identified no studies relevant to the UK setting in the population under consideration. A total of 29 studies were identified which reported HRQoL data.

The ERG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses conducted in a relevant population and setting. The ERG is therefore satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 11 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 11 NICE reference case checklist

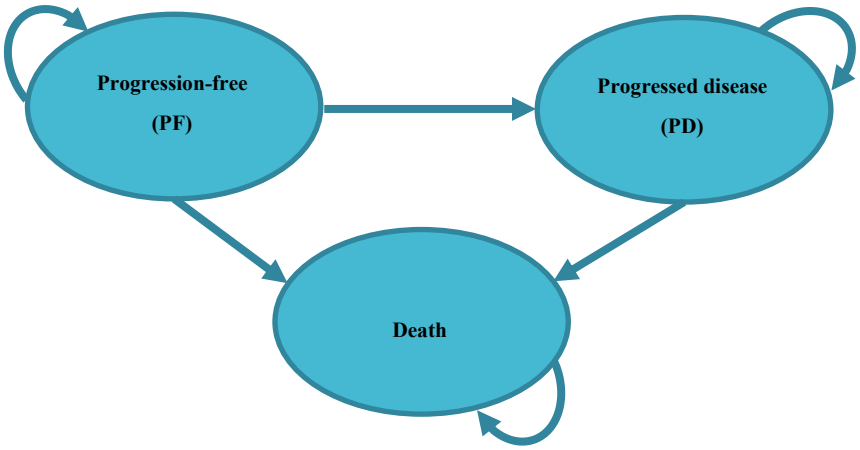
Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits to treated individuals were considered.
Perspective on costs	NHS and PSS	NHS and PSS costs have been considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model uses a 50-year time horizon. This is sufficient given the disease area.
Synthesis of evidence on health effects	Based on systematic review	The company initiated a systematic review to identify relevant sources of data.
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	EQ-5D-5L data was collected in the KEYNOTE 826 trial. These values were cross-walked to EQ-5D-3L values using the van Hout *et al.*[46] mapping function.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Derived from EQ-5D data directly obtained from patients in the KEYNOTE 826 trial.
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	Costs were based on UK sources including the BNF and NHS reference costs. Resource use rates were based on clinical advice.

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits have been discounted at 3.5% per annum. Scenario analysis was performed applying an annual discount rate of 1.5%.
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 developed a state transition model (STM) in Microsoft Excel to simulate the lifetime cost-effectiveness outcomes of patients with recurrent, persistent or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥ 1, who are on treatment with the standard of care (platinum-based chemotherapy +/- bevacizumab) compared to standard of care in combination with pembrolizumab. The model uses a one-week cycle length with no half-cycle correction applied. The model structure consists of three health states of 'progression-free', 'progressed disease' and 'death', See Figure 5.

Figure 5 Illustration of state transition model structure (CS Figure 16, Page 79)



In this model, the following transitions are permitted in each cycle, patients in the:

- 'Progression-free' health state could remain in the progression free state, transition into 'progressed-disease' health state or transition to the 'death' state,
- 'Progressed disease' health state could remain in the progressed disease state or transition into the 'death' state.
- 'Death' state will always remain in that state. This is an absorbing state.

At each model cycle, transition probabilities and health state occupancy were determined based on patient-level data from the KEYNOTE-826 trial for time to progression (TTP), progression-free

survival (PFS) and post-progression survival (PPS) extrapolated over the model time horizon using parametric survival models (see Section 4.2.6 for further details).

A key feature of the company's modelling approach is that it uses a STM rather than a partitioned survival model (PSM), which is typically adopted in advanced cancer evaluations. There are several key differences between a STM and a PSM in this context. Foremost among these is that a STM explicitly models the transitions between each health state, whereas a PSM model does not. This has consequences for how state occupancy is estimated. In a state transition model, state occupancy is a function of the transition probabilities applied to each health state. In a PSM, transitions between health states are not explicitly modelled. State occupancy is instead directly determined by the (observed and extrapolated) survival data (typically PFS and OS).

The company's justification for a state transition approach is described on page 37 of the CS and claims several advantages of adopting a state transition approach. A key part of this justification is founded upon the company's preferred extrapolations of TTP and PFS, which use a piece-wise approach (Kaplan-Meier (KM) data followed by parametric survival models fit from 37-weeks onwards). These preferred extrapolations lead to long tails in PFS with the consequence that extrapolated PFS and OS [redacted] for the pembrolizumab arm and standard of care (SoC) arm respectively (see Figure 6 and Figure 7 below). In a PSM (where state occupancy is determined directly from the survival curves), this would lead to inconsistencies in model predictions because the proportion of patients alive would be less than those in the progression-free state. The company's STM avoids this issue by imposing a structural surrogate relationship between PFS and OS. This surrogate relationship implies that PFS is the main determinate of predicted OS. Note this contrasts with a PSM model where OS is estimated directly using the OS curve.[47]

Figure 6 Illustration of PFS and OS KM data and parametric extrapolations; Pembrolizumab arm CPS≥1 population of KEYNOTE-826 (CS Figure 17, Page 81)

Key: Exp, exponential; GenGam, generalised gamma; K-M, Kaplan–Meier; LogLog, log-logistic; LogNor, log-normal; OS, overall survival; PFS, progression-free survival; SoC, standard of care; Wei, Weibull

Figure 7 Illustration of PFS and OS KM data and parametric extrapolations; SoC arm CPS≥1 population of KEYNOTE-826 (CS Figure 18, Page 82)

Key: Exp, exponential; GenGam, generalised gamma; K-M, Kaplan–Meier; LogLog, log-logistic; LogNor, log-normal; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; SoC, standard of care; Wei, Weibull

4.2.2.1 Points for critique

In principle, the ERG considers that the STM structure can have several advantages over a PSM when mature PFS and OS data are available. Specifically, the structural links imposed in STMs imply an explicit disease model that allows both the natural history of the disease and the effect of treatment to be reflected when extrapolating beyond the trial data. The assumptions underpinning these extrapolations are also made explicit and therefore subject to scrutiny and sensitivity analyses.[47] Importantly, PSMs and STMs are also expected to produce similar results for within-trial data because relationships between endpoints are reflected within the data.

An STM is, however, a substantially more complicated approach and has several drawbacks when data are immature. One important consequence of the STM approach is the structural link between PFS and OS which implies a surrogate relationship between PFS and OS. The CS does not fully justify this assumption. The CS states that elicited clinical opinion supported the concept of a positive relationship between the duration of progression and PPS survival. Appendix Q of the CS also provides evidence from a within trial analysis of KEYNOTE-826 examining the relationship between TTP/PFS and PPS, and reports a positive correlation between TTP and PPS. While the ERG considers this evidence broadly supportive of this assumption, no evidence is provided to suggest that TTP/PFS is a validated surrogate for OS, and notes that the observed correlation between PFS and PPS does not necessarily indicate a causal relationship. . The ERG considers the lack of supporting evidence for a surrogate relationship between PFS and OS to be an important omission. A failure to validate may lead to misleading cost-effectiveness estimates.[48, 49] Moreover, the NICE methods guide states: *"When the use of 'final' clinical endpoints is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling."* The ERG also highlights precedent from previous technology appraisals, which have raised concerns regarding the validity of PFS as a surrogate for OS (TA658).[50]

In the context of the current model, the ERG notes that the model predictions do not align well with the observed OS data from KEYNOTE-826. As illustrated in Table 12, the base-case model systematically overpredicts the proportion of patients alive at early time points and then underpredicts at later time points. The ERG is particular concerned about the underprediction at 24 months which is more pronounced in the SoC arm suggesting a bias in favour of pembrolizumab. The ERG notes this issue is persistent and is not sensitive to the parametric models used to extrapolate TTP, PFS, and PPS, suggesting it is a consequence of the modelling approach. The ERG considers that this is likely to be a consequence of how PPS transitions are modelled, as PFS predictions align relatively well

with the observed data. Specifically, this may result from the assumption that transitions in the PPS health state are unrelated to the timing of progression events. The duration of PPS is therefore the same regardless of whether a progression occurs in cycle one or cycle 1001. It is not clear if this is appropriate, and this assumption is not assumed in a PSM where PFS curves and OS curves are estimated independently.

Table 12 Comparison of model predictions and observed OS data

	Pembrolizumab		SoC	
	KEYNOTE 826	Economic model	KEYNOTE 826	Economic model
6 Months	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	[redacted]	[redacted]	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]	[redacted]
24 Months	[redacted]	[redacted]	[redacted]	[redacted]

In addition to the above, the ERG also has substantive concerns regarding the company's justification for the STM approach. As stated above, the company's justification is founded on the extrapolations of PFS data and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations. However, it is not clear that the PFS extrapolations preferred by the company are clinically plausible, and the ERG notes that the crossing of PFS and OS is solely because a piecewise approach is adopted to the extrapolation of PFS. Crossing does not occur when a single-parametric curve is fitted to the whole KM data.

The ERG further notes that the company's base-case analysis predicts that a non-negligible proportion of patients will achieve long-term survival of 5 or more years with a smaller proportion effectively cured and achieving survival near that of the general population. Importantly, the proportion of long-term survivors is substantially greater in the pembrolizumab arm of the model (22.7% in the pembrolizumab arm survive for 5 or more years compared with 8.9% of patients receiving SoC) and this drives a significant proportion of the benefits associated with pembrolizumab. The plausibility of these predictions is discussed in later sections but in terms of the model structure the ERG highlights that the long-term benefits of pembrolizumab predicted by the model are heavily dependent on the approach to extrapolating PFS, and are a direct consequence of the structural link between PFS and OS imposed by the STM.

4.2.3 Population

The modelled population is adults with untreated recurrent, persistent or metastatic cervical cancer whose tumours express PD-L1 (CPS≥1). This population aligns fully with the anticipated marketing authorisation for pembrolizumab but is a narrower population than that defined by the NICE scope which included all adult patients with untreated recurrent, persistent or metastatic cervical cancer.

In line with the narrower focus of the marketing authorisation, the modelled population is based upon CPS≥1 subgroup of KEYNOTE-826 which accounted for approximately 89% of the ITT population (n=548). The baseline characteristics of the modelled population are presented in Table 13 and include age, sex, weight, and body surface area. Age and sex were used to parameterise a general population mortality cap imposed in the model. Age also drives age-related utility adjustments to HRQoL. Weight and body surface area were used to inform the dose associated with several interventions and comparators, see Section 4.2.8.1 for details.

Table 13 Baseline patient characteristics of modelled population

Age	[redacted]
Sex	100% female
Weight	[redacted]
Body surface area	[redacted]

The NICE scope listed several subgroups of relevance, histology, pelvic disease status, PD-L1 expression (CPS<10, CPS ≥10) and tumour mutational burden. At the clarification stage the ERG also requested subgroup analysis according to whether patients received bevacizumab. The company did not consider any patient subgroups in the model, in the base-case or otherwise.

4.2.3.1 Points for critique

ECOG Performance Status

Inclusion criteria applied in KEYNOTE-826 restricted eligibility to patients with an ECOG performance status of either 0 or 1. Consequently, with the exception of one patient in the pembrolizumab arm, there were no patients in the trial with an ECOG status of 2. Discussions with the ERG's clinical advisors, however, suggested that some patients (circa 20-30%) with an ECOG status of 2 would receive systemic treatment in NHS practice. The ERG notes that the anticipated marketing authorisation for pembrolizumab does not restrict eligibility by ECOG status and therefore patients with an ECOG status of 2 could be eligible to receive pembrolizumab in practice (see Section 3.2.2.1). The ERG's clinical advisors considered this clinically plausible.

The lack of clinical evidence to support effectiveness in this sub-population represents a significant uncertainty. ECOG status is an established prognostic factor and may also impact on relative treatment effects, though the direction of this effect is unknown. The cost-effectiveness of pembrolizumab in an ECOG 2 population is therefore highly uncertain and the ERG considers that it would be inappropriate to extrapolate cost-effectiveness estimates from an ECOG <2 population to an ECOG 2 population given these uncertainties.

Eligibility for Bevacizumab

In base case cost-effectiveness analyses the company did not differentiate between patient subpopulations based on their eligibility for bevacizumab and did not provide relevant subgroup analysis following a request by the ERG at the clarification stage; their reasons for not differentiating the subpopulations are detailed in Section 3.2.3.1. The ERG considers that eligibility to receive bevacizumab defines two distinct decision problems as these represent distinct populations that may differ with respect to prognosis, relative treatment effects and costs. Pooling these populations, as has been done in the company's base-case analysis, therefore fails to recognise the potential for heterogeneity in cost-effectiveness estimates across these two populations. The ERG considers that further efforts to explore this uncertainty are necessary to establish the cost-effectiveness of pembrolizumab in both groups of patients.

Metastatic Patients

As discussed in Section 3.2.3.1, subgroup analysis presented in Figures 13 and 14 of CS Document B, demonstrates a substantial difference in the point estimates according to whether or not they were diagnosed with metastatic disease at their initial diagnosis (OS: HR 0.88, 95% CI (0.58, 1.35) vs HR 0.56, 95% CI (0.41, 0.75) respectively). Importantly, these analyses show no statistically significant treatment effect in the metastatic population, and additional analysis requested at clarification indicates a statistically significant interaction between treatment and metastatic status.

The ERG is conscious that the trial was not powered to formally investigate treatment effectiveness in subgroups but considers the results strongly suggestive of a difference in the relative treatment effects across these two groups. The company acknowledges that patients who are metastatic have a poorer prognosis, and according to the ERG's clinical advisors it is biologically plausible that treatment effect may differ in patients relative to baseline metastatic status. Therefore, the ERG considers that it would have been appropriate to explore this subgroup within the economic analysis and notes that the failure to do so means that heterogeneity in cost-effectiveness estimates is not fully reflected in the company's economic analysis.

4.2.4 Interventions and comparators

As described in Section 2.2, pembrolizumab is a humanised monoclonal anti-PD-L1 antibody, which binds to the PD-1 receptor expressed by tumour cells and thus allows the patient's immune system to target and destroy these cells. The anticipated marketing authorisation permits use of pembrolizumab only in combination with chemotherapy, with bevacizumab as an optional additional therapy.

The recommended dose of pembrolizumab in adults is either 200mg Q3W or 400mg Q6W, administered as an intravenous infusion over 30 minutes. Patients in KEYNOTE-826 received 200mg Q3W until discontinuation, or for up to a maximum of 24 months, or up to a maximum of 35 cycles. Pembrolizumab treatment is implemented in the economic model as per its use in KEYNOTE-826, i.e., 200mg Q3W up to a maximum of 35 cycles in combination with SoC.

The NICE scope identified several relevant comparators; platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel, topotecan, or etoposide. In addition, for those who would receive bevacizumab: paclitaxel and carboplatin or cisplatin with bevacizumab (15mg/kg Q3W). The company's submission did not address etoposide or topotecan, reasoning that cervical cancer is not included as an indication in the etoposide SmPC, and is used only in small cell cervical cancer, which was not covered in the KEYNOTE-826 trial. Topotecan was recommended in this population in TA183, but the company stated that their clinical experts agreed that topotecan was not currently in use in the NHS for this indication. Platinum-based monotherapy was also excluded from the list of comparators to align with options recommended by the BGCS guidelines[2] and clinician feedback.

The comparators as modelled by the company were platinum chemotherapy in combination with paclitaxel, with or without bevacizumab, up to a maximum of 6 treatment cycles. Carboplatin is modelled at a flat dose of 750 mg Q3W. Cisplatin is modelled at a dose of 50 mg/m^2 Q3W. Paclitaxel is modelled at a dose of 175 mg/m^2 Q3W. Bevacizumab is implemented in the model at a dose of 15 mg/kg Q3W.

The company submission noted that bevacizumab was available as an option through the Cancer Drugs Fund (CDF), but the ERG has clarified with NICE that bevacizumab is now in routine commissioning in this indication.

The composition of SoC was modelled according to the proportions on each treatment arm in KEYNOTE-826 and are reproduced in Table 14 below.

Table 14 Modelled comparator therapies (CS Table 21, Page 91)

Treatment	Pembrolizumab + SoC n (%), n total = 272	SoC only n (%), n total = 275
Pembrolizumab	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin + Carboplatin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]

Points for critique

Exclusion of etoposide and topotecan

The ERG considers the interventions and comparators included in the economic model to be broadly appropriate and consistent with the decision problem. The ERG's clinical advisor agreed with the exclusion of etoposide as a comparator but stated that topotecan was still used in some patients (circa 10%). The efficacy of topotecan is unlikely to differ significantly from SoC, and as the proportion of patients receiving this treatment on the NHS is unclear, the ERG does not consider this uncertainty to have meaningful implications for estimates of the cost-effectiveness of pembrolizumab.

Inclusion of bevacizumab as a comparator

The ERG accepts that bevacizumab combination therapy is used routinely in NHS practice for the treatment of recurrent, persistent or metastatic cervical cancer. However, the ERG considers a comparison with bevacizumab combination therapy to be problematic due to the unique circumstances in which it entered commissioning on the NHS. The ERG understands that bevacizumab underwent no formal public assessment of cost-effectiveness prior to its entry into the CDF and was not reviewed by NICE when it entered routine commissioning. The cost-effectiveness of bevacizumab is therefore unknown and it is plausible that bevacizumab is not a cost-effective technology.

Further, while the ERG recognises that consideration of the cost-effectiveness of bevacizumab is beyond the scope of this appraisal, its cost-effectiveness has implications for the cost-effectiveness of pembrolizumab and therefore the ERG considers it relevant to the current decision problem. The impact of this issue on cost-effectiveness estimates is difficult to untangle due to pembrolizumab being an adjunctive therapy, and ideally would be addressed by fully incremental analysis considering each of the four alternatives (doublet chemotherapy, doublet chemotherapy plus bevacizumab, doublet chemotherapy plus pembrolizumab, doublet chemotherapy plus bevacizumab and pembrolizumab) in

a bevacizumab eligible population. Lack of appropriate comparative evidence, however, makes any such comparison difficult. Resolution of this uncertainty may be partially addressed by considering subgroup analysis of KEYNOTE-826 stratifying by eligibility to receive bevacizumab. Subgroup analysis was requested by the ERG at the clarification stage but was not provided by the company in their response. The ERG considers that this issue should be further explored as part of the Technical Engagement process.

Bevacizumab monotherapy

Bevacizumab monotherapy was permitted to continue in KEYNOTE-826 beyond completion of the allowed cycles of platinum-based chemotherapy, with a median of [redacted] cycles in the pembrolizumab arm, and [redacted] cycles in the SoC arm. As noted in the CS, bevacizumab may only be used in conjunction with chemotherapy on the NHS. The company therefore adjusted the administration and acquisition associated with bevacizumab assuming a maximum treatment duration of 6 cycles. Clinical advice to the ERG suggests that, while official guidance restricts bevacizumab use to 6 cycles, it is sometimes used as a maintenance therapy. This appears to be confirmed by the company's clinical advisors, as reported in the advisory group meeting report.[22] The frequency with which bevacizumab maintenance therapy is used in the NHS is unclear, though it appears to be in a minority of patients. The ERG, notes that scenario analysis exploring this uncertainty results in a reduction in the ICER. The company's base case is therefore conservative with respect to this assumption.

Retreatment with pembrolizumab

The ERG noted that re-treatment with pembrolizumab was permitted in the KEYNOTE-826 protocol and requested that the company provide information on the proportion of patients receiving re-treatment and the duration of any such re-treatment. The company stated that while no patients received re-treatment as defined in the protocol, a small number of patients were treated with pembrolizumab following progression, amounting to [redacted] of progressed patients in the pembrolizumab arm, and [redacted] of progressed patients in the SoC arm. The company therefore provided a scenario analysis accounting for these costs. The ERG considers it unlikely that NHS England would approve retreatment with pembrolizumab. However, the effect of retreatment in terms of costs and predicted benefits is unlikely to have a significant impact upon the estimates of cost-effectiveness as illustrated by the scenario analysis.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[51] the company's analysis adopted a NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. The impact of alternative discount rates for costs and QALYs (1.5%) were explored in scenario analysis.

A lifetime horizon of 50 years was chosen to capture all relevant differences in costs and benefits between comparators. The impact of a shorter 40-year time horizon was also explored in scenario analysis. The use of a lifetime horizon is considered appropriate by the ERG and necessary to account for the claimed long-term survival gains associated with pembrolizumab.

4.2.6 Treatment effectiveness and extrapolation

As discussed in detail in Section 4.2.2, the company used a STM consisting of three health states: Pre-progression, Post-progression, and Death. Consistent with this model structure TTP, PFS and PPS were estimated. Each of these were informed by data from the KEYNOTE-826 trial which was the primary data source for the economic analysis. All model inputs from the KEYNOTE-826 trial are based on the interim May 2021 data cut. The ERG notes that a further and final data cut is expected to be available in [redacted] of [redacted].

4.2.6.1 Progression free health state

In line with the STM approach, transition probabilities were estimated to determine state occupancy. In the progression-free health state, patients could remain in the progression free health state, or transition to either the progressed disease or death health states. Transition probabilities were estimated using TTP and PFS data from the KEYNOTE-826 trial. Transition probabilities associated with remaining in the progression free health state or transitioning to the progressed disease state were informed by TTP, while transitions to the death state were modelled using the difference between TTP and PFS.

To inform the transition probabilities used in the progression free health state it was necessary to extrapolate the available TTP and PFS survival data. This was done using standard parametric models, with the same model type used for both TTP and PFS to ensure model results remained clinically plausible.

The company's base case model adopts a two-piece approach to modelling TTP and PFS. This two-piece approach directly applied observed TTP and PFS KM data from the KEYNOTE-826 trial to inform transition probabilities up to 37 weeks, followed by the use of parametric survival models fitted to the remaining observed data. This approach was adopted to inform the long-term extrapolations of the data after the company concluded that a single piece model (a parametric distribution fitted to the whole KM curve) had poor visual fit to the observed data and was unable to appropriately capture what they considered an emerging plateau in the observed survival data and the associated changes in the hazard function. In their justification for a two-piece approach, the company noted an 'inflection point' in the KM data between weeks 40 and 60, after which there is plateau in observed progression events. The company considered this plateau to exist in both the pembrolizumab and SoC arms, but that it was more pronounced in the pembrolizumab arm leading to divergence in

the KM curves. Cumulative hazard plots were reported as supportive evidence for this decline in the hazard rate. These are reported in in Figures 26 and 27 of the CS and show that the hazard rate begins to decline from approximately 37 weeks. Statistical assessment of a structural break was also assessed using a Chow test which supported a cut-off at 65 weeks for pembrolizumab and at 63 weeks for SoC.

In exploring alternative cut points, the company considered it preferable to align time points with the completion of tumour imaging assessment schedules. This suggested 37 weeks, 46 weeks or 55 weeks as potential cut-off points. Based on the number of patients at risk after each of these points a 55-week cut off was dismissed as inappropriate. A 37-week cut- off was selected for the base case analysis, with scenario analysis considering a 46-week cut-off.

The company's process for fitting survival models was by testing the proportional hazards assumptions (using log-cumulative hazards plots and Grambsch-Therneau correlation tests between Schoenfeld residuals); these indicated that the proportional hazards assumption was violated and independent models were fitted to each treatment arm. Model selection was based on: Akaike information criterion (AIC) and Bayesian information criterion (BIC); visual fit; the desire for common functional form of models to both arms; the plausibility of hazard assumptions and clinical plausibility of the survival predictions. The AIC and BIC for the models fitted to both arms of KEYNOTE 826 can be seen in Table 23 of the CS (p104); visual inspection of the models overlying the Kaplan-Meier data can be seen in Figure 25 of the CS (p103).

Based on the criteria outlined above, the log-logistic model was selected as the most appropriate and used in the base case analysis, see Figure 8 and Figure 9 for visual fit to KM data. The company also supplied a pessimistic analysis for both the SoC and pembrolizumab arms, which was an average of the Weibull and log-logistic piecewise models for TTP and PFS.

Figure 8 Modelled TTP (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 28, Page 109)

Figure 9: Modelled PFS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 29, Page 108)

Points for critique

Extrapolation of PFS

The ERG has substantive concerns regarding the company's approach to extrapolating PFS and the two-piece approach adopted by the company. The ERG considers the company's justification for adopting a two-piece approach to be inadequate and that it emphasises fit to the pembrolizumab PFS data without appropriate consideration of the clinical plausibility of the corresponding predictions in the SoC arm.

Considering the SoC arm, the ERG disputes the company's claim that a one-piece model does not adequately fit the data. The ERG considers that several one-piece extrapolations have good visual and statistical fit to this data and generate predictions that align reasonably well with the observed data, see Figure 11 for visual fit based on ERG's preference single piece extrapolation (log-logistic model). Moreover, the ERG sees no evidence of a plateau in PFS outcomes for SoC, and considers that the inflection point followed by a rapid decline in hazards as predicted by the two-piece approach to be unrealistic, and to result in clinically implausible predictions. Specifically, the ERG highlights that the model predicts that a non-negligible proportion of patients will remain progression-free beyond 5 years ([redacted]) leading to 5-year OS of [redacted]. Clinical advice provided to the ERG suggests that it is rare for patients to achieve such long-term freedom from progression and survival on SoC, with only a minority of patients surviving beyond 5 years. In this regard, the ERG also notes that company's own clinical advisors considered the long-term (20-year) predictions for SoC overly optimistic.

Figure 10 ERG preferred Single piece extrapolation to TTP (log-logistic model)

Figure 11 ERG preferred Single piece extrapolation to PFS (log-logistic model)

With regards to the company's parametric model selection process, the ERG also questions the company's use of GOG 240[4] to validate the long-term predictions of the model, and notes several weaknesses with this approach. Firstly, while GOG 240[4] reports data at 4 years, the numbers at risk are very small and thus the landmark PFS and OS used to validate the model predictions are based on very few patients and are thus subject to substantial uncertainty. Secondly, GOG 240[4] also has important external validity issues and may not be representative of patients treated in NHS practice. The ERG especially highlights a retrospective study carried out in the US which found that only 14.5% of patients treated with bevacizumab in clinical practice would be eligible for the GOG 240 trial.[52] The GOG 240[4] population therefore represents a highly restricted population and may not be an appropriate reference for validation.

With respect to the SoC arm, the ERG therefore considers the application of a two-piece model to be inappropriate and has a strong preference for a one-piece approach. Moreover, the ERG considers issues associated with a two-piece model in the SoC arm to be relevant to establishing the credibility of predictions in the pembrolizumab arm. NICE DSU TSD 19[47] recommends that the same model type should be adopted in both the treatment and comparator arms unless strong evidence to justify a differential approach is presented.

Considering the evidence for a two-piece approach, the ERG agrees with the company that KEYNOTE-826 shows some evidence of a reduction in hazards, with some evidence suggestive of a

plateau emerging in the relevant TTD and PFS KM curves. However, the company's approach to model selection and validation using visual fit and the hazard trends places too much emphasis on the tail of the KM curve, the shape of which is driven by very few events and small numbers at risk, and is subject to a high degree of censoring. Importantly, the rapidly declining hazards result in very substantial PFS and OS gains for pembrolizumab compared to SoC. These benefits are accrued almost entirely in the extrapolated region of the curves, and are not yet in evidence in the observed data. This is exemplified by the observed median gains from KEYNOTE-826 versus the mean PFS gains predicted by the model. In the trial, median PFS was 10.4 months on pembrolizumab compared to 8.2 months in the SoC group (i.e. 2.2-month improvement), whereas the model predicted a mean improvement of 2.7 years (32 months) for pembrolizumab compared to SoC.

Moreover, the long tails predicted by the two-piece approach lead to a very substantial proportion of patients achieving long-term survival. In the base case analysis, [redacted] of patients on pembrolizumab remain in the progression-free health state at 5 years and [redacted] at 10 years. These projections are highly optimistic and imply that a proportion of patients achieve cure-like benefits. When requested to comment on the plausibility of such benefits and the significant number of long-term survivors, the company emphasised the lack of clinical experience in using both bevacizumab and pembrolizumab in this indication, but noted that long tails are commonly associated with immunotherapies in other indications. The company further highlighted the small numbers of patients eligible for systemic treatment in the UK creates challenges to eliciting accurate expectations about long-survival, particularly for patients in the pembrolizumab arm of the model.

While the ERG acknowledges that immunotherapies have historically been associated with durable response rates in other indications, there is insufficient evidence in cervical cancer to suggest that short term treatment with an immunotherapy translates into such long survival gains, nor has a possible mechanism for cure been established. The ERG consequently does not consider existing evidence to be sufficient to demonstrate the paradigm shift in outcomes modelled by the company. Of the parametric models fitted by the company, there was a clear choice made to discount the single piece models which predicted more conservative PFS (and OS) gains, and instead it is assumed that a significant proportion of patients would instead survive for many years or even decades. See Table 15 for a comparison of landmarks associated with each approach. The final data cut from KEYNOTE-826, [redacted], will likely be helpful in resolving this uncertainty and may help substantiate the purported inflection point in hazards.

Table 15 Comparison of model predictions and observed OS data

	Pembrolizumab	SoC

	Two-piece (log-logistic)	Single-piece (log-logistic)	Two-piece (log-logistic)	Single-piece (log-logistic)
1 year	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]

Duration of treatment benefit

The company assumed a lifetime treatment effect of pembrolizumab in their base case analysis. Following a request at the clarification stage, the company also presented scenario analysis to explore the impact of a gradual loss of treatment effect between three and five years. In this scenario, the rate of progression on pembrolizumab is adjusted gradually to essentially switch the curve to be equal to that of the SoC arm after five years. It therefore assumes a complete loss of treatment effect five years after patients have discontinued treatment.

In defence of the base case assumption, the company highlights that treatment waning assumptions have been applied inconsistently in previous appraisals of immunotherapies, noting specific evidence for both nivolumab and pembrolizumab. The company also outline that they consider there to be no evidence of treatment waning in this indication and that longer-term follow-up on pembrolizumab in other indications shows only limited evidence of a waning effect (see response to PfC Question B3 part c).

While the ERG accepts that it may be biologically plausible for the maintenance of a treatment effect after stopping pembrolizumab, the duration of this effect is uncertain. Moreover, the ERG considers the company's characterisation of previous NICE decisions inaccurate, as the case for waning is not necessarily applicable to all immunotherapy appraisals and will depend on the length of trial follow-up and presence of a stopping rule. In the context of the current appraisal, the ERG highlights there is no indication-specific evidence to support a sustained treatment effect, and that the overall immaturity of the survival evidence means any such claimed benefit is highly uncertain. Importantly, the application of a stopping rule in the present appraisal implies the effect of pembrolizumab on PFS (and OS) persists long after patients have stopped receiving treatment (i.e. a patient who is alive 10 years after discontinuing pembrolizumab has a lower probability of PFS event and will have a better survival prognosis compared with an identical surviving patient who received SoC). Contrary to the company's response, the ERG notes that committees have routinely assumed a waning of the

treatment effect 3 to 5 years after discontinuation of treatment where a stopping rule has been applied.[7-12, 53-56]

In summary, given the short follow-up from KEYNOTE-826, the ERG believes that it is unknown whether, or for how long, the effects of pembrolizumab on PFS (and OS) are maintained after treatment discontinuation. This uncertainty may be resolved in part through more mature data from KEYNOTE-826.

4.2.6.2 Post-progression survival

State occupancy in the progressed disease health state was determined by PPS survival data from KEYNOTE-826. Transition probabilities were applied such that time in state was independent of when a patient entered the progressed disease health state, see Section 4.2.2 for further discussion of this point.

Single parametric models were fitted independently to both treatment arms of KEYNOTE-826, as the proportional hazards assumption was judged to have been violated. In line with the approach to modelling TTP and PFS, visual fit to the KM data together with cumulative and log-cumulative hazard plots were assessed for evidence of an inflection point. The company concluded standard parametric survival models were appropriate, and it was not necessary to explore other model types.

Model selection was undertaken using the same process as for TTP and PFS and has been outlined previously. On the basis of these criteria, the generalised gamma distribution was selected for the base case analysis, see Figure 36 of the CS for visual fit to KM data. Scenario analyses were also presented considering the log-normal and log-logistic functions, which demonstrated similar visual and statistical fit to the data while also generating predictions that the company considered clinically plausible.

Figure 12: Modelled PPS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 36, Page 116)

Points for critique

Model Selection

The ERG has several concerns regarding the company's approach to model selection for PPS and the use of GOG 240[4] to validate model predictions. As noted previously, the GOG 240[4] population is highly restricted, and there are notable differences in predicted PPS between GOG 240[4] and KEYNOTE-826, particularly at later time points. The use of GOG 240[4] as a source of data to validate model selection consequently results in preferences for curves that significantly over-predict the proportion of patients alive, as observed in KEYNOTE-826. This is evident in the company's preferred generalised gamma curve, as well as the secondary preferences (log-logistic and log-normal). Indeed, the best match to the observed data is the Weibull curve. Moreover, the ERG is concerned by the company's preference for models that exhibit decreasing hazards. The ERG accepts the description of the hazard trend as reported in the CS but is concerned that the long-tails predicted by these models lack clinical plausibility. Patients who have progressed in this population have very few treatment options with no established standard of care. Consequently, the prognosis for this population is very poor, with few if any patients achieving a durable response. The ERG therefore considers there to be uncertainty in the modelling of post-progression survival and that further clinical validation of model predictions would be useful.

Assumption of differential post-progression survival benefit

As modelled in the company's base case, it is assumed that patients progressing on pembrolizumab will have a sustained and persistent post-progression survival benefit. However, available KM data shows limited evidence to support this, with curves actually crossing at around week 63. The company do note in the CS that patients with longer pre-progression survival tend to have a longer post-progression and consider this supportive of the base case assumptions. However, the company do not present a formal statistical comparison of post-progression survival provided to justify the differential assumptions. The clinical plausibility of differential post-progression survival is also not clear. Treatment options following progression will be similar, if not identical between arms, and it is unknown whether any benefits of pembrolizumab will persist beyond progression. Given this absence of evidence, the ERG considers that a more conservative assumption where no treatment effect is assumed to persist beyond progression is preferable.

4.2.6.3 Adverse events

AEs included in the economic model were Grade 3+ and with ≥ 5% incidence in either treatment arm. The impact of AEs was modelled to account for both the incidence and duration of events, which were used to estimate per cycle disutilities and costs associated with each event. To inform the disutilities and costs associated with each AE, cycle-specific event rates were estimated independently for the pembrolizumab and SoC arms of the model. Event rates were estimated as function of incidence and time on treatment. The incidence of each AE and the rate per model cycle (week) are summarised in Table 16.

Table 16 Incidence and rate of AE by treatment arm (adapted from Table 30 of the CS)

	PEM+SoC		SoC	
Adverse event (grade 3+)	**Incidence**	**Rate per cycle**	**Incidence**	**Rate per cycle**
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

At the clarification stage the ERG noted that the company's approach accounts only for Grade 3 and 4 AEs and does not account for notable differences in some Grade 1 and 2 AEs of special interest. The company justified their approach noting the expectation that these AEs would not impact materially on the results of the economic analysis. The company did however provide scenario analysis in which

QALY losses and costs associated with Grade 1 and Grade 2 AEs of special interest occurring in >5% of patients are accounted for. These scenarios are presented in Section 5 and show that including these lower grade events has a minimal impact on the ICER.

Points for critique

The ERG considers the company's approach to modelling AEs to be broadly appropriate and to accurately reflect the burden of AEs associated with each treatment regimen. The ERG, however, notes the omission of Grade 3 and 4 adverse events occurring in less than 5% of people, which included leukopenia, fatigue and diarrhoea amongst many others. The overall impact of this omission is likely to be modest given the low incidence of these individual AEs, but will favour the pembrolizumab arm given the pattern of low frequency AEs observed in the trial.

The ERG notes AEs may manifest in patients on subsequent therapies; however, these events are not considered within the company's model. The impact of these AEs is also likely to be modest. It is unclear whether this omission would favour the pembrolizumab or SoC arm of the model given the limited information available on subsequent therapies received.

4.2.7 Health related quality of life

4.2.7.1 Health state utilities

Health state utilities in the economic analysis were estimated from health-related quality of life (HRQoL) data collected in KEYNOTE-826 and analysed using linear mixed regression to account for repeat observations. Data were collected using the EQ-5D-5L questionnaire, and mapped to the EQ-5D-3L using the van Hout *et al*. algorithm.[46] In the trial, EQ-5D assessments were taken every 3 weeks (on the first day of each treatment) for the first 14 cycles, and then every 6 weeks (every 2 treatment cycles) thereafter. After patients discontinued primary treatment or after disease progression, assessments were administered at the end of treatment, and 30 days after the last treatment or before the initiation of a new anti-cancer treatment, whichever came first.

The company base case analysis considered an approach for deriving health state utilities based on time to death (TTD) (Table 17), with scenario analysis also considering a progression-based approach (Table 18). The TTD utilities were derived based on the following time before death categories:

- Group 1: less than 30 days before death,
- Group 2: between 30 and 90 days before death,
- Group 3: between 90 days and 180 days before death,
- Group 4: between 180 and 360 days before death,
- Group 5: more than 360 days before death.

Table 17 Summary of health state utilities TTD approach (CS Table 32, Page 123)

Health state	Mean (SE)
Time to Death <30 days (intercept)	[redacted]
Time to Death 30-90 days (vs intercept)	[redacted]
Time to Death 90-180 days (vs intercept)	[redacted]
Time to Death 180-360 days (vs intercept)	[redacted]
Time to Death ≥ 360 days (vs intercept)	[redacted]
Grade3+ AEs	[redacted]

Key: SE, standard error; AEs, adverse events; TTD, time to death

Table 18 Summary of health state utilities progression status approach (CS Table 33, Page 124)

Health state	Mean (SE)
Progression free	[redacted]
Progression Status (PF vs PD)	[redacted]
Grade3+ AEs	[redacted]

Key: SE, standard error; AEs, adverse event; PF, progression-free; PD, progressed disease

The company justified the use of the TTD approach noting that progression-based methods typically used in oncology may be less appropriate when assessing immunotherapies due to patients experiencing "pseudo-progression" where the action of treatment is mistaken for disease. The company further notes that delays between progression and experiencing symptoms, as well as different types of progression, may blur the impact of progression on quality of life.

Points for critique

Appropriateness of TTD approach

The ERG has concerns regarding the TTD approach. Time to death is not a causal determinant of HRQoL, as it can only be measured retrospectively and an event that occurs in the future cannot determine something which has occurred in the past. The observed correlations between HRQoL and TTD are most likely due to confounding, with time to death acting as a proxy for severity of disease, which is likely to be highly correlated with both OS and HRQoL. This reversal of causality is inherently problematic and leads to predictions that either lack clinical plausibility or which are not substantiated by the current evidence base.

Firstly, the use of TTD death utilities severs the link between progression status and HRQoL and violates the accepted norm that progression status is major driver of HRQoL. The clinical plausibility of this is unclear, and the company offers no evidence to suggest that the underling mechanism of utility generation is based on TTD rather than progression. Moreover, the method used by the company to apply TTD utilities means that it is difficult to estimate how the predicted utility values evolve over time and as such how the utility values applied using the TTD approach align with a progression-based approach.

Secondly, the applications of TTD utilities imply a treatment related differential in the average utilities applied, which are higher for pembrolizumab. This is driven by the fact that TTD is longer on average in both health states. The justification for such a benefit is not clear and it notable that treatment specific utilities are not applied when considering a progression-based approach. This suggests that the company do not consider there to be specific HRQoL benefits associated with receiving pembrolizumab.

Given these conceptual issues with the TTD approach, the ERG favours a progression-based approach and notes that precedent from previous appraisals supports this position with the majority of previous appraisals of immunotherapies rejecting a TTD-based approach.

Mapping algorithm

As noted above the company used the van Hout *et al.* algorithm.[46] to map values from EQ-5D-5L to EQ-5D-3L. The ERG notes that the latest methods guide recommends that the Hernández-Alava algorithm should be used, and that this had been highlighted to the company at the decision problem stage. At the clarification stage the ERG asked the company to justify the use of the van Hout *et al.* algorithm.[46] In their response the company noted the recommendations in the latest NICE methods guide and advice provided by the ERG. The company, however, justified the use of the van Hout *et al.* algorithm[46] noting that the latest methods do not apply to this appraisal and that the choice of algorithm did not have a significant impact on the values generated.

Points for critique

The ERG considers that it would have been preferable for the company to use the Hernández-Alava algorithm as recommended in the latest methods guide (this updates previous guidance which recommended the van Hout *et al.* algorithm[46]). The ERG, however, notes analysis by the Policy Research Unit in Economic Evaluation of Health and Care Interventions suggesting that both algorithms produce similar predictions with differences only apparent in very poor health states. The ERG is therefore satisfied that the company's approach is acceptable in the context of the current appraisal, if not methodologically ideal.

4.2.7.2 Age adjustment

The model applies age adjustments to all utility values used in the model. These account for the impact of ageing on HRQoL. These are applied using a multiplicative approach in which a utility decrement is estimated relative to the utility of a 51-year-old (starting age) in the general population using data from Ara and Brazier.[57] This decrement is then subtracted from each health state utility value to generate an age-specific value.

Points for critique

The ERG considers the application of an age-related decrement appropriate, given the long-time horizon considered in the economic analysis and the long OS benefits predicted by the base case analysis.

4.2.7.3 Impact of AEs

To account for the impact of AEs on quality of life, utility decrements were applied in the model. The AE-specific utility decrement was based on regression analysis of HRQoL data captured in the KEYNOTE-826 trial, which was used to estimate an average decrement associated with experiencing a Grade 3/4 AE, See Table 17 and Table 18. This was then combined with evidence on the frequency and duration of Grade 3/4 AEs to estimate a treatment specific disutility that was applied on a per cycle basis while patients were on treatment.

Points for critique

The ERG considers that it was appropriate to capture the HRQoL impact of AEs and that the general approach taken by the company is reasonable though somewhat convoluted.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs, costs associated with management of adverse events, monitoring costs, costs of testing, cost of subsequent treatments, and the costs of end-of-life care.

The company's submission did not describe their approach to identifying resource use and cost data in this indication, stating only that the cost inputs used in TA183 were outdated and unsuitable for use in this submission. Resource use data appears to be at least in part based on the company's advisory board meeting.[22]

4.2.8.1 Treatment acquisition costs

Acquisition costs for pembrolizumab in the model were based on the anticipated licence and the dosing of pembrolizumab in KEYNOTE-826, i.e. a 200mg Q3W fixed dose. The cost per administration of pembrolizumab at list price is £5,260, comprising two 100mg vials at a unit cost of £2,630 each. A patient access scheme is available for pembrolizumab consisting of a simple discount of [redacted]. This reduces the acquisition costs associated with pembrolizumab to [redacted] per 100mg vial.

Dosing schedules and costs modelled for the comparators cisplatin, carboplatin, paclitaxel, and bevacizumab are summarised in Table 19. Cost of treatments with weight or body surface area-based dosing were based on the characteristics of the KEYNOTE-826 population, in which mean body weight was [redacted] kg, and mean body surface area was [redacted] m^2. The number of vials required for each

administration was estimated from the licensed dose. It was assumed that no vial sharing between patients would occur for weight or body surface area-based dosing, i.e. drug wastage was taken into account for paclitaxel, cisplatin, and bevacizumab.

Cisplatin, carboplatin, and paclitaxel are available in generic formulation, with costs sourced from the electronic market information tool (eMIT) where available. List prices for pembrolizumab and bevacizumab were based on the Monthly Index of Medical Specialities (MIMS) database. Bevacizumab is available as a number of biosimilar formulations, the company applied the list price for Alymsys (biosimilar) in a scenario analysis but used the list price of Avastin (originator) in the base case analysis. The ERG notes that there is a Commercial Medicines Unit discount available for Avastin. The prices of bevacizumab biosimilars are negotiated regionally and were also supplied to the ERG. Analyses inclusive of all confidential pricing arrangements are included in a confidential appendix to the ERG Report.

The distribution of patients across the modelled treatments was based on the KEYNOTE-826 trial and is presented in Table 19.

Table 19 Dosing schedule and costs applied in the company model (adapted from CS Tables 34 and 35)

Drug	Dosing per administration	Dosing frequency	Cost per administration	Source
Pembrolizumab	200 mg	Q3W	£5,260 (exclusive of PAS)	MIMS 2020
Paclitaxel	175 mg/m^2	Q3W	£37.44	eMIT 2020
Cisplatin	50 mg/m^2	Q3W	£5.66	eMIT 2020
Carboplatin	750 mg	Q3W	£35.27	eMIT 2020
Bevacizumab (Avastin)	15 mg/kg	Q3W	£2,375.11	MIMS 2020
Bevacizumab (Alymsys)	15 mg/kg	Q3W	£2,070.88	MIMS 2020

The company's base case analysis also accounted for missed doses using the proportion of administered vs expected doses observed in KEYNOTE-826. The proportion of actual vs expected doses for each modelled treatment arm are presented in Table 20. In all cases, patients treated with SoC alone received more of each drug on average than on PEM+SoC. Patients received more than the number of cycles permitted on the NHS for paclitaxel, cisplatin, and carboplatin in both treatment arms.

Table 20 Modelled treatment cycles derived from KEYNOTE-826 (CS Table 36, Page 128)

Percentage actual vs. expected number of cycles			
	Mean	**Standard Deviation**	**n**
PEM+SoC			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
SoC			
Paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]

Points for critique

The ERG considers the acquisition costs applied in the model to be largely appropriate. The ERG, however notes several uncertainties.

Firstly, the ERG considers it realistic that a significant proportion of patients initiated on bevacizumab will be given a biosimilar product. A scenario is therefore presented in Section 6 in which all patients receive biosimilar bevacizumab to explore the cost-effectiveness implications for pembrolizumab. Secondly, the ERG considers it potentially inappropriate to base the number of administered doses of paclitaxel, cisplatin, and carboplatin on KEYNOTE-826, as patients on average received over 100% of the permitted number of cycles. This is unlikely to represent NHS practice, and treatment costs should at the very least be capped to 100% of the number of cycles permitted on the NHS. However, the ERG notes that this has a very small impact on the ICER due to the low price of platinum-based chemotherapies. The ERG therefore does not consider this to represent an important uncertainty.

4.2.8.2 Treatment duration

The duration of treatment applied in the model was based directly on time on treatment (ToT) data from KEYNOTE-826. As there are stopping rules in place for pembrolizumab and bevacizumab, KM data were used to calculate the proportion of patients remaining on treatment until these respective cycle-based stopping rules were reached – 24 months for pembrolizumab, and 18 weeks for platinum-based chemotherapy, paclitaxel, and bevacizumab. The ToT curves and stopping rules applied in the model are reproduced in Figure 13.

Figure 13 Time on treatment KM data applied in the company model (CS Figure 38, Page 130)

Points for critique

The application of a stopping rule at 24 months may underestimate the real-world cost of treatment, and severs the link between treatment costs and health effects. In KEYNOTE-826, patients were strictly limited to 35 cycles of pembrolizumab treatment but in many cases [redacted] continued to receive treatment beyond 24 months. This reflects patients experiencing short breaks in treatment (perhaps due to AEs) before receiving further cycles. The application of a strict 24-month stopping rule in the model assumes that all these patients will discontinue therapy before reaching their full allocation of pembrolizumab doses. The ERG does not consider this reflective of practice and notes previous NHS England policy permits patients to receive a full allocation of doses under these circumstances. The exclusion of these costs also serves to break the link between benefits and costs in the model because patients receive the benefits associated with continued pembrolizumab treatment in the trial, but the accompanying costs are not accounted for. A scenario is therefore presented in Section 6 in which the effect of removing the modelled cap on pembrolizumab treatment is explored.

4.2.8.3 Treatment administration costs

All included treatments were administered intravenously. When multiple treatments are administered on the same day, modelled patients incur a unit cost of £329.75 (NHS Reference Cost SB13Z: deliver complex parenteral chemotherapy). When only one treatment is administered in one day, a unit cost of £295.92 was applied (NHS Reference Cost SB12Z: deliver simple parenteral chemotherapy).

Points for critique

The ERG considers the company's approach to modelling administration costs using the simple and complex parenteral chemotherapy costs appropriate, and in line with previous appraisals.

4.2.8.4 Subsequent treatments

The company applied a one-off cost associated with subsequent treatments at the point of disease progression, with the average duration of treatment based on data from KEYNOTE-826. The model assumed that [redacted] of patients would receive second-line treatment, which was based on advice from the company's advisory board. The company modelled paclitaxel monotherapy, doxorubicin, fluorouracil (5FU), and cisplatin + gemcitabine as second-line treatment options. This was based on the advice of the company's clinicians rather than on the KEYNOTE-826 trial, as there was little overlap in second-line therapies between the trial and NHS practice. The modelled proportion of patients on each, and the mean duration of treatment is detailed in Table 21. Acquisition costs are listed in Table 44 of the CS (Page 135).

Table 21 Subsequent treatments in company model (CS Table 43, Page 135)

Subsequent treatment	PEM + SoC		SoC	
	Proportion of patients	Mean treatment duration (days)	Proportion of patients	Mean treatment duration (days)
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]

The ERG requested further information on the subsequent treatments received in the KEYNOTE-826 trial, and that a scenario be constructed in which patients receive subsequent treatment per the distribution observed in the trial. The company included only subsequent therapies received by >3% of patients in the analysis submitted. In the data provided only [redacted] of patients who progressed received a second line treatment in the pembrolizumab arm, whilst this was [redacted] for the SoC arm – significantly lower than the [redacted] estimated by the company's clinicians.

Points for critique

The company stated that there was little overlap between the subsequent treatments in KEYNOTE-826 and NHS practice, but no details of the subsequent therapies used were provided in the submission or accompanying documents. Moreover, the company's response to clarification does little to resolve this uncertainty as the company's scenario only accounts for therapies received by >3% of patients. It is therefore unclear how many patients received subsequent therapy, or how this differed across treatment arms. The company state that this approach was adopted in the interests of time and the model is not sensitive to subsequent treatment costs. The ERG, however, cannot validate this claim given the partial answer provided by the company.

Given the limited information provided it is unclear if the company's base case assumptions are appropriate. The company's response while incomplete, indicates that far fewer patients went on to

receive subsequent therapy than modelled in the base case analysis. It also suggests that that more patients went on to receive subsequent therapies in the pembrolizumab trial arm than on SoC.

Moreover, advice from the ERG's clinical advisor raised concerns about the clinical plausibility of the modelled assumptions, stating that fewer than 50% of patients would proceed to subsequent treatment in NHS practice. Additional concerns were also raised regarding the composition of subsequent treatments modelled. Doxorubicin was highlighted as a treatment seeing very little use in cervical cancer, and it was suggested that topotecan may be used at this line of therapy. The assumption that 50% of patients would receive paclitaxel was also considered unrealistic and unreflective of UK practice.

The ERG considers both the proportion of patients receiving subsequent therapies, and the types of subsequent therapies received a potential source of uncertainty. The ERG's preference would be to base the proportions of subsequent therapies received on the full data for each treatment arm from the KEYNOTE-826 trial. Further information may also need to be elicited from UK clinicians on the composition of subsequent treatment in NHS practice.

4.2.8.5 Monitoring and health state costs

Healthcare resource use in the model was specific to each health state, and it was assumed that monitoring costs were the same regardless of treatment received. Health state resource use was based on clinician input, values applied in the model are summarised in Table 22 below. Pre-progression costs were applied on a per-cycle basis, while monitoring costs in the progressed disease health state were applied as a one-off cost upon progression for the [redacted] of patients who received a subsequent treatment.

The company assumed that monitoring costs for the remainder of patients who did not receive subsequent treatment would be captured in the one-off cost associated with end-of-life care. This one-off terminal care cost was applied at the time of death, and amounted to £4,611.54 based on Round *et al.*, which was inflated from 2015 to the 2019/20 cost year.

Table 22 Health state resource use applied in company model (Adapted from CS Table 40, Page 132)

	Unit cost	Progression-free			Progressed disease	
Resource		**Year 1**	**Year 2**	**Year 3+**	**On Tx**	**Off Tx**
Consultant outpatient appointment	£131.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	£107.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

GP visits	£33.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse/Nurse specialist visits	£81.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood-count	£2.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid function test	£2.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In response to the ERG's clarification request, the company provided a scenario in which a number of cost-elements typically included in advanced cancer models were added to the model. These costs comprised GP visits, nurse/nurse specialist visits, a blood count, and thyroid function count, and were assumed to occur at the same frequency as the health-state resources included in the original model.

Points for critique

In the original model submitted by the company, only two cost elements were considered in the pre- and post-progression health states (consultant outpatient appointment, CT scan). At the clarification stage the ERG requested that the company add cost items typically included in advanced cancer models, namely, GP visits, nurse/nurse specialist visits, and blood counts. The company provided a scenario analysis in which these cost items were considered, which is replicated in Section 5. This change had a minimal impact upon the apparent cost-effectiveness of pembrolizumab.

4.2.8.6 Adverse reaction unit costs and resource use

Costs associated with the management of adverse events were based on Grade 3 or higher events occurring in more than 5% of patients in KEYNOTE-826. Unit costs were derived from NHS Reference Costs 2019/20 and other recent appraisals of pembrolizumab, and were inflated to the current price year using the HCHS index. The AE costs and the sources cited by the company in their submission are summarised in Table 23.

Table 23 Adverse event costs applied in the company model (CS Table 39)

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
Anaemia	£2,700.00	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Neutrophil count decreased	£672.40	Assumed same as neutropenia	N/A
Neutropenia	£672.40	Weighted average of mean costs for HRG code WJ11Z: Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	NHS reference costs 2019/20[58]
Hypertension	£639.00	EB04Z, Hypertension, HRG	NHS reference costs 2019/20[58]
Thrombocytopenia	£782.31	TA600: Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small cell lung cancer (2018)	TA600: Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
Febrile neutropenia	£7,200.69	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2019-20 prices using the Hospital & community health services (HCHS) index	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Platelet count decreased	£672.40	Assumed same as neutropenia.	N/A
White blood cell count decreased	£1,515.42	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay	NHS reference costs 2019/20[58]
Key: HRG, Healthcare Resource Groups; SE, standard error.			

Points for critique

The methods used to derive the costs of AEs and implementing them into the model appear reasonable and are broadly comparable to other appraisals of pembrolizumab.

At clarification, the ERG requested that the cost associated with treatment of febrile neutropenia be inflated to the 2019-20 cost year, rather than 2017-18 as in the original submission. This was corrected and included as a scenario in the updated version of the company model.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections are inclusive of the PAS discounts for pembrolizumab unless otherwise stated. Results including commercial arrangements available for the comparator treatments are provided in a confidential appendix to the ERG report.

5.1.1 *Deterministic Results*

The company presents a series of ICERs for pembrolizumab versus a pooled SoC group of patients receiving platinum-based chemotherapy in combination with paclitaxel with or without bevacizumab. The use of a pooled analysis in the estimation of costs and effects of the SoC group of patients receiving/not receiving bevacizumab implies that the company views these populations as a homogenous group and not as distinct patient groups. As discussed in Section 2.2.1 and 4.2.3, the ERG does not consider this characterisation appropriate. The ERG considers there to be two relevant populations: i) those in whom bevacizumab is clinically indicated as they have better ECOG performance status, no significant comorbidities (e.g. hypertension), and low risk of bowel fistula formation and, ii) patients where bevacizumab is not clinically indicated.

The results of the company's cost-effectiveness analysis are summarised in Table 24. The company's base case exclusive of the PAS discount for pembrolizumab, is associated with increased costs (cost difference of [redacted]) but also greater benefits (QALY difference of [redacted]) yielding an ICER of [redacted] per QALY gained. After applying the PAS discount for pembrolizumab (only), the results suggest pembrolizumab is associated with increased costs (cost difference of [redacted]) with greater benefits (QALY difference of [redacted]) yielding an ICER of £34,017 per QALY gained. In all the scenarios, higher costs are primarily a result of the higher acquisition costs associated with pembrolizumab, while the QALY benefits are driven primarily by longer OS in the pembrolizumab arm compared to SoC arm.

Table 24 Company base case and scenario results: deterministic analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Company base case (Without PAS)							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case (With CAA for pembrolizumab)							
SoC	[redacted]	2.51	[redacted]				

Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,017
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.1.2 *Probabilistic Results*

The ERG performed probabilistic analyses on the company's base case model, running 5,000 iterations for each comparison. The results are presented in Table 25. The mean probabilistic ICER for pembrolizumab compared to SoC was £1,242 lower than the deterministic ICER. The ERG noted that because ToT for pembrolizumab is calculated directly from the KEYNOTE-826 data, acquisition cost calculations are independent of the number of patients remaining progression free at any time in a given model iteration. As pembrolizumab costs are essentially fixed and independent of QALY gain, the incremental costs across the PSA vary very little. Whilst there should generally be a positive relationship between acquisition costs and increasing QALYs, the scatter plot in the company's PSA shows no such trend. The PSA cannot therefore claim to represent the cost uncertainty associated with pembrolizumab.

Figure 14 presents the cost-effectiveness acceptability curve for the comparison of pembrolizumab versus SoC in the company's model. In this analysis, pembrolizumab had a 38% probability of being cost-effective versus SoC at a threshold of £30,000 per QALY gained, and 86% probability at a willingness-to-pay threshold of £50,000 per QALY gained.

Table 25 Company base case and scenario results: probabilistic analysis (including pembrolizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
SoC	[redacted]	2.60	[redacted]				
Pembrolizumab	[redacted]	5.46	[redacted]	[redacted]	[redacted]	[redacted]	£32,775
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

Figure 14 Cost-effectiveness acceptability curve for PEM+SoC versus SoC (generated from company's model, inclusive of PAS discount)

5.2 Company's additional analyses

At the clarification stage, the ERG requested that the company present a number of scenarios which explored alternative assumptions and parameter inputs. The results of this analysis are presented in Table 26. The scenarios explored were as follows:

i. Treatment waning effect applied for pembrolizumab for three and 5 years (2 to 5 or 7 year onset);
ii. Correction of general population mortality cap;
iii. The inclusion of any adverse event of special interest occurring in more than 5% of patients;
iv. Inclusion of subsequent treatment distribution from KEYNOTE-826;
v. Stopping rule removed for bevacizumab to match number of cycles in KEYNOTE-826;
vi. Inclusion of GP and nurse visits, blood counts, and thyroid function test costs;
vii. Correction to febrile neutropenia costs;
viii. Hernàndez-Alava algorithm used to map from EQ-5D-5L to EQ-5D-3L.

Table 26 Company's additional scenario analysis: deterministic analysis (inclusive of pembrolizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs company base case (£/QALY)
i) a) Inclusion of a treatment waning effect for pembrolizumab for three years							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	4.46	[redacted]	[redacted]	[redacted]	[redacted]	£43,647
ii) **b) Inclusion of a treatment waning effect for pembrolizumab for five years**							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	4.74	[redacted]	[redacted]	[redacted]	[redacted]	£39,209
iii) Correction of general population mortality cap							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,021
iv) The inclusion of any adverse event of special interest occurring in more than 5% of patients							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,215
v) Inclusion of subsequent treatment distribution from KEYNOTE-826							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£33,467
v) Stopping rule removed for bevacizumab to match number of cycles in KEYNOTE-826							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£32,881
vi) Inclusion of GP and nurse visits, blood counts, and thyroid function test costs							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£35,073
vii) Correction of inflation of febrile neutropenia cost to 2019/20							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,023
viii) Use of Hernàndez-Alava EQ-5D-3L mapping algorithm							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£33,923

Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

5.3 Company's deterministic sensitivity analyses

The company performed a series of one-way sensitivity analyses, setting the lower and upper bounds of each parameter to ±1.96*SE of the mean or base-case value, when the standard error (SE) was

derived from the data source. When this information was unavailable, SE was assumed to be within ±10% of the base-case value.

The input parameter with the greatest effect upon the ICER were dose intensity (actual vs. expected treatment cycles), followed by resource use estimators, and the mean treatment duration of paclitaxel in second line. The tornado diagram (Figure 15) showed that other parameters have a notably smaller effect on the ICER.

Figure 15 Tornado diagram showing DSA results of company model, PEM+SoC versus SoC, inclusive PAS discount.

5.4 Model validation and face validity check

5.4.1 *Validation undertaken by the company*

The CS stated that the outcomes of the model were clinically validated to ensure the face validity of predictions. This was undertaken by comparing PFS, OS and PPS data from the model to data from GOG 240[4] and KEYNOTE-826 trials, and was further supported by expert UK clinical opinion.

5.4.2 *Internal validation undertaken by ERG*

As part of the ERG assessment of the economic analysis, the ERG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Several minor model errors were identified as part of the ERG's validation checks. These related to the application of a general mortality cap for PFS and PPS curves to ensure that they are higher than the general population as they age. This meant that patients resided in the progression-free and progressed disease states longer than expected. This specifically impacted the cost and QALY outcomes per patient at the end of the model. The impact of this issue was relatively minor in the state transition model. All identified errors

were corrected by the company and verified by the ERG. Revised results correcting for this error are reported in Section 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. A number of alternative scenarios are presented in areas where the ERG felt that an alternative approach was more appropriate, or where it was considered important to explore the impact of uncertainty.

Descriptions of the exploratory analyses are described in Section 6.1and the impact of these analyses on the company's base case are presented in Sections 6.2 and 6.3 along with the ERG's preferred base case. Several scenarios were implemented by the company in response to the ERG's clarification questions, a number of which are reproduced in the present analysis.

Several further scenarios are included in the following section to illustrate the impact of alternative assumptions on the ERG base-case.

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted the following exploratory analyses after applying the corrections to the calculation of mortality, and using the correctly inflated cost for febrile neutropenia as described in Sections 4 and 5. Each of the following analyses are based upon this 'corrected' version of the company's model.

1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model

As described in Section 4.2.6.1, the ERG considers the use of a two-piece extrapolation approach to be potentially inappropriate given the immaturity of the data supporting the purported 'inflection point' in the TTP curve for pembrolizumab, and what this implies for long-term outcomes. The significant modelled QALY gain associated with pembrolizumab derives mostly from this long tail and results in predictions that the ERG considers highly optimistic. Moreover, the use of a simple parametric log-logistic model resulted in predictions in a pattern more reflective of long-term data available for the standard of care. Model fit statistics also supported the use of the log-logistic model to extrapolate PFS and TTP KM data. The final data cut from KEYNOTE-826 [redacted] may go some way to resolving the uncertainty associated with the apparent inflection point in hazards.

2. Pooled extrapolation of PPS

As described in Section 4.2.6.1, the ERG considers the use of a separate survival function to model PPS to be potentially inappropriate given the limited evidence to justify to support this assumption.

The clinical plausibility of the modelled parametric extrapolation is also uncertain and the ERG is concerned that the company's preferred generalised gamma distribution leads to an overly long tail with a small proportion of patients predicted to remain alive more than 3 years following progression. The ERG therefore considers two scenarios to explore this uncertainty. Scenario 2 (a) assumes a pooled PPS curve using a generalised gamma curve preferred by the company. Scenario 2 (b) assumes a pooled PPS curve using a Weibull curve. The Weibull curve is more pessimistic than the generalised gamma curve providing potentially more plausible predictions of PPS. The Weibull curve, however, does not offer as good a visual or statistical fit to the observed data as the generalised gamma.

3. Including treatment waning effect for pembrolizumab

As discussed in Section 4.2.6.1, the company have assumed a lifetime duration of the treatment effect associated with pembrolizumab on the basis of an observed effect for up to 2 years, in which patients were yet to discontinue treatment. The ERG considers, a lifetime treatment effect requires substantial supporting clinical evidence, which has not been presented by the company. The ERG notes that previous appraisals of immunotherapies have applied a waning effect, in which mortality rates gradually return to those of the comparator therapy over a number of years following the discontinuation of treatment.

To explore uncertainty associated with the longevity of the treatment effect, and to explore the potential impact of waning efficacy upon cost-effectiveness, the ERG presents scenarios in which the mortality rate experienced by patients previously treated with pembrolizumab returns to that of patients on SoC. In line with previous TA's waning over 3 and 5 years is considered.

4. Progression based utilities

The company's base case analysis uses a time to death approach to model HRQoL. As discussed in Section 4.2.7.1, the ERG considers this approach to have conceptual limitations and results in predictions that do not align well with accepted norms regarding the impact of progression on HRQoL. This scenario therefore replicates analysis implemented by the company in which progression-based utilities are used.

5. Subsequent therapy distribution from KEYNOTE-826

As discussed in Section 4.2.8.4, the ERG requested that the company use the treatment arm-specific distributions of subsequent therapies received by patients in the KEYNOTE-826 trial. As this analysis included only those treatments received by >3% of patients, the ERG does not consider it sufficiently representative of the distribution of treatments received in the trial. However, the ERG prefers this approach to modelling subsequent therapies to that based on estimates from the company's clinical

advisers. The ERG's preference is for this scenario to be implemented in full in future iterations of the model.

6. Full pembrolizumab ToT KM curve used to calculate costs

As discussed in Section 4.2.8.2, the ERG disagreed with the imposition of a 24 month stopping rule to pembrolizumab treatment in KEYNOTE-826, as a 35-cycle stopping rule was already in place in the trial. By removing the cost of pembrolizumab treatment beyond 24 months, the company still receive the QALY benefits of this treatment but not model all treatment costs. The ERG therefore considers it appropriate to apply the ToT KM curve from KEYNOTE-826 in full to calculate pembrolizumab acquisition costs.

7. All patients receive a biosimilar bevacizumab

The ERG explored a scenario where all patients received biosimilar bevacizumab (Alymsys). This was to assess the cost implications of all patients using cheaper alternatives to proprietary bevacizumab (Avastin). This does not include the available commercial arrangements for biosimilar bevacizumab – analysis inclusive of all discounts will be provided in a confidential appendix.

8. Bevacizumab maintenance therapy allowed

As described in Section 4.2.4, the ERG considers it plausible that patients may continue to be administered bevacizumab beyond the recommended 6 cycles. This more closely matches the use of bevacizumab in the KEYNOTE-826 trial.

9. GP visits, nurse/nurse specialist visits, blood-counts, and thyroid function tests costs

As described in Section 4.2.8.5, the ERG requested that the company include a number of health state costs typically applied in cancer appraisals, including GP and nurse visits, blood counts, and thyroid function tests. This scenario replicates that analysis.

10. All AEs of special interest occurring in more than 5% of patients modelled

The ERG replicated the scenario offered by the company in their clarification response which accounted for all adverse events of special interest regardless of their grading.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the scenario analyses are presented in Table 27. The results include the pembrolizumab PAS only.

Table 27 ERG Exploratory Scenario Analyses (Including Pembrolizumab PAS)

Scenario	Technology	Total			Incremental			ΔICER vs corrected BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
ERG-corrected company base-case	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,021	-
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.09	[redacted]	[redacted]	[redacted]	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	SoC	[redacted]	2.53	[redacted]				
	Pembrolizumab	[redacted]	5.21	[redacted]	[redacted]	[redacted]	£36,231	£2,209
2. b) Pooled survival curve for PPS using Weibull curve.	SoC	[redacted]	2.41	[redacted]				
	Pembrolizumab	[redacted]	5.16	[redacted]	[redacted]	[redacted]	£34,832	£811
3. a) Treatment waning for pembrolizumab between 2 and 5 years	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	4.48	[redacted]	[redacted]	[redacted]	£42,919	£8,897
3. b) Treatment waning for pembrolizumab between 2 and 7 years	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	4.76	[redacted]	[redacted]	[redacted]	£38,823	£4,802
4. Progression based utilities	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£36,591	£2,569
5. Subsequent therapy distribution from KEYNOTE-826	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£33,472	-£549
6. Full Pembro ToT KM curve used to calculate costs	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,952	£930
7. All patients receive biosimilar bevacizumab	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,056	£34
8. Bevacizumab maintenance treatment allowed	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£32,885	-£1,136
9. GP/nurse visits, blood-counts, and thyroid function tests costs	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£35,072	£1,051
	SoC	[redacted]	2.51	[redacted]				

10. All AEs of special interest occurring in more than 5% of patients modelled	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,220	£198

6.3 ERG's preferred assumptions

The cumulative impact of the ERG's preferred assumptions are presented in Table 28. The ERG base-case adopts the following scenarios described in Section 6.1:

Scenario 1: One-piece log-logistic extrapolation of the PFS and TTP curve;
Scenario 2 (a): Pooled PPS using the generalised gamma curve;
Scenario 3 (a): Treatment waning for pembrolizumab (3-year treatment);
Scenario 4: Progression based utilities;
Scenario 6: Full pembroliumab ToT KM curve used to calculate costs;
Scenario 9: GP/nurse visits, blood-counts, and thyroid function tests costs;
Scenario 10: All AEs of special interest occurring in more than 5% of patients.

The choice of extrapolation had by far the largest incremental impact on the ICER in the ERG's alternative preferred base-case, accounting for an increase of £37,886 per QALY. In the ERG preferred base-case, pembrolizumab was predicted to generate [redacted] incremental QALYs, at an additional cost of [redacted] versus SoC to get an ICER for pembrolizumab of £95,529 per QALY gained.

Table 28 ERG's preferred model assumptions (Deterministic)

Scenario	**Section of ERG Report**	**Cumulative ICER**	**ΔICER vs corrected BC**
ERG-corrected company base-case	4 & 5	£34,021	
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	6.1.1	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	6.1.3	£83,725	£49,704
3(a) Treatment waning for pembrolizumab (3 year treatment effect)	6.1.4	£88,795	£54,774
4. Progression based utilities	6.1.6	£89,909	£55,888
6. Full Pembro ToT KM curve used to calculate costs	6.1.7	£92,442	£58,421
9. GP visits, nurse/nurse specialist visits, blood-counts, and thyroid function tests costs	6.1.9	£93,709	£59,687
7. All AEs of special interest occurring in more than 5% of patients	6.1.11	£95,529	£61,508
ERG base case			
ERG preferred base-case (Scenarios 1, 2 (a), 3 (a), 4, 6, 9 & 10)	**Inc. costs**	**Inc. QALYs**	**ICER**
	[redacted]	[redacted]	£95,529

Probabilistic results for the ERG's alternative base-case are presented in Table 29. The model was set to the ERG's preferred assumptions and run with 5,000 iterations. As discussed in Section 5.1.2, the ERG did not consider the PSA to have been constructed appropriately, which was an issue the ERG was unable to resolve given the model structure and limitations in the data available. The probabilistic ICER was £93,159 – somewhat lower than the deterministic ICER. This difference was driven both by lower average incremental costs and higher average incremental QALYs than in the deterministic analysis.

Table 29 ERG's alternative base-case analysis results (probabilistic)

Scenario	Technology	Total			Incremental		
		Costs	LYs	QALYs	Costs	QALYs	ICER
ERG-corrected company base-case (probabilistic)	SoC	[redacted]	2.11	[redacted]			
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£93,159

6.3.1 Additional scenario analysis on the ERG's base case

In addition to the ERG base case, the ERG presents the results of several scenario analyses on the ERG base-case. Table 30 presents the results of this analysis.

Table 30 ERG Exploratory Scenario Analyses on the ERG base case

Scenario	Technology	Total			Incremental			ΔICER vs corrected BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
ERG-base case	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£95,529	-
2. b) Pooled survival curve for PPS using Weibull curve.	SoC	[redacted]	1.99	[redacted]				
	Pembrolizumab	[redacted]	2.82	[redacted]	[redacted]	[redacted]	£95,550	£21
3. b) Treatment waning (5 year treatment effect)	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£92,595	-£2,934
5. Subsequent therapy distribution from KEYNOTE-826	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£94,021	-£1,508
7. All patients receive biosimilar bevacizumab	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£95,622	£93
8. Bevacizumab maintenance treatment allowed	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£90,604	-£4,925

6.4 Conclusions of the cost effectiveness section

The company submitted a de novo economic analysis to assess the cost-effectiveness of pembrolizumab versus SoC in the treatment recurrent, persistent or metastatic cervical cancer. The company's analysis was based on STM consisting of three health states (pre-progression, post-progression, and death). The company's base-case economic analysis suggested that pembrolizumab is more costly but is also more effective than both SoC. The company's deterministic base case ICER was £34,017 per QALY. The company's probabilistic base case ICER was £32,775 per QALY. At a £30,000 per QALY threshold, the probabilistic analysis suggests a [redacted] probability that pembrolizumab is cost-effective. At a £50,000 per QALY this increase to [redacted] probability. Note that these results are based on the net price of pembrolizumab but are exclusive of confidential discounts for bevacizumab and other treatments.

6.4.1 Conclusions of ERG's Critique

The ERG considers the submitted evidence to broadly reflect the decision problem defined in the final scope, and that the submitted analyses meet the requirements of the NICE reference case. The ERG's review of the company submission identified several key uncertainties, which the ERG has sought to address in the revised base case and scenario analyses.

A key area of uncertainty relates to the model structure adopted by the company. The STM approach used in the company's base case implies a structural link between PFS and OS which assumes a surrogate relationship between PFS and OS. The CS does not fully justify this assumption, providing only limited evidence based on clinical opinion and statistical analysis of KEYNOTE-826. The ERG considers the lack of supporting evidence to be an important omission. Moreover, the ERG is concerned that the model's predictions do not align well with the observed OS data from KEYNOTE-826 and it systematically under-predicts the proportion of patients alive in both treatment arms at 24 months. Importantly, this issue is more pronounced in the SoC arm suggesting a bias in favour of pembrolizumab.

The ERG also has substantive concerns regarding the company's justification for the STM approach. The company's justification is founded on the extrapolations of PFS data and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations. However, as discussed below, it is not clear that the PFS extrapolations preferred by the company are clinically plausible and the ERG notes that the crossing of PFS and OS is solely because a piecewise approach is adopted to the extrapolation of PFS. Crossing does not occur when a single-parametric curve is fitted to the whole KM data.

A key uncertainty relates to the approach taken to extrapolation of TTP and PFS in the model, as these are drivers of cost-effectiveness. The company's base-case analysis approach adopts a two-piece approach to modelling TTP and PFS curves to capture a purported point of inflection around 40 to 60 weeks in the KM curve from KEYNOTE-826. This approach leads to very long tails in TTP (& PFS) and results in the model predicting that a substantial proportion of patients will remain alive for five or more years, with a non-negligible proportion of patients achieving survival that could be considered akin to cure. While the ERG acknowledges that immunotherapies have historically been associated with durable response rates in other indications, there is insufficient evidence in cervical cancer to suggest that short term treatment with immunotherapy translates into such long survival gain, nor has a possible mechanism for cure been established. The ERG also notes that the two-piece approach appears to produce optimistic estimates of survival in the SoC arm, while these broadly align with data from GOG 240 they do not align with clinical expectations regarding long-term survival in this patient population. The final data cut from KEYNOTE-826 expected [redacted] may go some way to resolving the uncertainty associated with the apparent inflection point in hazards.

Related to the above, the economic analysis also makes strong assumptions about the durability of the treatment effect, assuming that the benefits to mortality gained while on treatment are maintained beyond treatment discontinuation. Although it is biologically plausible for the treatment effect to continue after pembrolizumab, its duration is uncertain. Given the short follow-up from KEYNOTE-826, the ERG believes that it is unknown whether, or for how long, the effects of pembrolizumab are maintained after treatment discontinuation. As a result, survival benefits predicted by the company's base-case analysis may be overly optimistic.

The ERG also has concerns regarding the company's approach to modelled HRQoL. In the company's base case, a TTD approach is used in which utility values are determined by proximity to death. The ERG has conceptual issues with this approach as it relies on future death events to predict current HRQoL status. The ERG is also concerned that the TTD approach severs the link between progression and HRQoL, and violates the accepted norm that progression status is major driver of HRQoL. Moreover, the predictions of the TTD approach are difficult to reconcile with a progression-based approach.

Additionally, the ERG identified several resource use issues, which have a smaller impact on the results. These include the use of the full pembrolizumab ToT curve; inclusion of GP visits, nurse/nurse specialist visits, blood-counts and thyroid function tests costs; and bevacizumab use. These issues were explored in scenario analysis presented by either the company or the ERG and were all demonstrated to have a modest impact on the cost-effectiveness of pembrolizumab.

The impact of these uncertainties was considered in a series of exploratory analyses. The results of which demonstrate that the extrapolation modelling approach adopted for TTP and PFS is a key driver of overall benefits and cost-effectiveness. Taking the ERG base-case, which uses a single piece log-logistic model, the comparison of pembrolizumab against SoC resulted in an ICER of £95,529 per QALY, which is £61,508 higher than the company base case ICER. Results are exclusive of confidential price discounts for the other drugs.

7 END OF LIFE

The CS (Table 19, p73 CS) presents evidence to support pembrolizumab as an end-of-life therapy.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The reported median OS for SoC patients was 16.3 months (95% CI 14.5 to 19.4) based on data from KEYNOTE-826. Similar estimates were also obtained from GOG 240[4] which reports median survival ranging between 13.3 and 16.8 months. Based on parametric extrapolations used in the company base case analysis economic analysis, mean life expectancy for patients receiving SoC was 2.51 years (30.12 months). Based on the ERG preferred assumptions, mean life expectancy was estimated to be 2.08 years (24.96 months). These data suggest that there is uncertainty over whether the first criterion is met. The ERG notes that the EoL criteria are typically interpreted with respect to mean or average life expectancy. This is in line with decision making for cost-effectiveness which is based on mean costs and QALY gains. Such an interpretation would suggest that the first criterion for end of life is not met. The ERG, however, notes several mitigating factors that may imply that mean OS is overestimated in the KEYNOTE-286 trial informing the economic analysis. As noted in Section 2.2.1, some patients in NHS practice may receive a monotherapy chemotherapy regimen which may be less effective than the doublet and triplet chemotherapy considered in the KEYNOTE-826 trial. Further, the KEYNOTE-826 population excluded patients with performance status of >1; clinical advice suggests that a proportion of ECOG status 2 patients receive systemic treatment and that in principal ECOG 2 patients may be eligible for pembrolizumab combination therapy. It is widely accepted that performance status is a prognostic indicator.

Criterion 2: There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

Median OS for pembrolizumab has not been reached in the KEYNOTE 826 study and therefore a comparison of median OS gains based on observed data is currently not possible. Based on extrapolated evidence used in the economic analysis, median survival gains are predicted to be 7.13 months. Further, based on the company's base-case economic analysis, mean extension to life is estimated to be 2.80 years (33.64 months). In the ERG's base-case analysis, which makes more conservative assumptions about the benefits of pembrolizumab, this is reduced to a mean extension of 0.82 years (9.84 months). Despite stated uncertainties regarding the extrapolations of OS, the ERG considers that there is strong evidence to indicate that the second criterion is met.

The ERG concludes that there is substantial uncertainty regarding whether pembrolizumab meets the end of life criteria given current life-expectancy on SoC. It is highly likely that Criterion 2 is met.

Uncertainties regarding life expectancy on current SoC, however, mean it is uncertain whether Criterion 1 is met.

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9 APPENDICES

9.1 Appraisal of company search strategies

9.1.1 Clinical Evidence Searches

The original company submission included searches to identify clinical evidence for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix D (pp. 4-15). The embedded systematic literature review (SLR) report on page 4 of Appendix D was included in the original company submission but was not reviewed as it would not open.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG

Table 31 ERG appraisal of clinical evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Inaccessible Data** The embedded systematic literature review (SLR) report on page 4 of Appendix D was included in the original company submission but was not reviewed initially as it would not open: this was raised as a PfC. In response to PfCs, the company sent through the full SLR which provided some of the missing search strategies. **Missing Search Strategies:** In the original submission, there was insufficient information on the searches of the clinical trials registries and conference proceedings (listed in Appendix D, D.1.1, pp. 4-5). Additional data was provided in the response to PfCs with fully documented searches of conference proceedings through the Northern Light Life Sciences Conference Abstracts database (mistakenly referred to as the Northern Nights database in parts of the SLR). However, the clinical trials registries that were searched were not documented. **Error in Description of Date Limits for Conference Proceedings:** The search strategy for ASCO 2019 was not contained in the document 'ID3798 MER36645 Cervical cancer UK SLR report UK' but has since been provided. The ERG can now confirm that searches of conference proceedings were carried out as detailed on page 18 of the document 'ID3798 MER36645 Cervical cancer UK SLR report UK'. **Error in Search Results:** Appendix D, D.1.3. lists the total figures from the databases as 4,417. However, the number of results listed for Medline, Embase, and CENTRAL combined comes to 4,416. The figure 4,416 is also reported in the PRISMA diagram. **EUCTR not in PRISMA diagram:** The PRISMA diagram does not list the number of records from 'European Union Clinical Trials Registry' (EU CTR) even though this source is listed as one of the sources searched on Appendix D, D.1.1, page 4. In the response to PfCs the company indicated that this is because the database retrieved 0 relevant records. **Errors with explode function (exp) on databases**

		In several instances, exp was used in front of a subject heading when the subject heading could not be exploded. This will not affect the number of hits, but gives the false impression that all these subject headings have narrower subject headings: Appendix D, pages 5-6 (Embase strategy): exp pembrolizumab/, exp cisplatin/, exp paclitaxel/, exp bevacizumab/, exp topotecan/, exp carboplatin/, exp gemcitabine/, exp etoposide/, exp vinorelbine/ [the correct Emtree term is vinorelbine tartrate/], exp ifosfamide/, exp docetaxel/, exp fluorouracil/ Appendix D, pages 7-8 (Medline strategy), and pages 9-10 (Cochrane CENTRAL strategy): uterine cervical neoplasms/, exp cisplatin/, exp bevacizumab/, exp topotecan/, exp carboplatin/, exp etoposide/, exp vinorelbine/, exp ifosfamide/, exp docetaxel/
Were appropriate sources searched?	YES	A range of relevant databases, conference proceedings, and trials registry databases were searched. The searches could have benefitted from searching a larger number of databases though.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the intervention and the study type.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** Although the truncation and adjacency on line 2 of each of the database searches will successfully capture several terms for the condition, the following terms would be missed: • carcinoma colli uteri • endocervical carcinoma • endocervix carcinoma • uterine cervix adenocarcinoma Notably, adenocarcinoma is even listed as an eligible subtype in Appendix D, Table 2, page 11. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant. **Missed Field Codes:** There are field codes that could have been used for the free-text term lines for the interventions, in addition to the title and abstract. On Medline these are rn (registry name / name of substance), or nm (name of substance word). On Embase these are: tn (drug trade name), or du (drug index terms). The same comment may apply to Cochrane but we do not have access to the Cochrane CENTRAL via Ovid. Exclusion of these field codes could have missed relevant papers. **Emtree Subject Headings used outside of Embase** On Medline and Cochrane CENTRAL, the following Emtree Terms were used: exp pembrolizumab/, exp gemcitabine/ but these are not MeSH terms and not appropriate for these databases. However, as there are no equivalent MeSH terms that represent these intervention terms, it is unlikely any relevant papers would have been missed as a result.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	For Ovid Medline and Embase, study design filters by the Scottish Intercollegiate Guidelines Network were used for clinical trials. The filter was referenced, though it is not a validated filter.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.2 Cost-Effectiveness Searches

The original company submission included searches to identify cost-effectiveness for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 32 ERG appraisal of cost-effectiveness evidence identification

TOPIC	ERG RESPONSE	NOTE:
Is the report of the search clear and comprehensive?	PARTLY	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Missing Search Strategy** There is mention of searches on the NICE website on page 19 of the embedded document on page 50 of Appendix G, but the searches are not documented.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with economics study filters.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com and the search of PubMed (in the economic review searches: pages 9-11 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant.

		The search strategy for the economic review searches using the CRD databases NHS EED, HTA, and DARE (page 11 of the document embedded on page 50 of Appendix G) is very basic and no MeSH terms were used. A search for just the MeSH term Uterine Cervical Neoplasms on its own will bring back 541 hits (which is more than the strategy in the company submission retrieved). Therefore, relevant papers may have been missed. Moreover, a search just for 'cervical cancer' is also quite limited. This was raised as a PfC and the company response was that this was unlikely to miss relevant papers due to the databases being out-of-date and indexed in other sources that were searched.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.3 Health-Related Quality of Life Searches

The original company submission included searches to identify health-related quality of life studies for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and all of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included clarifications on issues raised by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 33 ERG appraisal of HRQoL evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Errors with explode function on databases**

		In the searches of Cochrane CENTRAL a MeSH subject heading (uterine cervical neoplasms) was exploded when the subject heading does not have narrower terms (on page 13 of the document embedded on page 50 of Appendix G). This will not affect the number of hits but gives the false impression that the subject heading has narrower subject headings.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with a health-related quality of life study filter.
Were appropriate search terms used?	YES	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com, the search of PubMed, and the searches of Cochrane CENTRAL and CDSR (in the humanistic review searches: pages 11-13 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.4 Cost and Healthcare Resource Identification, Measurement, and Valuation Searches

The original company submission included searches for cost and healthcare resource identification, measurement, and valuation for patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 34 ERG appraisal of cost and healthcare resource evidence identification

TOPIC	ERG RESPONSE	NOTE:
Is the report of the search clear and comprehensive?	PARTLY	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Missing Search Strategy** There is mention of searches on the NICE website on page 19 of the embedded document on page 50 of Appendix G, but the searches are not documented.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with economics study filters.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com and the search of PubMed (in the economic review searches: pages 9-11 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant. The search strategy for the economic review searches using the CRD databases NHS EED, HTA, and DARE (page 11 of the document embedded on page 50 of Appendix G) is very basic and no MeSH terms were used. A search for just the MeSH term Uterine Cervical Neoplasms on its own will bring back 541 hits (which is more than the strategy in the company submission retrieved). Therefore, relevant papers may have been missed. Moreover, a search just for 'cervical cancer' is also quite limited. This was raised as a PfC and the company response was that this was unlikely to miss relevant papers due to the databases being out-of-date and indexed in other sources that were searched.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 **5pm on Monday 13 June 2022** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Depiction of impact of ECOG status on generalisability of population from KEYNOTE-826 to the NHS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 13, 21, and 34. The company considers the ERG's proposals that ECOG score of 0 is over-represented in KEYNOTE-826, and that results on clinical effectiveness derived from the study are not directly relevant to those with ECOG score of 2, to be potentially misleading.	We propose that ERG amends the text to read, "The largest proportion of patients were categorised as ECOG PS 0 in KEYNOTE-826".	The inclusion of patients with an ECOG PS of <2 is in alignment with other studies evaluating pembrolizumab. The company considers that data are not available on the percentage of patients receiving systemic therapy stratified by ECOG PS. Additionally, the treatment pathway outlined in guidance from the BGCS (May 2020) is not determined by ECOS PS grouping. The guideline states: '*Those patients with a WHO performance status (WHO PS) 0/1 should be considered for systemic treatment, whereas those with lower performance status should be carefully risk assessed as to their suitability and likely benefit from treatment, with the patient fully informed of expectations and limitations of chemotherapy. Best supportive care or palliative radiotherapy may be a more preferable option for these patients*.'	Not a factual inaccuracy.

Issue 2 Inaccurate description of bevacizumab usage in NHS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 51. Secondly, in the NHS, bevacizumab would not be continued for as many cycles as was used in KEYNOTE-826 (where the number of permitted cycles was unlimited).	The company suggests amending the text to: 'In the NHS, bevacizumab can be continued for more than six cycles if well tolerated and with a planned reduction in chemotherapy dose regimen.'	The company have received advice from several clinicians who indicated that there is variation in number of treatment cycles with respect to use of bevacizumab.	Not a factual inaccuracy.

Issue 3 Description of lack of efficacy of pembrolizumab plus chemotherapy in those with metastatic disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41. The company considers it inappropriate for the ERG to compare the HRs of comparative clinical effectiveness in two clinically distinct subgroups (metastatic disease at initial diagnosis and those of the subgroup PD-L1 status of CPS <1) and, in the same sentence, refer to the restriction applied in the EMA's marketing authorisation excluding authorisation for one of the subgroups.	Recommendation to omit the sentence beginning 'The apparent lack of effect…'.	There is no statistical comparison of the subgroups of metastatic disease at diagnosis and PD-L1 status of CPS <1, which are clinically distinct subgroups. The company considers it inappropriate to compare the two subgroups directly and to draw inferences from the comparison. Additionally, the marketing authorisations issued by the MHRA and EMA both include those with metastatic disease at diagnosis.	Not a factual inaccuracy.

Issue 4 Description of KEYNOTE-826

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 22. The ERG comments that, "However, KEYNOTE-826 does not provide a randomised head-to-head comparison of chemotherapy plus pembrolizumab versus chemotherapy plus bevacizumab".	For clarity, please consider amending to "….KEYNOTE-826 ***was not designed to*** provide randomised…"	The company proposes that the ERG's text could be open to interpretation, with the potential for inference that there were defects in the design and/or conduct of KEYNOTE-826 that led to the unavailability of head-to-head data on chemotherapy plus pembrolizumab versus chemotherapy plus bevacizumab rather than the study not	Amended as suggested.

		being designed to capture the comparison in a randomised manner.	

Issue 5 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 18 and 100. Mean OS predicted for the standard of care arm is 2.5 years using the company preferred assumptions and 2.08 using the ERG's preferred assumptions. These suggest that the EoL criteria are not met. Furthermore, the ERG concluded that there is substantial uncertainty regarding whether pembrolizumab meets the end of life criteria given current life-expectancy on SoC. It is highly likely that Criterion 2 (treatment offers an extension to life, normally of at least an additional 3 months) is met. Uncertainties regarding life expectancy on current SoC, however, mean it is uncertain whether Criterion 1 is met.	We suggest that the EOL criteria are met for this indication.	NICE precedent demonstrates that at a mean LYG of 2.08 EoL is met.	Not a factual error. While the committee have the flexibility to interpret the EoL criteria as they see fit, 2.08 years is greater than 2 years and therefore does not meet Criterion 1.

Issue 6 Inaccurate statement about the models estimates vs. empirical data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 98. The sentence beginning "The ERG also notes that the two-piece approach appears to overestimate survival in the SoC arm…" is misleading.	We propose an amendment along the lines of "The company's two-piece approach accurately estimates the only long term empirical data for OS on the SoC. The one-piece approach preferred by the ERG underestimates empirical data for OS on the standard of care."	The only long term empirical data for OS on SoC come from the GOG240 trial. These are 17.7% at 4 years for patients on bev and 10.6% for patients not on bev. A weighted average of the two would be ~15%. We used this figure in our model selection criteria, which are detailed extensively in the CS. The two-piece approach estimates OS to be 12.7% on SoC. The one-piece approach preferred by the ERG estimates OS to be 9.7%. It is misleading to stakeholders to suggest that the one-piece model is "more reflective of the long-term data available for SoC."	The text has been amended as follows: "The ERG also notes that the two-piece approach appears to produce optimistic estimates of survival in the SoC arm, while these broadly align with data from GOG -240 they do not align with clinical expectations regarding long-term survival in this patient population."

Issue 7 Omission of company evidence about surrogacy of PFS for OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
a. The report frequently cites the lack of evidence that PFS is a good "surrogate" for OS and asserts the company has submitted no empirical evidence, which is not accurate.	At each instance where ("lack of") evidence on the surrogate relationship is discussed, please include reference to Figure 21, Appendix Q and state that the company has provided empirical	It is misleading to stakeholders to suggest that no empirical evidence exists that PFS is a good surrogate for OS and that the company's view is based on clinical opinion alone.	a) Thank you for highlighting Appendix Q of the CS. We agree this should have been referenced in the ERG report and have therefore amended the text. This, however, does

b. The ERG mention multiple times that their clinical advisors have said that it is possible that increased PFS doesn't necessarily lead to increased OS for "a proportion of patients" (e.g. p.31) and "can delay progression without extending survival" (p.23). This statement may be misleading. It is not clear what question was asked of these advisors and whether they were thinking about individual patients or had access to a dataset for TTP and PPS to estimate this correlation. If it is the former, then we consider the comment reflects individual, natural variability in clinical outcomes and is not meant to be generalised in the way that is implied in the ERG report. The ERG has not reviewed or omitted the company's submission of empirical evidence suggesting that time pre-progression is not 'traded' for time post-progression. Figure 21 in Appendix Q of the CS shows the relationship between TTP and PPS among patients who died in KN826 and finds no association at aggregate level. If it were true that increased PFS did not lead to increased OS this association would be negative. That increased PFS doesn't necessarily lead to increased OS for "a proportion of patients" (p.31) is evident from Figure 21, Appendix Q but the converse (patients with short TTP and long PPS) is also true. Without having done an analysis such as this, it is misleading to say that, on the	evidence that length of PPS is independent of TTP among all patients who died in KN826 in both trial arms and that the company believes this provides some empirical evidence that PFS is likely to be a good surrogate for OS in this population. Specific instances that need amending are:- Page 13 "…providing only limited evidence based on clinical opinion." Page 57 "…providing only limited evidence based on clinical opinion." Page 57 "The ERG considers the lack of supporting evidence for a surrogate relationship between PFS and OS to be an important omission" Page 97 "…providing only limited evidence based on clinical opinion." It should also be clarified at each instance that the ERG's advisors are basing their assumptions on individual (or subgroups of) patients who have had long TTP but short PPS, that the converse is also likely at the individual or subgroup level and that it is the aggregate relationship between TTP and PPS *in the whole cohort* that determines whether PFS is a good surrogate for OS.	It is also misleading to stakeholders to suggest that clinical advice about individual patients who may have had long TTP but short PPS or vice versa is reason to doubt that there is a strong relationship between PFS and OS at the population level. It is misleading to stakeholders to suggest that evidence of surrogacy is required by NICE for all models where OS isn't modelled independently of other health states.	not alter the ERG's broad conclusions. The evidence for surrogacy remains limited and has only been partially justified. b) Not a factual error. The ERG clinical advisors were reflecting on a broad relationship not individual patients as implied by the company. The NICE methods guide is very clear on the requirement for evidence of surrogacy. Further, the ERG considers that its interpretation is appropriate given the somewhat novel approach adopted in the economic analysis. The use of a state-transition model is atypical in oncology and it is reasonable that the assumptions imposed by this approach are properly justified. TA 658 illustrates that the committee haven't automatically accepted assumptions of surrogacy.

aggregate level, PFS may not be a good surrogate for OS. Figure 21, Appendix Q provides the only empirical evidence that PPS is independent of TTP on the aggregate level, which in turn implies PFS is a good surrogate for OS. It is unclear what specific analysis the ERG would request to see. It is also misleading to suggest that definitive evidence on surrogacy is required by NICE. By this rationale, every model submitted to NICE that does not independently model OS would be called into question. The reality is that most models submitted to NICE model OS based on its relationship with other health states. That progression of disease has a strong relationship with OS in advanced cervical cancer at the population level should not be open to question. It also misleading to cite the precedent of TA658, which sought to predict OS using estimates of surrogacy sourced from the literature. The economic model for this appraisal uses only the observed data on the components of OS from within the trial to model OS.			

Issue 8 Inaccurate reference to clinical advisers' comments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 66 and 67. "Clinical advice provided to the ERG suggests that it is rare for patients to achieve such long-term freedom from progression and survival on SoC, with only a minority of patients surviving beyond 5 years. In this regard, the ERG also notes that company's own clinical advisors considered the predictions for SoC overly optimistic" is inaccurate. The company's advisers were referring to 1.3% of patients being alive at the 20-year time point whereas this section discusses the 5-year time point. It is unclear what is meant by "rare" in this context but data from Tewari et al 2017 show ~5% of patients are still PFS at 4-years.	We suggest that this be removed.	The statement misleads stakeholders about the time-point that clinical advisors were discussing when saying the economic model looked slightly optimistic.	Not a factual error. The ERG is referencing broad concerns raised by the company's advisors. Reflecting the company's concerns, we have amended the text for clarity.

Issue 9 Inaccurate description of the US retrospective study and relevance of GOG240

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68. "The ERG especially highlights a retrospective study carried out in the US which found that only 14.5% of patients treated with bevacizumab in clinical practice	We suggest this should be removed as it mischaracterises the evidence. GOG240 excluded patients with	GOG240 is the evidence that underpins the standard of care. It reports 4-year data and is an important point of validation for	Not a factual error. While the ERG recognises that it is not abnormal for clinical trials to impose strict

would be eligible for the GOG 240 trial.[52] The GOG 240[4] population therefore represents a highly restricted population and may not be an appropriate reference for validation" is an inaccurate summary of this study's findings and implications. This study was a retrospective analysis of all metastatic/recurrent CC patients treated with any intervention at a single centre in the US, not "patients treated with bevacizumab" as claimed. The study concludes that only 14.5% of patients in their centre would have been eligible for bevacizumab, had it been available at the time, because of the large preponderance of comorbidities among their cohort. Additionally, chart reviews of patients presenting in the US are not generalizable to UK clinical practice because the presence of the cervical cancer screening programme in the UK, as well as a variety of cultural and health service related factors are likely to significantly influence the morbidity of presenting patients.	certain comorbidities but that practice is common in clinical trials.	longer term survival estimates. It is misleading to stakeholders to discredit it in this way.	inclusion criteria, the cited study demonstrates that a substantive proportion of patients who are treated in practice were not represented in the GOG 240 study. This will inevitably impact the generalisability of GOG 240 and its value as a source of data with which to validate the model.

Issue 10 Omission of the weighted survival analysis by responder status

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 68 “These projections are highly optimistic and imply that a proportion of patients achieve cure-like benefits. When requested to comment on the plausibility of such benefits and the significant number of long-term survivors…” this section and others that deal with the plausibility of long term predictions for OS on pembrolizumab are inaccurate by omission of key evidence provided by the company.

In addition to the responses documented here by the ERG, we provided a weighted survival analysis report as part of the Clarification Questions step. This report provides important statistical validation for the economic model and should be reviewed and discussed by the ERG.

The ERG state that “…nor has a possible mechanism for cure been established”, while this statement is accurate it omits that a mechanism for long term OS has been established and discussed at</td>
<td>We suggest that the ERG provides a full discussion of the data on OS by response status and the weighted survival analysis that was provided at the CQ step.

The reasons why the ERG finds the predictions made by the model to be implausible are unclear so we would like them to comment on what proportion of Complete Responders, ~90% of whom are alive at 2 years, they would expect to be alive at 3, 5, 10 and 20 years along with their rationale.

We also suggest that rather than dichotomise the choice between one-piece and two-piece models, the ERG presents a scenario where the two-piece model’s OS on pembrolizumab is dampened by a treatment waning effect between 3 and 5 years post treatment.

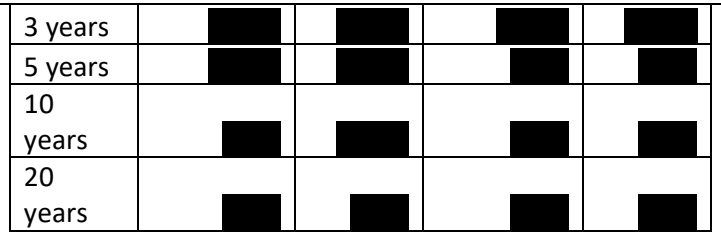
For reference we provide the landmark analysis from the weighted survival analysis compared to single piece SoC and 2-piece pembrolizumab with treatment waning. It would be helpful to include this as well. It shows a close match between the one-piece SoC model and the 2-piece pembrolizumab model if treatment waning is included.

<table>
<tr><th></th><th>Pembro weighted survival analysis</th><th>Pembro 2-piece + waning</th><th>SoC weighted survival analysis</th><th>SoC one-piece</th></tr>
<tr><td>1 year</td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>The ERG report mischaracterises the company’s response and the evidence presented in the original submission about the plausibility of long term OS on pembrolizumab.

The extremely good outcomes (~90% Overall Survival at 2 years) among Complete Responders in the pembrolizumab arm do represent a “paradigm shift” and a very real reason to be optimistic aboutnot to ignore the a small proportion of patients achieving long term survival.

The discussion of OS outcomes by responder status is key to enabling stakeholders to understand the benefits of pembrolizumab in this population and should not be omitted. We presented these data in Figure 22 of the CS and mentioned multiple times in the submission that the excellent outcomes</td>
<td>Not a factual error.

The ERG recommends that the company raise these arguments at technical engagement. The ERG agrees additional analysis inclusive of a waning effect may be useful.</td>
</tr>
</table>

length in the CS. The OS data by response status (Figure 22 in the CS) clearly show the extremely positive outcomes for patients with complete response (~90% OS at 2 years). These clinical data are referred to frequently throughout the CS as key evidence to support the 2-piece model, the turn in hazards and the plausibility of the long term OS estimates.		among complete responders are a key reason why we believe there will be evidence of a cohort of long term survivors and why it is reasonable to expect that the observed turn in hazards is a real phenomenon..	

Issue 11 Inaccurate characterisation of evidence from other immunotherapy trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69. "While the ERG acknowledges that immunotherapies have historically been associated with durable response rates in other indications, there is insufficient evidence to suggest that short term treatment with an immunotherapy translates into such long survival gains…" In response to CQs, we provided the ERG with 3 references for trials reporting 5-year data on pembrolizumab, all of which included unprecedented 5-year OS data. For example, in NICE TA531, 5-year OS in mNSCLC prior to the introduction of immunotherapy was acknowledged to be just 5%. KEYNOTE-024 has recently reported 5-year OS data with OS at 32%	We suggest that the ERG acknowledge that the modelled absolute OS and differential is conservative compared to observed data in other pembrolizumab trials, despite Complete and Response rates being among the highest ever recorded in an immunotherapy trial to date (we highlighted this in Figure 15 of the CS).	The statement misleads stakeholders by stating that there is insufficient evidence from other immunotherapy trials to indicate that the economic model's predictions are reasonable. It is misleading to state that a "paradigm shift" is not to be expected when it has already been seen in other areas with more mature immunotherapy data such as mNSCLC. In terms of median difference in PFS, PFS and OS HR, absolute modelled mean and median survival, KEYNOTE-826 does not	Not a factual error. The ERG acknowledges that substantive benefits have been demonstrated in other indications. There is, however, insufficient evidence in cervical cancer. We have amended for clarity.

(control arm OS was 16% because patients could access I/O second line). This differential and absolute difference in 5-year OS is greater than that in the economic model for KEYNOTE-826. This is despite Complete Response rates in KEYNOTE-024 being just 4% vs. 24% in KEYNOTE-826 and the population being much older. It is worth pointing out that half of the KEYNOTE-826 cohort are in their 30s and 40s and non-cancer related mortality is not a factor that meaningfully influences OS unlike in NSCLC. KEYNOTE-024 is also relevant in that PFS is 2 months longer at the median but the difference in median OS is 13 months and the difference in mean OS appears very large. Fitting a single-piece OS curve to the 5-year pembrolizumab data yields mean life years of 6.6.		appear to be substantially different to KEYNOTE-024.	

Issue 12 Inaccurate representation of company position supporting differential PPS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72. “The company do note in the CS that patients with longer pre-progression survival tend to have a longer post-progression and consider this supportive of the base case assumptions. However, no details of this analysis are included in the CS, nor is a formal statistical comparison of	We suggest that the ERG state that the company provided some empirical and biological justification for maintaining the observed difference in PPS within the economic model rather than ignoring	The reasons why the company believes that using the trial data on PPS are reasonable have been inaccurately described or omitted.	We have amended the text to more accurately reflect the statistical analysis provide in Appendix Q. The ERG, however, notes that the company do not provide any

post-progression survival provided to justify the differential assumptions. The clinical plausibility of differential post-progression survival is also not clear" is not accurate. We provided the analysis of the relationship between TTP and PPS in Appendix Q of the CS. It is correct that there is little evidence of an association between TTP and PPS but if any trend exists, it is positive. There is biological justification on two fronts which has not been discussed by the ERG in this section. Firstly, it is known that some progression events in I/O can be mischaracterized (the so called pseudo-progression phenomenon) and secondly, because of the higher rate of Complete Response in the pembrolizumab arm. Complete Response is defined as no tumour detectable on imaging, a patient progressing from this state is likely to have less severe disease than a patient progression from the other response categories and may live longer in the PPS health state.	the data and assuming they are equal.		clinical rationale for the differential PPS in the CS. The ERG recommends that the points raised are noted in the company's technical engagement response.

Issue 13 Misrepresentation of the reasons the company chose the STM structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55. "The company's justification for a state transition approach…" is founded on the decision to fit piecewise PFS curves from 37 weeks misrepresents the reasons laid out in the CS, which were:- 1. The relative maturity of the KEYNOTE-826 PFS versus OS data, and the observed plateauing of PFS data in the pembrolizumab arm, which causes parametric survival models fitted to PFS and OS data to cross. 2. The importance of the fuller and more explicit use of information on prognostic intermediate endpoints (i.e., progression) to inform mortality extrapolations, particularly when PFS is an appropriate surrogate for OS and mortality data are immature. 3. The importance of being able to assess the clinical and biological plausibility of survival extrapolations by performing scenario analyses given the immaturity of the KEYNOTE-826 OS data. 4. Data analysis examining OS among response subgroups within the trial shows that most patients in the post-	We would like the ERG to fully acknowledge the reasons why the company deems the STM structure most appropriate.	The statement about the reasons for choosing a STM is misleading for stakeholders.	Not a factual error. The ERG recognises that the company puts forward several arguments in favour of a STM approach. However, the crossing of the PFS and OS curves is clearly a primary concern given the impossibility of using a partition approach under these circumstances. For clarity, the ERG has edited the text to make readers aware that the company raised several points in favour of a STM approach and cross reference page 37 of the CS.

trial period will be complete or partial responders with low and declining event rates, particularly in the PEM+SoC arm.			

Issue 14 Update to reported data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49. Footnote to Table 10 stating, "† In Table 5 in Appendix D in the CS, the company reported 6.7 (5.7, 8.1) and 9.6 (7.2, 12.7) for median PFS for the cisplatin + paclitaxel and cisplatin + paclitaxel + bevacizumab treatment arms respectively. However, the ERG was not able to locate these results in any published literature (Insert Refs: Tewari 2017,4 Tewari 2017,45 on GOG-240 and any available supplementary material".	Please update reference to GOG-240 entry from ClinicalTrials.gov. The data are available on the "study results" tab on the trial record. The company apologies for the error in referencing.	Update citation to correct reference. Reported results are available here: https://clinicaltrials.gov/ct2/show/results/NCT00803062	Amended as suggested.

Issue 15 Update to SLR methods

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Page 106. Text in Table 31 detailing an error in description of date limits for conference proceedings. ERG states “In the document ‘ID3798 MER36645 Cervical cancer UK SLR report UK’, the methodology on page 18 lists that conference proceedings were searched for the past three years (2019-2021) but on page 35 of the document two of the strategies (Table 7 and Table 8) are limited to 2021 only”.</td>
<td>Please amend text to reflect that conference proceedings for ASCO were also searched in 2019, as detailed in the table below.

Search strategy for ASCO 2019 Conference Abstracts in Northern Nights Database Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 22; Search executed: June 11, 2021
<table>
<tr><th>No.</th><th>Criteria</th><th>Strings</th><th>Hits</th></tr>
<tr><td>1</td><td>Population</td><td>exp Uterine Cervical Neoplasms/</td><td>10886</td></tr>
<tr><td>2</td><td>Population</td><td>(cervi* adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.</td><td>8129</td></tr>
<tr><td>3</td><td>Population</td><td>1 or 2</td><td>11907</td></tr>
<tr><td>4</td><td>Conference</td><td>American Society of Clinical Oncology.cf.</td><td>60254</td></tr>
<tr><td>5</td><td>Combined</td><td>3 and 4</td><td>609</td></tr>
<tr><td>6</td><td>Restriction</td><td>limit 5 to yr="2019"</td><td>57</td></tr>
</table>
</td>
<td>Change requested to provide clarity that searches were carried out as detailed in the methods for the SLR.</td>
<td>Amended as suggested.</td>
</tr>
</table>

Issue 16 Incorrect data values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65. “and Weibull distribution (pembrolizumab arm only), which was included as a pessimistic scenario.” This statement is incorrect. The company included an average of the Weibull and log-	This statement can be corrected to “the company supplied a pessimistic analysis for both the SoC and pembrolizumab arms, which was an average of the Weibull and log-	The comment incorrectly refers to the company’s pessimistic analysis.	Amended as suggested.

logistic models for both arms as the pessimistic scenario. The Weibull model alone was discarded during the curve selection process.	logistic piecewise models for TTP and PFS.”		
Page 67. Figure 10 and 11 do not show the single-piece fits. Instead they show the two-piece fits.	We would like the ERG to change these graphs to the one-piece fits and to comment on the extremely poor visual fit for the one-piece model to the pembrolizumab arm.	The figures do not show what they are supposed to.	Amended as suggested.
Page 69 Table 15. Incorrect 5-year OS reported	ERG reports that 5-year OS for Pembrolizumab is [redacted], this should be [redacted]	Minor rounding error in the report table.	Amended as suggested.
Page 79. NHS reference cost SB13Z for deliver complex parenteral chemotherapy is incorrectly cited as £295.92 instead of £329.75	Cost of administering multiple treatments in the same day should be changed to £329.75.	The unit cost is incorrect in the report.	Amended as suggested.
Page 72 Table 16. Data reported under the ‘rate per cycle’ column in the ERG report are incorrect; these values are off by one row (see Table 30 of the company submission). This applies to all rates per cycle in the ERG report but the incidence data are aligned.	The ERG could remove the ‘total’ row from Table 16. Either way, please correct the values in the ‘rate per cycle’ column to match the correct AE row.	Pasting error in the report table.	Amended as suggested.
Page 85 Figure 14 Tornado diagram showing DSA results of company model, PEM+SoC versus SoC The title of this figure should refer if list of PAS pembrolizumab price was used here. From the provided text on the page 85 the	We would like the ERG to amend title addressing pembrolizumab discount status for the figure, update the figure with appropriate values and mark appropriately (BiC).	Error in labelling figure and what information was intended to be discussed	Amended as suggested (CiC).

figure does not match the discussed values.			
Page 88 Figure 15 Cost-effectiveness acceptability curve for PEM+SoC versus SoC (generated from company's model) The title of this figure should refer if list of PAS pembrolizumab price was used here. From the provided text on the page 85 the figure does not match the discussed values.	We would like the ERG to amend title addressing pembrolizumab discount status for the figure, update the figure with appropriate values and mark appropriately (BiC).	Error in labelling figure and what information was intended to be discussed	Amended as suggested (CiC).

Issue 17 Incorrect mark up of confidential data

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
Page 20 2.1 Introduction Page 21 & 23 2.3 Critique of company's definition	The application for marketing authorization with the EMA in this indication is currently ongoing. EMA approval was received in March 2022[1] and MHRA approval was expected in [redacted] This matches the NICE scope [redacted] yielding an ICER of [redacted] per QALY gained	MHRA approval was granted in May 2022 'and the granted licence indication' yielding an ICER of £34,017 per QALY gained	Amended as suggested in light of the MHRA approval.

Pages 93-94 Table 27 – Incorrect scenario labels for the starting year in the ERG report (scenario 3a. 3 and 5 years, and scenario 3b. 5 and 7 years); this mismatches the ERG model (scenario 3a. 2 and 5 years, and scenario 3b. 2 and 7 years)	Please update the labels in Table 27 of the ERG report to match the ERG model as below: • Scenario 3a) Treatment waning for pembrolizumab between 2 and 5 years i.e. 3 years Scenario 3b) Treatment waning for pembrolizumab between 2 and 7 years i.e. 5 years	Incorrect scenario titles in the ERG report.	Amended as suggested.
Page 36 of ERG report, text describing Figure 1 and Figure 2	Figures 1 and 2 are marked as AiC. The company considers that the text describing the curves should be marked as AiC.	There is a [redacted] between the curves in Figure 2, suggesting [redacted]. This is consistent with the data from the subgroup analysis that showed [redacted]	AiC marking added as suggested.
Page 55 of the ERG report, text describing Figures 6 and 7	Figures 6 and 7 are marked as AiC. The company considers that the text describing the curves should be marked as AiC.	These preferred extrapolations lead to long tails in PFS with the consequence that extrapolated PFS and OS [redacted] for the pembrolizumab arm and standard of care (SoC) arm respectively	AiC marking added as suggested.
Page 76 Section 4.2.8.1	Please remove confidential pembrolizumab PAS	Please removed the confidential pembrolizumab PAS from the ERG report and CE model. By keeping it in the model there is an increased chance of confidentiality breaches and that it will	This has been removed from the model but remains included in the report as agreed at the clarification teleconference.

ERG CEM Model “ID3798 2982 - PEM +SoC Cervical - CE Model [ACIC]” We request to remove pembrolizumab confidential pricing information and that the PAS is only referenced in the company submission Document B.		be shared by mistake with other stakeholders.	
Page 80. Table 21 - Missing percentage sign in the proportion of patients receiving fluorouracil as a subsequent treatment in the SoC arm	Please add the percentage sign in the data value in the table.	Minor typographical error in the report table.	Amended as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Sections 1.3 to 1.6).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **21st July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	MSD
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Applicability of the KEYNOTE-826 trial to the NHS population	No	**Based on feedback received at the UK MSD advisory board, we believe KEYNOTE-826 is generalisable to the NHS population and disagree with the statement that pembrolizumab maybe less efficacious when used in the NHS.** KEYNOTE-826 did not include patients with ECOG PS of 2 and therefore the company submission reflects the trial and there is no evidence of the effectiveness of pembrolizumab in this patient group. Bevacizumab is not available through NHS England for PS 2 patients, according to the criteria set by the organisation (1). Pembrolizumab use across all NICE approved indications, available on the NHS in England, is restricted to patients with PS0 or 1. We have no reasons to expect NHSE to take a different view for cervical therefore the trial and the economic model reflects expected UK use.
Issue 2: Immature overall survival data	No	MSD acknowledges that not all OS events have occurred. The next database lock for KEYNOTE-826 is scheduled to take place in [redacted]

		It is the company's position that sufficient OS data are available to conclude that pembrolizumab has a beneficial treatment effect on survival outcomes for women with cervical cancer. **Importantly, the KM data by response status shows that the OS event rate observed to date is largely driven by non-responders to treatment and therefore there are insufficient OS data for the responding patient population. OS is therefore not mature enough to accurately model long-term survival directly, across both responders and non-responders, particularly Complete Responders. This is the key reason why a state-transition model, in this specific population and given the data available, is more accurate than a partitioned survival model, which relies on direct extrapolation from observed OS event rates.**
Issue 3: Uncertain relationship between progression-free survival and overall survival	No	The company understands that the ERG is concerned that, given the similarity in PPS time between the arms, the economic model results in a treatment effect on OS that is similar in magnitude to that observed for PFS. **The company acknowledges that the relationship between PFS and OS has not been formally validated but considers that the OS treatment effect implied by the economic model is plausible for the following reasons**:- 1) The OS and PFS HRs observed within KEYNOTE-826 are of similar magnitude (respective point estimates are 0.62 and 0.64 in the CPS>1 population) 2) There have, to date, been four clinical trials of pembrolizumab in advanced cancer where OS HR has been lower than PFS HR (KEYNOTE-010, KEYNOTE-045, KEYNOTE-189 and KEYNOTE-426), which demonstrates that a roughly equal HR is not implausible. This has been observed despite I/O use typically being allowed after progression in the SoC arm, which can confound the PFS-OS relationship. (2-5) 3) Within cervical cancer, the magnitude of PFS and OS treatment effects are similar for bevacizumab in the GOG240 4-year data (respective HRs are 0.68 and 0.73) (6) 4) For PFS gain not to be a reasonable surrogate for OS gain, average TTP time would have to be 'traded' for average PPS time. The analysis in Appendix Q of the CS shows that this is not the case. If there is any emerging trend in that data, it is that

		longer TTP on pembrolizumab leads to longer PPS rather than the converse. The correlation in TTP and PPS time was ~0 for SoC. 5) Individual patients may experience short TTP and long PPS or long TTP and short PPS but this individual variability does not indicate a reason to disbelieve that pembrolizumab's PFS gain would translate into similar OS gains on the aggregate level. 6) Biologically, PFS is a plausible surrogate for OS in advanced cervical cancer. This is because no good 2nd line treatment options exist to confound the relationship between PFS and OS and because non-cancer mortality is not likely to meaningfully influence OS in this indication because the population are relatively young. This means that the disease itself accounts for the vast majority, if not all, OS events.
Issue 4: Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	No	**MSD does not support separate recommendations for this group based on lack of statistical power and because such a recommendation would worsen health inequalities.** <u>Lack of statistical power</u> KEYNOTE-826 was not designed or powered to look at benefit specifically in metastatic-at-diagnosis (FIGO [2009] stage IVB) patients. While the magnitude of improvement varies between subgroups, the treatment effect in KEYNOTE-826 is positive and consistent across all subgroups. There were >100 participants per arm with stage IVB disease at initial diagnosis. The point estimates on treatment effects (PFS: 0.92 (0.64, 1.30) and (OS: 0.84 (0.56, 1.26)) were favourable, though not statistically significant. Although this group were a stratification factor in the trial, this was merely to guard against confounding, just as stratification by region and ECOG status would. It is not an indication that clinicians would or should treat them differently. <u>Health inequalities issue</u>

		Clinical advice to MSD is that patients who are metastatic at diagnosis are more likely to come from groups with poorer health literacy and poorer engagement with the heath system including the national screening and HPV vaccination programmes. This may be for reasons correlated with culture, ethnicity and/or economic deprivation. MSD considers that a recommendation excluding this group would not be in line with NICE's commitments to reducing health inequalities between groups, particularly those with protected characteristics. For example, patients in Scotland with cervical cancer are more likely to have stage IV disease at diagnosis if they live in the most deprived quintile vs. the least (15.4% vs 9.2%). (7) The same data are not available for England and Wales but clinical advice to MSD is that the pattern would be similar. A recommendation excluding eligible (as per the marketing authorisation) patients with metastases at initial diagnosis (would risk disproportionately disadvantaging those in the highest deprivation quintile who have 16.8 years fewer of disability free-life expectancy than the least deprived. (8)
Issue 5: Application of two-year stopping rule	No	**Treatment stopping rule should be based on the KEYNOTE-826 study where patients were allowed to receive pembrolizumab up to 35 cycles (Q3W).** MSD understands in common with other pembrolizumab indications the 35 cycle stopping rule will be implemented by NHS England. This is in line with the KEYNOTE-826 where patients were allowed to receive pembrolizumab up to 35 cycles (Q3W), approximately two years. The economic model includes the option to cap the Time on Treatment (ToT) curve later than 2 years to account for patients experiencing longer treatment duration. The KM curve for ToT reaches zero at 26 months.
Issue 6: Appropriateness of state transition model	Yes	**A Partitioned Survival Model (the alternative structure suggested by the ERG) is considered inappropriate in this specific case for the following reasons:-** 1) Parametric curves fitted to the OS data are dominated by the fast event rate observed in non-responders in the early part of the trial. The expected plateauing effect typical of I/O is only beginning to emerge.

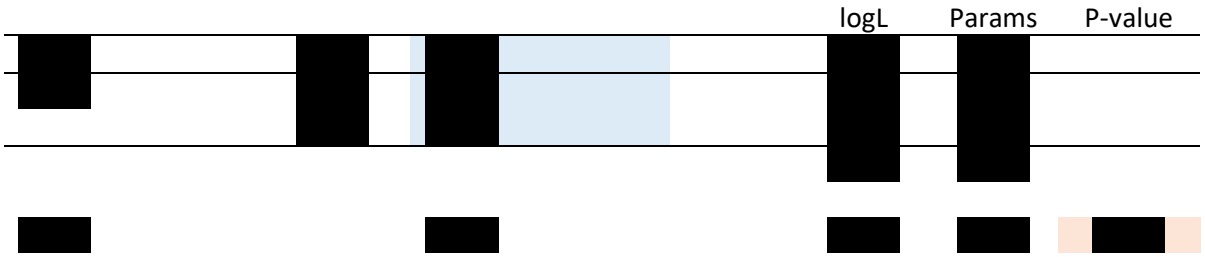
		2) As demonstrated in the company's "weighted survival analysis" report. The OS event rate in the within trial period is largely driven by patients who did not respond well to treatment. These patients have mostly died at 2 years of follow up. The remaining patients are largely those who achieved Complete Response (CR) or Partial Response (PR) and have a much slower event rate. For example, ~[redacted] of patients with CR are alive at 2 years. These patients have a slow event rate and now make up a much larger proportion of living patients. 3) In common with other immunotherapy trials, a plateau has emerged in the pembrolizumab PFS curve, which is expected to become apparent in the OS curve over time. 5-year data on pembrolizumab in other cancers are available from KEYNOTE-024, KEYNOTE-010 and KEYNOTE-006, which all show the clear emergence of a plateau first in the PFS curve and later in the OS curve. Please refer to the "Supporting analysis from other pembrolizumab trials" document submitted by the company as part of this response. This phenomenon fits with the mechanism of action of the drug and clinical experience of using it in practice. It is important that the economic model reflects this. 4) The economic model's estimates of restricted mean OS at 2 years are only very slightly different to the KM curves' restricted mean OS (+0.04 life years in both arms).
Issue 7: Extrapolation of PFS	Yes	Our understanding is that the ERG's main concerns around this issue are: 1) Too many patients on SoC have a durable PFS in the company's two-piece model and they prefer a one-piece model 2) Because the one-piece model does not provide an obviously poor fit to the observed SoC Kaplan-Meier data, a one-piece model should be used for the pembrolizumab arm, regardless of fit 3) Too many patients have durable response in the pembrolizumab arm In response to (1) we would reiterate that the company's two-piece based model produces the best fit to the observed 4-year GOG240 OS and that some patients on SoC do receive durable benefit. To directly quote GOG240 "At greater than 50 months of maximal follow-up,

		many patients continue to benefit from stable disease, and some have been cured with no evidence of clinical and radiologic disease." Clinical experience is that these occurrences are rare, with individual clinicians commenting to both MSD and the ERG that they have only seen 1 or 2 cases in their careers. Bevacizumab has only been available via the CDF for ~7 years, however, and clinicians only see a handful of cases per year. These "1 or 2" cases over 10+ years of treating advanced cervical cancer patients would appear to be consistent with the single-digit percentages (e.g. 3% at 10 years) of long term survivors estimated by the company's economic model. We would also highlight that using the one-piece curve, the economic model underestimates 4-year OS vs. GOG240 (10% vs. 15%). In response to (2) we do not think that if a one-piece model is deemed appropriate for SoC arm, this places an obligation to fit a one-piece model to the intervention arm regardless of visual fit or any other factors. Although this is encouraged in the relevant TSD guidance, visual fit and the biological plausibility of different models are also important considerations. **We consider the one-piece model a very poor visual fit to the pembrolizumab arm and therefore inappropriate.** Pembrolizumab as an 'add-on' treatment has a different mechanism of action to SoC alone and it may be that a separate model type is appropriate on these grounds. TSD 14 suggests that three criteria must be considered when justifying the selection of different survival models to each arm. There is sufficient evidence to defend all three in the instance of comparing PEM+SOC to SOC alone: • Biological plausibility ○ A difference in survival and morphology of survival between IO and chemotherapy is well known in clinical practice. Pembrolizumab as an add-on treatment provides not a replacement but an additional mechanism by which patients can respond to treatment. ○ There is also precedent in this area. A similar approach, with different parametric models fitted to either arm, was used in TA798 comparing durvalumab to best supportive care in the treatment of NSCLC. (9). Different

		parametric models between arms were also accepted in TA801 comparing pembrolizumab+SoC vs. SoC in Triple Negative Breast Cancer. (10)
		• Clinical validation
		  ○ Given their experience with IO therapies in other advanced cancer indications and noting the strong response data in KEYNOTE-826, clinicians expected the plateau seen in PFS data to be replicated in a significant minority of patients (9).
		• Statistical evidence
		  ○ The KM data for PFS shows a clear divergence in outcomes between arms at 1-year. The fact that the EAG does not dispute the plateauing of PFS in the KM solidifies this evidence.
		  ○ Similar morphology of PFS curves is seen in KEYNOTE-024, a trial of pembrolizumab in 1L mNSCLC with 5 years of follow-up (3)
		
		In response to (3) we have supplied a report detailing 5-year outcomes from other advanced cancer trials. The observed outcomes in these trials show clear plateauing in both PFS and OS curves as durable responders begin to dominate the hazard rates after the acute treatment period, after which most non-responders will have died. [redacted]
		
		[redacted]
		Figure 1: KEYNOTE-024 Original NICE submission two-piece OS predictions vs. observed data at 5 years
		
		[redacted]
		Figure 2: KEYNOTE-024 original NICE submission predictions based on IA2 data vs actual 5-year follow up

		We would also reiterate the data in the CS showing that levels of complete and partial response are some of the highest observed in any immunotherapy trial to date and draw the ERG and committee's attention to the weighted survival analysis, which shows that [redacted] of complete responders are still alive at 2 years. These patients make up [redacted] of the pembrolizumab cohort and are expected to have particularly slow PFS and OS rates. <u>Comparison of economic model's outputs with weighted survival analysis</u> At Clarification Questions stage MSD provided a "Weighted survival analysis". This modelled OS for each arm as a weighted combination of one-piece parametric curves by response status. The purpose of this was to provide a biologically coherent justification for why the model's predictions are reasonable and to suggest who the long-term survivors might be. The key figures from that report are here:- Figure 3: Weighted Survival Analysis for Pembro Arm compared with Company's Economic Model Estimates for OS [redacted] Figure 4: Weighted Survival Analysis for SoC Arm compared with Company's Economic Model Estimates for OS [redacted] The results of the weighted survival analysis were quite close to the model's predictions of OS suggesting that those predictions are not unreasonable in light of the data available. The model estimates slightly higher long-term OS than the weighted survival analysis in both arms, suggesting that incremental OS is not overestimated. Complete Responders had a 2 year OS of [redacted] in KEYNOTE-826 and this group may drive the tail of the curves. Here, we compare the results of this analysis with those produced by the ERG's preferred model settings:-

		Figure 5: Economic model estimates compared to weighted survival analysis - pembro  Figure 6: Economic model outputs compared to weighted survival analysis - SoC  These graphs find that, while both the company's model and the ERG's preferred settings model match quite well with the weighted survival analysis for the SoC arm, **the ERG's preferred settings model produces notably discordant results in the pembrolizumab arm.** **The company's economic model matches the weighted survival analysis quite well in the pembrolizumab arm, however, particularly if treatment waning assumptions (gradual wane from 3 to 5 years post treatment discontinuation) are applied.** The weighted survival analysis does not provide evidence to reject either a two-piece or one-piece based model for SoC but provides some evidence to reject a one-piece model for the pembrolizumab arm. Once again, we would reiterate that despite the wording of the TSD guidance, the fact that a one piece model is plausible for SoC should not place an immutable obligation to fit the same type of model for the pembrolizumab arm in spite of data on goodness of fit, biological reasoning and long term plausibility. Evidence on long term plausibility comes from clinical experience, from the 5-year data of other pembrolizumab trials and from the weighted survival analysis by response status.
Issue 8: Extrapolation of PPS	Yes	The ERG is concerned that the small incremental PPS benefit that was observed in KEYNOTE-826 has been used in the economic model and prefer instead to treat patients in both arms as having equal PPS. **We believe there are five good reasons to use the observed data instead of making this assumption:-**

		1) The default expectation should be to use the data rather than making an unsubstantiated assumption, especially if there is reasonable rationale for accepting the data 2) Longer PPS in the bevacizumab arm of GOG240 was observed at all time points suggesting that a better treatment option provides a lasting benefit in this disease area 3) Progression is assessed from "nadir", meaning the smallest extent of the disease. Since there are more complete and partial responders in the pembrolizumab arm, it is reasonable to expect that patients classified as PD have relatively less severe disease than those in the SoC arm. 4) The differences between the arms are small and thus the magnitude of the observed benefit is not clinically implausible 5) The likelihood ratio test finds that the statistical fit for two independent generalised gamma curves, as measured by AIC, is superior to the statistical fit of a single generalised gamma curve. Data using logL (=Nparams – AIC/2) obtained from R output below:- **Comparison of models** 
Issue 9: Including treatment waning effect for pembrolizumab	Yes	We reiterate that there is no evidence for this assumption and there does not appear to be any treatment waning effect in the three available 5-year follow-up studies of pembrolizumab. It is therefore inappropriate to include any treatment waning effect prior to 5 years. Please refer to the company's "supporting analyses from other pembrolizumab trials" document. Comparison of hazard ratios reported at 1-year, 2-years, 3-years and 5-years

Technical engagement response form

		from the KEYNOTE-024 provided in this document does not find any evidence of waning of PFS or OS hazard ratios through time. **In the ERG's version of the economic model treatment waning appears to be implemented from two years post discontinuation of treatment for a period of 3 years, which is not supported by the above evidence.** **It is MSD's experience across multiple pembrolizumab appraisals that the start and end point of the treatment waning assumption has been imposed inconsistently. For example, in NICE TA737, NICE TA525, NICE TA770 the assumptions accepted by the committee began at 3 years post treatment (so 5 years in the model) and ended at 5 years post treatment. (11, 12) In TA661 and TA801 the committee's accepted a 5-year treatment effect duration. (10, 13) In several appraisals including TA709, TA540 and TA772 there was no treatment waning assumption mentioned in the FAD. (14-16)** We understand the ERG's views and precedent in this area, however, so we suggest incorporating **gradual wane from 3-5 years post treatment is the most conservative sensitivity analysis that should be examined**. It may be more appropriate to assume waning from 5-7 years post treatment, given no waning at all has been observed in the 5-year pembrolizumab trials to date.
Issue 10: Health state utilities	No	**MSD believes that TTD approach is more suitable for the base case of this evaluation.** A number of published economic evaluations of IO treatments have used the TTD-based utility approach, noting that such an approach avoids a number of issues typically attributed to progression-based analyses. (17-19) TTD-based utility values are becoming a more common approach for economic evaluations of IO treatments. A recent review of IO appraisals performed by NICE found that of the 21 identified company submissions, 11 defined health states by progression status, seven by TTD, and three by using a model that had aspects of both elements.(20)

		There are some advantages to using TTD utilities relative to a progression-based approach:- 1) Progression-based utilities distinguish between 2 health states while TDD utilities distinguish between 4 health states, which can allow for finer gradations in utility across patients. 2) Whereas limited utility assessments are typically available in IO trials following disease progression (e.g., at treatment discontinuation and a 30-day post-treatment safety visit only) for being able fully model the trajectory of health utility for this health state, time-to-death utility data are captured for at least a subset of patients across the full spectrum of possible health states (e.g., to within 30 days from death) which allows for the imputation of lower utility values near the point of death for patients for whom a death event utility was not assessed during the trial due to a lack of utility assessment post-progression. 3) A progression based approach assumes that patients within the health states are the same between the arms, which may not be true. Within the Progression Free state, a greater proportion of patients in the pembrolizumab arm will have had a Complete vs. Partial Response. In the progressed disease state they may have progressed from a more complete response and I/O has been associated with “pseudo progressions” where the mechanism of action of the drug is mistaken for radiological progression. The company provided both TTD as a base case and progression-based utilities as scenario.
Issue 11: Resource use	No	**The resource implications of 35 cycles vs 2 years cap vs complete ToT curve and switch to KEYNOTE-826 subsequent treatments vs expected in the UK practice are minimal.** KEYNOTE-826 allowed patients to received pembrolizumab for up to 35 cycles (Q3W), approximately two years, if there is no treatment break. The Kaplan-Meier curve reaches 0

		at approximately 26 months. It is possible that some patients in the trial had a short break in treatment and hence continued shortly beyond the normal 2-year stop. The model can be set to have a cap of 38 cycles to reflect this, which has a marginal effect on the ICER, increasing it from approx. £34,000/QALY to approx. £34,900/QALY in the company's base case analysis. MSD provided the subsequent treatment data based on the KEYNOTE-826 results in the Clarification questions document question B8 (supplemented with updated cost-effectiveness model). Switching model assumptions from the expected in UK to the trial data had a minimal effect on the ICER.
Issue 12: Relevance of bevacizumab and availability of bevacizumab biosimilar	No	The list prices for bevacizumab and associated biosimilars are within close range. (21) Therefore using these prices the impact would be minimal, however this does not take into account any confidential discount provided by the manufacturer. As discussed at the Technical Engagement meeting, this is not expected to be a major issue due to the use of bevacizumab in both arms of the model.
Issue 13: End-of-life criteria	No	**MSD believe that the EoL criteria should be applied for this population. The provided evidence from the study, literature and clinicians suggest that this indication is likely to meet both criteria. A pragmatic approach that takes account of the totality of the evidence on life expectancy and the high incremental health gain would be of great benefit to patients within a therapy area where treatment options are limited and patients typically have poor outcomes.** The EoL criteria are applied in cases where patients can "normally" expect to live for less than 2 years. We note that NICE has never formally specified whether mean or median is the excepted standard for normality. We believe that patients with advanced cervical cancer can normally expect to live for less than 2 years for the following reasons:- 1) Median life expectancy on the SoC in both KEYNOTE-826 and the GOG240 trial is approximately 1.3 years 2) Only 35% of patients are alive at 2 years in the economic model in the company's preferred assumptions.

		3) The company's preferred assumptions for the SoC estimate a mean life expectancy of 2.5 years on the SoC, which is driven by a tail of longer term responders. This is a rare outcome, experienced by a small minority of patients who do well on bevacizumab, which results in the mean being significantly higher than the median. The ERG's preferred assumptions result in a mean life years of 2.08, which is only slightly higher than 2 years. 4) The ERG consider that patients in the SoC arm of KEYNOTE-826, on whom the model is based, are fitter than might be seen in UK clinical practice, perhaps indicating that they would consider a mean of 2 years or lower is plausible. 5) Some models included in the CS e.g. the 2-piece log-logistic/Weibull model for the SoC have a mean below 2 years. **6)** We note from the recent avelumab appeal (NICE TA788) and our own experience with recent appraisals of pembrolizumab that NICE committees can interpret the 2-year life expectancy criterion flexibly, especially in cases where the mean is heavily influenced by a small minority of patients that do not reflect the normal patient experience. The upheld appeal for TA788 considered a situation where the mean life expectancy under the committee's preferred assumptions was 27.8 months and median was 12-18 months. These data are similar to those for this appraisal, where the median is 15 months and the mean 25-30 months, depending on the model selected.

Additional issues

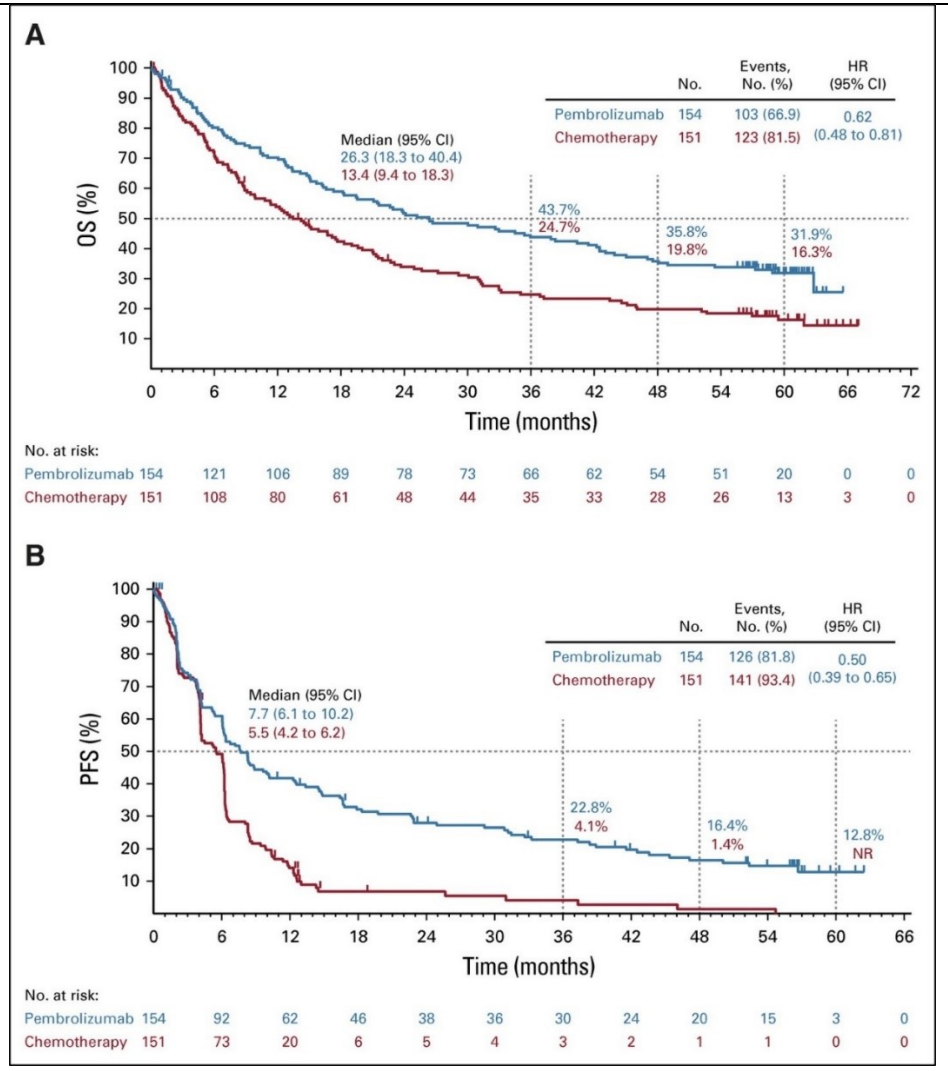
All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The ERG's preferred one-piece curve for the pembrolizumab arm is implausible	Page 67 of ERG Report	No	The ERG prefer one-piece log-logistic parametric models for SoC and pembrolizumab for both TTP and PFS. While the company consider the one-piece model a worse fitting but plausible alternative to the base-case two-piece model, we consider that the two-piece model provides a very poor fit to the pembrolizumab data. [redacted] We have illustrated in our responses to Key Issue 2, 6 and 7 why the observed plateau in TTP/PFS in the pembrolizumab arm of the trial is consistent with clinical expectation, biological plausibility given high and durable response levels in this trial and long term data from other I/O trials. Based on these data and the poor visual fit, we conclude the ERG's preferred curve would dramatically underestimate outcomes for the proportion of patients who have responded well and durably to immunotherapy in this trial. Two-piece curves are routinely accepted in immunotherapy appraisals because it is acknowledged that these drugs are associated with PFS and OS hazard functions that are difficult to model accurately using one-piece curves and short term event rates. In the Company

			Submission (section B.3.3.2) we outlined the poorness of fit of the single-piece models and the process by which we derived the 37-week inflexion point in detail.
Additional issue 2: Evidence from other immunotherapy trials	Page 69 where the ERG discuss the plausibility of the OS projections for pembrolizumab	Yes	At the Technical Engagement meeting, the Company agreed to supply additional analyses from longer term immunotherapy trials to support the plausibility of the KEYNOTE-826 OS projections. This analysis is detailed in a separate report entitled **"Supportive analysis from other pembrolizumab trials".** The Executive Summary is here for convenience:- There have been, to date, three RCTs that have reported 5-year data for pembrolizumab in advanced solid tumours. The analyses within this document show that the predictions made by the company's economic model are reasonable in the context of this evidence. In the 5-year data for pembrolizumab it is clear:- • There is a marked turn in hazards in both PFS and later, OS, leading to extended plateaus in these curves. These plateaus are consistent with clinical experience that a proportion of patients respond extremely well and durably to treatment with pembrolizumab. • KEYNOTE-024, a trial of pembrolizumab vs. chemotherapy in 1L mNSCLC was selected as the most relevant of the three trials for additional analysis. o Although the difference in median PFS in KEYNOTE-024 is just 2 months, observed differences in median OS, predicted mean OS and proportion of patients alive at 5 years are large and are greater than those predicted in the company's model for KEYNOTE-826 (graphs below) o One and two-piece parametric curves were fitted to the 1-year OS data, as in the company's original submission for TA447/531. These curves significantly underpredict observed 5 year OS. • Taken together, the company believes this evidence shows that the modelling approach is reasonable given the pattern of response to pembrolizumab observed in other advanced cancer trials and produces differences in life years

			that are smaller than have been observed elsewhere, despite comparable outcomes on SoC and comparable clinical trial data. • There is no evidence of treatment waning on PFS or OS within the 5-years of KN024 • The model's predictions may even be conservative in light of the extremely high Complete Response rates observed in KN-826, which is much higher than in KN024.


A
OS (%)
Time (months)
No.
Events, No. (%)
HR (95% CI)
Pembrolizumab 154 103 (66.9) 0.62 (0.48 to 0.81)
Chemotherapy 151 123 (81.5)
Median (95% CI)
26.3 (18.3 to 40.4)
13.4 (9.4 to 18.3)
43.7%
24.7%
35.8%
19.8%
31.9%
16.3%
No. at risk:
Pembrolizumab 154 121 106 89 78 73 66 62 54 51 20 0 0
Chemotherapy 151 108 80 61 48 44 35 33 28 26 13 3 0
B
PFS (%)
Time (months)
No.
Events, No. (%)
HR (95% CI)
Pembrolizumab 154 126 (81.8) 0.50 (0.39 to 0.65)
Chemotherapy 151 141 (93.4)
Median (95% CI)
7.7 (6.1 to 10.2)
5.5 (4.2 to 6.2)
22.8%
4.1%
16.4%
1.4%
12.8%
NR
No. at risk:
Pembrolizumab 154 92 62 46 38 36 30 24 20 15 3 0
Chemotherapy 151 73 20 6 5 4 3 2 1 1 0 0

<table>
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<td>Additional issue 3: Possible compromise</td>
<td>ERG's preferred settings</td>
<td>Yes</td>
<td>
The company suggests a compromise between the ERG's preferred settings and the company's base case be considered by the committee.
The only one of the ERG's preferred assumptions which moves the ICER above the £50,000/QALY threshold is the selection of a one-piece model for TTP and PFS for the pembrolizumab arm.
We do not agree with the pooled PPS curve, progression based utilities or treatment waning assumptions but have supplied results of an updated company base case with the following amendments:-

One-piece TTP and PFS curve for the SoC but two-piece for pembrolizumab
Treatment waning from 5-7 years after end of treatment (years 7-9 in the model)
Full ToT KM curve for treatment cost

The results are as follows:-
<table>
<tr><th></th><th>Costs</th><th>LYs</th><th>QALYs</th><th>Δ Costs</th><th>Δ LYs</th><th>Δ QALYs</th><th>ICER</th></tr>
<tr><td>Pembro + SoC</td><td>[redacted]</td><td>4.25</td><td>[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">2.19</td><td rowspan="2">[redacted]</td><td rowspan="2">£38,407</td></tr>
<tr><td>SoC</td><td>[redacted]</td><td>2.06</td><td>[redacted]</td></tr>
</table>
If treatment waning is imposed between years 3-5 post treatment (years 5-7 in the model) the results are as follows:-
<table>
<tr><th></th><th>Costs</th><th>LYs</th><th>QALYs</th><th>Δ Costs</th><th>Δ LYs</th><th>Δ QALYs</th><th>ICER</th></tr>
<tr><td>Pembro + SoC</td><td>[redacted]</td><td>3.95</td><td>[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">1.89</td><td rowspan="2">[redacted]</td><td rowspan="2">£42,853</td></tr>
<tr><td>SoC</td><td>[redacted]</td><td>2.06</td><td>[redacted]</td></tr>
</table>
Landmark overall survival results for the different models:-
</td>
</tr>
</table>

			Overall Survival predictions [redacted] For context when assessing the plausibility of these predictions, 5-year OS in KEYNOTE-024 (1L mNSCLC) was 31% despite 5-year OS being ~5% before the introduction of immunotherapy. That is despite much lower Complete Response rates in that trial than were observed in KEYNOTE-826.
Additional issue 4:	ERG Scenarios	No	It would be more helpful to display the scenario where one-piece curves are applied last in the list if these analyses are to be shown at the committee meeting. All the other ERG scenario analyses have a relatively small effect on the ICER, even when combined, and that may be important information to help guide committee discussion.
Additional issue 5: Uncaptured value	General	No	**When assessing the cost-effectiveness of this intervention, we hope the NICE committee will take into account the comments of consultees who have illustrated that this is an area with very few treatment options. There have been no NICE Technology Appraisals in cervical cancer for 13 years, and even that treatment is rarely indicated for use. Persistent/recurrent/metastatic cervical cancer is an aggressive cancer that affects predominantly younger women, many of whom have caring responsibilities for young children and elderly parents. The impacts of significantly extending a patient's survival on these groups are not captured in the analysis. A quarter of patients on pembrolizumab achieved Complete Response, meaning no evidence of cancer after treatment and [redacted] of**

			these patients remained alive at two years. These outcomes are unprecedented in this disease area. **We also note that cervical cancer is the most common cancer in women under 35, however it affects women of all ages and disproportionately affects those from deprived and ethnic minority groups. The Women's Health Strategy for England, is a central government policy which has prioritised cervical cancer as one of the gynaecological cancers in which to improve screening, access to treatment and increase survival rates for at least 5 years after diagnosis.(22)**

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
5, 7, 9, 11	The company's base case included a cap on treatment at 2 years, two-piece PFS/TTP curves for SoC and no treatment waning assumption.	We have changed the SoC curve to one-piece, included the full KM curve for ToT and imposed treatment waning assumptions from 3-5 years post treatment and 7-9 years post treatment.	Original company base case ICER: £34,017/QALY New analysis with waning 5-7 years post treatment ICER: £38,407/QALY New analysis with waning 3-5 years post treatment ICER: £42,853/QALY

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Table 1: Mean PSA results – analysis with waning 5-7 years post treatment

	Totals per treatment arm			Incremental results			ICER (£/QALY)
Treatment	**LYs**	**QALYs**	**costs**	**LYs**	**QALYs**	**Costs**	
SoC	2.12	[redacted]	[redacted]	2.26	[redacted]	[redacted]	£36,634
PEM+SoC	4.38	[redacted]	[redacted]				
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 2: Mean PSA results – analysis with waning 3-5 years post treatment (mean of 2,000 iterations)

	Totals per treatment arm			Incremental results			ICER (£/QALY)
Treatment	**LYs**	**QALYs**	**costs**	**LYs**	**QALYs**	**Costs**	
SoC	2.12	[redacted]	[redacted]	1.93	[redacted]	[redacted]	£41,253
PEM+SoC	4.06	[redacted]	[redacted]				
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

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12. NICE. TA525 Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy 2018 [Available from: https://www.nice.org.uk/guidance/ta525.

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14. NICE. TA540 Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma 2018 [Available from: https://www.nice.org.uk/guidance/ta540.
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Supportive Analyses from Other Pembrolizumab Trials

Executive Summary

During the Clarification Questions and Technical Engagement steps for this appraisal, the ERG were concerned that the company's economic model may have over-predicted survivors at future landmarks such as 5, 10 and 20 years. They were concerned about the company's choice to fit a two-piece model and to model OS dependent on PFS rather than directly from the observed trial data. We agreed to provide some data from other pembrolizumab trials to contextualise the KEYNOTE-826 economic model's predictions.

There have been, to date, three RCTs that have reported 5-year data for pembrolizumab in advanced solid tumours. The analyses within this document show that the predictions made by the company's economic model are reasonable in the context of this evidence. In the 5-year data for pembrolizumab it is clear:-

- There is a marked turn in hazards in both PFS and later, OS, leading to extended plateaus in these curves. These plateaus are consistent with clinical experience that a proportion of patients respond extremely well and durably to treatment with pembrolizumab.
- KEYNOTE-024, a trial of pembrolizumab vs. chemotherapy in 1L mNSCLC was selected as the most relevant of the three trials for additional analysis.
    - Although the difference in median PFS in KEYNOTE-024 is just 2 months, observed differences in median OS, predicted mean OS and proportion of patients alive at 5 years are large and are greater than those predicted in the company's model for KEYNOTE-826.
    - One and two-piece parametric curves were fitted to the 1-year OS data, as in the company's original submission for TA447/531. These curves significantly underpredict observed 5 year OS.
- Taken together, the company believes this evidence shows that the modelling approach is reasonable given the pattern of response to pembrolizumab observed in other advanced cancer trials and produces differences in life years that are smaller than have been observed elsewhere, despite comparable outcomes on SoC and comparable clinical trial data.
- There is no evidence of treatment waning on PFS or OS within the 5-years of KN024
- The model's predictions may even be conservative in light of the extremely high Complete Response rates observed in KN-826, which is much higher than in KN024.

Introduction and trial selection

Three trials have reported 5-year data on pembrolizumab. No trials have reported longer follow-up. These trials are:-

- KEYNOTE-024, a trial of pembrolizumab monotherapy vs. chemotherapy in first line metastatic non-small cell lung cancer (NSCLC) in patients with PDL1>50% (NICE TA531)
- KEYNOTE-010, a trial of pembrolizumab monotherapy vs. chemotherapy in second line metastatic NSCLC in patients with PDL1>1% (TA428)
- KEYNOTE-006, a trial of pembrolizumab vs. ipilimumab in second line advanced melanoma patients (TA366)

PDF documents of the relevant journal publications are provided separately. The relevant PFS and OS Kaplan-Meier (KM) plots are below:-

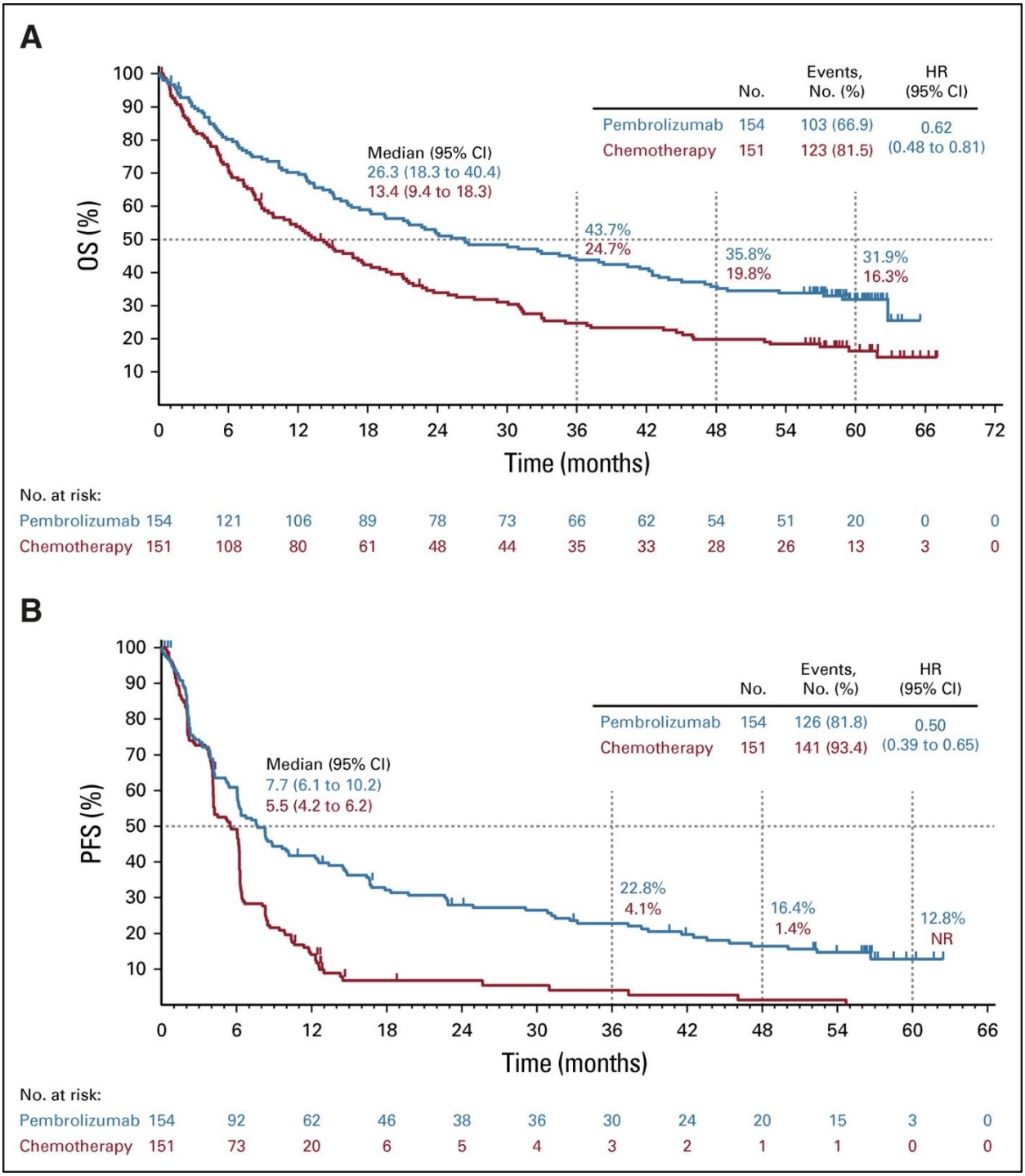

Figure 1: OS and PFS Kaplan-Meier curves from KEYNOTE-024 (1)

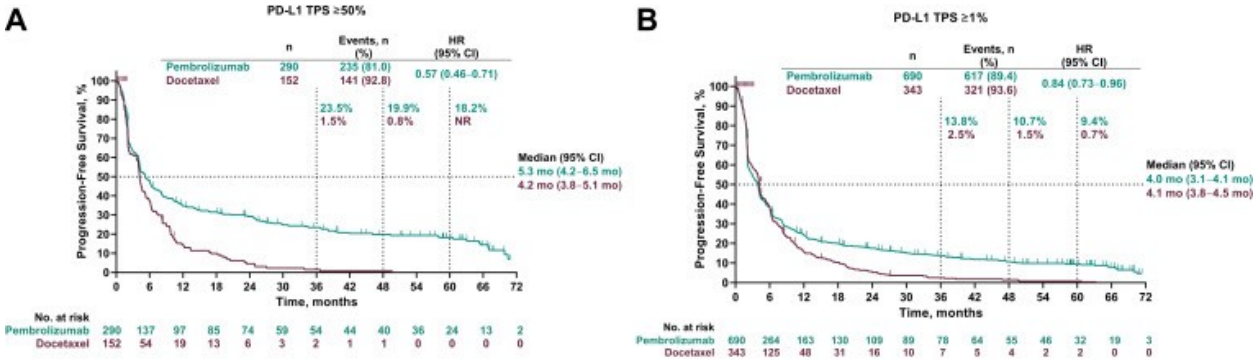

Figure 2: PFS Curves from KEYNOTE-010 (2)

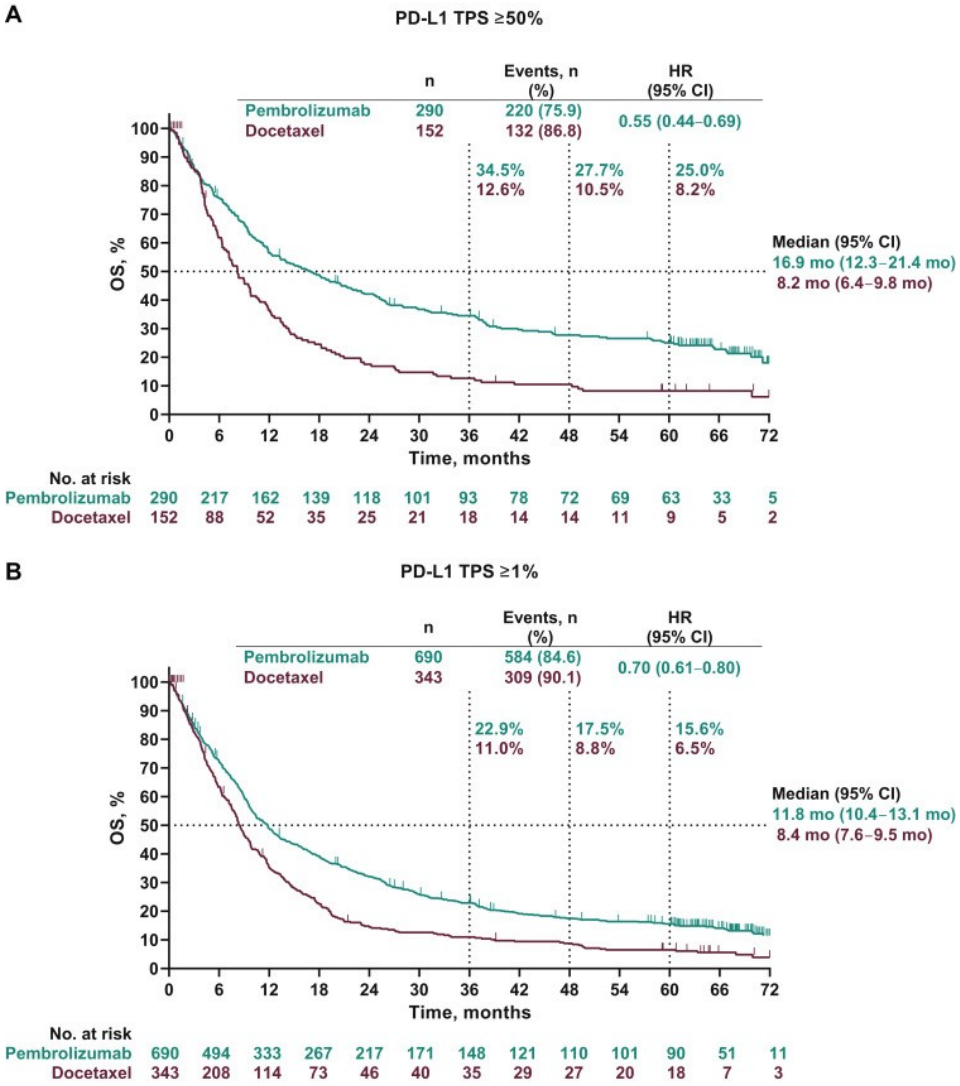

Figure 3: OS Kaplan-Meier curves from KEYNOTE-010 (2)

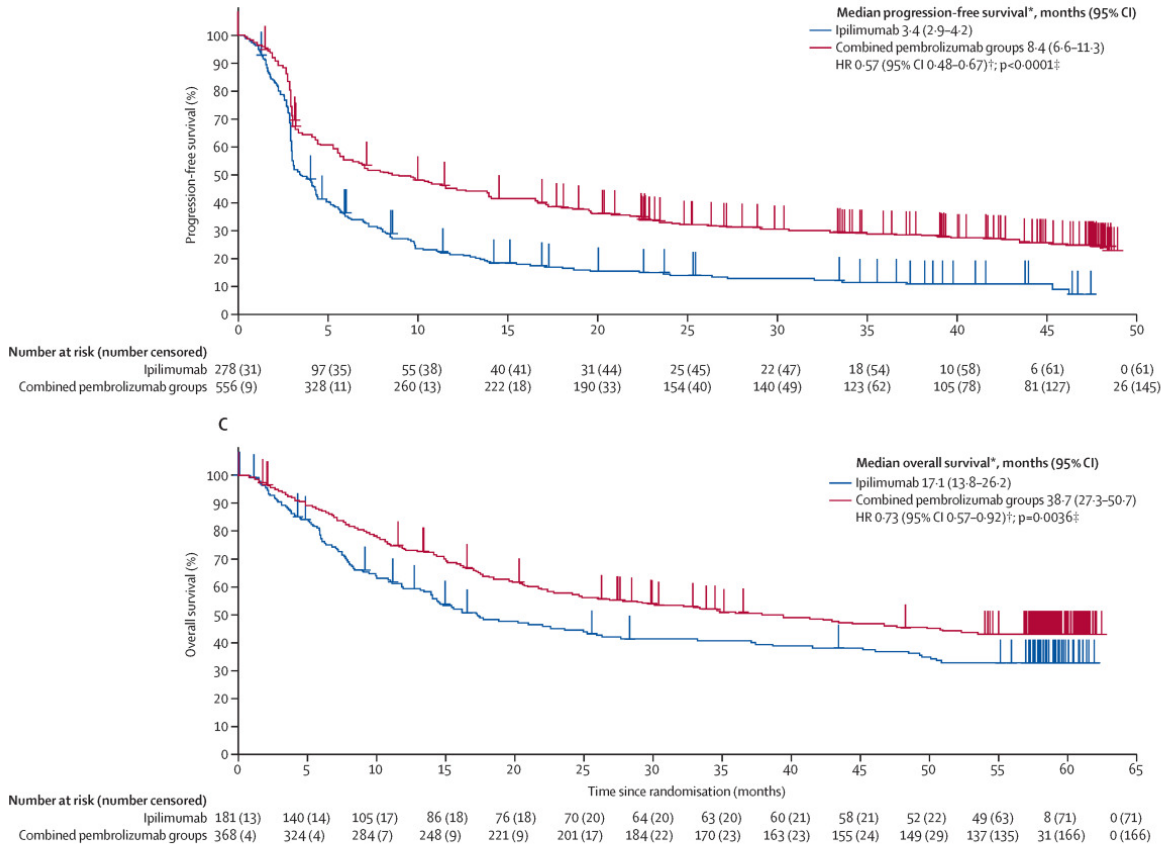

Figure 4: OS and PFS curves from KEYNOTE-006 (3)

The data show marked plateaus in both PFS and OS for all three trials. The fact that (lower) plateaus exist in the control arm of all studies is likely due to crossover to pembrolizumab being allowed in all trials and, in the case of KN-006, because of the presence of ipilimumab immunotherapy in the control arm. This may also explain why OS hazard ratios largely have less favourable point estimates than PFS hazard ratios. Crossover effects on OS wouldn't be seen in the KN826 economic model where I/O does not exist in the SoC arm at all.

The purpose of showing these curves is to demonstrate the 5-year morphology of PFS and OS curves in patients treated with immunotherapy, which show first fast and then slow rates of progression and death, and to show that the 5-year outcomes for KEYNOTE-826 predicted by the company's economic model (PFS=18%, OS=23% on pembrolizumab) are not unreasonable in the context of observed data elsewhere.

Detailed Analysis from KEYNOTE-024

In the time available, the company was able to conduct detailed analysis from only one of these trials. KEYNOTE-024 has been selected as the most relevant trial for the following reasons:-

- It is the only study of the three that is in the first line advanced solid tumour setting.
- The comparator is chemotherapy rather than immunotherapy.
- The PFS and OS curves are morphologically similar with similar medians for both arms.
- The difference in median PFS is short, as observed in KEYNOTE-826, but the observed difference in mean OS and PFS within the five years is much longer, as predicted for KEYNOTE-826.
- Prior to KEYNOTE-024 similarly poor outcomes were seen in advanced NSCLC as in advanced cervical cancer. The FAD for NICE TA531 notes that OS on chemotherapy was approximately 5% at 5 years.
- There is very little censoring in this trial, which means the tail of the curve provides strong evidence about medium-term survivorship.

The following analyses have been produced:-

1. One-piece parametric fit to the five-year data forecasting proportions alive at 5, 10, 15 and 20 years and mean life years
2. One-piece and two-piece survival curve predictions from two-year data compared to observed five year data
3. Chow test showing time-points for changes in hazards for PFS and OS
4. PFS hazard ratio for each year

One-piece parametric fit to OS

Standard one-piece parametric curves were fitted to the KN-024 5-year IPD. [redacted]

Table 1: AIC/BIC Statistics for one-piece parametric curves fitted to pembrolizumab OS data from KN-024

Fitted Function	Pembrolizumab	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]

[redacted]

Figure 5: Best fitting parametric curves and 5-year OS KM data from KN-024

Figure 6: Log-logistic curve and survival at landmark timepoints

It can be seen from Figure 6 that the best fitting single-piece OS curve produces landmark survival estimates that were unprecedented before the era of immunotherapy. As acknowledge in the FAD for NICE TA531, 5-year overall survival on chemotherapy for 1L metastatic NSCLC was just 5% before the introduction of immunotherapies.

The landmark survival on pembrolizumab at 5, 10, 15 and 20 years in KEYNOTE-024 is greater than that predicted by the company's economic model for KEYNOTE-826, despite OS on the SoC being lower in KEYNOTE-024.

In NICE TA531, the committee acknowledged that mean life expectancy on standard care was less than 24 months. The area-under-the log-logistic curve for pembro, which equals mean life expectancy, is [redacted] years. This is a far greater differential than predicted by the company's preferred model for KEYNOTE-826 ([redacted] years vs. [redacted] years). It is worth noting that the median difference in PFS in KEYNOTE-024 was only two months and yet years of difference in life expectancy has been observed at 5 years.

Comparison of two-year extrapolations to observed 5-year data

In the company's original submission for TA447/531, we submitted a two-piece parametric OS curve with KM-data up to 22 weeks and a single parametric curve thereafter. This extrapolation significantly underpredict the OS that was observed on pembrolizumab. This is because the OS data was immature and not enough time had passed for the eventual plateau to become fully apparent.

Figure 7: Company's 2-piece extrapolation from KEYNOTE-024 Interim Analysis 2 (as used in the original NICE submission) vs. Observed OS at five years

The same is true for the PFS data in KEYNOTE-024 where the original submission used KM data to 9 weeks followed by a single parametric curve. This under-prediction is also explained by the full extent of the plateau not becoming apparent. We had to base this analysis on PFS-INV rather than the PFS-BIRC that was originally submitted as no BIRC assessments took place after 2 years in KEYNOTE-024. The analysis otherwise remains the same.

Figure 8: Company's extrapolation from KEYNOTE-024 Interim Analysis 2 (as used in the original NICE submission) vs. Observed PFS at five years

Chow test results for changing hazards

Below are Chow test plots that have been produced to help ascertain when distinct changes in the slope of the hazard function for pembrolizumab occurred across the follow-up time.

The Chow test peaks at week [redacted] for PFS and at week [redacted] OS. This provides some evidence that the greatest turn in hazards occurs later for OS than PFS, which is expected given the pattern of response to immunotherapy and the relationship between disease progression and OS. For OS this occurred well into the second half of the trial where patients at risk would have been smaller. This suggests that the plateauing in OS is likely to become concretely observed at later timepoints than 2 years maximal follow-up as in KEYNOTE-826.

Figure 9: Chow test plot for KEYNOTE-024 PFS

Figure 10: Chow test plot for KEYNOTE-826 OS

Comparison of Hazard Ratios at different time periods

The following tables show the PFS and OS hazard ratios from KEYNOTE-024 reported in the 1-year, 2-year, 3-year and 5-year publications. If treatment waning began at 2 years we should expect some upward drift in the hazard ratios by the 5 year cut-off, which is not observed, despite crossover being allowed in the study and 66% of patients in the chemotherapy arm receiving immunotherapy on

progression. These data, along with visual inspection of the curves in KEYNOTE-010 and KEYNOTE-006 provide no evidence in support of a treatment waning effect within the first 5 years.

KN024 Analysis	PFS HR	OS HR	Source
1-year	0.5	0.62	(4)
2-year	NR	0.63	(5)
3-year	NR	0.65	(6)
5-year	0.5	0.60	(1)

References

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Sections 1.3 to 1.6). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **22nd July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating recurrent, persistent or metastatic cervical 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	Alexandra Taylor
2. Name of organisation	The Royal Marsden NHS Trust
3. Job title or position	Consultant in Clinical Oncology
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 recurrent, persistent or metastatic cervical cancer? ☒ A specialist in the clinical evidence base for recurrent, persistent or metastatic cervical 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.	No links

Clinical expert statement

8. What is the main aim of treatment for recurrent, persistent or metastatic cervical cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve survival (and potentially cure) for women with cervical cancer, without causing significant toxicity.
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)	Increasing the median time to disease progression by at least 2 months. To have a greater proportion of long term survivors (beyond 18 months) by at least 10%
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent, persistent or metastatic cervical cancer?	There is definitely unmet need for women with advanced and recurrent cervical cancer. Treatment with chemotherapy has very limited efficacy and there are no standard second line treatments as response rates are so low. Median survival with chemotherapy is only 13-14 months. While cure rates are high for treating localised primary disease, the outcomes for recurrent and metastatic disease are very disappointing and we need new approaches.
11. How is recurrent, persistent or metastatic cervical 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?	Recurrent and metastatic cervical cancer is currently treated with combination chemotherapy comprising carboplatin (or cisplatin) with paclitaxel, and with the addition of bevacizumab when there is not a high risk of fistulation. This is established care internationally for which guidelines include the ESGO guidelines and NCCN guidelines. The pathway is well defined with all centres using this treatment. The only variation is the percentage of women receiving bevacizumab alongside chemotherapy – since there is a high risk of fistulation when radiotherapy has been given previously (up to 15%), some centres use this more frequently than others (range from 50-80%). Bevacizumab is currently funded in England through the Cancer Drug Fund to be given in combination with carboplatin and paclitaxel. While the standard regimen is 6 cycles of chemotherapy, in the clinical trial GOG 240 chemotherapy +/- bevacizumab was given until progression so can be continued for longer in the CDF (although maintenance bevacizumab alone is not funded).

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	This technology entails the addition of pembrolizumab to the current standard of care treatment. Therefore it is unlikely to change the initial pathway of care with combination chemotherapy and pembrolizumab for the first 6 cycles. The changes will be that following 6 cycles, pembrolizumab is then continued up to 2 years in total. Whereas some centres currently continue chemotherapy and bevacizumab beyond 6 cycles, this will not occur if the patient will be receiving pembrolizumab instead.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The chemotherapy and bevacizumab used in this technology is the same as the current care in NHS clinical practice. It will be delivered in the oncology specialist clinics. Variance from current care includes: Testing for PDL-1 status on the histology specimen (pathologist). Addition of pembrolizumab to chemotherapy (additional 30 minutes chair time) Blood tests including viral serology (once before starting treatment), thyroid function each cycle. Additional visits for the maintenance pembrolizumab Potentially reduction in chemotherapy / bevacizumab use for centres that continue beyond 6 cycles currently
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I expect this treatment to significantly improve progression free survival and overall survival compared to standard care. This will be due to improvement in median survival but also by having a much greater proportion of long term survivors (beyond 2 years) which is so uncommon with chemotherapy.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Women with tumours that express PDL-1 (>1%)
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)	Treatment delivery would be similar to current standard of care. The additional / different toxicities that can occur with immunotherapy compared to chemotherapy are managed by protocols already established in every hospital since many patients with other tumour types are now routinely treated with checkpoint inhibitors. There are additional blood tests (thyroid function, cortisol) taken alongside standard blood tests but do not require additional visits for this. Health care professionals treating gynaecological cancer may need to become familiar with the toxicity profiles and management of these.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would be stopped in the event of disease progression, significant toxicity or patient choice. Imaging for response assessment and ongoing monitoring would generally be as per 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
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, this treatment provides a large step-change in the management of advanced and recurrent cervical cancer with a significant survival benefit on a

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?	different scale to the results in previous studies in this patient group (eg GOG 240).
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?	Potential toxicities due to immunotherapy are usually managed by stopping the relevant drug, either temporarily or permanently, and often require steroids. The management of this is well established due to the wide use of these drugs for other tumour types. There can rarely (<1%) be very severe toxicity including death.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I think the clinical trial does reflect current UK clinical practice, and therefore the trial results are applicable to our patients. The most important outcome was the significant improvement in both progression free survival and overall survival. The survival curves show a large early separation of the Kaplan Meier curves for the two arms which is maintained and suggest a longer term plateau in the immunotherapy arm.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA183]?	Since TA183 assessed cisplatin with topotecan, there was a large phase 3 study GOG 204 which compared 4 different chemotherapy doublets, all of which included cisplatin. There was no significant difference between the arms but

	cisplatin-paclitaxel was the preferred regimen due to the highest response rate and OS of 12.8 months. GOG 240 then compared cisplatin and paclitaxel with the addition of bevacizumab, and median survival increased from 13.3 months to 16.8 months. CECILIA study: This is a single arm phase 2 study evaluating bevacizumab, carboplatin (rather than cisplatin) and paclitaxel, and in contrast to GOG240 in which bevacizumab was only given with chemotherapy, maintenance bevacizumab was allowed. (Gyn Onc 2020:159;142-149). This study included 150 patients with persistent, recurrent and metastatic cervical cancer receiving carboplatin, paclitaxel and bevacizumab until progression or unacceptable toxicity to assess results using carboplatin rather than cisplatin in the combination treatment. Response rate was 61% and median PFS 10.9 months. Maintenance bevacizumab was allowed, and used in 57% patients. Median chemotherapy cycles was 6 (1-21) and median cycles of bevacizumab was 9 (1-53) with median duration 6.7 months. There was at least one fistulation episode in 11% patients despite rigid patient selection. Relating to second line options, there has also been a randomised phase 3 study of cemiplimab versus systemic chemotherapy for second line treatment irrespective of PDL-1 status (Tewari et al, N Engl J Med 2022;386:544-55.DOI: 10.1056/NEJMoa2112187). This showed improvement in OS with immunotherapy, and this may impact on second line options. It also confirms activity with checkpoint inhibitors for recurrent cervical cancer. Median OS was 12 months with cemiplimab versus 8.5 months with chemotherapy, while PFS was 2.8 months versus 2.9 months. Of note, there was a similar benefit for both squamous cell carcinoma and adenocarcinomas.
23. How do data on real-world experience compare with the trial data?	We have very limited real world data to compare to the immunotherapy arm as compassionate use has only been available for a few months in UK.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any	No concerns.

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Applicability of the KEYNOTE-826 trial to the NHS population	The results are applicable to the NHS population. As with all clinical trials, there is selection of patients that occurs and in KEYNOTE-826 there was a higher proportion of patients with stage 4B disease (30% in study is higher than UK population), and only 55% had previously received chemoradiation. The trial was limited to patients with ECOG 0,1 whereas we would have patients with PS 2 that would be considered for chemotherapy. To be considered for the 4 drug combination treatment, clinicians would still consider fitness and there would be a proportion of patients with PS2 due to disease (particularly pain from pelvic disease) who would be treated with this regimen. The study therefore would be overestimating survival for the whole cohort of patients with advanced/recurrent cervical cancer (with respect of End of Life criteria), but unlikely to be overestimating benefits of the addition of immunotherapy to carbo/taxol/bevacizumab.

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Issue 2: Immature overall survival data	Whilst longer term follow up would provide more data, with a median follow up of 22 months (18 months PDL-1>1%), the median OS has not been reached in the pembrolizumab arm, compared to 16.3 months in the chemotherapy arm which is very similar to GOG 240 mature data.
Issue 3: Uncertain relationship between progression-free survival and overall survival	In KEYNOTE-826, there is early separation of the curves for PFS and OS which continue to increase in separation with time. In all previous studies in advanced cervical cancer (including cisplatin versus cisplatin-topotecan and GOG 240 (cisplatin/paclitaxel +/- bevacizumab), there has been a relationship between PFS and OS, with the OS benefit greater than PFS. I think it would be extremely unlikely that PFS benefit does not translate into a significant overall survival benefit. The clinical situations in which PFS does not translate into OS benefit are where there are effective second line options of treatment, high mortality from other causes, or very prolonged survival despite progressive disease. None of these reasons apply to advanced cervical cancer. There is a lack of effective second line options with very poor PFS and OS in second line studies. Current guidelines state there is no standard second line option due to the lack of effect and clinical trials are recommended. The median age of patients is 55 years in the study (and similarly in the UK population), with few co-morbidities, and deaths unrelated to cervical cancer is rare. Treatment related deaths were similar in both arms.
Issue 4: Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	Although the hazard ratio is less than for patients without metastatic disease at presentation, there is still benefit with pembrolizumab for those with metastases at diagnosis (it just does not reach statistical significance). It is very difficult to draw conclusions from an unplanned subgroup analysis, particularly as despite 30% had stage 4B disease, only 19% had no prior treatment in the study so it is unclear how these patients were treated. We have not been provided with specific data on survival in this group, just a hazard ratio. It is implausible that there is a significant differential treatment effect. It is unclear from the data provided whether the difference is due to chemotherapy being more effective when there is no prior exposure to chemotherapy (ie survival is better for the whole cohort) or if survival is overall worse.

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	I would not expect to differentiate treatment choice based on this subset analysis and would apply the trial results to the whole cohort.
Issue 5: Application of two-year stopping rule.	Two years (or 35 cycles) is an appropriate time to stop and this is in keeping with other immunotherapy studies.
Issue 6: Appropriateness of state transition model	I am not very familiar with the options of modelling. As discussed previously, I do think it is very reasonable to extrapolate from PFS to OS, and there may be further OS benefits due to the durable responses seen in patients with complete responses of which there is higher percentage in the pembrolizumab arm. With our experience with chemotherapy, patients with a prolonged response to first line treatment are more likely to respond to subsequent treatments and it is reasonable to anticipate even further benefits with immunotherapy.
Issue 7: Extrapolation of PFS	The extrapolation of PFS is reasonable, and the longer follow up data from GOG 240 does fit with the modelling with a long term tail.
Issue 8: Extrapolation of PPS	This follows on: since PPS is not worse with pembrolizumab, this supports extrapolation of PFS and PPS. It is an important point that PPS data is only available for those patients who have relapsed: since there are more patients on the pembrolizumab arm that have not relapse, it is a reasonable assumption that PPS will actually increase further for the pembrolizumab arm once data is more mature. In other immunotherapy studies in lung cancer, the relapse rate up to 5 years remains very low in patients with a complete response at the end of treatment.
Issue 9: Including treatment waning effect for pembrolizumab	We do not have long term data and have to extrapolate from other immunotherapy studies about the ongoing treatment effect. In other studies we do see a prolonged tail with maintained separation of the curves although the effect beyond 5 years remains uncertain. In KEYNOTE 010 (pembrolizumab versus docetaxel in second line non-small cell lung cancer PDL-1 >50%), the long term follow up confirmed an ongoing effect with 5 year OS 25% versus 8% with median follow up 60 months. Among 79 patients who completed 35 cycles/2 years of pembrolizumab, the OS rate at 5 years from randomization was 83.0% demonstrating an ongoing response in those who respond well. Similarly, KEYNOTE 024 assessed

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	pembrolizumab versus chemotherapy as first line treatment of non-small cell lung cancer and after 5 years follow up, there was a maintained benefit despite crossover, and 5 year overall survival was 82% for those patients who received 2 years of treatment. Based on clinical experience and extrapolation from other studies, I think the estimates for 5 and 10 year overall survival in the company case are reasonable.
Issue 10: Health state utilities	
Issue 11: Resource use	Subsequent treatment options depend on duration of response to first line treatment. Combination platinum-based chemotherapy may be used if there has been a long (>6 months) duration, whereas single agent drugs including weekly paclitaxel or liposomal doxorubicin are used. In the UK , weekly paclitaxel is probably the most commonly used agent, although to date clinical trials are the preferred option due to the poor outcomes with chemotherapy. More recently, the outcome from trial of cemiplimab versus chemotherapy for recurrence less than 6 months from chemotherapy means there will be increased use of immunotherapy in the second line option if patients have not had pembrolizumab previously (currently available via named patient compassionate access scheme).
Issue 12: Relevance of bevacizumab and availability of bevacizumab biosimilar	The use of bevacizumab biosimilar drugs may occur although I am uncertain how widespread this would be. I would raise that it is very likely that bevacizumab would be used less (either concurrently with chemotherapy and certainly in the maintenance setting) when pembrolizumab is being given than when pembrolizumab is not being used. Patients not eligible for pembrolizumab are likely to receive chemotherapy and bevacizumab for more than 6 cycles (as per CDF criteria) whereas a maximum of 6 cycles would be given with pembrolizumab. If maintenance bevacizumab is an option, it is more likely to be given when pembrolizumab is not used. This does not seem to have been modelled.
Issue 13: End-of-life criteria	In GOG 240, median overall survival was **16.8 months** in the bevacizumab plus chemotherapy group vs **13.3** months in the chemotherapy-alone group (HR = 0.77, P =0 . 007). In GOG 204, median survival was **12.0** months. KEYNOTE-826 included selected patients with better PS and less co-morbidities than the

	overall population with this disease due to the use of 4 systemic agents, and in the control arm the median survival is still only **16.3** months. I therefore believe the end of life criteria are met as the average survival for the UK population is less than 2 years (will be less than the trial data as discussed previously).
Are there any important issues that have been missed in ERG report?	Whilst not covered by the ERG, I have a few queries in terms of practical use of this regimen to ensure equitable care. Availability of bevacizumab for women with PDL-1 negative tumours (including maintenance option). This is currently available through CDF approval and no plans for NICE review. It will be important that women who are ineligible for pembrolizumab are not denied access to bevacizumab when women with PDL-1 positive tumours will be eligible for both maintenance bevacizumab and pembrolizumab. PDL-1 status is assessed on a tumour biopsy which is often an archived specimen from primary diagnosis which can take time (often several weeks) to access and then to be processed by the pathology department. Although pembrolizumab is given with each cycle in the trial, would It be possible to start treatment with chemotherapy and add the pembrolizumab with the second cycle if there would otherwise be an unacceptable delay to starting treatment? Otherwise waiting for the PDL-1 status could result in those patients with very symptomatic disease (who cannot wait for starting treatment) missing out on the option of pembrolizumab. Vaginal cancer: Primary vaginal cancer is very rare (<250 cases per year in UK) but has identical aetiology and treatment to cervical cancer. We would use the same chemotherapy agents for women with vaginal cancer, as no trials can be done specifically for vaginal cancer due to rarity. Since the aetiology (HPV-related cancer) is identical, we would want this technology to apply to women with vaginal cancer as well as cervical cancer.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The significant improvement in progression free and overall survival with the addition of pembrolizumab is a big step forward in treating women for whom treatment to date has been very disappointing.
Due to lack of effective second line options, improving progression free survival does result in improved overall survival.
There is an acceptable toxicity profile with the combination of chemotherapy and pembrolizumab.
Durable (cure-like) responses are seen with immunotherapy for other tumour types, and it is anticipated this would be similar for women with cervical cancer.
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.

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

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Sections 1.3 to 1.6). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **22nd July 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating recurrent, persistent or metastatic cervical 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	Susan Lalondrelle
2. Name of organisation	NCRI Gynaecology CSG
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 recurrent, persistent or metastatic cervical cancer? ☒ A specialist in the clinical evidence base for recurrent, persistent or metastatic cervical 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.	

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8. What is the main aim of treatment for recurrent, persistent or metastatic cervical cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve symptoms and quality of life, alongside increasing the time to disease progression through disease response and to extent life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In this setting any treatment that improves overall survival and progression free survival that is well tolerated (side effects not impacting on QoL).
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent, persistent or metastatic cervical cancer?	Yes, whilst first line treatment has improved in the last decade with bevacizumab, OS remains poor and there are no available established other therapies. This is a young population, often with young families. There is a definite unmet need to improve outcomes
11. How is recurrent, persistent or metastatic cervical 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?	Current SOC is carboplatin or cisplatin plus paclitaxel plus bevacizumab (through NCDF) This has been standard since bevacizumab introduced. Some clinicians are wary of giving bevacizumab after radiation, particularly if disease recurrence is in the pelvis due to the 6% incidence of severe fistula associated with bevacizumab. The current technology would be added to this SOC backbone. Current UK practice for the use of bevacizumab is as per the trial presented as evidence. Introduction of pembrolizumab in the PDL1 positive patients would improve PFS and OS without detriment to QoL
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?	It will be in addition to the SOC currently, but given on the same timescales. Should be delivered in specialist cancer centre with experience of immunotherapy and managing side effects Training for clinicians not familiar with immunotherapy may be needed although would expect that most have delivered this technology before for other tumor sites

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• 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)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, although the OS data is not mature, would expect that the improvement in PFS would translate into improved OS. The submitted data suggests that QOL is improved with the technology
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Apart from standard exclusion therapy for immunotherapy, No. The population is selected based on biomarker positivity (PDL1 CPS>=1)
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)	The addition of another drug to the treatment regime could lead to more side effects, The safety data shows that these side effects are predictable in line with other immunotherapy use.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	AS above, entry is based on PDL1 CPS >=1. This requires access to laboratory testing

Clinical expert statement

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
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?	Yes, this technology is not available at any other point in the pathway. Immunotherapy is available for use in cervix cancer in the adjuvant or second line setting. Introduction in first line that improves OS is a leap forward for a disease with limited options.
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?	The side effects of immunotherapy are well established with guidelines for management well developed and readily available. The incidence of severe side effects (G3+ is lower than with cytotoxic therapy).
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, UK SOC practice is C/T/bev The most important outcomes are PFS and OS as were measured in the trial. In addition the SE profile did not impair QoL OS is currently extrapolated and shows a long tail with a proportion of long term responders. I would agree that this assumption is correct and is similar to the long tail seen with other immunotherapy studies in the relapsed disease setting

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• 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. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA183]?	No
23. How do data on real-world experience compare with the trial data?	This technology has only just been made available through a CAP thus there is limited information on real world experience
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No

• 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.	

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For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Applicability of the KEYNOTE-826 trial to the NHS population	Yes, the trial is directly applicable to the UK population. In the study 63% of patients received bevacizumab in addition to chemotherapy, I would agree that is broadly the same proportion as in the UK. Those not receiving bevacizumab would have either been due to previous radiation to the pelvis or contraindications to bev (bowel serosal disease at risk of perforation). Otherwise bevacizumab as accessed through NCDF is SOC. The trial includes only PS0-1 patients; I estimate this is applicable to 60% of recurrent or metastatic disease patients in the UK. No data on pembrolizumab in PS=2 patients is available.
Issue 2: Immature overall survival data	The OS is immature but would expect that this would follow PFS and demonstrate improvement. This opinion is based on the outcome data from other immunotherapy trials in the relapsed setting. A tail to the curve would also be expected, highlighting a proportion of patients who are long term responders – in other tumour sites this is up to 15% of cases.

Clinical expert statement

Issue 3: Uncertain relationship between progression-free survival and overall survival	AS above, other immunotherapy studies have demonstrated a maintained improvement in PFS with OS following accordingly. The data presented should no narrowing of the curves, therefore would expect PFS to be a surrogate of OS
Issue 4: Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	Patients presenting with metastatic disease often have a higher burden of disease and symptoms. Their response to chemotherapy is also worse than patients who have relapsed after primary therapy. I would not exclude metastatic patients from the group likely to benefit, they have no other opportunity to access immunotherapy. Only 20% in trial were metastatic at presentation.
Issue 6: Appropriateness of state transition model	Unable to comment
Issue 7: Extrapolation of PFS	I agree that one would expect to see a tail on the projection with a number of longer term survivors. Based on current data the expected SOC outcome would be 16.8 months OS with bev and 13.3 months without. I find it hard to comment on the best model for this but agree that the % of patients alive at each time pint would be maintained at a higher level than that see for chemo plus bev alone, with maintenance of the tail in the trial arm.
Issue 8: Extrapolation of PPS	Agree that post progression survival would be expected to be longer in the immunotherapy group due to an ongoing effect beyond discontinuation in responders.
Issue 9: Including treatment waning	In responders who stop after 2 years/ 35 cycles I would expect to see an ongoing response and further response to immunotherapy if reintroduced at subsequent relapse.

Clinical expert statement

effect for pembrolizumab	
Issue 10: Health state utilities	QoL would be expected to be decreased closer to death as the burden of disease increases and symptoms worsen. QoL over time will depend on burden of disease and sites of metastasis leading to symptoms and functional impairment
Issue 11: Resource use	All centres will have expertise in administering immunotherapy. The technology will result in additional appointments which have been included in the financial considerations
Issue 12: Relevance of bevacizumab and availability of bevacizumab biosimilar	Access to bevacizumab should be maintained for maximal benefit It is not an alternative to pembrolizumab but the evidence demonstrates the benefit of all 4 drugs
Issue 13: End-of-life criteria	As above
Are there any important issues that have been missed in ERG report?	Consideration of continued access to bevacizumab especially for those not eligible for pembrolizumab

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The technology represents a key advance in improving outcomes in this group of patients
There are no other established treatments in advanced cervical cancer providing equivalent benefit (PFS and OS)
The technology is well tolerated with predictable side effects and maintains QoL
The trial population is directly applicable to the UK population
Click or tap here to enter text.

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Single Technology Appraisal (STA)

Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

ERG addendum: review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD
Date	3rd August 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135578.

Declared competing interests of the authors

None

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.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 Overview

This addendum to the Evidence Review Group (ERG) Report presents the ERG's critique of the additional evidence provided by the company in their responses to the technical engagement key issues emerging from the ERG report. The ERG has not addressed separately the additional issues raised by the company as it considers that these are covered by the ERG's response to the key issues.

The technical engagement covered 13 key issues for consideration (see Table 1). The company's technical engagement response indicated that they accepted the ERG's judgement on some aspects of Issues 5, 8, 9, and 11. The company's responses are discussed in Section 2. Section 3 presents an overview of the company's revised base-case analysis. As no further evidence has been provided by the company, and none of the resolved issues have implications for the ERG's base-case analysis, no additional ERG analyses are presented.

Table 1 Summary of company's Technical Engagement response

Issue #	**Status**
Issue 1: Applicability of the KEYNOTE-826 trial to the NHS population	Resolved
Issue 2: Immature overall survival data	Unresolved
Issue 3: Uncertain relationship between progression-free survival and overall survival	Unresolved
Issue 4: Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	Unresolved
Issue 5: Application of two-year stopping rule	Resolved
Issue 6: Appropriateness of state transition model	Unresolved
Issue 7: Extrapolation of PFS	Unresolved
Issue 8: Extrapolation of PPS	Unresolved
Issue 9: Including treatment waning effect for pembrolizumab	Partially resolved (uncertainty remaining)
Issue 10: Health state utilities	Unresolved
Issue 11: Resource use	Partially resolved (uncertainty remaining)
Issue 12: Relevance of bevacizumab and availability of bevacizumab biosimilar	Unresolved
Issue 13: End-of-life criteria	Unresolved

2 Description and critique of additional evidence

2.1 Issue 1: Applicability of the KEYNOTE-826 trial to the NHS population

The company have clarified that across NICE approved indications for pembrolizumab, treatment is limited to patients with an ECOG performance status (PS) of 0 or 1. The company do not anticipate this to differ in the current indication. The company also note that bevacizumab is not available through NHS England for PS 2 patients.

Points for critique

The ERG considers this issue resolved, presupposing that the final NICE guidance will restrict use of pembrolizumab to patients with an ECOG status of 0 or 1.

2.2 Issue 2: Immature overall survival data

The company have clarified that the

[redacted]

Points for critique

The ERG considers that the improved maturity of the OS data from KEYNOTE-826 will serve to reduce uncertainty around the long-term efficacy of pembrolizumab. The ERG does not consider the response-based analysis an appropriate substitute for imminently available OS data with [redacted] more follow-up than that in the current model.

2.3 Issue 3: Uncertain relationship between progression-free survival and overall survival

The company has provided no evidence further to that already considered in the ERG Report in support of the surrogate relationship between PFS and OS.

Points for critique

The ERG agrees that a surrogate relationship is plausible, but this issue cannot be considered resolved until it has been validated clinically. As in Issue 2, the company have clarified that the final trial analysis [redacted]. This may help validate whether observed improvements in PFS will translate into equivalent OS benefits.

2.4 Issue 4 Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis

The company did not implement subgroup analysis in the economic model for the patient group diagnosed with stage IVB disease. The company state that analysis of the metastatic subgroup is inappropriate, as KEYNOTE-826 was not designed to detect benefits specifically in patients with

metastases at baseline, and thus such an analysis would not have appropriate statistical power. The company considers the outcomes in this group (PFS HR 0.92 [95% CI 0.64 to 1.30] and OS HR 0.84 [95% CI 0.56 to 1.26]) to be indicative of a 'positive and consistent' treatment effect.

The company also considered a recommendation by NICE which excludes patients with stage IVB disease at diagnosis to present a health inequalities issue, reasoning that this population is more likely to come from groups with poorer health literacy and engagement with the health system. This may be for reasons correlated with culture, ethnicity, and/or economic deprivation. They consider such a recommendation would risk disproportionately disadvantaging those in the highest deprivation quintile.

Points for critique

The KEYNOTE-826 statistical analysis plan (SAP) describes pre-specified subgroup analyses based on the six stratification factors (including metastatic status at diagnosis) "to determine whether the treatment effect is consistent across various subgroups".

While point estimates for patients who were metastatic at initial diagnosis favoured pembrolizumab, the magnitude of effects were noticeably smaller than for other subgroups. The ERG considers the interpretation of the subgroup PFS HR of 0.92 (0.64 to 1.30) as favourable to be a very optimistic reading of these data. The ERG considered this to be a source of uncertainty to be addressed through the economic model and/or clinical opinion on the biological plausibility of a differential treatment effect. No new evidence or analyses have been presented.

The relevance of health inequalities to this issue is unclear. Current data from KEYNOTE-826 suggests a lack of effectiveness of pembrolizumab relative to chemotherapy alone among patients with metastatic disease at baseline. The ERG does not consider a recommendation excluding a patient group who would gain little benefit from treatment to present an equality issue.

2.5 Issue 5: Application of two-year stopping rule

The company states that a 35-cycle stopping rule has been implemented by NHS England in other pembrolizumab indications, and anticipates this would be the case in the present indication.

Points for critique

The ERG agrees with the company's response and the inclusion of the full ToT curve in the company's revised base-case; the ERG considers this issue resolved.

2.6 Issue 6: Appropriateness of state transition model

The company argues that the PSM structure preferred by the ERG is inappropriate for the following reasons:

- Parametric curves fitted to OS data are dominated by early events in non-responders and thus don't capture the expected plateau.
- Patients achieving a complete response or partial response have a much lower OS event rate, [redacted] of patients with CR remain alive at 2 years.
- The company expect the PFS plateau for pembrolizumab emerging in KEYNOTE-826 to be replicated in the OS curve.
- The estimates of restricted mean OS at 2 years generated by the company's economic model largely resemble the KM curves restricted mean OS.

In support of these arguments, the company provided an additional supporting document with analysis of three selected pembrolizumab trials with longer follow-ups. These three trials were:

- KEYNOTE-024: pembrolizumab vs chemotherapy in first-line NSCLC
- KEYNOTE-010: pembrolizumab vs chemotherapy in second-line NSCLC in patients with PDL1>1%
- KEYNOTE-006: pembrolizumab vs ipilimumab in second-line advanced melanoma

The company focus their supportive analysis on KEYNOTE-024, which they considered the most relevant trial due to its first-line advanced solid tumour setting, a chemotherapy comparator arm, morphological similarities between PFS and OS curves, contextual similarities with regards to unmet need, and minimal censoring in the tail of the KM curves. The company fitted one-piece parametric curves to 5-year OS data from KEYNOTE-024. The three best fitting curves are illustrated in Figure 1; the [redacted] had the best fit to the observed KM data.

Figure 1 KEYNOTE-024 parametric model fit (Supporting document Figure 5, Page 7)

The company highlights that the landmark survival estimates predicted in this analysis are far above those achieved in a population not treated with immunotherapy and are greater than those predicted by the current cervical cancer model. The company implies that the greater difference in mean predicted life expectancy between SoC and pembrolizumab ( ) in KEYNOTE-024 compared to the company's preferred model of KEYNOTE-826 data (vs) means this prediction is conservative.

The company also present Chow hazards plots of OS and PFS in KEYNOTE-024. These plots show that peak hazards occurs at week for PFS and week for OS, suggesting that any plateau in OS is likely to be observed at a later time point than currently available from KEYNOTE-826.

Points for critique

The ERG's concerns regarding the clinical plausibility of the model's predictions remain, with signs that the model may not adequately predict the observed data. The ERG notes that pembrolizumab has been studied in a very wide range of tumour types, exhibiting a range of long-term OS patterns.

The ERG maintains the point that a partitioned survival model may be more appropriate when more mature data from KEYNOTE-826 are made available.

2.7 Issue 7: Extrapolation of PFS

The company reiterate their preference for a two-piece model for modelling PFS outcomes on pembrolizumab. The company consider the one-piece model a very poor visual fit to the pembrolizumab arm, and therefore inappropriate. The company also argue that the benefits predicted by the two-piece model are a biologically plausible outcome, given the differences in immunotherapies and chemotherapy. The company state they do not believe that if a one-piece model

is deemed appropriate for SoC arm, they should be obligated to fit a one-piece model to the intervention arm, in spite of TSD guidance advising otherwise.

The supplementary analysis of KEYNOTE-024 previously described in Issue 6 is again discussed in reference to this issue. The company considers the plateaus emerging in 5-year data from pembrolizumab trials in other indications (primarily KEYNOTE-024, mNSCLC) supportive of the assumption of a plateau in the present model. The company also reproduces figures from the weighted analyses presented in their clarification response, arguing that this alternative analysis supports the model predictions and rejects the one-piece model for the pembrolizumab arm.

Points for critique

The ERG suggested that clinical validation of long-term PFS predicted by the company's model may help to reduce the uncertainty associated with this issue. In their technical engagement response, the company stated "Clinicians expected the plateau to be replicated in a significant minority of patients.' In support of this statement the company cite a recent TA of durvalumab for maintenance treatment of unresectable non-small-cell lung cancer following platinum chemotherapy. The EAG highlights that this TA considered an indication where curative intent was the objective of treatment, and where there was already an established paradigm of long-term survival. The relevance of this statement is therefore unclear. The company provide no further clinical validation of the predictions of the two-piece model, which predicted PFS of [redacted] at 5 years and [redacted] at 10 years. The ERG received clinical advice suggesting these figures were optimistic.

The ERG does not necessarily regard evidence from pembrolizumab trials conducted in other indications to be supportive of the company's position that the two-piece model is the most appropriate extrapolation. Much of the evidence provided by the company focuses on the extrapolation of OS and the relative plausibility of one- vs two-piece models. The company base-case model, however, does not use OS directly to inform survival predications and two-piece models of OS have thus far not been put forward by the company as a possible extrapolation approach. The direct relevance of this information is therefore unclear. Further while additional evidence provided by the company does explore two-piece extrapolations of KEYNOTE-024 PFS data, no analysis is presented using a one-piece model. It is therefore not possible to compare the relative performance of both approaches. The ERG also notes that the two-piece model fitted to the KEYNOTE-024 data uses a 22-week cut-off whereas the two-piece model used in the company model uses a 37-week cut-off. This undermines the company position that a two-piece model may be pessimistic, as it is likely that a later cut-off would produce more optimistic predictions.

The ERG further highlights that the presented analysis does not represent a systematic assessment of all evidence on long-term treatment effects in immunotherapies, rather the examples have been

selected because they illustrate the declining hazard trends purported by the company. As such, while the evidence presented may broadly support the company's position, it is not conclusive evidence that this pattern of declining hazards is observed across all indications. In this regard, the ERG highlights the KEYNOTE-048 trial in head and neck squamous cell carcinoma. This trial demonstrates that an apparent inflection point and emerging plateau on pembrolizumab is not necessarily indicative of persistently reduced hazards.[1]

2.8 Issue 8: Extrapolation of PPS

The company argue that the ERG's preferred approach to modelling a consistent PPS across treatment arms regardless of prior treatments received is inappropriate. The company state that longer PPS in the bevacizumab arm of GOG240 was observed at all time points, which is suggestive of a lasting treatment benefit. The company also argue that as disease progression is assessed relative to the maximum treatment response, the pembrolizumab population with a higher number of complete and partial responders will have less severe disease at the point of progression than those in the SoC arm. The company also present the results of a likelihood ratio test, which found that the statistical fit (AIC) of independently fit generalised gamma curves is superior to the fit of a single generalised gamma curve.

Points for critique

The ERG remains concerned about the use of GOG240 to inform model selection, and reiterates concerns that due to the limited treatment options beyond progression in this population, regardless of previously received treatments, prognosis is likely to be very poor. The ERG acknowledges the company's argument regarding the higher proportion of complete and partial responders on pembrolizumab, but clinical evidence demonstrating improved PPS in this these patients has not been presented. The ERG again notes that available KM data from KEYNOTE-826 was not necessarily supportive of a PPS benefit on pembrolizumab, with the curves for pembrolizumab and SoC crossing at week 63. Until more mature PPS data are presented in support of this assumption, the ERG prefers to maintain the more conservative assumption where the treatment effects do not persist beyond progression.

2.9 Issue 9: Including treatment waning effect for pembrolizumab

The company reiterate their position that modelling a waning of the treatment effect is inappropriate.

The supplementary analysis of KEYNOTE-024 included a comparison of hazard ratios over time for PFS and OS, which the company suggest did not show evidence in support of effect waning over the first five years in KEYNOTE-024 (See Table 2)

Table 2 KEYNOTE-024 PFS and OS HR over time (Supporting document, Page 11)

KN024 Analysis	PFS HR	OS HR
1-year	0.5	0.62
2-year	NR	0.63
3-year	NR	0.65
5-year	0.5	0.60

The company note that the time at which effect waning has been applied is consistent over past appraisals. In TA737, TA525, and TA770, the committee has accepted the assumption that waning begins at 3 years post-treatment and ends at 5 years post-treatment. In TA661 and TA801 the committee accepted a 5-year effect duration. In TA709, TA540, and TA772, there was no assumption of a waning effect mentioned in the FAD. The company therefore suggest that the most conservative analysis that should be examined incorporates a gradual waning effect from 3 – 5 years after treatment cessation.

The company present two revised base-case analyses in their TE response which include the application of effect waning at 3 – 5 years post-treatment, and 5 – 7 years post-treatment.

Points for critique

The implementation of effect waning has been done in a number of different ways across historical appraisals, but as noted by the company in their response, the approach preferred by the ERG has been accepted many times by the committee in immunotherapy appraisals. The ERG notes that effect waning may have been inappropriate in three cited examples of appraisals in which waning was not applied, e.g. a poorer prognosis meant KM data was more mature, or treatment was given with curative intent. The ERG also does not consider the evidence provided from KEYNOTE-024 to provide convincing evidence against treatment waning. This study provides only up to three years of data following the cessation of treatment and shows a small increase in hazards for OS in the first year after treatment is stopped. There remains significant censoring between years four and five (~63% of remaining patients censored). This means the small reduction in hazards at year 5 (year 3 post-treatment) is of uncertain significance, and caution should be given to interpreting this as evidence against treatment effect waning.

The ERG considers this issue partially resolved, as the company have included waning scenarios in their revised base-case. However, the appropriate timing of effect waning remains unclear from the data available.

2.10 Issue 10: Health state utilities

The company reiterated their preference for time to death-based utilities, noting what they consider limitations of progression-based utilities. The company highlights a recent review of immunotherapy appraisals by NICE which found that of 21 company submissions, seven defined utilities by TTD. The company did not provide a comparison of the fit of progression-based and TTD-based utilities to determine which is statistically the most appropriate.

Points for critique

The ERG does not consider the company's response to provide clarity on the appropriateness of the TTD approach for this appraisal. As stated in the ERG Report, the observed correlations between HRQoL and TTD are most likely due to confounding, with time to death acting as a proxy for severity of disease, which is likely to be highly correlated with both OS and HRQoL. As has been discussed in previous appraisals, TTD utilities are based on reversed causality (i.e. previously experienced HRQoL can only be determined upon death), and cannot be clinically validated.

The ERG notes in the majority of appraisals in which this approach has been adopted in company submissions, TTD-based utilities have been rejected. As requested in the ERG Report, the ERG would have preferred to see an appropriate statistical comparison of each utility set with the observed data in KEYNOTE-826, and a more thorough examination of which patients contributed data over time to examine the effect of confounding on the generated utilities.

2.11 Issue 11: Resource use

The company argues in their response that the resource implications of modelling patients to receive the full allocation of pembrolizumab doses as per the trial are minimal (ICER increases by ~£900). The company appear to confirm that the patients who continued treatment to 26 months had experienced a short break in treatment. It was, however, unclear whether they agreed with the ERG's alternative approach to modelling time on treatment as described in the ERG Report.

The company stated that data from KEYNOTE-826 on subsequent treatments were provided by the company in their clarification response, and therefore no further information as requested in the ERG Report was provided.

Points for critique

The ERG considers the first issue regarding time on treatment resolved, as modelled time on treatment should reflect patients receiving the full allocation of 35 treatment cycles as per KEYNOTE-826 and anticipated NHS practice. The company included the full KM curve for ToT in their updated base-case model.

The ERG requested further information on the subsequent treatments received by patients in KEYNOTE-826, as data on only those treatments received by >3% of patients was provided in the company's clarification response. The company's technical engagement response did not provide any further data.

The ERG also suggested additional UK clinical opinion may be necessary to inform the composition of subsequent treatments used in NHS practice. The company offer no further insights into the composition of subsequent treatments used in NHS practice.

2.12 Issue 12: Relevance of bevacizumab and availability of bevacizumab biosimilar

The company does not anticipate this issue to have a significant impact on cost-effectiveness due to the use of bevacizumab in both arms of the model.

The company presented no evidence regarding the relevance of bevacizumab as a comparator.

Points for critique

The ERG is satisfied that the use of biosimilar prices for bevacizumab will have a limited impact on cost-effectiveness and has explored relevant scenarios accounting for the confidential price discounts.

While the ERG recognises that consideration of the cost-effectiveness of bevacizumab is beyond the scope of this appraisal, it reiterates that the cost-effectiveness of bevacizumab has implications for the cost-effectiveness of pembrolizumab and as such is relevant to the current decision problem. The ERG considers that this should ideally be addressed by fully incremental analysis considering each of the four alternatives (doublet chemotherapy, doublet chemotherapy plus bevacizumab, doublet chemotherapy plus pembrolizumab, doublet chemotherapy plus bevacizumab and pembrolizumab). The ERG accepts that data to conduct this analysis is not available, but is disappointed that the company did not provide the relevant subgroup analysis requested in the ERG Report. This analysis would have helped resolve some of the uncertainty associated with this issue.

2.13 Issue 13: End-of-life criteria.

The company reiterate their position that EoL criteria should be applied in this population based on the use of median life expectancy. The company note the following reasons why they believe patients could normally expect to live for less than 2 years:

- Median life expectancy on SoC in KEYNOTE-826 and GOG240 is approximately 1.3 years;
- 35% of patients remain alive at 2 years in the economic model under the company's preferred assumptions;
- The company's preferred assumptions generate 2.5 LYs on SoC, which they consider to be driven by a small but long tail;

- The ERG's preferred assumptions generate 2.08 LYs on SoC
- The ERG consider patients on SoC in KEYNOTE-826 to be fitter than those seen in UK clinical practice;
- Some of the parametric models fitted by the company predict below 2 LYs
- The recent upheld appeal for TA788 considered a situation where the committee did not apply EoL where mean life expectancy was 27.8 months but the median was 12 – 18 months. The present data show a similar pattern.

Points for critique

The EoL criteria are typically interpreted with respect to mean life expectancy. Because the QALY gains and costs to which end-of-life weighting is applied are based on means, life expectancy is usually calculated on the basis of mean rather than the median.

The ERG acknowledges the prediction of a mean life expectancy of 2.08 years in the ERG-preferred base case. The ERG also re-states the caveat that some patients in NHS practice may receive a monotherapy chemotherapy regimen which may be less effective than the doublet and triplet chemotherapy considered in the KEYNOTE-826 trial. As discussed in Issue 1, the point that patients in the KEYNOTE-826 may be fitter on the basis of performance status than the NHS population may not apply, as treatment is likely to be limited to patients with a PS of 0 – 1.

The ERG considers that under the company's base-case assumptions, it is unlikely that criterion 1 should apply. In order to accept the 2.08 years in the ERG base case (and the resulting uncertainty over whether EoL should apply), it would be necessary for the company to accept the extrapolations preferred in the ERG's base-case analysis (Issues 7 and 8).

The ERG also considers that TA788 is inappropriate to consider as precedent. The appraisal committee did not conclude that the EoL was met in TA788. This is clearly stated in the FAD, where it is explained that the committee "firmly believed that the best estimate of life expectancy came from the mean survival for the eligible patient population, based on the decision model submitted by the company." The decision to consider EoL was instead imposed on the committee by the appeal panel, who consider median OS a more relevant indicator of usual life expectancy. Aligning with the committee in TA788, the ERG does not consider the median an appropriate statistic with which to assess EoL.

3 Updated modelling assumptions

In response to the issues noted in the ERG Report, and following the technical engagement teleconference, the company updated their base case cost-effectiveness analyses.

The following ERG-preferred assumptions are incorporated within the company's revised model:

- Issue 5: Application of two-year stopping rule
- Issue 9: Including treatment waning effect for pembrolizumab

In addition, the following issues have been partially accommodated in the company's revised model:

- Issue 8: Extrapolation of PPS (one-piece model fitted to SoC)
- Issue 11: Resource use (full ToT curve for pembrolizumab)

The company maintain their original position on the following assumptions:

- Issue 3: Uncertain relationship between progression-free survival and overall survival (pembrolizumab arm)
- Issue 8: Extrapolation of PPS for pembrolizumab
- Issue 10: Health state utilities

3.1.1 Results of updated company analysis

The results presented in Table 3 include only the confidential PAS discount for pembrolizumab, and are exclusive of confidential commercial arrangements for the comparator treatments. Probabilistic results of these scenarios are presented in Table 4. Results with the PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix to this report.

In the company's revised base case which considered a waning effect starting at 3 years post-treatment discontinuation, pembrolizumab generated [redacted] incremental QALYs versus SoC, at a cost [redacted] higher than SoC. The ICER was £42,853 per QALY gained. When considering waning beginning 5 years after treatment discontinuation, pembrolizumab generated [redacted] incremental QALYs versus SoC, at a cost [redacted] higher than SoC. The ICER was £38,407 per QALY gained.

Table 3 Changes to the company's cost-effectiveness estimates (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Original company base case							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	2.80	[redacted]	£34,017
Company's revised base case 1 (3 – 5-year effect waning)							
SoC	[redacted]	2.06	[redacted]				
Pembrolizumab	[redacted]	3.95	[redacted]	[redacted]	1.89	[redacted]	£42,853
Company's revised base case 2 (5 – 7-year effect waning)							
SoC	[redacted]	2.06	[redacted]				
Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	2.19	[redacted]	£38,407

Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 4 Changes to the company's cost-effectiveness estimates (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Company's revised base case 1 (3 – 5-year effect waning)							
SoC	[redacted]	2.12	[redacted]				
Pembrolizumab	[redacted]	4.06	[redacted]	[redacted]	1.93	[redacted]	£41,253
Company's revised base case 2 (5 – 7-year effect waning)							
SoC	[redacted]	2.12	[redacted]				
Pembrolizumab	[redacted]	4.38	[redacted]	[redacted]	2.26	[redacted]	£36,634

Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

4 References

1. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, Jr., et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;**394**:1915-28. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31679945

Waning scenarios on post-TE company base-case (Including Pembrolizumab PAS)

Scenario	Technology	Total			Incremental			ΔICER vs TE BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
Company's post-TE base-case (with 5 – 7 year treatment waning)	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,407	-
Company's post-TE base-case (with 3 – 5 year treatment waning)	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.95	[redacted]	[redacted]	[redacted]	£42,853	
Company's post-TE base-case (with 2 – 5 year treatment waning)	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.85	[redacted]	[redacted]	[redacted]	£44,804	

Table 1 ERG Exploratory Scenario Analyses on post-TE company base-case (Including Pembrolizumab PAS)

Scenario	Technology	Total			Incremental			ΔICER vs TE BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
Company's post-TE base-case (with 5 – 7 year treatment waning)	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,407	-
Company post-TE base-case including corrections from ERG Report	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,413	£6
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.05	[redacted]	[redacted]	[redacted]	£75,660	£37,253
2. a) Pooled survival curve for PPS using generalised gamma curve.	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	4.14	[redacted]	[redacted]	[redacted]	£41,276	£2,869
2. b) Pooled survival curve for PPS using Weibull curve.	SoC	[redacted]	1.96	[redacted]				
	Pembrolizumab	[redacted]	4.09	[redacted]	[redacted]	[redacted]	£39,453	£1,046
3. a) Treatment waning for pembrolizumab between 3 and 5 years	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.95	[redacted]	[redacted]	[redacted]	£43,126	£4,719
3. b) Treatment waning for pembrolizumab between 5 and 7 years	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,407	£0
4. Progression based utilities	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£41,446	£3,039
5. Subsequent therapy distribution from KEYNOTE-826	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£37,756	-£651
6. Full Pembro ToT KM curve used to calculate costs	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,407	£0
7. All patients receive biosimilar bevacizumab	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,445	£38
	SoC	[redacted]	2.06	[redacted]				

8. Bevacizumab maintenance treatment allowed	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£37,147	-£1,260
9. GP/nurse visits, blood-counts, and thyroid function tests costs	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£39,450	£1,043
10. All AEs of special interest occurring in more than 5% of patients modelled	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	4.25	[redacted]	[redacted]	[redacted]	£38,645	£238