

Single Technology Appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission from MSD:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
 - a. Clarification addendum
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. UK Cervical Cancer
- 4. Expert personal perspectives from:**
 - a. Dr Asma Sarwar – clinical expert, nominated by British Gynaecological Cancer Society
 - b. Dr Alexandra Taylor – clinical expert, nominated by MSD
- 5. External Assessment Report prepared by SCHARR**
 - a. Survival probability different timepoints
 - b. Additional data
- 6. External Assessment Report – factual accuracy check**

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Single technology appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Company evidence submission



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ID6138 pembrolizumab Company Submission Document [No CON].docx	1	Yes	10 th March 2025

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Abbreviations

Abbreviation/acronym	Definition
AE	Adverse event
AEOSI	Adverse Event Of Special Interest
AIC	Akaike Information Criterion
APaT	All participants as treated
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIN3	Cervical intraepithelial neoplasia-3
COPD	Chronic obstructive pulmonary disease
CPS	Combined Positive Score
CC	Cervical cancer
CCRT	Concurrent chemoradiotherapy
CR	Complete response
CRT	Chemoradiotherapy
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DSU	Decision Support Unit
EAG	External Assessment Group
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	Euroqol-5D
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FIGO	International Federation of Gynecology and Obstetrics
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
IMRT	Intensity-modulated radiation therapy
ITT	Intention to treat
IV	Intravenous
KM	Kaplan—Meier
LACC	Locally advanced cervical cancer
LS	Least square

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LYs	Life years
MA	Marketing authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD1	First disease progression
PD2	Second disease progression
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PLD	Patient level data
PPS	Post progression survival
PR	Partial response
PRO	Patient reported outcome
PSS	Personal social services
Q3W	Pembrolizumab every 3 weeks
Q6W	Pembrolizumab every 6 weeks
QALYs	Quality-adjusted life years
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SUV	Standardised uptake value
TEW	Treatment effect waning
TOT	Time on treatment
TSD	Technical Support Document
TTD	Time to discontinuation
TTP	Time to progression
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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

Summary of the decision problem, technology, and clinical care pathway

- The company submission covers the full anticipated marketing authorisation for pembrolizumab in cervical cancer - Adults with FIGO 2014 Stage III-IVA locally advanced cervical cancer who have not received prior definitive therapy.
- Pembrolizumab is a humanized monoclonal antibody which binds to the programmed death-ligand 1 (PD-L1) receptor that is involved in the control of T-cell immune responses, thereby potentiating an immune response to tumour cells.
- Cervical cancer is a malignancy that is preventable and if detected early and adequately treated, it is also curable. A total of 2,641 new cervical cancer cases were recorded in England for 2022, with over half being in women aged between 15-49.
- Cervical cancer diagnosis age standardised rates per 100,000 population in 2022 are nearly twice as high for people who live in the most deprived quintile in England compared with the least deprived, with rates of 12.1 versus 7.3, respectively.
- Lack of engagement with the national cervical screening programme is an important risk factor for more advanced LACC.
- The current standard of care for the population under review is cisplatin based chemoradiotherapy (EBRT followed by brachytherapy). The proposed treatment pathway would see pembrolizumab added to this treatment combination.

1.1 Decision problem

The company submission (CS) covers the technology's full marketing authorisation for the indication for which NICE recommendation is sought. The decision problem relevant to the Technology Appraisal is set out 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 high-risk, locally advanced cervical cancer	Adults with FIGO 2014 Stage III-IVA locally advanced cervical cancer who have not received prior definitive therapy	To align with licensed population
Intervention	Pembrolizumab with chemoradiation	As per NICE scope	N/A
Comparator(s)	Chemoradiotherapy (cisplatin-based, unless contraindicated)	As per NICE scope	
Outcomes	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life.	As per NICE scope	N/A
Special considerations including issues related to equity or equality		Deprivation	MSD considered deprivation to be an important characteristic to explore due to the inequalities experienced by those from the most deprived quintile.

1.2 Description of the technology being evaluated

Pembrolizumab (KEYTRUDA®) is a humanised monoclonal antibody (mAb) against the programmed death-1 (PD-1) receptor. Expression of PD-1 protein, and its ligands PD-L1 and PD-L2, triggers a signalling cascade that culminates in the suppression of T cell proliferation, cytokine release and cytotoxicity, a process that modulates the immune response (to prevent destruction of healthy cells). (1) Expression of PD-L1 and PD-L2 is frequently upregulated on the surface of tumour cells, as well as other cells in the tumour microenvironment. By binding to the PD-1 receptor, and thus blocking its interaction with PD-L1 and PD-L2, pembrolizumab reverses PD-1-mediated T-cell suppression, thereby reactivating tumour-specific cytotoxic T lymphocytes and restoring antitumour immunity.

A description of pembrolizumab and its proposed use for the treatment of cervical cancer is available in Table 2. The draft Summary of Product Characteristics (SmPC) is provided in Appendix A.

Table 2: Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor, thereby potentiating an immune response to tumour cells.
Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 19th September 2024 recommending approval of pembrolizumab for use in the indication listed in the application. The date of EMA Marketing Authorisation (MA) was 21st October 2024. An application for a MA for Great Britain was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in ■■■■, using the EMA as the reference regulatory body. The anticipated date of approval by the MHRA is ■■■■.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication wording is: KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III-IVA locally advanced cervical cancer in adults who have not received prior definitive therapy. Pembrolizumab has also obtained regulatory approval for the management of the following conditions: • Melanoma; • Non-Small Cell Lung Cancer • Classical Hodgkin lymphoma; • Urothelial carcinoma; • Head and neck squamous cell carcinoma • Renal cell carcinoma;

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	• Microsatellite instability high or mismatch repair deficient cancers; • Colorectal cancer; • Oesophageal carcinoma; • Triple-negative breast cancer; • Endometrial carcinoma; • Cervical cancer; • Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma; • Biliary tract carcinoma.
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.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	£2,630 per 100 mg vial.
Patient access scheme (if applicable)	A Commercial Access Agreement (CAA) for pembrolizumab is in place. Please refer to Appendix J for details.

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

1.3.1 Health condition

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. (2) 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-A18 includes patients with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma histologies. (3) 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. (4, 5)

An estimated 99.8% of cervical cancer cases are preventable, and, if the cancer is detected early and adequately treated, it is also curable. (6) 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. (6) 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. (7, 8) 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. (8) Additional risk factors associated with developing advanced-stage cervical cancer include low-socioeconomic status, older age, black or Hispanic ethnicity, and lower education level. (9)

The HPV immunisation 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). (10) CIN3 is important to detect early as women with this condition have a two fold increase in the risk of developing cervical cancer compared to the general female population. (11) 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 and people with a cervix aged 25–64 years. (12) In 2023/24, 5.12 million women in England were invited for screening, of Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

whom 68.8% were adequately screened. (13) In 2023 NHS England announced their ambition to eliminate cervical cancer by 2040 through improved vaccine and cervical screening uptake. (14)

The successful eradication of cervical cancer will be dependent on a combination of maintenance of the high rate of vaccination against HPV and engagement of those with a cervix with the national screening programme available in England and Wales, both of which have contributed to reducing the incidence of cervical cancer. However, despite the introduction of education programmes, advertising campaigns, and other strategies to raise awareness of cervical cancer, uptake of both programmes is not universal and data show there is a proportion of patients who present with LACC and who require effective treatment options to manage their disease. (15, 16) Additionally, research shows that migrant women born in Eastern Europe and living in the UK are at higher risk of being diagnosed with LACC. Migrant women from Eastern Europe are less likely to engage with the cervical cancer screening programme in the UK, and are therefore at higher risk of presenting with later stage disease. (17-19) Universal factors that have been found to contribute to lower rates of uptake of cervical cancer screening include fear and embarrassment, cultural and ethnic factors, and awareness and education. (20, 21) Additional barriers for migrant women also include difficulty communicating with healthcare professionals due to language differences, unfamiliarity with the NHS, and potential fear of divulging immigration status. (17-19) A lower uptake of the HPV vaccination has also been observed in Polish and Eastern European women residing in the UK. (22)

Deprivation is also a key factor in the observed inequality in the diagnosis and prognosis of people with cervical cancer (discussed in more detail in Section 1.3.3).

Outside of screening, the main symptoms of cervical cancer are vaginal bleeding that is unusual for the patient (e.g. bleeding during or after sex), changes to vaginal discharge, pain during intercourse and pain in lower back, pelvis or stomach. (23) Nearly two-thirds of women were unable to attribute symptoms after diagnosis to having cervical cancer. (24)

1.3.2 Epidemiology

The WHO states that rates of cervical cancer incidence and mortality are higher in low- and middle-income countries due to a 'lack of access to national HPV vaccination, cervical screening and treatment services and social and economic determinants'. (25)

In 2022, 2,641 new cervical cancer cases (ICD10 code C53) were registered in England, corresponding to an incidence rate of 9.3 per 100,000 population. (15) Over half of cases, 54.1%, were in women aged 15–49 years. (15) The incidence of new diagnoses of cervical

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cancer per 100,000 females has fallen from 12.0 in 1995 to 9.3 in 2022. (15, 26) The peak age of cervical cancer diagnosis is expected to move to an older age group (from 25–29 years to 55–59 years) due to the lack of vaccination in women born between 1975 and 1990. (27) There were 737 cervical cancer deaths in 2022 registered in England, a rate of 2.3 per 100,000. (28)

The English cancer registry reported that 49.9% of cervical cancer cases were diagnosed at Stage 1 or 2, 23.9% were Stage 3 or 4, and for 26.2% of cases the stage was missing or unstageable. (15) Of the stage 3 and 4 patients, 51.6% were aged 54 and under. (15)

The Welsh cancer registry data for 2019–2021 provides a breakdown by stage and has a lower percentage of missing data, which gives a more complete picture of stage distribution: stage 1, 40.1%, stage 2, 15.4%, stage 3, 22.1%, stage 4, 13.1% and unknown 9.2%. (16)

Patients diagnosed with Stage 3 or 4 cervical cancer have a much lower survival rate compared with earlier stages, with, for example, with 44.2% of Stage 3 patients surviving to 5-years compared with 94.6% for stage 1 patients (Table 3). (29)

Table 3: Non-standardised net cancer survival rates for women diagnosed with cervical cancer in England for the period 2015–2019

Non-standardised net cancer survival	Stage at diagnosis			
	Stage 1	Stage 2	Stage 3	Stage 4
1-year	99.1	94.4	78.9	48.7
2-year	97.3	86.4	61.2	29.2
3-year	95.9	79.6	53.2	22.8
4-year	95.1	74.5	48.6	19
5-year	94.6	71.9	44.2	18.3
Source: NHS Digital (29)				

1.3.3 Deprivation and cervical cancer

Inequalities exist across the pathway for cervical cancer between deprivation quintiles for various parameters, including diagnosis rates and survival. Cervical cancer diagnosis age standardised rates per 100,000 population in 2022 are nearly twice as high for people who live in the most deprived quintile in England compared with the least deprived, with rates of 12.1 versus 7.3, respectively (see Figure 1). (15) The higher rate is attributed to multiple factors including lower uptake of cervical screening, higher prevalence of smoking, teenage conception rates and earlier onset of sexual activity. (30, 31) Research has shown the HPV immunisation programme is ‘associated with a substantial reduction in the expected number of women with cervical cancers and CIN3 in all fifths of deprivation’, (32) however the gap between the most and least deprived persists.

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Mortality rates per 100,000 population are twice as high in the most deprived areas compared with the least deprived, 4.1 versus 1.8, respectively (see Figure 1). (33) Survival at various timepoints is also poorer for those falling into the most deprived category compared with the least deprived, with 5-year survival being 56.2% for the most deprived compared with 65.7% for the least deprived (see Figure 2). (34)

Figure 1: Diagnosis and mortality rate for cervical cancer in England by deprivation quintiles

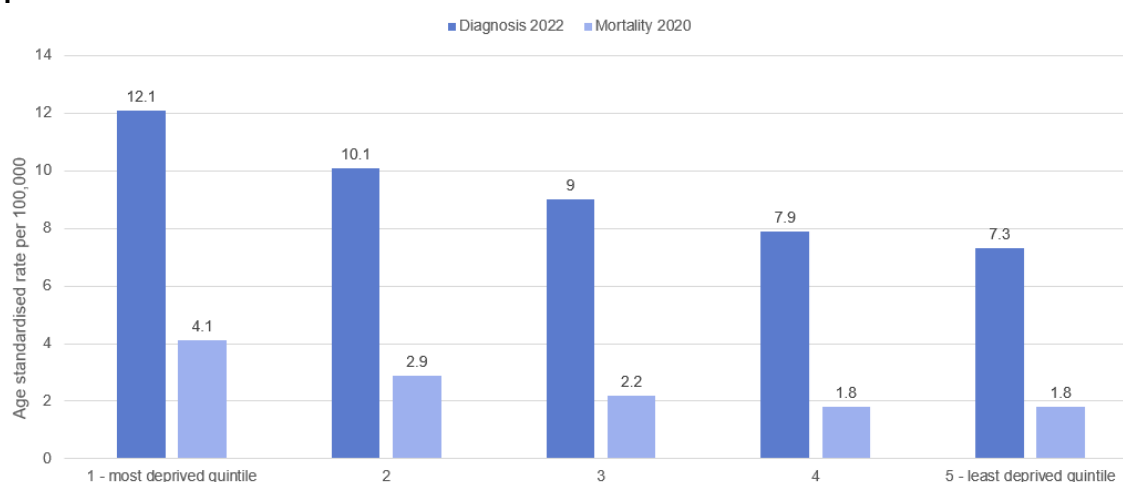
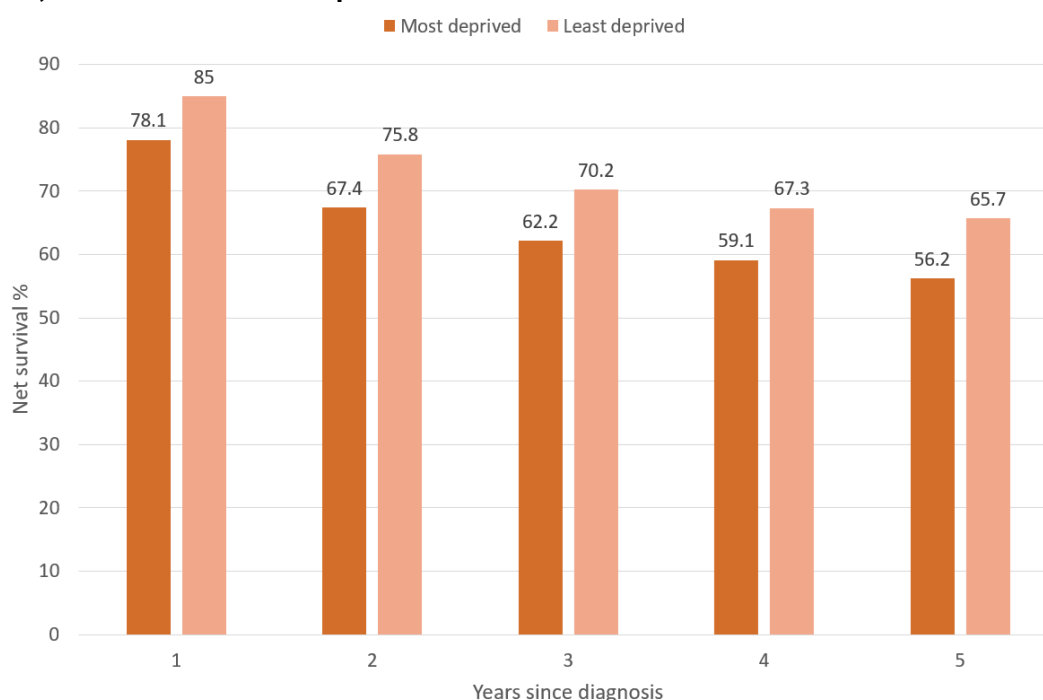


Figure 2: Net survival for cervical cancer diagnosed between 2016 and 2020, followed up to 2021, for most and least deprived



1.3.4 Quality of Life Impact

Jo's Cervical Trust conducted a survey in 2016 with 35 women who had been diagnosed with cervical cancer in the previous two years to understand their experience of cervical cancer and what they valued throughout the treatment pathway. (24) After diagnosis, a range of emotions and experiences were reported including, feeling isolated in decision making, being concerned about future fertility, trust in clinicians, and being comfortable with the treatment plan proposed. Women reported being given lots of information, mainly in the form of paper leaflets and being directed to patient group websites. Many of the respondents, who received chemotherapy, experienced physical and psychological side effects of treatment such as nausea, anxiety and feeling lonely. Radiotherapy was also considered to be a challenging treatment. Throughout treatment women found life to be challenging due to the side effects, the time required to attend appointments and recover and changes to their lives. The women also considered the impact on the wider family unit such as disruptions to their children's routine, lack of energy to play, becoming closer to their partners emotionally but, in majority of cases, intimate relationships were negatively affected. Finally, for those who were employed, some were able to use sick leave whilst others had to take early retirement.

A 2014 report found the cost to a woman of having cervical cancer was £5,844 over the course of a year due to increase living costs (car parking, energy bills, childcare) and loss of income. (35)

1.3.5 Treatment pathway and proposed positioning of the technology

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. (36) The European Society for Medical Oncology (ESMO) has also published guidance on the treatment of cervical cancer. (37)

The BGCS recommended treatment for patients with locally advanced cervical cancer (LACC; FIGO 2018 Stage IIIA/IIIB, IVA) is 'definitive chemoradiation (CRT) and brachytherapy with an additional radiation boost to the involved lymph nodes in those patients with unequivocally involved pelvic lymph nodes on imaging'. (36)

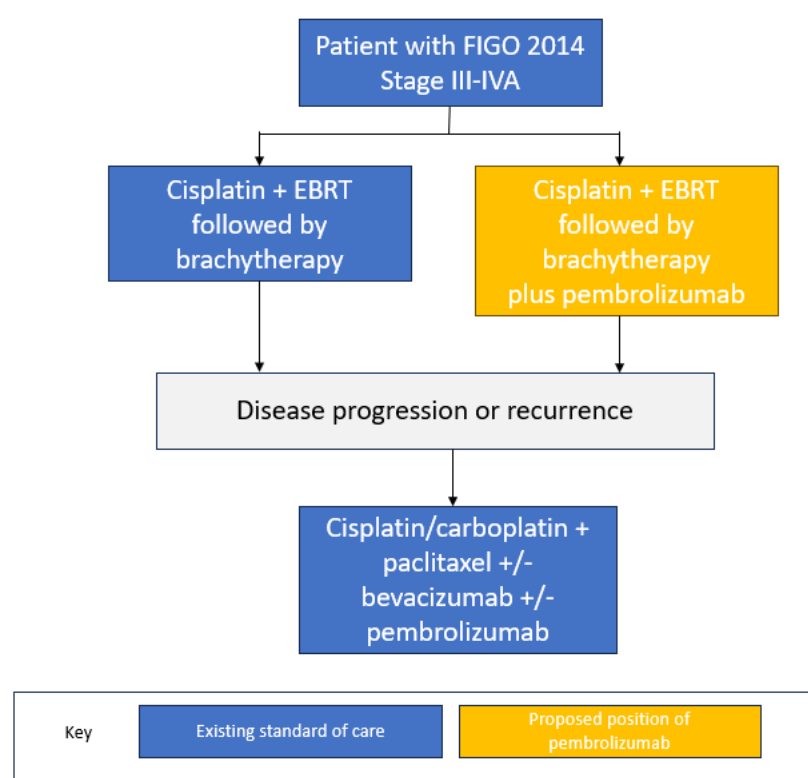
Chemoradiotherapy (CRT) comprises external beam radiation therapy (EBRT), intracavitary brachytherapy and concomitant chemotherapy with cisplatin. The BGCS guidelines state 'combined intracavity / interstitial brachytherapy should be used where appropriate (such as significant residual disease in parametria) in order to achieve a sufficiently high radiation dose to the target and / or reduce dose to organs at risk.' (37) The most commonly used dose for a cisplatin based regimen is 40 mg/m² and the recommended 'pelvic EBRT dose should be 45-

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50.4 Gy in 1.8 Gy per fraction to the central disease and the elective nodes.’ In image-guided adaptive brachytherapy (IGABT) the aim should be to deliver a brachytherapy dose of 40-45 Gy (EQD2)(D90) to reach a total EBRT + brachytherapy dose of 85-90 Gy to the high-risk volume. (37) CRT has been the standard of care for LACC for ‘almost two decades.’ (37)

Error! Reference source not found. presents the clinical pathway for patients and the proposed positioning of pembrolizumab in the treatment pathway. Adding pembrolizumab to CRT, as has been evaluated in KEYNOTE-A18, provides a step change in the treatment for patients with LACC.

Figure 3: Clinical pathway of care for patients with FIGO Stage III-IVA cervical cancer and the proposed placement of pembrolizumab



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, most patients will go on to receive systemic anti-cancer therapy (SACT), which primarily consists of platinum doublet chemotherapy ± bevacizumab ± pembrolizumab (NICE TA939).

1.4 Equality considerations

As discussed in Section 1.3.3, those in most deprived quintiles have a higher rate of cervical cancer, and a poorer prognosis, compared with those in the least deprived. As a consequence, the company has provided a Distributional Cost-effectiveness Analysis (DCEA) in section 3.13.

No other equity or equality considerations are anticipated.

2 Clinical effectiveness

Summary of key clinical effectiveness information

Randomised controlled trial:

- A SLR was conducted (search date of November 2024) with eligibility criteria of the decision problem.
- KEYNOTE-A18 is a Phase III, randomized and double-blind trial comparing pembrolizumab plus chemoradiotherapy with chemoradiotherapy in patients with FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stages III-IVA. A total of 1,060 patients, including 6 from the UK, were enrolled.
- KEYNOTE-A18 trial results presented in this submission are based on a data cut from the second interim analysis of data (IA2) conducted in January 2024. Results from the final analysis are expected in [REDACTED].
- **In line with the anticipated licence wording, this submission is focussed on the results of the FIGO 2014 stage III-IVA patients .**
- The OS hazard ratio (HR) was 0.57 (95% CI: 0.39, 0.83) in favour of pembrolizumab plus CCRT, which represents a 43% reduction in the risk of death.
- The PFS HR was 0.57 (95% CI:0.43, 0.76) in favour of pembrolizumab + CCRT, representing a 43% reduction in the risk of progression.
- EQ-5D-5L analyses showed no clinically meaningful differences between participants treated with pembrolizumab + CCRT compared with placebo + CCRT.
- The safety profile of pembrolizumab + CCRT at IA2 was generally consistent with well-established safety profiles of a cisplatin-based chemoradiotherapy regimen and of pembrolizumab monotherapy.

Clinical effectiveness conclusions

- For the subgroup of patients with LACC, KEYNOTE-A18 demonstrated clinically meaningful improvements across both of its primary endpoints of OS (HR 0.57 [95% CI 0.39, 0.83]) and PFS (HR 0.57 [95% CI 0.43, 0.76]), as well as key secondary endpoints of ORR where a continued improvement with durable responses was also observed.

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was carried out as per NICE guidance and according to a pre-specified protocol to identify and select relevant evidence on the efficacy and safety of pembrolizumab and any comparator treatments for the indication of interest for this appraisal. As the manufacturer of pembrolizumab, MSD are aware of all relevant clinical trials for pembrolizumab for the indication under review. Full details of the SLR methodology followed to identify and select the clinical evidence relevant to the technology being evaluated are provide in Appendix B

2.2 List of relevant clinical effectiveness evidence

The SLR was initiated on the 5th of November 2024. A total of 3,197 unique records were retrieved, from which one randomised controlled trial (RCT) – KEYNOTE-A18 (38) – was identified that provided evidence of the clinical effectiveness and tolerability profile of pembrolizumab in the patient population relevant to this appraisal (Table 4).

MSD note that evidence on the use of pembrolizumab in the indication for which a recommendation is being sought is derived from a subpopulation of patients from KEYNOTE-A18. As detailed in Table 4, KEYNOTE-A18 enrolled adults with cervical cancer of FIGO 2014 stage IB2 through to IVA, whereas MSD, in line with the anticipated marketing authorisation of pembrolizumab in this indication, focused on adults with treatment-naïve high-risk LACC of FIGO 2014 stage III-IVA. Randomisation in KEYNOTE-A18 was stratified by stage of cervical cancer at screening – FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease). The implementation of stage as a stratification factor mitigates against an imbalance between the two treatment arms in the RCT in the FIGO stage III-IVA subgroup, and allows for a more robust analyses of treatment effects in the population of interest. MSD recognise that there are limitations associated with the use of subgroup analyses, but consider that the large number of patients forming the relevant cohort (n=601) and the observed balance in baseline characteristics between the treatment groups (Table 8) lead to confidence in the results and that the estimates of effectiveness of adding pembrolizumab to CCRT represent a true effect in clinical outcomes.

Table 4: Clinical effectiveness evidence

Study	KEYNOTE-A18 (NCT04221945)
Study design	Phase III, randomized and double-blind
Population	Adults aged 18 or over with high risk locally advanced cervical cancer with FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stages III-IVA
Intervention(s)	Pembrolizumab with chemoradiotherapy (CRT)

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Study	KEYNOTE-A18 (NCT04221945)
	CRT: Cisplatin plus external beam therapy followed by brachytherapy
Comparator(s)	Phase III, randomized and double-blind
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	<u>Primary outcomes</u> • Progression free survival (PFS) as assessed by investigator • Overall survival (OS) <u>Key Secondary outcomes</u> • Complete response rate at 12 weeks after completion of concurrent CRT • Objective response rate as assessed by investigator • Complete response rate at 12 weeks after completion of concurrent CRT • Objective response rate as assessed by BICR • Health Related Quality of Life (HRQoL) assessed by EORTC QLQ-C30 and EORTC QLQ-CX24 • Adverse events
All other reported outcomes	EQ-5D-5L

2.3 Summary of methodology of the relevant clinical effectiveness evidence

Table 5: Summary of trial methodology

Study name	KEYNOTE-A18 (NCT04221945)
Trial design	Phase III, randomized and double-blind
Eligibility criteria for participants	Key inclusion criteria: 1. Has high-risk LACC (a or b below): a. FIGO 2014 Stage IB2-IIB (with node-positive disease) – must meet criteria below for positive pelvic lymph node OR para-aortic lymph node involvement up to the L1 cephalad body level. i. Pelvic lymph node involvement as assessed by one of the following criteria: 1. Histopathologic, biopsy-proven pelvic node involvement (high-risk LACC

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	patient with locally evaluable disease is eligible if removal of positive lymph node[s] is documented), or 2. 2 or more positive pelvic nodes by MRI or CT (≥ 1.5 cm shortest dimension), or 3. 2 or more positive pelvic nodes by PET / CT with SUV (max) ≥ 2.5 ii. Para-aortic lymph node involvement as assessed by one of the following criteria: 1. Histopathologic, biopsy-proven para-aortic node involvement (high-risk LACC patient with locally evaluable disease is eligible if removal of positive lymph node[s] is documented), or 2. 1 or more positive para-aortic nodes by MRI or CT (≥ 1.5 cm shortest dimension), or 3. 1 or more positive para-aortic nodes by PET / CT with SUV (max) ≥ 2.5 b. FIGO 2014 Stages III-IVA (either node-positive or node-negative disease) Refer to Appendix 9 for further details of FIGO 2014 staging for cervical cancer. 2. Has histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix. 3. Has not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents, and is immunotherapy naïve. Note: Previous surgical procedure for localized cervical tumor is allowed. 4. Has an ECOG performance status of 0 or 1 within 7 days prior to the first dose of study intervention. 5. Is female, at least 18 years of age at the time of documented informed consent. 6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: Is not a WOCBP OR Is a WOCBP and using a contraceptive method that is highly effective, with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis). 7. Has radiographically evaluable disease, either measurable or non-measurable per RECIST 1.1, as assessed by the local site investigator/radiology. 8. Has adequate organ function as defined in the study protocol. Key exclusion criteria: 1. Has histological subtypes other than those allowed per inclusion criterion 2

	2. Has FIGO 2014 Stage IVB disease. Evidence of metastatic disease per RECIST 1.1 including lymph nodes above the L1 cephalad body or in the inguinal region. 3. Has undergone a previous hysterectomy defined as removal of the entire uterus or will have a hysterectomy as part of their initial cervical cancer therapy. Note: Women who have had a partial/subtotal hysterectomy for reasons other than cervical cancer are eligible to participate in the study. 4. Has 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. 5. Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization. 6. Has any contraindication to the use of cisplatin. The full eligibility criteria is in Appendix E.
Settings and locations where the data were collected	A multinational multicentre study conducted at 176 centres in 30 countries. Six patients across two UK sites were randomised in KEYNOTE-A18.
Trial drugs	Intervention arm • Pembrolizumab 200 mg every 3 weeks (Q3W) for 5 infusions • With cisplatin 40 mg/m² weekly for 5 infusions plus External Beam Radiation (EBRT) followed by brachytherapy • Followed by pembrolizumab 400 mg every 6 weeks (Q6W) for 15 infusions Comparator arm • Placebo Q3W for 5 infusions • With cisplatin 40 mg/m² weekly for 5 infusions plus EBRT followed by brachytherapy Followed by placebo Q6W for 15 infusions
Primary outcomes	PFS OS
Other outcomes used in the economic model/specified in the scope	Health utilities assessed using EQ-5D-5L. Adverse Events
Pre-planned subgroups	• Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT • Stage at screening of cervical cancer: FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease) • Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy versus ≥70 Gy • Age group (<65 years versus ≥65 years) • Race (white, non-white) • ECOG performance status (0, 1)

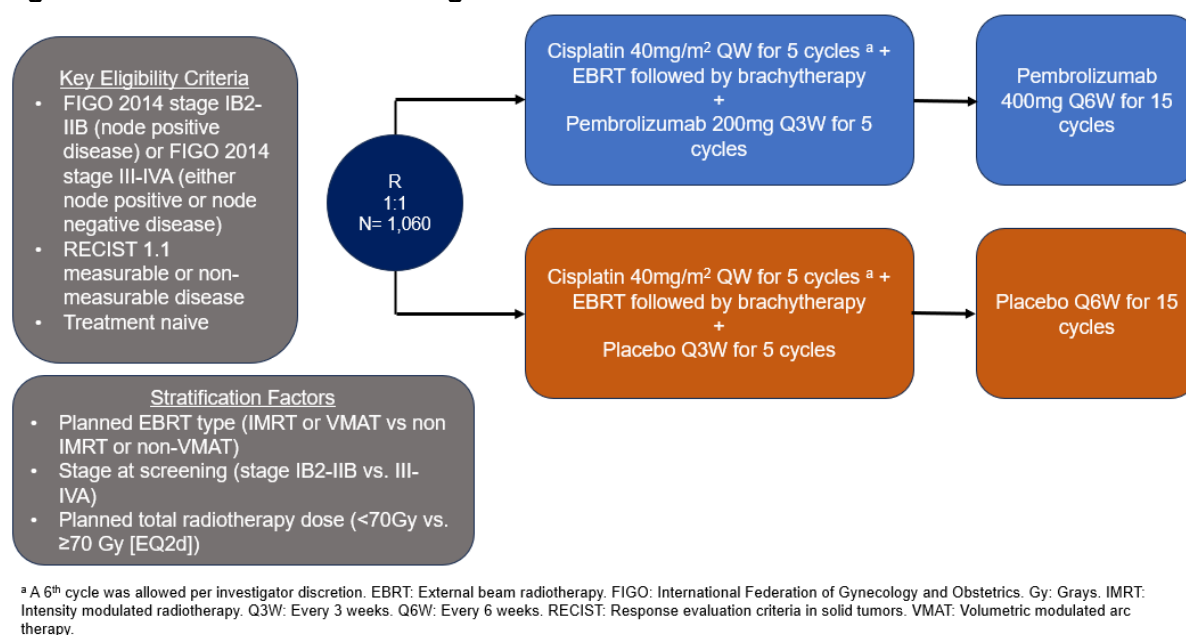
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Summary of the methodology of the KEYNOTE-A18 study

2.3.1 Trial design

KEYNOTE-A18 is an ongoing phase 3 randomized, multicentre, double-blind study. A graphical outline of the trial is given below, Figure 4.

Figure 4: KEYNOTE-A18 trial design



The trial compares pembrolizumab in combination with cisplatin and radiotherapy followed by monotherapy pembrolizumab versus placebo in combination with cisplatin and radiotherapy followed by monotherapy placebo. Participants in the study had either FIGO 2014 stage IB2-IIB (node positive disease) or stage III-IVA (any nodal status) along with being treatment naïve.

2.3.2 Allocation, randomisation, and blinding

Treatment allocation occurred centrally used an integrated interactive voice-response (IRT) system. Participants were assigned randomly in a 1:1 ratio to pembrolizumab plus concurrent chemoradiotherapy (CCRT) or to placebo plus CCRT.

Randomisation was stratified by:

1. Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT.
2. Stage at screening of cervical cancer: FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease).

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3. Planned total radiotherapy dose (EBRT + brachytherapy dose): <70 Gy versus ≥70 Gy [equivalent dose of 2 Gy; EQ2D]).

A double-blinding technique with in-house blinding was used. The participant, the investigator, and Sponsor personnel or delegate(s) who were involved in the study intervention administration or clinical evaluation of the participants were unaware of the intervention assignments. Pembrolizumab and placebo were prepared and/or dispensed by a blinded pharmacist, or other qualified site personnel, so that masking to treatment was maintained.

2.3.3 Eligibility criteria

Key eligibility criteria are provided in Table 5. A full list of eligibility criteria is available in Appendix E.

2.3.4 Settings and locations where the data were collected

KEYNOTE-A18 is a multinational multicentre study that was conducted at 176 centres in 30 countries covering Asia Pacific, Europe, the Middle East and Africa (EMEA), North America and Latin America (Table 6). Six patients from the UK were randomised from two sites, three of these patients are FIGO 2014 stage III-IVA.

Table 6: KEYNOTE-A18 countries with trial sites by region

Asia Pacific	EMEA	North America	Latin America
Australia	Austria	Canada	Brazil
China	Belgium	United States	Chile
Japan	Czech Republic		Colombia
Republic of Korea	France		Guatemala
Taiwan	Germany		Peru
Thailand	Greece		
	Hungary		
	Ireland		
	Israel		
	Italy		
	Norway		
	Russia		
	Spain		
	Sweden		
	Türkiye		
	Ukraine		
	United Kingdom		

2.3.5 Trial drugs and concomitant medications

Treatment doses and periods are presented in Table 7.

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The trial drugs were administered until the maximum number of cycles was reached or one the following: participant request, occurrence of unacceptable adverse events, disease progression, recurrence of malignancy, or interruption of study intervention for more than 12 weeks due to adverse events. Participants who discontinued from study intervention continued to be monitored in the study.

Table 7: KEYNOTE-A18 trial drugs

Component	Treatment	Unit dose strength(s)	Dosage level(s)	Route of administration	Treatment period
Initial phase					
Pembrolizumab	Pembrolizumab	25 mg/mL	200 mg	IV infusion	Day 1 of each 21 day cycle for 5 cycles
Placebo	Normal saline	N/A	N/A	IV infusion	Day 1 of each 21 day cycle for 5 cycles
Chemotherapy	Cisplatin	Variable	40 mg/m ²	IV infusion	Day 1 of each 7 day cycle for 5 infusions ^a
Radiation	EBRT	23–28 fractions (1.8 Gy to 2 Gy per fraction)	45 Gy to 50 Gy ± boost doses	External	40 days
	Brachytherapy	4–6 fractions (5 Gy to 7 Gy per fraction)	25 Gy to 30 Gy	Internal	Total treatment duration should not exceed 50 days ^b with radiotherapy including brachytherapy ^c
Monotherapy phase					
Pembrolizumab	Pembrolizumab	25 mg/mL	400 mg	IV infusion	Day 1 of each 42

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					day cycle for 15 cycles
Placebo	Normal saline	N/A	N/A	IV infusion	Day 1 of each 42 day cycle for 15 cycles
^a An optional sixth infusion may be administered according to local practice ^b With an extension to a maximum of 56 days for unforeseen delays ^c Brachytherapy sessions should be performed immediately after EBRT sessions					

All treatments that the investigator considered necessary for a participant's welfare may have been administered at the discretion of the investigator in keeping with the community standards of medical care. The medicines that were prohibited can be found in Appendix E.

2.3.6 Pre-planned subgroups

To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect for PFS and OS (with a nominal 95% CI) was estimated and plotted by treatment group within each category of the following classification variables:

- Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT.
- Stage at screening of cervical cancer: FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease).
- Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy versus ≥70 Gy (EQ2D).
- Age group (<65 years versus ≥65 years).
- Race (white, non-white).
- ECOG performance status (0, 1).

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above.

2.3.7 Baseline characteristics of trial participants

The demographic and baseline disease characteristics were representative of a patient population with FIGO 2014 stage III-IVA high-risk LACC and were generally balanced between the pembrolizumab plus CCRT and placebo plus CCRT groups.

All participants were female. The majority were white or Asian, not Hispanic or Latino, and had a baseline ECOG PS of 0. The median age was 51 years (range: 22 to 87 years). Out of 601

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participants with known CPS tumour status, 93% of participants had PD-L1 positive tumours (CPS ≥ 1). Most participants had squamous histology at baseline.

Table 8: Baseline characteristics of FIGO 2014 Stage III-IVA participants in KEYNOTE-A18

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	296		305		601	
Sex						
Female	296	100	305	100	601	100
Age (Years)						
< 65					502	83.5
≥ 65					99	16.5
Mean					51.5	
SD					12.3	
Median					51	
Range					22 to 87	
Race						
American Indian Or Alaska Native					41	6.8
Asian					203	33.8
Black Or African American					9	1.5
Multiple					129	21.5
Native Hawaiian Or Other Pacific Islander					2	0.3
White					217	36.1
Ethnicity						
Hispanic Or Latino					230	38.3
Not Hispanic Or Latino					369	61.4
Not Reported					2	0.3
Geographic Region						
Asia Pacific					202	33.6
EMEA					148	24.6
North America					31	5.2
Latin America					220	36.6
Geographic Region 2						
North America					31	5.2
Western Europe					107	17.8
Rest of the World					463	77
Age Group (Years)						
< 65					502	83.5
65 - 74					91	15.1

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75 - 84	■	■	■	■	7	1.2
85+	■	■	■	■	1	0.2
Baseline ECOG						
0	■	■	■	■	406	67.6
1	■	■	■	■	195	32.4
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic	■	■	■	■	425	70.7
No Positive Pelvic nor Para-Aortic	■	■	■	■	176	29.3
Histology Subtype						
Non-squamous	■	■	■	■	99	16.5
Squamous	■	■	■	■	502	83.5
Planned Type of EBRT						
IMRT or VMAT	■	■	■	■	519	86.4
non-IMRT and non-VMAT	■	■	■	■	82	13.6
Planned Total Radiation Therapy Dose per (EQD2)						
< 70 Gy	■	■	■	■	61	10.1
>= 70 Gy	■	■	■	■	540	89.9
PD-L1 Status						
CPS <1	■	■	■	■	34	5.7
CPS >=1	■	■	■	■	559	93
Missing	■	■	■	■	8	1.3
Key: EMEA, Europe, the Middle East and Africa; EBRT, External beam radiotherapy; IMRT, Intensity modulated radiotherapy; VMAT, Volumetric modulated arc therapy.						
Database Cutoff Date: 08JAN2024						
Source: KEYNOTE-A18 IA2 TLF						

2.3.8 Eligibility criteria

The key inclusion criteria for the trial were as follows:

- Had high-risk LACC FIGO 2014 Stage IB2-IIB (with node-positive disease) or Stage III-IVA (either node-positive or node-negative disease).
- Had histologically-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix.
- Had not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents, and was immunotherapy-naïve. Previous surgical procedure for localized cervical tumour was allowed.
- Had an ECOG PS of 0 or 1 within 7 days prior to the first dose of study intervention.

The key exclusion criteria for the trial were as follows:

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- Had a FIGO 2014 Stage IVB disease.
- Had a known additional malignancy that was progressing or had required active treatment within the past 3 years.
- Had a diagnosis of immunodeficiency, received chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication.
- 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, OX40, CD137).
- Had received prior systemic anticancer therapy, including investigational agents, within 4 weeks prior to randomization.

Further eligibility criteria are listed in Table 5.

2.3.9 Outcomes assessed

The key outcomes used in the model are below. The full list of primary and secondary outcomes in KEYNOTE-A18 are listed and defined in Table 9.

Primary outcomes

KEYNOTE-A18 had primary co-primary endpoints of PFS (investigator assessed) and OS.

- PFS investigator (INV) assessed is defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator or per histopathologic confirmation of disease progression (in the absence of radiographic disease progression per RECIST 1.1) or death due to any cause, whichever occurs first.
- OS is defined as time from randomization to death due to any cause.

Other outcomes

The key secondary outcomes used in the economic model are

- Changes to Visual Analog Scale (VAS) assessed using the EQ-5D-5L instrument. In addition, utilities will also be characterized using the EQ-5D-5L instrument.
- Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values and vital signs.

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

2.4.1 Objectives, hypotheses, and endpoints

Table 9: KEYNOTE-A18 study objectives, hypotheses, and endpoints

Objective	Endpoint and definitions
Primary	
1. To evaluate PFS as per RECIST 1.1 assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) as assessed by investigator	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To evaluate OS	OS: The time from randomization to death due to any cause
Secondary	
To evaluate PFS as assessed by BICR	PFS BICR: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To evaluate the proportion of participants that are PFS event-free at 2 years per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)	PFS INV at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
To evaluate the proportion of participants that are PFS event-free at 2 years per RECIST 1.1 as assessed by BICR	PFS BICR at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
To evaluate the proportion of participants are OS event-free at 3 years	OS at 3 years: The proportion of participants that are overall survival event-free at 3 years
To evaluation the proportion of participants that achieve CR at 12 weeks after CCRT per RECIST 1.1 as assessed by investigator and BICR, respectively	CR rate at 12 weeks: Complete response rate at 12 weeks after completion of concurrent chemoradiotherapy
To evaluate the proportion of participants in the analysis population who have an OR, defined as a CR or a PR per RECIST 1.1 as assessed by investigator and BICR, respectively	ORR: Complete response or partial response
To evaluate the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression, by PD-L1 status (by combined positivity score)	PFS INV by PD-L1: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To evaluate the PFS per RECIST 1.1 as assessed by BICR, or death due to any cause, whichever occurs first, by PD-L1 status (by combined positivity score)	PFS BICR by PD-L1: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

To evaluate the time from randomization to death due to any cause, by PD-L1 status (by combined positivity score)	OS by PD-L1: The time from randomization to death due to any cause
To evaluate the time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first	PFS2: The time from the date of randomization until disease progression on next-line treatment or death due to any cause, whichever occurs first
To assess change from baseline score in global quality of life and physical function using the EORTC QLQ-C30 global health status/Quality of Life scale and Physical Function subscale	PRO: EORTC QLQ-C30
To assess change from baseline score in symptom experience using the EORTC Quality of Life Questionnaire (Symptom Score for Cervical Cancer) the EORTC CX24 symptom specific scale	PRO: EORTC QLQ-CX24
To evaluate the safety and tolerability of pembrolizumab in combination with concurrent chemoradiotherapy	AEs and study treatment discontinuation due to adverse events
Relevant exploratory objectives	
To evaluate changes in the Visual Analog Scale and characterize utilities using the European Quality of Life (EQ-5D-5L) instrument	PRO: EQ-5D-5L

2.4.2 Analysis populations

Efficacy analysis population

Analyses of the co-primary endpoints of PFS and OS, and of the secondary clinical efficacy outcomes, are based on the ITT population, which includes all randomized participants, who were analysed in the treatment arm to which they were randomized.

For the results on clinical effectiveness presented in the CS, the modified ITT (mITT) population refers to the subgroup of patients diagnosed with FIGO Stage III-IVA cervical cancer, which is the population relevant to the decision problem, and comprises 601 patients.

Safety analysis population

Analyses of safety data are based on the 'all participants as treated' (APaT) population, which included randomized participants who received at least 1 dose of allocated study treatment. Participants were analysed according to the study intervention they received.

The APaT population for those with FIGO Stage III-IVA cervical cancer comprises 599 participants.

Patient reported outcome analysis population

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The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study medication.

Statistical methods

Table 10: Summary of KEYNOTE-A18 statistical methods

Study design and overview	A Randomized Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer
Treatment assignment and stratification	Approximately 980^a participants will be randomized in a 1:1 ratio between 2 treatment arms: Arm 1: CCRT + pembrolizumab Arm 2: CCRT + placebo Stratification factors are as follows: 1. Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT 2. Stage at screening of cervical cancer FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease) 3. Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy versus ≥70 Gy (EQ2D)
Analysis populations	Efficacy: ITT The analysis population for ORR consists of all randomly assigned participants with measurable disease. Safety: APaT
Primary endpoint	• PFS as assessed by investigator or by histopathologic confirmation of suspected disease progression as assessed by investigator • OS
Key other endpoint	• EQ-5D • Safety and tolerability
Statistical methods for key efficacy analyses	The primary hypotheses will be evaluated by comparing the treatment groups with respect to PFS and OS using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Progression-free survival at 2 years and OS at 3 years will be estimated using the Kaplan-Meier method.
Statistical methods for key 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

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	3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method. (39)
Interim and final analyses	Two IAs and 1 final analysis are planned in this study. Comparisons between 2 treatment arms will be conducted at the IAs and final analysis. Results of the IAs will be reviewed by an external data monitoring committee. Details are provided in Section 9.7. • IA1 (interim analysis for PFS and OS): around 28 months after the first participant is randomized, on completion of enrollment and when approximately 237 PFS events are observed. • IA2 (final analysis for PFS and interim analysis for OS): around 34 months after the first participant is randomized, when approximately 304 PFS events are observed. • Final analysis (final OS analysis): around 42 months after the first participant is randomized, when approximately 240 OS events are observed. Note for IA1, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to an additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. For IA2 and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to an additional 6 months of follow-up, or when the specified number of events is observed, whichever occurs first.
Multiplicity	The overall Type I error rate over the multiple endpoints will be strongly controlled at 2.5% (1-sided) with initially 2.5% allocated to test PFS superiority. No initial alpha is allocated to the OS hypothesis. The graphical approach of Maurer and Bretz will be applied to reallocate alpha among the hypotheses of PFS and OS. In particular, OS can be tested hierarchically following the successful outcome of PFS. (40) Lan-DeMets O'Brien-Fleming group sequential methods will be used to allocate alpha among the interim and final analyses for the PFS and OS endpoints.
Sample size and power	The planned sample size is approximately 980 participants with 490 participants in each arm ^a . The study is event-driven and completes after substantial evidence of efficacy is observed for PFS and/or OS. The PFS hypothesis testing is designed for one-sided $\alpha = 0.025$ and power of 95% to detect an HR of 0.660 with approximately 237 and 304 events between the 2 arms at the planned PFS interim and final analyses. The OS hypothesis testing is designed for one-sided $\alpha = 0.025$ and power of 86% to detect an HR of 0.671 with approximately 132, 182 and 240 events between the 2

	arms at the planned OS interim and final analyses.
^a The planned sample size and the assumptions made to estimate the required sample size are based on the full planned population for KEYNOTE-A18, that is stage IB2 to stage IVA and not the subgroup of patients forming the basis of the company submission. Key: AE, adverse event; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ2D, Equivalent Dose; FA, Final analysis; HR, hazard ratio; Gy, Gray; IA, Interim Analysis; OS, overall survival; PFS, progression-free survival;	

Table 11: Patient flow - FIGO 2014 stage III-IVA participants

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	296		305		601	
Status for Trial						
Discontinued						
Death						
Lost To Follow-Up						
Withdrawal By Subject						
Participants Ongoing						
Status for Study Medication in Trial						
Started						
Completed						
Discontinued						
Adverse Event						
Clinical Progression						
Excluded Medication						
Lost To Follow-Up						
Non-Compliance With Study Drug						
Non-Study Anti-Cancer Therapy						
Physician Decision						
Progressive Disease						
Radiographic Progression						
Withdrawal By Subject						
Participants Ongoing						
If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.						
Database Cutoff Date: 08JAN2024						

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The Cochrane collaboration's risk of bias tool version 2 was used to assess the risk of bias for KEYNOTE-A18. The trial has low risk of bias across the five domains and therefore is assessed to have an overall low risk of bias.

MSD acknowledge that the evidence forming the basis of its submission is taken from a subpopulation of patients from KEYNOTE-A18, and, therefore, analyses of trial outcomes are associated with the recognised limitations of subgroup analyses (e.g., increased risk of Type I and Type II errors). However, MSD note that stage of disease was a stratification factor (IB2-IIB versus III-IVA), which mitigates against potential confounding introduced by the breaking of randomisation in subgroup analyses. Additionally, 601 patients (296 with pembrolizumab plus CCRT versus 305 with placebo with CCRT) inform the analyses, which is sufficiently large to provide robust evidence on clinical effectiveness of adding pembrolizumab to CRT in LACC.

Full details are provided in Appendix B.

2.6 Clinical effectiveness results of the relevant studies

All results are for FIGO stage III-IVA participants, unless otherwise stated.

2.6.1 Primary Endpoints

2.6.1.1 Overall survival

At IA2, KEYNOTE-A18 results showed that pembrolizumab + CCRT was superior to placebo + CCRT with a statistically significant and clinically meaningful improvement in OS in participants with high-risk LACC. A total of 116 OS events were observed at this interim analysis.

The OS HR was 0.57 (95% CI: 0.39, 0.83) in favour of pembrolizumab + CCRT, representing a 43% reduction in the risk of death (Table 12). Median OS has not reached in either group.

The KM curves for OS separated at approximately 10.5 months and remained separated over the follow-up period in favour of pembrolizumab + CCRT (Figure 5).

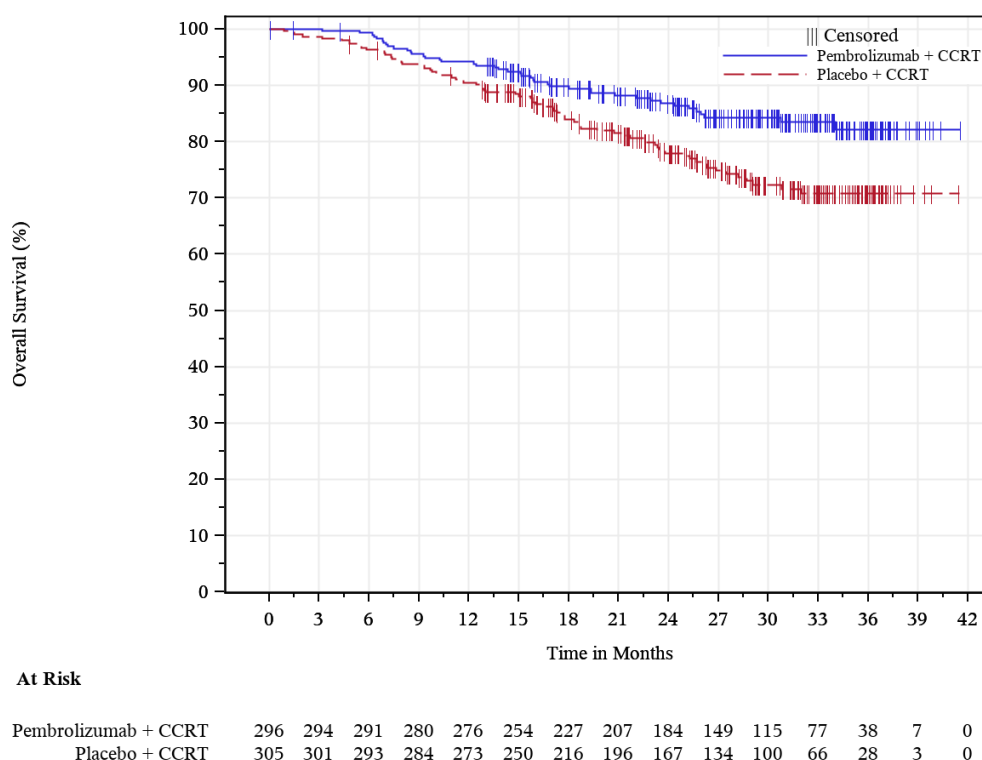
Table 12: Analysis of Overall Survival (ITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)	43 (14.5)	73 (23.9)
Kaplan–Meier Estimates (months) ^a Median (95% CI)	NR (NR, NR)	NR (NR, NR)

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Hazard Ratio (95% CI) ^b	0.57 (0.39, 0.83)	
p-value ^c	████	
OS Rate at month 6 (%) (95% CI)	████	████
OS Rate at month 12 (%) (95% CI)	████	████
OS Rate at month 18 (%) (95% CI)	████	████
OS Rate at month 24 (%) (95% CI)	████	████
OS Rate at month 30 (%) (95% CI)	████	████
OS Rate at month 36 (%) (95% CI)	████	████
^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. ^c One-sided p-value based on log-rank test. Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; OS, overall survival. Database Cutoff Date: 08JAN2024		

Figure 5: Kaplan–Meier Estimates of Overall Survival (mITT Population)



2.6.1.2 Progression Free Survival per RECIST assessed by Investigator Assessment

The PFS HR was 0.57 (95% CI:0.43, 0.76) in favour of pembrolizumab + CCRT, representing a 43% reduction in the risk of progression (Table 13).

PFS was not statistically tested at IA2 as at IA1 results showed a statistically significant and clinically meaningful improvement in PFS for all patients within the study (Stage IB2 to IVA) (IA1 HR of 0.70 [95% CI: 0.55, 0.89]).

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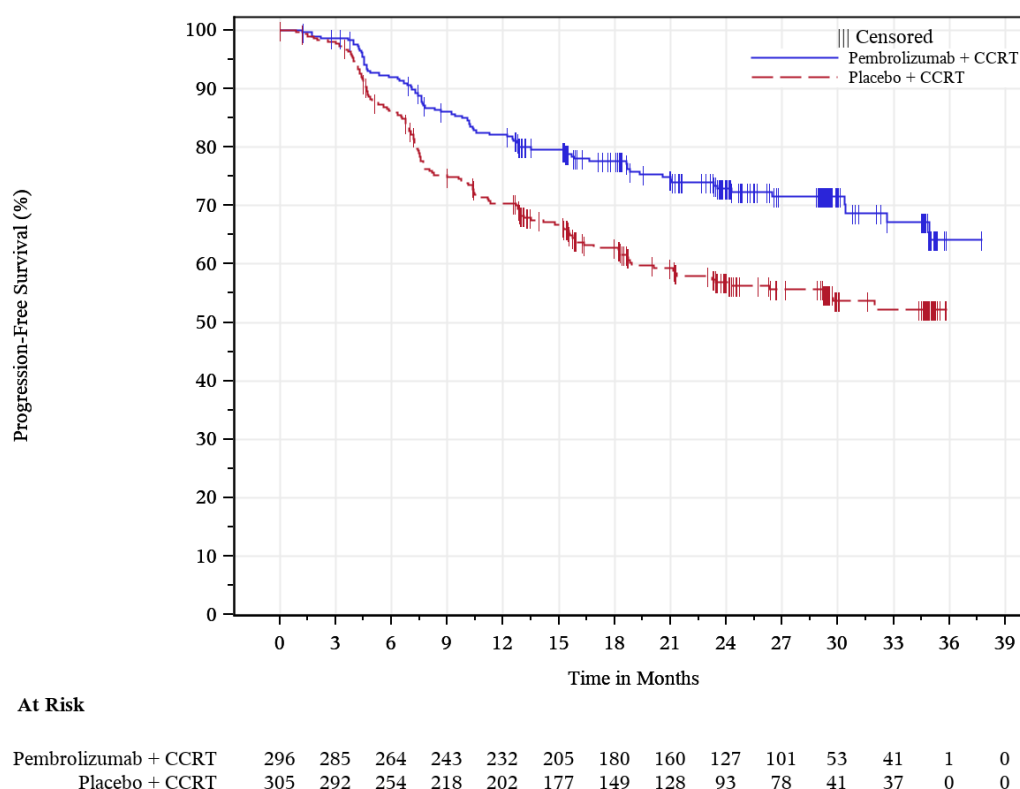
Median PFS had not been reached in either group. PFS rates were higher in the pembrolizumab + CCRT group compared with the placebo + CCRT after 6 months.

The KM curves for PFS separated early at approximately 3 months and remained separated over the follow-up period in favour of pembrolizumab + CCRT (Figure 6).

Table 13: Analysis of Progression Free Survival (Primary Censoring Rule) Based on Investigator Assessment (mITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)	79 (26.7)	125 (41.0)
Kaplan–Meier Estimates (months) ^a Median (95% CI)	NR (NR, NR)	NR (26.3, NR)
Hazard Ratio (95% CI) ^b	0.57 (0.43, 0.76)	
p-value ^c		
PFS Rate at month 6 (%) (95% CI)		
PFS Rate at month 12 (%) (95% CI)		
PFS Rate at month 18 (%) (95% CI)		
PFS Rate at month 24 (%) (95% CI)		
PFS Rate at month 30 (%) (95% CI)		
PFS Rate at month 36 (%) (95% CI)		
^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. ^c One-sided p-value based on log-rank test. Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; PFS, progression-free survival. Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) Database Cutoff Date: 08JAN2024		

Figure 6: Kaplan–Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (mITT Population)



2.6.2 Key Secondary Endpoints

2.6.2.1 Objective Response Rate per RECIST as assessed by investigator

In participants with measurable disease at baseline, the point estimate of ORR per RECIST 1.1 by investigator assessment was █% in the pembrolizumab + CCRT group compared with █% in the placebo + CCRT group (Table 14). The treatment difference was █.

Table 14: Analysis of Objective Response Based on investigator assessment per RECIST 1.1 (Participants With Measurable Disease at Baseline)

NR (Participants With Measurable Disease at Baseline)		
	Pembrolizumab + CCRT (n = 292)	Placebo + CCRT (n = 300)
Number of objective responses	██████████	██████████
ORR, % (95% CI)	██████████	██████████
Difference (pembrolizumab + CCRT versus placebo + CCRT), %		
Estimate (95% CI) ^a	██████████	
Nominal p-value ^b	██████████	
^a Based on unstratified Miettinen & Nurminen method. ^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; ORR, objective response rate. Database Cutoff Date: 08JAN2024		

Table 15: Summary of Best Objective Response based on Investigator Assessment per RECIST 1.1 (Participants with measurable disease at baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	%	95% CI ^a	n	%	95% CI ^a
Number of Participant in Population	292			300		
Complete Response (CR)	■	■	■	■	■	■
Partial Response (PR)	■	■	■	■	■	■
Overall Response (CR+PR)	■	■	■	■	■	■
Stable Disease (SD)	■	■	■	■	■	■
Disease Control (CR+PR+SD)	■	■	■	■	■	■
Progressive Disease (PD)	■	■	■	■	■	■
Not Evaluable (NE)	■	■	■	■	■	■
No Assessment	■	■	■	■	■	■
^a Based on binomial exact confidence interval method. Investigator assessed responses per RECIST 1.1 are included in this table. Database Cutoff Date: 08JAN2024.						

2.6.2.2 Progression Free Survival after next line treatment (PFS2)

Analysis of PFS after next-line treatment following discontinuation of study treatment administration (PFS2) showed ■, representing a ■ in the risk of disease progression or death (Table 16 and Figure 7). ■.

Table 16: Analysis of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (mITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)	■	■
Kaplan–Meier Estimates (months) ^a Median (95% CI)	■	■
vs Placebo + CCRT	■	■
Hazard Ratio (95% CI) ^b	■	■
p-value ^c	■	■
^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. ^c One-sided p-value based on log-rank test Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached. Database Cutoff Date: 08JAN2024		

Figure 7: Kaplan–Meier Estimates of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (mITT Population)

■

2.6.2.3 Patient Reported Outcomes

EQ-5D

The compliance rate of the EQ-5D-5L was above █% at baseline and similar in both the pembrolizumab + CCRT and placebo + CCRT groups (█) and remained high at week 36 (█; Table 17 and Figure 8).

EQ-5D-5L analyses showed █ between participants treated with pembrolizumab + CCRT compared with placebo + CCRT.

Results for EORTC QLQ-C30 and QLQ-CX24 are presented in Appendix E.

Table 17: Analysis of Change from Baseline in EQ-5D-5L VAS Score to Week 36 FAS population

	Baseline		Week 36		Change from Baseline to Week 36	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab + CCRT	█	█	█	█	█	█
Placebo + CCRT	█	█	█	█	█	█
Pairwise Comparison					Difference in LS Means ^a	p-Value ^a
					(95% CI)	
Pembrolizumab + CCRT vs. Placebo + CCRT					█	█
^a Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction. For baseline and Week 36, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group. Database Cutoff Date: 08JAN2024						

Figure 8: Line Plot of Empirical Mean Change from Baseline and 95% CI for the EQ-5D-5L Over Time by Treatment Group FAS population



2.7 Subsequent oncologic treatments used in KEYNOTE-A18

The percentage of patients who had received at least 1 subsequent oncologic therapy was higher in the placebo + CCRT group compared with the pembrolizumab + CCRT group (█). This is most likely a product of fewer number of patients who have progressed in the pembrolizumab + CCRT group.

The most frequently reported subsequent oncological therapy (≥5% of participants in both groups) included █ (Table 18).

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Not all of the subsequent treatments reported in KEYNOTE-A18 are available for use or licensed in England for the treatment of cervical cancer. The cost effectiveness modelling results in section 3 take into account those available in English clinical practice.

Table 18: Subsequent oncologic therapies APaT

	Pembrolizumab + CCRT (n=70) n (%)	Placebo + CCRT (n=111) n (%)
Participants who did not receive subsequent oncologic therapies	■	■
Participants who died	■	■
Participants who are alive	■	■
Participants who received subsequent oncologic therapies	■	■
1st subsequent line	■	■
carboplatin + paclitaxel	■	■
bevacizumab + carboplatin + paclitaxel	■	■
cisplatin + paclitaxel	■	■
bevacizumab + carboplatin + paclitaxel + pembrolizumab	■	■
bevacizumab + cisplatin + paclitaxel	■	■
carboplatin + paclitaxel + pembrolizumab	■	■
cisplatin	■	■
paclitaxel	■	■
paclitaxel nanoparticle albumin-bound	■	■
bevacizumab + carboplatin + cisplatin + paclitaxel	■	■
bevacizumab + carboplatin + paclitaxel nanoparticle albumin-bound	■	■
pembrolizumab	■	■
bevacizumab + cadonilimab + capecitabine + catequentinib + cisplatin + paclitaxel	■	■
bevacizumab + cisplatin + paclitaxel + paclitaxel nanoparticle albumin-bound	■	■
bevacizumab + cisplatin + paclitaxel + pembrolizumab	■	■
bevacizumab + denosumab + paclitaxel + topotecan	■	■
bevacizumab + paclitaxel + pembrolizumab + topotecan	■	■
bevacizumab + paclitaxel nanoparticle albumin-bound	■	■
bevacizumab + zimberelimab	■	■
cadonilimab	■	■

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carboplatin	■	■
carboplatin + catequentinib + docetaxel	■	■
carboplatin + gemcitabine + paclitaxel + pembrolizumab	■	■
carboplatin + paclitaxel + paclitaxel nanoparticle albumin-bound	■	■
carboplatin + paclitaxel nanoparticle albumin-bound	■	■
cisplatin + gemcitabine + paclitaxel	■	■
cisplatin + paclitaxel + zoledronic acid	■	■
cisplatin + paclitaxel nanoparticle albumin-bound	■	■
cyclophosphamide + doxorubicin + vincristine	■	■
paclitaxel + topotecan	■	■
2nd subsequent line	■	■
bevacizumab + carboplatin + paclitaxel	■	■
bevacizumab	■	■
bevacizumab + cisplatin + paclitaxel	■	■
bevacizumab + paclitaxel	■	■
bevacizumab + pembrolizumab	■	■
gemcitabine	■	■
topotecan	■	■
carboplatin + paclitaxel + pembrolizumab	■	■
cadonilimab	■	■
carboplatin + paclitaxel	■	■
cemiplimab	■	■
cisplatin + gemcitabine	■	■
cisplatin + paclitaxel	■	■
doxorubicin	■	■
gemcitabine + pemetrexed	■	■
marsdenia tenacissima stem	■	■
paclitaxel nanoparticle albumin-bound + zimberelimab	■	■
pembrolizumab	■	■
tisotumab vedotin	■	■
vinorelbine	■	■
3rd subsequent line	■	■
angelica sinensis + paeonia lactiflora + poria cocos + rehmannia glutinosa + reynoutria multiflora	■	■
bevacizumab + carboplatin + paclitaxel	■	■

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bevacizumab + cisplatin + paclitaxel + pembrolizumab	■	■
cisplatin + gemcitabine	■	■
irinotecan	■	■
pembrolizumab	■	■
cemiplimab	■	■
4th subsequent line	■	■
bevacizumab + carboplatin	■	■
5th subsequent line	■	■
doxorubicin	■	■
Number of participants: all-participants-as-treated population Every participant is counted once for each applicable row and column. Percentages are based on the number of participants who progressed based on Investigator Review. If a treatment reflects a combination of regimens, the duration is derived using the first initiation date of any treatment within the regimen and the last date at which any treatment within the regimen is observed. To be included in this summary, start date of individual component must be on or after date of progression based on Investigator Review. Database Cutoff Date: 08JAN2024		

2.8 Subgroup analysis

The treatment benefit in OS and PFS for pembrolizumab + CCRT across all prespecified subgroups was generally consistent with the overall ITT population, noting that data in the subgroups with small sample sizes and events should be interpreted with caution (Figure 9 and Figure 10).

Figure 9: Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT Population)



Figure 10: Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment (Primary Censoring Rule) (ITT Population)



2.9 Evidence synthesis

Based on the SLR results, there is only one phase III randomised, controlled trial evaluating pembrolizumab with CCRT versus the relevant comparator in our specific population of interest (patients with FIGO stage III-IVA LACC): KEYNOTE-A18. (38, 41) Therefore, it was not possible to conduct a pairwise meta-analysis.

The decision problem (Table 1) indicates the comparator of interest to the Technology Appraisal to be CCRT. MSD consider that the CCRT regimen administered in the experimental

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and control arms of KEYNOTE-A18 reflects the standard of care in UK clinical practice, as recommended in the BGCS guidelines, and that the estimates of comparative clinical effectiveness derived from KEYNOTE-A18 provide the best source of evidence on the efficacy of pembrolizumab in FIGO stage III-IVA LACC.

However, for completeness, MSD have assessed the generalisability of studies evaluating other combinations of chemotherapy and radiotherapy, with a focus on those involving CCRT in combination with either induction and/or consolidation chemotherapy, together with the feasibility of comparing such interventions through an indirect treatment comparison (ITC) via the control arm of KEYNOTE-A18. After assessing the relevant studies, MSD concluded that an ITC was not feasible and any ITC carried out would be associated with severe limitations, as discussed below in more detail. Full details of the methods and descriptions of the included studies are available in the Appendices, section B.1.2.4.

In brief, 19 records pertaining to six unique clinical trials were identified that matched the PICOTS study selection criteria. Four of the six eligible trials were phase III studies (Table 19). KEYNOTE-A18 was the only double-blinded RCT. CIRCE, INTERLACE and OUTBACK were open-label in design, while one study (ACTLACC) was single-blinded, and level of masking was not reported in one study (Tang 2012). The number of randomized patients ranged from 107 in the CIRCE trial to 1,060 in KEYNOTE-A18 (Table 19). Three of the six studies — CIRCE, INTERLACE and Tang 2012 — compared the efficacy of neoadjuvant chemotherapy plus CCRT to CCRT alone. INTERLACE and Tang 2012 evaluated the effectiveness of neoadjuvant carboplatin plus paclitaxel, whereas CIRCE utilized cisplatin combined with gemcitabine. ACTLACC and OUTBACK compared CCRT with adjuvant carboplatin plus paclitaxel versus without adjuvant carboplatin plus paclitaxel. KEYNOTE-A18 was the only study that assessed CCRT plus an immune checkpoint inhibitor. The cisplatin dose across all the trials was 40 mg/m² administered weekly for 3–6 cycles.

In assessing the feasibility of carrying out an ITC (discussed in more detail in Appendix B, Section B.1.2.4), two important sources of clinical heterogeneity were identified — subgroup analysis of the populations enrolled across the trials and the types of EBRT administered in the control arm that would form the common node in a potential network of evidence.

None of the studies was conducted exclusively in patients with FIGO stage III-IVA cervical cancer but four studies evaluated efficacy within the relevant subpopulation — ACTLACC, INTERLACE, KEYNOTE-A18 and OUTBACK. However, ACTLACC did not present data in a format that could be utilised in an ITC (HRs and 95% CIs were not reported and Kaplan–Meier [KM] curves were not available). As CIRCE and Tang 2012 did not present results for FIGO stage III-IVA subgroup, MSD deemed it would not be appropriate to include the studies in a Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

ITC. Baseline characteristics for patients with FIGO 2014 stage III-IVA LACC are available for only KEYNOTE-A18.

MSD appraised the information and data presented in the full-text publications of INTERLACE and OUTBACK to ascertain whether it would be feasible to include the subgroup data in an ITC to derive comparative estimates of effect for pembrolizumab plus CCRT versus CCRT with either induction or consolidation chemotherapy. MSD consider it important to note that FIGO stage III-IVA LACC patients comprise a minority of the population enrolled into each of these studies (13.8% for INTERLACE versus 23.9% for OUTBACK) so numbers would be comparatively small. Additionally, neither of the studies reported a statistically significant treatment effect in the FIGO stage III-IVA subgroup for either PFS or OS. It is unclear whether the treatment modalities in the experimental arm would be considered appropriate for the subpopulation, given no treatment effect was observed in these small subgroups in either study.

It should also be noted that both INTERLACE and OUTBACK excluded some patients with evidence of disease in the lymph nodes of the pelvis or para-aortic region: INTERLACE excluded those with FIGO 2008 stage IIIA disease and presence of para-aortic nodes, whereas those with para-aortic nodal involvement above the level of the common iliac nodes or above L3/L4 were not eligible for enrolment in OUTBACK. Presence of cancerous cells in the lymph nodes is associated with a more severe form of disease and a worse prognosis and may be a treatment effect modifier. Of the ITT population of KEYNOTE-A18, 83% had any nodal involvement, which is markedly larger than reported for either INTERLACE or OUTBACK, of which 43% and ~50% of enrolled patients, respectively, were identified as having disease present in lymph nodes. The proportion of patients with lymph node involvement in the subgroups with FIGO stage III-IVA disease is not known for the analyses of clinical outcomes reported by INTERLACE and OUTBACK. Additionally, because baseline characteristics are not available for the subgroup of FIGO stage III-IVA LACC from INTERLACE or OUTBACK, it is unclear whether there may be imbalances between treatment groups in other prognostic factors that were not stratification factors. Given the disparity in proportion of patients with nodal involvement across the studies, and uncertainty about potential imbalances in characteristics across treatment groups in the other RCTs, MSD consider that the results of an ITC would be uncertain and the extent and direction of bias is difficult to quantify.

It is important to note that many of the studies meeting the eligibility criteria recruited patients over a lengthy period of time. KEYNOTE-A18 recruited patients between 2020 and 2022, whereas OUTBACK enrolled patients over a 6-year period (2011 to 2017) and INTERLACE

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10 years (2012 to 2022). Assessment of the studies identified considerable disparity in the radiotherapy regimens applied in the CCRT alone arm across the trials that MSD consider precludes carrying out an ITC. During the past decade, there have been considerable advances in radiation techniques implemented in the management of LACC. (42) Initially, there was a shift from using a two-dimensional (2D) approach based on anatomical bony landmarks for delivery of EBRT and brachytherapy to sophisticated image-guided three-dimensional (3D) techniques. Image-guided 3D procedures, such as IMRT and VMAT (types of EBRT), are highly precise techniques that conform the radiation dose to the unique size, shape and position of the tumour, with the goal of delivering doses more precisely to the target area, thus minimising the risk of radiating healthy organs and tissues.

IMRT and VMAT have been adopted as the standard of care for EBRT for LACC in UK clinical practice, and planned use of IMRT or VMAT was a stratification factor in KEYNOTE-A18. The baseline characteristics of the subgroup of patients with FIGO stage III-IVA LACC indicate that 88.6% of patients comprised the category of planned IMRT or VMAT. By contrast, in INTERLACE, only 40% of full trial population was treated with IMRT. Similarly, the OUTBACK trial employed 4-field radiation therapy, with a stipulation that IMRT was not allowed.

MSD consider the marked differences across the trials in the types of EBRT used to be too varied to generate a sufficiently homogeneous network through the control (CCRT alone) arm of the included studies. There are limited overlaps in the populations between the studies and results of, and heterogeneity between, overlapping subgroups is a concern. Results derived from an ITC would be too uncertain to draw conclusions on the comparative effectiveness of pembrolizumab plus CCRT versus other forms of CCRT in the relevant patient population, that is, FIGO stage III-IVA LACC. Moreover, MSD consider that the high planned use of IMRT and VMAT in KEYNOTE-A18 signify that, of the included studies, the control arm most closely aligns with current UK clinical practice for FIGO stage III-IVA LACC and maintain that results from KEYNOTE-A18 are the most robust source of evidence on the clinical effectiveness of pembrolizumab plus CCRT.

Table 19. Summary of trial methodology

Trial identifier	Principal publication	Secondary publications	Trial design	N	Intervention	Comparison	Locations	Pre-planned subgroups	Key limitations precluding inclusion in ITC
ACTLACC (NCT02036164)	Tangjitgamol et al., 2019 (43)	Tovanabutra et al., 2021 (44)	Phase III, single-blinded, RCT	259	Cisplatin + radiotherapy	Cisplatin + radiotherapy + adjuvant chemotherapy (carboplatin + paclitaxel)	Thailand	Age, stage, histology, and duration of radiation therapy	Data not presented in a format that could be used in ITC Substantial difference in EBRT implemented in trial versus KEYNOTE-A18 FIGO Stage III-IVA forms a small proportion of trial population
CIRCE (NCT01973101)	Da Costa et al., 2019 (45)	Nunes De Arruda et al., 2020 (46)	Phase II, open-label, RCT	107	Neoadjuvant chemotherapy (cisplatin + gemcitabine) + cisplatin + radiotherapy	Cisplatin + radiotherapy	Brazil	--	Subgroup analysis in FIGO stage III-IVA not reported
INTERLACE (NCT01566240)	McCormack et al., 2024 (47)	McCormack et al., 2023 (48) Ledermann et al., 2024 (49) Eminowicz et al., 2024 (50)	Phase III, open-label, RCT	500	Cisplatin + radiotherapy	Carboplatin + paclitaxel (followed by cisplatin + radiotherapy)	Brazil, India, Italy, Mexico, UK	FIGO stage, tumour volume, nodes involvement	Substantial difference in EBRT implemented in trial versus KEYNOTE-A18

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								histology, age and recruiting site	FIGO Stage III-IVA forms a small proportion of trial population
KEYNOTE-A18 (NCT04221945)	Lorusso et al. 2024 (41)	Lorusso et al., 2024 (51) Duska et al., 2024 (52) Lorusso et al., 2024 (53) Lorusso et al., 2023 (54) Randall et al., 2024 (55) Xiang et al., 2024 (56) KEYNOTE- A18 HTA report, KEYNOTE- A18 CSR	Phase III, double- blind, RCT	1060	Pembrolizuma b + cisplatin + radiotherapy	Placebo + cisplatin + radiotherapy	Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Greece, Guatemala, Hungary, Ireland, Israel, Italy, Japan, South Korea, Norway, Peru, Russia, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, USA	Age, race, ECOG score, EBRT, FIGO stage, planned radiotherapy dose	N/A
OUTBACK (NCT0141460,8 ACTRN1261000 0732088)	Mileshkin et al., 2023 (57)	--	Phase III, open- label, RCT	157	Cisplatin + radiotherapy	Cisplatin + radiotherapy + adjuvant chemotherapy	Australia, China, Canada, New Zealand,	Nodal involvement, EBRT, FIGO stage, age, country,	Substantial difference in EBRT implemented in trial versus

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						(carboplatin + paclitaxel)	Saudi Arabia, Singapore, USA	smoking status, histology	KEYNOTE-A18 FIGO stage III-IVA forms a small proportion of trial population
Tang 2012	Tang et al., 2012 (58)	--	--	880	Cisplatin + radiotherapy	Neoadjuvant chemotherapy (cisplatin + paclitaxel) + cisplatin + radiotherapy + consolidation chemotherapy (cisplatin + paclitaxel)	China	--	Subgroup analysis in FIGO stage III-IVA not reported
Notes: Double dash indicates that the data are not reported. Key: BICR, blinded independent central review; CR, complete response; CSR, clinical study report; HTA, health technology assessment; IA, investigator assessed; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; UK, United Kingdom; USA, United States of America.									

2.10 Adverse Events

The safety profile of pembrolizumab + CCRT at IA2 was generally consistent with well-established safety profiles of a cisplatin-based chemoradiotherapy regimen and of pembrolizumab monotherapy.

The observed safety profile of pembrolizumab + CCRT was generally similar compared with placebo + CCRT. The incidences of participants with AEs leading to death and with AEs leading to discontinuation of study intervention were similar between the 2 treatment groups.

2.10.1 Extent of exposure

At the second interim analysis data cut off (8th January 2024), the median duration on therapy was higher in the pembrolizumab + CCRT group compared with the placebo + CCRT group (■■■ months vs ■■■ months) (Table 20).

More patients in the pembrolizumab + CCRT arm completed ≥12 months of treatment compared with placebo + CCRT (Table 21).

Table 20: Summary of drug exposure APaT

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=295)	(N=304)
Duration on Therapy (Months)		
n	295	304
Mean (SD)	■■■	■■■
Median	■■■	■■■
Range	■■■	■■■
Number of Cycles		
n	295	304
Mean (SD)	■■■	■■■
Median	■■■	■■■
Range	■■■	■■■
Number of cycles of Pembro/Placebo refer to Q3W cycles from C1 to C5 and Q6W from C6 onward. Database Cutoff Date: 08JAN2024		

Table 21: Exposure by duration APaT

	Pembrolizumab + CCRT			Placebo + CCRT		
	(N=295)			(N=304)		
	n	(%)	Person-months	n	(%)	Person-months
Duration of Exposure						
>0 m	■■■	■■■	■■■	■■■	■■■	■■■

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≥1 m	■	■	■	■	■	■
≥3 m	■	■	■	■	■	■
≥6 m	■	■	■	■	■	■
≥12 m	■	■	■	■	■	■
≥18 m	■	■	■	■	■	■
≥24 m	■	■	■	■	■	■
Each participant is counted once on each applicable duration category row.						
Duration of exposure is the time from the first dose date to the last dose date.						
Database Cutoff Date: 08JAN2024						

2.10.2 Summary of adverse events

The overall incidence of participants with AEs was similar in the pembrolizumab + CCRT group and the placebo + CCRT group (Table 22). Differences were observed in the AE categories of grade 3-5, grade 3-5 drug related, serious drug related and discontinuation of any drug.

Table 22: Adverse Event Summary APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events	■	■	■	■
with no adverse event	■	■	■	■
with drug-related adverse events	■	■	■	■
with toxicity grade 3-5 adverse events	■	■	■	■
with toxicity grade 3-5 drug-related adverse events	■	■	■	■
with serious adverse events	■	■	■	■
with serious drug-related adverse events	■	■	■	■
who died	■	■	■	■
who died due to a drug-related adverse event	■	■	■	■
discontinued any drug due to an adverse event	■	■	■	■
discontinued PEMBROLIZUMAB/ PLACEBO	■	■	■	■
discontinued CISPLATIN	■	■	■	■
discontinued EBRT	■	■	■	■
discontinued BRACHYTHERAPY	■	■	■	■
discontinued All Drugs	■	■	■	■
discontinued any drug due to a drug-related adverse event	■	■	■	■
discontinued PEMBROLIZUMAB/PLACEBO	■	■	■	■
discontinued CISPLATIN	■	■	■	■
discontinued EBRT	■	■	■	■
discontinued BRACHYTHERAPY	■	■	■	■

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discontinued All Drugs	████	████	████	████
discontinued any drug due to a serious adverse event	████	████	████	████
discontinued PEMBROLIZUMAB/ PLACEBO	████	████	████	████
discontinued CISPLATIN	████	████	████	████
discontinued EBRT	████	████	████	████
discontinued BRACHYTHERAPY	████	████	████	████
discontinued All Drugs	████	████	████	████
discontinued any drug due to a serious drug-related adverse event	████	████	████	████
discontinued PEMBROLIZUMAB/ PLACEBO	████	████	████	████
discontinued CISPLATIN	████	████	████	████
discontinued EBRT	████	████	████	████
discontinued BRACHYTHERAPY	████	████	████	████
Discontinued All Drugs	████	████	████	████
^a Determined by the investigator to be related to the drug. Grades are based on NCI CTCAE version 5.0. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 08JAN2024				

2.10.3 Most frequently reported adverse events

The types and severity of the most frequently reported AEs (incidence $\geq 10\%$) were generally similar in both intervention groups (████ in the pembrolizumab + CCRT group, █████% in the placebo + CCRT group). The three most frequently reported AEs in both treatment groups were █████, which are events commonly associated with chemoradiotherapy.

Frequently reported AEs (incidence $\geq 10\%$) with a greater risk difference for pembrolizumab plus CCRT (i.e., the lower bound of the 95% CI for the treatment difference is >0) were █████. These events were primarily Grade 1 or 2 in severity, and most did not result in discontinuation of study intervention. █████ are well-established immune-related AEs associated with pembrolizumab.

There were no frequently reported AEs (incidence $\geq 10\%$) with a greater risk difference for placebo plus CCRT.

Table 23: Adverse events $\geq 10\%$ APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population				
with one or more adverse events	████	████	████	████

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with no adverse events				
Anaemia				
Nausea				
Diarrhoea				
White blood cell count decreased				
Neutrophil count decreased				
Vomiting				
Urinary tract infection				
Platelet count decreased				
Hypomagnesaemia				
Hypokalaemia				
Hypothyroidism				
Alanine aminotransferase increased				
Constipation				
Aspartate aminotransferase increased				
Neutropenia				
Weight decreased				
Decreased appetite				
Fatigue				
Leukopenia				
Lymphocyte count decreased				
Blood creatinine increased				
Pyrexia				
Abdominal pain				
Hyperthyroidism				
Hyponatraemia				
Dysuria				
Thrombocytopenia				
Pelvic pain				
Back pain				
COVID-19				
Hyperglycaemia				
Asthenia				
Arthralgia				
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 08JAN2024				

2.10.4 Grade 3 to 5 adverse events

The Grade 3 to 5 AEs observed for participants treated with pembrolizumab + CCRT were generally consistent with the well-established safety profiles of pembrolizumab monotherapy and a cisplatin-based chemoradiotherapy regimen. There were no specific trends noted that suggest any new safety concerns.

The overall incidence of participants with Grade 3 to 5 AEs was higher in the pembrolizumab + CCRT group compared with the placebo + CCRT group (████) (Table 24).

Table 24: Grade 3-5 Adverse events ≥1% APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more grade 3-5 adverse events	████	████	████	████
with no adverse events	████	████	████	████
Anaemia	████	████	████	████
White blood cell count decreased	████	████	████	████
Neutrophil count decreased	████	████	████	████
Lymphocyte count decreased	████	████	████	████
Neutropenia	████	████	████	████
Lymphopenia	████	████	████	████
Leukopenia	████	████	████	████
Hypokalaemia	████	████	████	████
Platelet count decreased	████	████	████	████
Diarrhoea	████	████	████	████
Urinary tract infection	████	████	████	████
Hypertension	████	████	████	████
Hypomagnesaemia	████	████	████	████
Weight decreased	████	████	████	████
Alanine aminotransferase increased	████	████	████	████
Hydronephrosis	████	████	████	████
Sepsis	████	████	████	████
Thrombocytopenia	████	████	████	████
Hypocalcaemia	████	████	████	████
Hyponatraemia	████	████	████	████
Acute kidney injury	████	████	████	████
Febrile neutropenia	████	████	████	████
Pleural effusion	████	████	████	████
Pyelonephritis	████	████	████	████
Urosepsis	████	████	████	████
Abdominal pain	████	████	████	████

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Aspartate aminotransferase increased				
Pelvic pain				
Radiation proctitis				
Urogenital fistula				
Vomiting				
Myelosuppression				
Vaginal haemorrhage				
Appendicitis				
COVID-19				
Nausea				
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 5.0. Database Cutoff Date: 08JAN2024				

2.10.5 Deaths due to adverse events

The number and incidence of participants with AEs or drug-related AEs resulting in death were similar in the pembrolizumab + CCRT and placebo + CCRT groups.

Table 25: Participants With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events				
with no adverse events				
Large intestine perforation				
Sepsis				
Urosepsis				
Vaginal haemorrhage				
Acute myocardial infarction				
Bone marrow failure				
Completed suicide				
Death				
Neutropenic colitis				
Every participant is counted a single time for each applicable row and column. Serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 08JAN2024				

2.10.6 Adverse events of special interest

A larger proportion of patients receiving pembrolizumab + CCRT experienced an adverse event of special interest (AEOSI) compared with placebo + CCRT, ████% versus ████% respectively; Table 26). Hypothyroidism and hyperthyroidism were the most common AEOSI in the pembrolizumab + CCRT arm.

**Table 26: Participants With AEOSI (Incidence > 0% in One or More Treatment Groups)
(All-Participants-as-Treated Population)**

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events	████	████	████	████
with no adverse events	████	████	████	████
	████	████	████	████
Hypothyroidism	████	████	████	████
Hyperthyroidism	████	████	████	████
Gastritis	████	████	████	████
Colitis	████	████	████	████
Pneumonitis	████	████	████	████
Hypersensitivity	████	████	████	████
Autoimmune thyroiditis	████	████	████	████
Drug hypersensitivity	████	████	████	████
Enterocolitis	████	████	████	████
Erythema multiforme	████	████	████	████
Infusion related reaction	████	████	████	████
Dermatitis bullous	████	████	████	████
Nephritis	████	████	████	████
Pancreatitis	████	████	████	████
Thyroiditis	████	████	████	████
Autoimmune colitis	████	████	████	████
Autoimmune hepatitis	████	████	████	████
Autoimmune hypothyroidism	████	████	████	████
Autoimmune nephritis	████	████	████	████
Diabetic ketoacidosis	████	████	████	████
Encephalitis	████	████	████	████
Gastritis erosive	████	████	████	████
Graves' disease	████	████	████	████
Guillain-Barre syndrome	████	████	████	████
Haemolytic anaemia	████	████	████	████
Immune-mediated thyroiditis	████	████	████	████
Interstitial lung disease	████	████	████	████
Myocarditis	████	████	████	████

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Nephrotic syndrome	■	■	■	■
Sarcoidosis	■	■	■	■
Secondary adrenocortical insufficiency	■	■	■	■
Silent thyroiditis	■	■	■	■
Thyroid disorder	■	■	■	■
Type 1 diabetes mellitus	■	■	■	■
Uveitis	■	■	■	■
Vasculitis	■	■	■	■
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Database Cutoff Date: 08JAN2024				

2.11 Ongoing studies

The pivotal trial for this indication, KEYNOTE-A18, is ongoing and the final analysis database lock is expected to take place in ■. It is expected to provide ■ months of additional follow up. Results for this analysis are expected to be available in ■.

2.12 Interpretation of clinical effectiveness and safety evidence

2.12.1 Summary

For the subgroup of patients with LACC, KEYNOTE-A18 demonstrated clinically meaningful improvements across both of its primary endpoints of OS (HR 0.57 [95% CI 0.39, 0.83]) and PFS (HR 0.57 [95% CI 0.43, 0.76]), as well as key secondary endpoints of ORR where a continued improvement with durable responses was also observed.

The results from the IA2 of KEYNOTE-A18 provide evidence that treatment with pembrolizumab + CCRT is superior to CCRT alone for patients with FIGO 2014 stage III-IVA locally advanced cervical cancer. Pembrolizumab + CCRT has a generally acceptable safety profile.

Those who are considered to be the most deprived in England have nearly twice as high cervical cancer diagnosis rates compared with the least deprived, 12.1 per 100,000 versus 7.3, respectively. Morality from cervical cancer are comparatively even higher for this group, 4.1 per 100,000 versus 1.8 in the least deprived. These figure highlight the need to address inequalities in cervical cancer.

2.12.2 Internal Validity

KEYNOTE-A18 is a multi-centre, randomised, double-blind, placebo controlled phase III trial of pembrolizumab + CCRT versus placebo + CCRT in patients with FIGO 2014 Stage IB2-IIB Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

(with node-positive disease) or FIGO 2014 Stages III-IVA who have not received definitive treatment. Prior to randomisation eligible subjects were first stratified by planned EBRT type, stage at screening and planned total radiotherapy dose.

The primary endpoints were to compare OS and PFS (per RECIST 1.1 as assessed by investigator) in subjects treated with pembrolizumab + CCRT versus placebo + CCRT is a clinically relevant endpoint, that was directly referenced in the final scope for this appraisal and the decision problem. This selected endpoint is consistent with that used in studies of other therapeutic agents in the population of locally advanced cervical cancer. The definition of progression when evaluating PFS in KEYNOTE-A18 followed an established response evaluation criterion (RECIST 1.1), in line with European Guidance. (59)

HRQoL was explored under secondary and exploratory endpoints in the KEYNOTE-A18 study, with changes from baseline in patients treated with pembrolizumab + CCRT compared to placebo + CCRT using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC QLQ-C30 and EORTC QLQ-CX24.

KEYNOTE-A18 is a double-blind study, with study sponsor, investigator and participant not aware of the treatment administered. This ensures the absence of bias in study results and the credibility of study conclusions.

2.12.3 External Validity

KEYNOTE-A18 is a global study conducted in 176 centres in 30 countries, including the UK. Of the patients participating in the study, 6 were from the UK and 3 were in the stage III-IVA group, in line with the anticipated marketing authorisation.

Baseline characteristics of stage FIGO 2014 III-IVA patients enrolled in KEYNOTE-A18 were as expected for a global trial conducted in locally advanced cervical cancer patients. The median age was 51 and 36.1% were white. The treatment arms were generally well balanced by all baseline characteristics.

The observed safety profile of pembrolizumab + CCRT in KEYNOTE-A18 reflects the known safety profiles of the components i.e. generally well-tolerated. The types and severity of adverse events observed in the pembrolizumab + CCRT group were generally consistent with the established pembrolizumab safety profile. No new safety signals were identified.

Some of this study was conducted during the COVID-19 pandemic. There were no changes in the planned conduct of the study implemented by protocol amendment due to the COVID-19 pandemic.

The baseline characteristics of enrolled patients and study design (including the modality of chemoradiotherapy) of KEYNOTE-A18 were discussed with clinicians treating LACC in the UK at an advisory board. The clinicians advised that the study design and participants are reflective of current UK clinical practice and the evidence is therefore directly applicable. For example, the chemoradiotherapy regimens were concordant with those currently recommended in BGCS guidelines. (36)

3 Cost effectiveness

Summary of key cost effectiveness information

Objective:

- To examine the cost-effectiveness of pembrolizumab + CCRT versus CCRT alone for patients with LACC

Model structure:

- A de novo 4 state transition model was developed with states; progression free, first progression, second progression, and death
- An SLR of published cost-effectiveness analyses in this indication was conducted, but no studies were directly applicable to the decision problem.

Model inputs:

Patient population inputs:

- The modelled patient population is patients with FIGO 2014 stage III-IVA local advanced cervical cancer.

Clinical efficacy inputs:

- Clinical data from the KEYNOTE-A18 trial has been used to model progression free patients with clinical data from KEYNOTE-826 being used to model patients after progression.
- Extrapolations of PFS, time-to-progression (TTP) and post-progression survival (PPS) outcomes from the two studies were conducted in accordance with NICE TSD 14 and 21 to obtain long-term estimates to support the model. Direct KM data were used for time-to-discontinuation (TTD) due to its availability up to the end of the treatment period
- Treatment stopping rules included in the model base case are in line with the administration of treatments in KEYNOTE-A18, which are also in line with UK practice
- Due to the curative intent of treatment, a cure assumption was applied to an increasing proportion of the progression free population in both arms of the model from years 5-7, culminating at a 95% cure assumption at 7 years
- To be consistent with the NICE committee's preferred assumptions in TA939 (the appraisal for the KEYNOTE-826 indication), treatment effect waning assumptions have been implemented from years 5-7.

Utility inputs:

- Utility inputs were informed by EQ-5D-3L data (UK value set) sourced directly from the KEYNOTE-A18 trial.

Costs and resource use inputs:

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

Base-case results and sensitivity analyses:

- In the deterministic base case, pembrolizumab + CCRT was associated with [REDACTED] incremental costs and 2.05 incremental QALYs compared to CCRT, which corresponds to an ICER of [REDACTED] per QALY gained.
- The probabilistic results are closely aligned with the deterministic results, and show that at a WTP threshold of £30,000, the probability of pembrolizumab + CCRT being cost-effective is [REDACTED]
- In a one-way sensitivity analysis parameters relating to [REDACTED] had the greatest effect on the ICER, although varying them around their standard error didn't not affect the cost-effectiveness conclusion at a WTP of £30,000/QALY
- Distributional Cost-Effectiveness Analysis suggested the addition of pembrolizumab to standard care would improve health inequalities

Scenario analyses:

- Extensive scenario analyses were conducted to address underlying uncertainty
- The most influential scenarios include assumptions around [REDACTED], [REDACTED] and [REDACTED], although the ICER was below £30,000/QALY gained in all scenarios

Cost effectiveness conclusions:

- This analysis is the first within the UK to assess the cost-effectiveness of pembrolizumab + CCRT as treatment for LACC.

- Results of this cost-effectiveness analysis show that pembrolizumab is a cost-effective addition to standard care for patients having CCRT for LACC in the UK.
- The results of the extensive sensitivity and scenario analyses yielded results consistent with that of the base case ICER value, suggesting a high degree of confidence that pembrolizumab is cost-effective in this setting.
- Adding pembrolizumab to standard care would improve health inequalities

3.1 Published cost-effectiveness studies

An initial SLR was conducted on 31st Oct 2021, to identify published cost-effectiveness studies that met the inclusion criteria relating to adult patients with locally advanced cervical cancer that had not previously received prior systemic therapy. The searches were updated on 23rd Aug 2023. Full details of the review are provided in Appendix F.

A total of 20 reports were found to meet the inclusion criteria. Of the 20, no studies were from the perspective of the UK healthcare system. Only 2 of the 20 reported ICERs in terms of the QALY. Six of the 20 used a Markov model structure, with a further 2 using a decision analysis model where it was unclear if this was based on a Markov or decision tree. No publications used a partition survival model.

No NICE appraisals for relevant treatments in LACC were identified at the time of this submission. Although TA939 (60) is an appraisal of interest, as this represents the next line of treatment after progression from CCRT, and has been used within this submission.

3.2 Economic analysis

No published health economic evaluations that were directly relevant to the decision problem were found in the search so a *de novo* analysis was developed.

3.2.1 Patient population

The modelled patient population for high-risk locally advanced CC reflects the final NICE scope and the anticipated marketing authorisation for pembrolizumab + CCRT for first-line treatment of high-risk locally advanced CC in adults.

The primary source for the clinical effectiveness evidence used in the model is drawn from the stage III/IVA population of KEYNOTE-A18 (38) as no other directly relevant studies were retrieved in the search.

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3.2.2 Baseline patient characteristics

Baseline patient characteristics used in the model were sourced from KEYNOTE-A18. Weight and body surface area (BSA) were used to calculate drug dosing, where applicable. Population inputs are summarised in Table 27.

Table 27: Summary of population inputs

Variable	Mean	N	SD	SE	Source
Age (years)	51.5	601	12.3	0.5	KEYNOTE-A18
Female (%)	100		NA	NA	
Weight (kg)	63.1		15.2	0.6	
BSA (m ²)	1.7		0.2	0.0	

Key: BSA, Body surface area; kg, kilograms; m, metre

KEYNOTE-A18 included two UK sites and discussions with UK clinicians indicated that the trial population was broadly similar to the patients seen in real-world clinical practice in the UK. (61) It was noted that stage III-IVA patients are the minority of presenting LACC patients due to the UKs cervical screening program.

3.2.3 Model structure

The economic model developed to assess the cost-effectiveness of pembrolizumab + CCRT in LACC follows a 4-state state transition modelling approach. The model has been built referencing best practice guidance on developing cost-effectiveness models, including NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 13, 14, and 21. (62-64) The model structure was determined after considering each of the following factors:

1. The relative maturity of the KEYNOTE-A18 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, and data from the final analysis of KEYNOTE-826, both arms of which encompass the two second line treatment choices for this patient population, are available. (65)
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-A18 OS data.

This assessment showed that a state transition model consisting of the health states:

- Progression-free (PF)

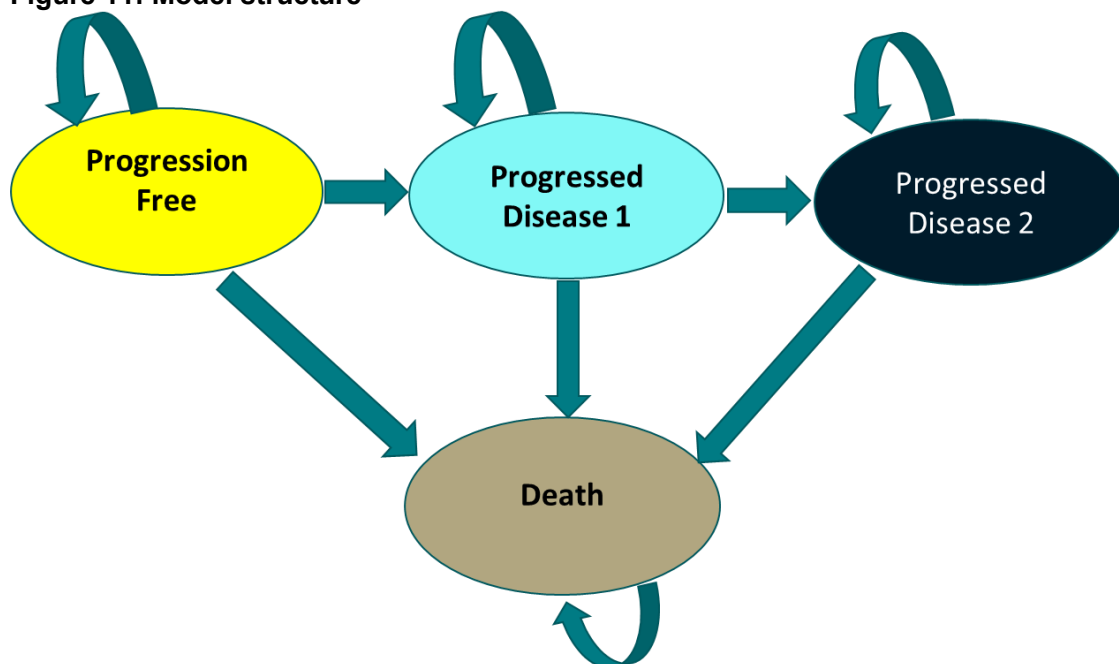
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- First disease progression (PD1)
- Second disease progression (PD2)
- Death

is the most appropriate approach for assessing the cost-effectiveness of pembrolizumab + CCRT (Figure 11). Broadly, a state-transition model was appropriate because of the immaturity of OS and the expectation that PFS benefit is highly prognostic of OS benefit in the curative setting (this assumption is consistent with several other NICE appraisals of pembrolizumab in early settings, where OS has never been directly extrapolated) and two separate Progressed Disease states were necessary because pembrolizumab is an important and effective treatment in the 'PD1' health state that needed to be accounted for explicitly. (66-69)

The model compares pembrolizumab + CCRT to CCRT alone in terms of costs, life years (LYs), and quality-adjusted life years (QALYs). The model considers drug costs, administration costs, monitoring costs, costs of adverse events, other health care resource use costs, end-of-life costs.

Figure 11: Model structure



The de novo state transition model uses modelled PFS, time to progression (TTP – these survival times are the same as in the PFS data but where the PFS event is a death it counts as a censor rather than as an event), OS (for validation only), and TTD curves from KEYNOTE-A18 as well as PFS, TTP and post-progression survival (PPS) curves from KEYNOTE-826 (TA939) to estimate health state occupancy over time. (60) Time to discontinuation Kaplan-

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Meier data from KEYNOTE-A18 were used directly to estimate the proportion of patients receiving treatment such that all treatment-associated costs and impact can be assigned accordingly to reflect actual use observed in the trial.

Progression free state

All patients enter the model in the progression-free health state. Progression-free survival in KEYNOTE-A18 was assessed by the investigator and reported as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. (41)

The possible transitions from the PF health state were as follows:

- PF → PF
- PF → DP1
- PF → death

First disease progression state

Patients who had experienced disease progression from the PF state could make the following transitions:

- PD1 → PD1
- PD1 → PD2
- PD1 → death

Transition from the PD1 health state are informed by PFS and TTP data from KEYNOTE-826 (TA939), defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first. (60)

Second disease progression state

From the PD2 state patients can either remain in PD2 or move to the death state. These state transitions were informed by the post progression survival (PPS) from KEYNOTE-826, defined as the time from first disease progression to death in that study.

Death state

Death is an absorbing health state in which a one-off cost and no LY/QALY benefit is accrued upon entry.

General model settings

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The mortality risk at each model cycle is capped by age-matched general population mortality, sourced from the latest available Office for National Statistics Life Tables, such that modelled mortality risk did not fall below that of general population mortality at any time point. (70) Due to there being some expected comorbidities in this population a standardized mortality ratio (SMR) has been applied to the background mortality rate (Section 3.3.2.5).

The model uses a 1-week cycle length. The length was considered appropriate to reflect the dosing and administration frequency for both arms, allowing precise calculation of drug acquisition and administration costs over time. Half-cycle correction is not applied due to the short cycle length of the model. The economic analysis is undertaken using the perspective of NHS and personal social services (PSS), with a discounting of 3.5% applied for costs and effects as per NICE reference case. A lifetime time horizon of 50 years was chosen to reflect a horizon that is sufficiently long to reflect all differences in costs or outcomes between pembrolizumab + CCRT and CCRT only. (71)

3.2.4 Intervention technology and comparators

Pembrolizumab + CCRT arm

The intervention, pembrolizumab + CCRT, is implemented within the model as per BGCS guidelines (for the CCRT element) and its anticipated MHRA marketing authorisation. (36) In KEYNOTE-A18, pembrolizumab + CCRT were administered in the combination phase for a maximum of 5 cycles as follows:

- Pembrolizumab: 200 mg intravenous (IV) every three weeks (Q3W) for 5 infusions
- CCRT(36)
 - Cisplatin 40mg/m² IV once a week (QW) for 5 infusions
 - EBRT (45 Gy in 25 fractions)
 - Brachytherapy (40-45 Gy in 4 fractions)

Thereafter, patients receive IV pembrolizumab in the maintenance phase at 400mg once every 6 weeks (Q6W) until progression or for a duration of up to 15 cycles.

A maximum of 20 cycles of treatment with pembrolizumab is permitted (approximately 2 years of treatment). This is reflected within the economic model (further details on duration of treatment provided in section 3.3.2.4).

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

Drug	Dose	Route	Frequency
Concurrent radiotherapy			

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EBRT	45 Gy	N/A	25 fractions
Brachytherapy	40-45 Gy	N/A	4 fractions
Combination phase			
Pembrolizumab	200 mg	IV	Once every 3 weeks for a maximum of 5 cycles
Cisplatin	40mg/m ²	IV	Once every week for a maximum of 5 cycles
Maintenance phase			
Pembrolizumab	400 mg	IV	Once every 6 weeks for a maximum of 15 cycles

Key: IV, intravenous; mg, milligram; m, meter; Gy, Gray

CCRT arm

The relevant comparator is cisplatin based concurrent chemoradiotherapy alone, consisting of a combination of cisplatin, external beam radiotherapy and brachytherapy, as per BGCS guidelines and confirmed by UK clinical experts. (36, 61, 72) The administration schedule for CCRT in current clinical practice is the same as the placebo + CCRT arm in KEYNOTE-A18.

Table 29: Dosing schedule for CCRT applied within the model

Drug	Dose	Route	Frequency
Concurrent radiotherapy			
EBRT	45 Gy	N/A	25 fractions
Brachytherapy	40-45 Gy	N/A	4 fractions
Combination phase			
Cisplatin	40mg/m ²	IV	Once every week for a maximum of 5 cycles

Key: IV, intravenous; mg, milligram; m, meter; Gy, Gray

3.3 Clinical parameters and variables

3.3.1 Overview of clinical data and outcomes in the economic model

The primary source of clinical data for the economic model is KEYNOTE-A18 (Jan 2023 datacut) because it provides direct evidence for pembrolizumab + CCRT versus placebo + CCRT in the population of interest. Data from KEYNOTE-A18 is used to model state transitions related to PFS and time on treatment (TOT). After progression, data from KEYNOTE-826 is used to model all state transitions from PD1 and PD2.

KEYNOTE-826 was the pivotal trial underpinning the TA939 NICE appraisal (Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer), the two arms of the trial represent the main two second line treatment options for patients that progress after CCRT ($\pm$ pembrolizumab), as confirmed by MSD's 2024 advisory board. (60, 61) The final analysis of the ITT CPS>1 population from KEYNOTE-826 (Oct 2022

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datacut) has been used for all analysis. The CPS>1 population has been used as pembrolizumab is only available in these patients. While chemotherapy is available to all patients, irrespective of CPS, results from final analysis indicate that CPS is not a treatment effect modifier for those receiving chemotherapy. A comparison of the CPS>1 and full population PFS results are presented in appendix K.

3.3.2 Approach

Parametric survival curves were fitted to individual patient level time-to-event endpoints from KEYNOTE-A18 and KEYNOTE-826 to inform outcomes in the pembrolizumab with CCRT and CCRT arms of the model. Parametric survival curves were fitted to PFS and time to progression (TTP) data from KEYNOTE-A18 and KEYNOTE-826, PPS data from KEYNOTE-826 and observed TTD from KEYNOTE-A18 was used to model time on treatment. Extrapolation was undertaken by fitting standard parametric survival curves, or flexible spline models where appropriate, each being fitted to patient level data (PLD). Curves were fitted separately to the intervention and comparator treatment arms, as it is generally considered unnecessary to rely on a proportional hazards assumption when PLD are available, as reported in NICE Technical Support Document 14 and 21. (63, 64)

Base-case parametric functions were chosen based on the following criteria:

- Visual fit to the observed Kaplan–Meier (KM) data within the trial period for KEYNOTE-A18 and KEYNOTE-826
- Clinical plausibility of the long-term extrapolations
- Assessment of the underlying hazard functions
- Statistical goodness-of-fit indicated by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values
- Clinical validation of extrapolated models was obtained from clinical experts, and extrapolations were compared against relevant evidence from the published literature and real-world data where possible.

The most appropriate and clinically plausible models were used in the base-case analysis, with alternative clinically plausible models tested in scenario analyses. Definitions of endpoints, and what they were used to model can be found in Table 30.

Table 30: Baseline summary of transition probability approaches

Transition(s)	Estimation approach	Data source(s)

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PF → PD1 PD → Death	• The pembrolizumab and placebo arms were based on a parametric survival modelling approach in which different parametric functions were fitted to PFS and TTP to calculate the cycle-specific probabilities of a PFS event and a TTP event. • The TTP curve dictates the cycle-specific probabilities of transition into the PD1 state, with the probability of a PFS event minus the probability of a TTP dictating the cycle-specific probabilities of transition into the death state, subject to the constraints that probabilities could never be negative or lower than general population mortality. • A cure assumption was applied among patients who achieve long-term PFS. Specifically, the per-cycle probabilities of transitions from the PF state were gradually reduced by 95% over 2 years for patients who achieve are still PFS at 5 years, subject to the rule that the transition from PF->Death must always be at least as high as background mortality.	• Patient-level data from KEYNOTE-A18. • UK national life tables were used as minimum transitions to death and as the only PFS->Death transition for cured patients. (70)
PD1 → PD2 PD1 → Death	• The same approach as the above was employed for the downstream health states but using PFS and TTP data from KN-826. • The outcomes for patients assumed to be treated with pembrolizumab + chemo +/- bevacizumab and chemotherapy +/- bevacizumab, the two principal treatment options in the PD1 health state, were based on the trial data from KN-826. Curves had been validated by the NICE committee in TA939. • KN-826 TTP dictated the transition into PD2. PFS-TTP dictated the transition probability into the death state. • Patients that receive no further treatment after progression from PF we're also modelled by applying a HR to the PFS extrapolations. • The proportion of patients receiving either pembrolizumab + chemotherapy, chemotherapy only,	• Patient-level data from KEYNOTE-826 • UK national life tables were used for minimum transitions to death.

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	or no treatment in each arm is used to produce a weighted transition probability out of this state. The model uses matrix multiplication to handle the time dependency of the downstream transition probabilities correctly i.e. the weighted transition probabilities are a function of time in state for all cohorts entering the PD1 health state at different time points.	
PD2 → Death	Transition probabilities from PD2 to death were based on a parametric modelling approach in which different parametric functions were fitted to PPS from KN-826. Consistent with the committee's preferences in TA939, there was a slight advantage for patients assumed to have received pembrolizumab in the PD1 health state.	- Patient-level data from KEYNOTE-826 - National life tables - for minimum transitions to death

Key: PF, progression free; PD1, progressed disease 1, PD2, progressed disease 2; TTP, time to progression; PPS, post progression survival; HR, hazard ratio

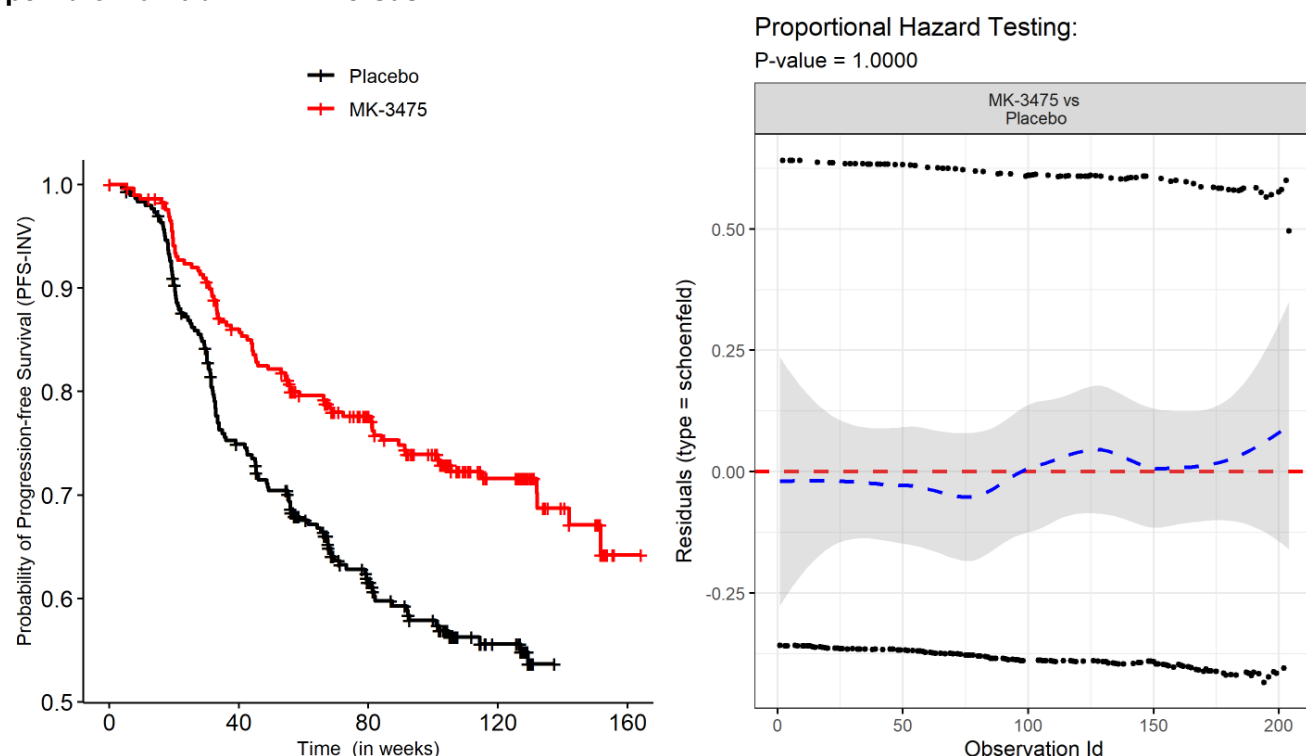
3.3.2.1 *Modelling transitions from progression-free state*

The transition probabilities starting from the progression-free state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-A18 trial, in accordance with best practice methods and guidance from NICE DSU TSD 14. (63) Parametric models were fitted to both PFS and TTP.

Parametric models fitted to TTP were used to determine the time dependant transition probability of progressing, while difference between the weekly hazard of PFS and TTP determines the transition from the progression free state, straight to death.

Progression-free survival was defined via investigator assessment per RECIST, this was a primary endpoint of the KEYNOTE-A18 trial, and most closely represents how progression would be assessed in the UK.

Figure 12: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-A18 PFS – pembrolizumab + CCRT versus CCRT



Key: MK-3475, Pembrolizumab; PFS-INV, investigator assessed progression free survival

Figure 13: Cumulative hazard plot – PFS – pembrolizumab + CCRT versus CCRT

Key: MK-3475, Pembrolizumab

Standard parametric models

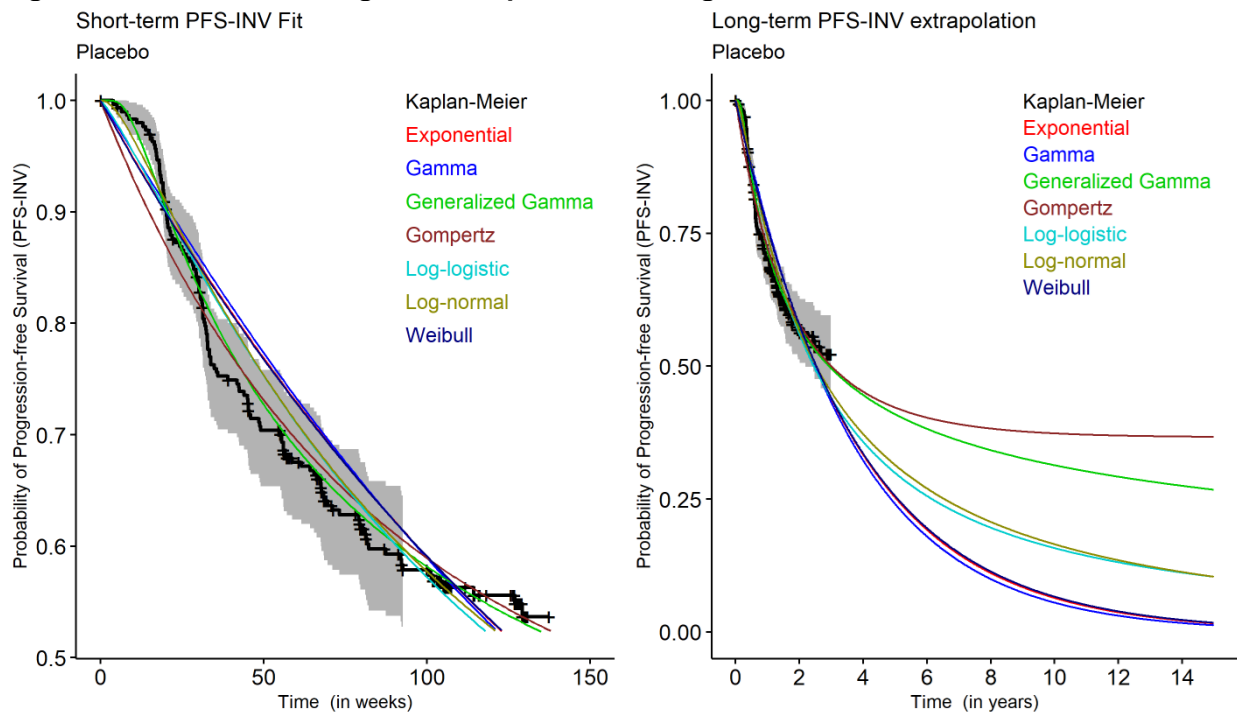
The standard parametric models along with the observed PFS KM data from KEYNOTE-A18 are shown in Figure 14 and Figure 15 for CCRT and pembrolizumab + CCRT respectively. Table 31 summarises goodness-of-fit for the parametric models to the observed data as assessed by the AIC and BIC statistics. The following conclusions were drawn:

- Five of the seven standard parametric curves provided poor visual fit to the observed KMs and severely underestimated PFS from week 120 onwards for both arms (Figure 14 and Figure 15); The generalised gamma and Gompertz curves were the only ones to fit the observed data well. This is clear for both CCRT and pembrolizumab + CCRT arms
- Of these two, the generalised gamma outperformed the Gompertz in terms of AIC and BIC. No curves are within 5 points of the generalised gamma model in the CCRT arm, and only the log-normal is within 5 in the pembrolizumab + CCRT in the pembrolizumab arm

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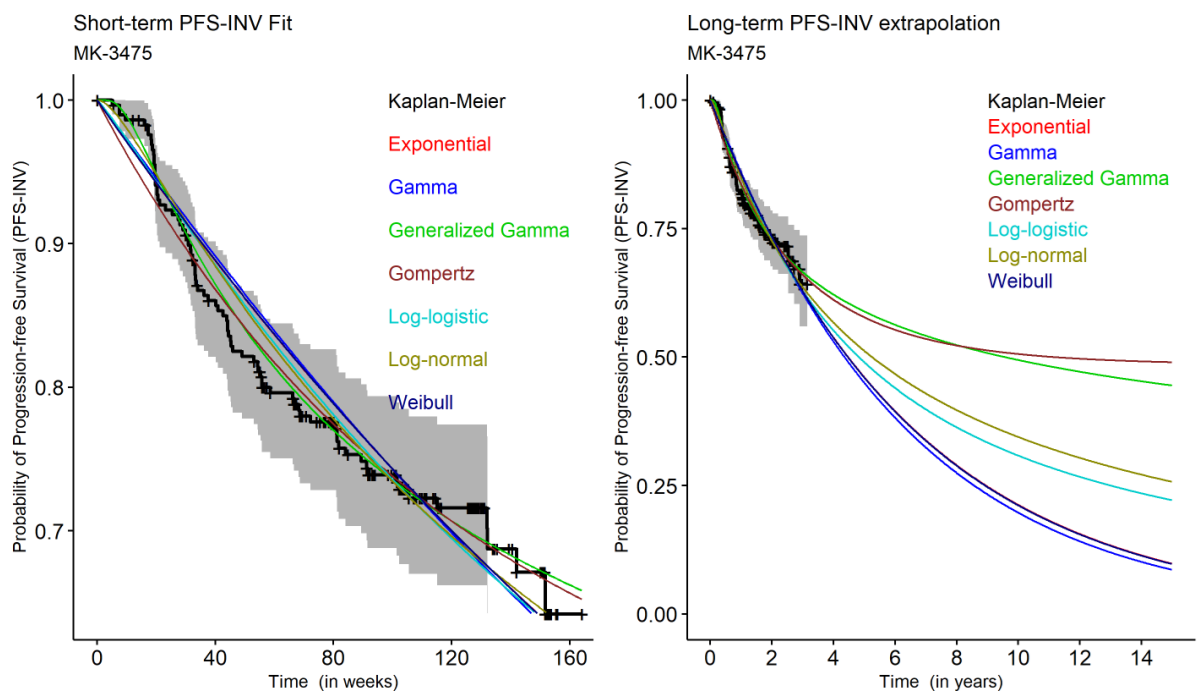
- Given the sufficient fit to observed data, more complex models were not considered necessary for PFS

Figure 14: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PFS - CCRT



Key: PFS-INV, Investigator assessed progression free survival

Figure 15: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PFS - Pembrolizumab + CCRT



Key: MK-3475, Pembrolizumab, PFS-INV, Investigator assessed progression free survival

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Table 31: Summary of parametric fitting performances of KEYNOTE-A18 PFS for pembrolizumab + CCRT and CCRT

Treatment	Pembrolizumab + CCRT			CCRT		
	AIC	BIC	Average	AIC	BIC	Average
Extrapolation						
Exponential	1080	1083	1081	1564	1568	1566
Gamma	1081	1089	1085	1566	1573	1569
Gen. Gamma	1064	1075	1070	1530	1541	1536
Gompertz	1078	1086	1082	1557	1565	1561
Log-Logistic	1078	1086	1082	1555	1562	1558
Log-Normal	1071	1078	1075	1544	1551	1547
Weibull (AFT)	1082	1089	1085	1566	1573	1570

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

Note: Shaded blue represents the model with the best statistical fit, shaded green represents the models within 2 points from the best statistical fit.

Cure

Clinical advice to the company is that a substantial proportion of patients with LACC are cured by chemoradiotherapy and that PF patients are no longer followed up after 5 years in UK practice. The model allows a cure period to be implemented whereby the per-cycle risk of progression (movement to PD1) from the progression-free state is reduced by 95%; the risk reduction to 95% is applied with a linear rate during the cure period (i.e. from 0% to 95%). The same risk reduction is applied to the risk of transitions from progression-free to death subject to the constraint that the risk of progression-free to death must always be at least as high as background mortality. In the absence of evidence to the contrary, the cure proportion and time point is equal across both arms. This approach along with a 95% cure proportion has been used in numerous other indications where cure is the intent of treatment (e.g. TA830, TA1017, and TA1037). However, the true cure proportion is unknown. The company were unable to identify the sort of very long term epidemiological data that would allow this to be calculated but suspect that no observational study would have long enough follow up since the introduction of modern radiotherapy techniques.

The base-case assumes a cure period from 5 to 7 years. This is based in part on feedback from clinical experts from the 2024 Clinical Advisory Board, which confirmed that all patients are treated with curative intent and suggested that it is reasonable to assume there will be very few recurrences or disease-related deaths after 5 years, and that this is reflected in that patients are not routinely followed up in secondary care after this point. (36, 61) Scenarios looking at 3-5, 5-7, and 7-9 years were presented at the advisory board for both arms and the 5-7 scenario was also selected on the basis of plausible long-term outcomes. The model Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

contains the functionality for sensitivity analyses to be conducted on both the cure proportion and time points.

Validation and selection

CCRT

1. Due to poor visual fit to observed data, all models bar the generalised gamma and Gompertz were rejected. All other curves also underestimated survival towards the end of follow up and did not capture the beginning of the plateau seen in KEYNOTE-A18
2. The generalised gamma had the best AIC and BIC with no other model being with 5 points
3. One key difference between the generalised gamma and Gompertz curve is the different long term predictions, but when a cure point is applied this difference is significantly reduced with there being less than a 3% difference in the long term PFS outcome at both 10 and 20 years, reducing further towards the end of the time horizon
4. Clinical validation at the 2024 advisory board confirmed that the generalised gamma with 5-7 year cure point provided the most plausible long term PFS estimates (61)

As such the generalised gamma curve with a cure assumption on 95% patients between 5-7 is used within the base-case modelling. The Gompertz fit, along with the cure assumption are further explored in the sensitivity analysis.

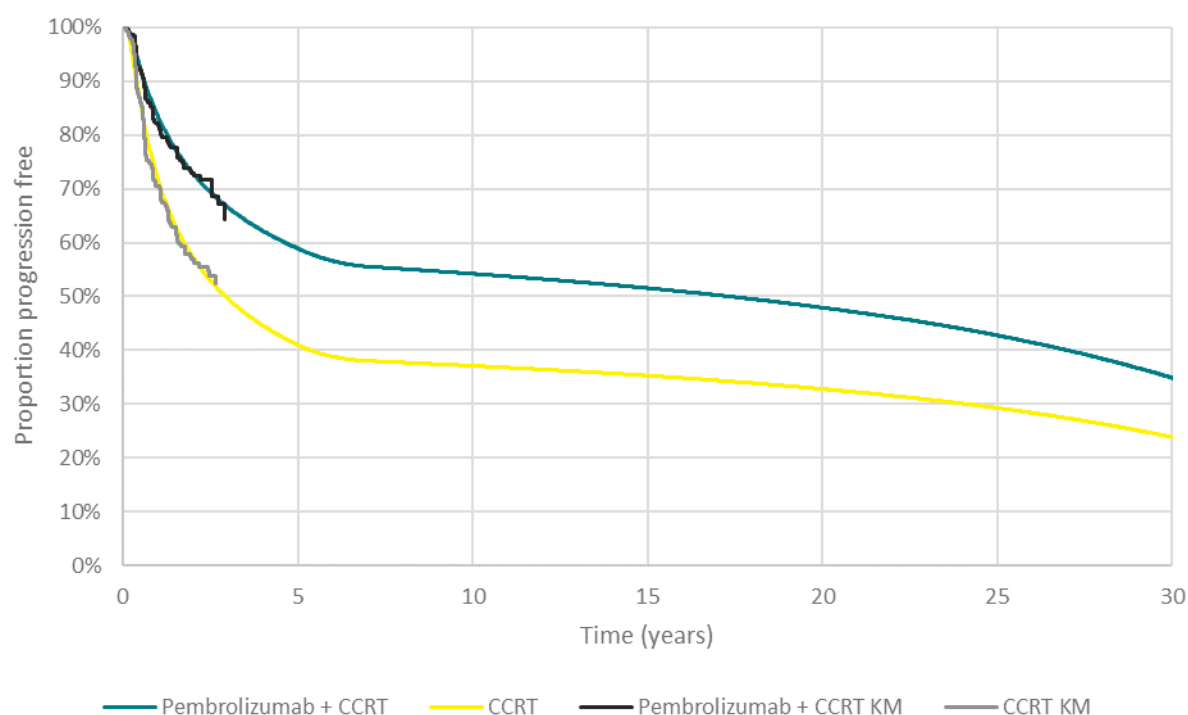
Pembrolizumab +CCRT

1. Due to poor visual fit to observed data all but generalised gamma and Gompertz were rejected.
2. The generalised gamma had the best AIC and BIC with only the log-normal model being with 5 BIC.
3. As with the CCRT arm the one key difference between the generalised gamma and Gompertz curve is the different long term predictions, but again when a cure point is applied this difference is significantly reduced with there being less than a 2% difference in the long term PFS outcome at both 10 and 20 years, reducing further towards the end of the time horizon
4. Clinical validation at the 2024 advisory board confirmed that the generalised gamma with 5-7 cure point provided the most plausible long term outcomes. (61)

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NICE TSD14 recommends using the same parametric form in both arms when there is not a strong rationale to do otherwise. (63) Helpfully for model selection, the generalised gamma curve had the lowest AIC and BIC in both arms and visually appeared to fit the data well. As such the generalised gamma curve with a cure assumption on 95% patients between 5-7 is used within the base-case modelling. The Gompertz fit, along with the cure assumption are further explored in the sensitivity analysis.

Figure 16: Base-case progression free survival selections



Key: CCRT, concurrent chemoradiotherapy; KM, Kaplan-Meier

Progression from progression free to first progression

Progressions from PF → PF, PF → PD1, and PF → Death are reliant on parametric models fitted to both PFS and TTP. Due to PFS and TTP being codependent outcomes (PFS is a composite of TTP + Death), the KM curves and fits for each are very similar with only [REDACTED] events (deaths) in the PFS KM for the pembrolizumab + CCRT arm and [REDACTED] events (deaths) in the CCRT arm.

Therefore, the same distribution has been picked for each PFS/TTP pair in either arm. This approach was used in TA939 and preferred by the EAG for that appraisal. (60) The company consider it logical that PFS and TTP should follow the same parametric form to avoid illogical extrapolations. Detailed charts and tables are presented for TTP in appendix K including details on visual and statistical fit. As with PFS, the generalised gamma curves had the lowest

AIC and BIC in both arms. As such the generalised gamma curve with a cure assumption on 95% patients between 5-7 is used within the base-case modelling.

In the event the cycle-specific hazard of PFS minus TTP is less than general background mortality, the model ensures the hazard of PF-> death is at least that of background mortality, and appropriately adjusts the hazard of TTP to account for this, with PFS being fixed.

3.3.2.2 First disease progression (PD1)

On progression, patients have 3 main treatment options available to them:

- Pembrolizumab + chemotherapy $\pm$ bevacizumab (TA939)
- Chemotherapy $\pm$ bevacizumab
- No treatment

Due to the immaturity of trial data regarding states post first progression, mainly due to median PFS not yet being reached in either arm of KEYNOTE-A18, modelling of transitions from the PD1 state is informed by the KEYNOTE-826 trial. This trial has reached final analysis and was the pivotal RCT that informed the modelling TA939 ("Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer", TA939 was itself a CDF exit for TA885). (60) All data relating to the survival analysis and curve selection are copied directly from TA939 but are reproduced here for convenience.

The arms of this trial represent the 2 main treatment options for progressed patients:

- Intervention arm; Pembrolizumab + chemotherapy $\pm$ bevacizumab
- Control arm; Chemotherapy $\pm$ bevacizumab

Over and above introducing more mature data into the post progression modelling than would be the case if relying on post-progression data from KEYNOTE-A18, the use of KEYNOTE-826 also allows for:

- The NHS specific subsequent treatment mix to be better modelled and explored, by allowing treatment specific efficacy to be linked to subsequent treatment inputs within the model, as opposed to relying on data derived from the subsequent treatment in the KEYNOTE-A18 trial.
- KEYNOTE-826 was the pivotal trial used in TA939. This provides a robust set of assumptions that have already been scrutinised via an EAG and committee during the NICE process, and were found satisfactory for decision making.

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KEYNOTE-826 PFS and TTP

As per TA939, one piece fits for PFS and TTP in both arms were rejected due to poor visual fits. Within the appraisal, flexible spline models were agreed to be appropriate by both the EAG and the committee as they better modelled the more complex pattern of hazards that was seen in the trial population, particularly in the pembrolizumab arm.

Spline-based models

One, 2 and 3 knot spline models on the normal, hazard and odds scales were fitted, providing nine options for each KM curve. The locations of the knots were predetermined by the R package (flexsurvspline) at the relevant standard event quantiles.(73)

To assess which curves to implement in the economic model we examined:-

- Visual fit to the KM and smooth hazard curves
- Statistical fit assessed via AIC
- Clinical plausibility of long-term survival vs. estimates confirmed as plausible at the UK advisory board and NICE ACM meetings for TA885

The spline models provide significantly improved visual fit to the data over the best fitting one-piece models, particularly in the pembrolizumab arm (Figure 17).

Figure 17: PFS visual fits of (hazard) spline and one-piece models



Key: GenGam, Generalised Gamma

We also examined the visual fit to the smooth spline hazards observed in the trial. These plots did not provide a strong rationale to pick between models, with all models appearing to capture the trend in hazards in the latter part of the trial well. We note that the 1-knot models fit the quadratic shape of the hazard function with the apex around 37 weeks somewhat less well than the 2-knot and 3-knot models.

Figure 18: PFS visual fits of all 1, 2 and 3 knot models to the smooth spline hazards



Key: k, Knot; PFS, Progression free survival

Figure 19: TTP visual fits of all 1, 2 and 3 knot models to the smooth spline hazards



Key: k, Knot; TTP, Time to progression

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The spline models also provide superior statistical fit compared to the one-piece models in both arms, but particularly in the pembrolizumab arm. In terms of comparison between the AIC scores for the nine spline options, there is little to choose between any option for the SoC models. For the pembrolizumab+SoC arm, the 2 and 3-knot models had better fit than the 1-knot models. The hazard scale had the best fitting 1-knot model, fit was comparable among the 2-knot models and the hazard scale had a slightly worse fitting 3-knot model than the other two options. Overall, AIC did not provide a strong rationale to pick between spline models.

Table 32: AIC for spline models for PFS

	Pembrolizumab + SoC			SoC		
	knots=1	knots=2	knots=3	knots=1	knots=2	knots=3
hazard	■	■	■	■	■	■
odds	■	■	■	■	■	■
normal	■	■	■	■	■	■

Key: SOC, standard of care; PFS, progression free survival

Table 33: AIC comparing one-piece with spline models

		Pembrolizumab		SoC	
One-piece	Model	AIC	AIC Rank	AIC	AIC Rank
	Exponential	■	■	■	■
	Weibull	■	■	■	■
	Log-normal	■	■	■	■
	Log-logistic	■	■	■	■
	Gompertz	■	■	■	■
	Generalised gamma	■	■	■	■
Spline (hazard scale)	1-knot	■	■	■	■
	2-knot	■	■	■	■
	3-knot	■	■	■	■

Key: AIC, Akaike information criterion; SOC, standard of care

Decisions on whether extrapolations were plausible or not were made via a company advisory board and the clinical experts at NICE ACM1 and ACM2. These original estimates were 7% OS at 20 years for the pembrolizumab+SoC arm and 1.3% OS in the SoC arm, although the clinical advisors noted that this was slightly optimistic and 0.5%-1% might be more plausible.

The table below gives the landmark OS estimates generated by the economic model when all nine spline methods are implemented for PFS and TTP and when treatment waning 3-5 years (post treatment) is applied. It is notable that for the models on the hazard scale, all three options provide estimates close to those confirmed plausible at ACM2. The hazard scale

options also provide low (1-knot), middle (3-knot) and high (2-knot) values to test in sensitivity analysis.

Table 34: Landmark OS estimates from the economic model using all spline options for PFS/TTP

Scale	Knot	Treatment	5-year survival	10-year survival	15-year survival	20-year survival
Normal	1	Pem+SOC	■	■	■	■
	1	SOC	■	■	■	■
Normal	2	Pem+SOC	■	■	■	■
	2	SOC	■	■	■	■
Normal	3	Pem+SOC	■	■	■	■
	3	SOC	■	■	■	■
Odds	1	Pem+SOC	■	■	■	■
	1	SOC	■	■	■	■
Odds	2	Pem+SOC	■	■	■	■
	2	SOC	■	■	■	■
Odds	3	Pem+SOC	■	■	■	■
	3	SOC	■	■	■	■
Hazard	1	Pem+SOC	■	■	■	■
	1	SOC	■	■	■	■
Hazard	2	Pem+SOC	■	■	■	■
	2	SOC	■	■	■	■
Hazard	3	Pem+SOC	■	■	■	■
	3	SOC	■	■	■	■

Key: OS, overall survival; PFS, progression free survival; TTP, Time to progression; SOC, standard of care

For any given number of knots, there were not big differences between the scales (hazard, odds and normal) in terms of statistical or visual fit but we noted the hazard models provided a reasonable range for sensitivity analysis that was close to estimates that had already been confirmed by experts.

For the company base case, we selected the 3-knot hazard model with waning from 3-5 years post treatment for both arms as it produced estimates close to those previously considered and was the middle option. We examined 1-knot and 2-knot models as low/high sensitivity analysis. This approach was seen to be appropriate by the committee when making their recommendation for TA939 (60). This base-case pick and exploration of further splines is explored in scenario analysis.

As with the progression free state, we selected the same model for TTP as PFS, based on the two datasets comprising very similar data but PFS having more events and being a primary trial outcome. This was the preferred method in TA939 (60).

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No treatment

Feedback from clinicians at the 2024 advisory board, as well as 2 individual clinician consultancies, highlighted that around 20% of patients that progressed after CCRT ($\pm$ pembrolizumab) would not go on to get further treatment, for reasons such as a personal choice or unsuitability for further chemotherapy due to lack of fitness or other contraindication. (61)

Given the fact these patients would not receive any additional anti-cancer therapy and move directly to palliative care, it is assumed that these patients would have a higher risk of death in any cycle compared to the chemotherapy arm KEYNOTE-826.

OS is not modelled directly within the PD1 state in the model but rather, the probability of dying within the state and not moving through the PPS state is dictated by the difference between PFS and TTP. For the patients receiving no treatment, we therefore assigned them a TTP of 0, such that every PFS exit transition became a death. OS for patients receiving no treatment within the PD1 health state was then able to be modelled by giving these patients a no-treatment-specific PFS curve.

Given the disposition of these patients (frailty or unwillingness for further treatment) it is highly unlikely that data specifically relating to these patients' outcomes would be available from a published clinical trial. Desktop research was conducted in an attempt to find survival estimates for these patients but nothing was found.

To estimate the survival of these patients, we conducted 2 clinical validation consultancy meetings with 2 clinical oncologists. (72) The modelled OS estimates from KEYNOTE-826 chemotherapy arm were presented alongside multiple HR adjusted PFS curves, such that all curves sat below the OS curve. The curves were unlabelled and the clinicians selected which curves they felt best represented OS for patients receiving no treatment in this setting.

Both clinicians agreed that the options relating to curves adjusted by HRs of 2 implying a median OS of less than 6 months seemed appropriate. A HR of 2 has been applied to the chemotherapy arm PFS curve to model no treatment OS in the base case, with a HR of 1.5 and 3 explored in sensitivity analysis. A no treatment proportion of 10% has also been explored on the advice of one clinician. (72)

Figure 20: Overall survival estimates for no treatment after first progression



Key: OS, Overall survival; PFS, Progression free survival; HR, Hazard ratio

Within the model it is assumed the proportion getting no treatment after progression with CCRT $\pm$ pembrolizumab is equal in both arms.

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Due to the inherent uncertainty of the OS outcomes in this specific population, scenarios have been explored within scenario analysis. Results from the GOG 240 and GOG 204 studies also allow us to create an upper bound for the survival of these patients. These trials provide survival outcomes for patients that received the chemotherapy regimen prior to the introduction of bevacizumab. (74, 75) Survival at one year is approximately 50% for patients receiving cisplatin+paclitaxel (the regimen which became the SoC after GOG 204) and 40% for patients receiving the suboptimal chemotherapy regimens and therefore curves with better outcomes than this (e.g. KN-826 PFS curve with HRs ≥ 1) would not hold face validity. It should be noted that all patients in the GOG studies were fit enough for chemo and to enter a clinical trial and are therefore likely to have a substantially better prognosis than the patients receiving no treatment in this setting within the model.

It should be noted that no residual treatment effect from using pembrolizumab in this setting is assumed once patients progress. However, given this was observed in KEYNOTE-826 and validated in TA939 by the NICE committee, it may well be that the PD1 outcomes for patients previously treated with pembrolizumab are underestimated and the model's results may be conservative.

Summary of fits

Figure 21 shows the base case extrapolations for each of the three possible 2nd line treatment choices. The curves for chemotherapy $\pm$ pembrolizumab represent (second) progression free survival after progression from CCRT $\pm$ Pembrolizumab. These patients either progress straight to the death state or to the post progression survival state. The curve for no active treatment represents overall survival, with all no active treatment patients moving directly to death.

Figure 21: Extrapolations to each 2nd line treatment choice



Key: OS, Overall survival

Figure 22 represents the extrapolations of progression free survival after 1st progression, weighted to the base-case subsequent treatment mix in section 3.5.3. It should be noted that the CCRT curve sits above the pembrolizumab + CCRT curve as the majority of progressed CCRT patients receive pembrolizumab via TA939, while within the first 2.5 years no patients that have progressed on pembrolizumab + CCRT would receive pembrolizumab via TA939. At 2.5 years pembrolizumab + CCRT patients follow the CCRT curve as it is expected that rechallenge would be allowed after this point.

Figure 22: Weighted extrapolations for progression free survival after 1st progression

Key: CCRT, Concurrent chemoradiotherapy

3.3.2.3 *Post 2nd progression survival*

Within the post 2nd progression population the only transitions are to remain in the post progression state or move straight onto death. As with the transitions out of the progressed state, these have been modelled using individual patient level KN-826 data on PPS. All data relating to the survival analysis and curve selection are copied directly from TA939 but have been reproduced here for convenience.

We fit parametric curves to the data for use in the economic model. Our criteria for model selection were as follows:-

- Prioritization of one-piece model unless hazard function complex
- Visual and statistical fit
- Prioritise using the same model type between the arms unless there is a strong rationale not to, consistent with EAG advice detailed in the TA885 and TA939 FADs. (60)
- Mean life years longer in the pembrolizumab arm than SoC arm (curves don't cross), consistent with NICE committee's conclusions in the TA885 FAD.

The visual fit of the standard one-piece parametric models was good and we did not need to explore more flexible survival analyses. The log-normal and generalised gamma models had the lowest AIC and BIC among the options for the pembrolizumab combination arm and log-normal, log-logistic and generalised gamma models had the lowest AIC and BIC among the options in the SoC arm.

We compared the projections to those that had been considered in the previous NICE ACMs and found that, given the greater observed survival time, median and mean PPS was understandably slightly longer than the 1.04 and 0.9 mean PPS life years produced by the independent generalised gamma models preferred by the committee during TA885. We selected the base case models conscious of the guidance we received from the EAG about using the same model in both arms unless there is a strong rationale not to. We compared pairs of curves and found that the log-normal and log-logistic curves crossed each other, leading to longer mean PPS life years in the SoC arm, which was contrary to the NICE committee's stated conclusions in the FAD. We therefore excluded these models.

We selected the independently fitted generalised gamma curves as the most appropriate as they had among the lowest AIC, had the best visual fit to the data and were a pair where mean PPS was longer in the pembrolizumab arm/the curves did not cross. This is consistent with the committee's stated preferences in section 3.8 of the TA885 FAD (also independently fitted generalised gamma models with slightly longer PPS in the pembrolizumab arm). (60) The EAG and committee for TA939 raised no concerns with these curve selections.

Table 35 below summarises the rule-in and rule-out criteria above. Visual fit was assessed as amber if it was notably worse than the best fitting curve but not so poor that it could be directly ruled out.

Table 35: Rule-in and rule-out criteria applied to one-piece parametric curves

	Exponential	Weibull	Lognormal	Log-logistic	Gompertz	Generalised gamma
AIC/BIC for pembro among lowest						
AIC/BIC for SoC among lowest						
Visual fit for Pem+SoC						
Visual fit for SoC						
Mean PPS longer for Pem+SoC for pair						

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; SOC, Standard of care; PPS, Post progression survival

Table 36: Statistical fit of parametric survival models fit to the PPS KM data for Pem+SoC and SoC in the CPS≥1 population of KEYNOTE-826 Final analysis

	Pem+SoC			SoC		
Model	AIC	BIC	Average	AIC	BIC	Average
Exponential						
Weibull						
Log-normal						
Log-logistic						
Gompertz						
Generalised gamma						

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, Combined positive score; KM, Kaplan-Meier; SOC, Standard of care; PPS, Post progression survival

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Figure 23: Base-case post progression survival curves, by treatment received 2nd line



Key: SoC, Standard of care

Figure 24 below shows the weighted post second progression extrapolations used for modelling, taking into account the 2nd line treatment mix detailed in section 3.5.2.

Figure 24: Post second progression survival estimates, by model arm



Key: CCRT, Concurrent chemoradiotherapy

3.3.2.4 Time to discontinuation

Time to discontinuation is defined as the time from the date of the first dose until the date of the last dose of the protocol regimen for any treatment components for participants who discontinued study treatment for any reason, and is used directly to estimate the proportion of patients who are on or off treatment in each model cycle. TTD is censored at the date of the last known treatment dose prior to the database cutoff date should a patient still be on treatment. TTD is expressed in months, and the KM curve is shown in Figure 25.

More patients in the pembrolizumab + CCRT arm were on treatment for longer than those in the placebo + CCRT arm, although in both arms the median time to discontinuation was limited by the stopping rule at 2 years. The KM curves were largely similar up to around 30 weeks and diverged thereafter. It is likely this coincides with the first scan 12 weeks post CCRT at which asymptomatic progressors would be identified and discontinued from treatment. A small proportion of patients were still on treatment after 2 years, likely due to delays in earlier cycles of treatments, or treatment holidays, no one in the trial received more than 20 cycles of pembrolizumab, in line with the cycle based stopping rule.

Given that the KM curve is available up to the end of the pembrolizumab treatment period, the KM estimates from the trial are used directly to inform the duration of treatment in the model. A stopping rule is applied at the maximum number of pembrolizumab cycles (5 Q3W + 15 Q6W) within the model with 100% relative dose intensity (RDI).

Figure 25: Kaplan–Meier curve of TTD



Key: TTD, time to treatment discontinuation; CCRT, Concurrent chemoradiotherapy

3.3.2.5 Background mortality

General population mortality was sourced from national life tables for England and Wales. (70) General population mortality was applied using the baseline age (51.5 years old) observed in KEYNOTE-A18, such that at any time point, the hazard of PFS cannot fall below that of general population mortality risk. Background mortality is also used to determine the hazard of death in the cured population.

Feedback from the 2024 advisory board highlighted that even in patients that had had successful treatment, and remained progression free past 5 year, that the hazard of death is unlikely to revert all the way back to the general background mortality. (61) This would be due to the fact the typical patient also presents with other underlying comorbidities, and as a result the cured population would still likely have a hazard of death greater than the general population.

Using a standardised mortality ratio (SMR) to adjust the background mortality for the cured population is an approach that has been used before e.g. in TA1037re, an appraisal of pembrolizumab in early stage non-small cell lung cancer (69). For TA1037, specific registry data were available that allowed for SMR to be taken from literature. This SMR (x1.453) was deemed to be “double-counting” by the NICE committee because the economic model already allowed some recurrences (just as the model for this appraisal does by setting the cure proportion to 95%).(69) The true SMR for cured resected lung cancer patients was thought to be lower than this. The company consider that 1.453, while offering a recent precedent is likely to be significantly higher than the SMR that would be appropriate for cured cervical cancer patients. This is because resected lung cancer patients can experience significant morbidity in relation to the removal of part of their lung and often have smoking related comorbidities such as COPD that significantly reduce life expectancy. These factors, in addition to the NICE committee’s conclusion about double-counting, suggest that any SMR applied to cervical cancer patients cured by CCRT should be substantially lower than x1.453.

No directly relevant registry data could be found in either the stage III-IVA, nor the total population, for LACC patients that were progression free post 5 years. The company considers that it is unlikely that directly relevant data exist, given that radiotherapy techniques have advanced substantially in the past few years.

On advice from clinicians it was suggested that IMD specific life tables could be used to estimate an SMR, where those in the bottom 1-5 deciles compared to the total population could be used as a proxy to account for socioeconomic factors and health disparities (61).

Using the age specific European standard population, the total expected number of deaths for each 5 year age band between the ages of 50-89 were calculated for each IMD decile by applying the age sex specific mortality taken from the 2018-2022 IMD specific ONS life tables. (76, 77) The SMR was then calculated by dividing the total expected number of death per capita in deciles 1-5 by the total expected number of deaths per capita across all deciles.

With this method we calculated the SMR for those aged 50-89 (reflecting the time horizon of the model from the mean age of entry) to be x1.19. This SMR has been used in the base case and a scenario exploring its removal have been explored in sensitivity analysis.

3.3.2.6 *Treatment effect waning*

While MSD does not endorse the application of treatment effect waning in patients that have received immunotherapy, within this submission it has been explored in the base case due to precedent in past NICE appraisals, particularly the assumptions agreed by the committee in TA939.

Within this submission TEW was applied from 3 - 5 years after pembrolizumab stopping rule (~2 year stopping rule in both KEYNOTE-826 and KEYNOTE-A18). Although there is no published evidence supporting the assumption of treatment effect waning in patients who have received immunotherapy, this assumption was agreed as appropriate in TA939 and has therefore been applied across all pembrolizumab related transitions in the model for this appraisal.

The company's view is that any expected convergence of the hazards between the arms is adequately handled by the cure assumption, which takes effect at the same time point as typical treatment waning assumptions have in the metastatic setting.

Within the model, waning of pembrolizumab specific hazards towards the control arm hazards between years 3 and 5 post stopping treatment has been applied to all of the time-dependant transition probability in the progression free and first progression state that relate to pembrolizumab. Immunotherapy is not modelled in the post progression survival state and is therefore not applied for transitions from PD2 – Death.

3.3.2.7 *Summary of base-case modelling approach*

The model structure reflects the treatment pathway for LACC, with separate health states being used to capture resource use, HRQoL and outcomes for each of the notable treatment options. Data from RCTs specific to the health states and treatment options within the model were available. The model is conceptually similar to the model that was accepted for decision-

making in TA939 but with an additional PFS health state to reflect that the setting for this appraisal is one step earlier in the patient pathway.

A comprehensive assessment of appropriate survival models for PFS and TTP in both KEYNOTE-A18 and KEYNOTE-826 was conducted (Section 3.3.2.1 and 3.3.2.2 respectively) and PPS in KEYNOTE-826 (Section 3.3.2.3). This process considered the visual and statistical fit of the extrapolated curves to the observed data, the clinical plausibility of long-term extrapolations and NICE TSD guidance. The KEYNOTE-826 extrapolations were validated as part of TA939 and are based on mature Final Analysis data. Directly observed TTD data was used to model the use of pembrolizumab and other treatments with no further extrapolations needed, given the completeness of the KM curves. The most appropriate and clinically plausible models for PFS, TTP and PPS were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses (Table 37).

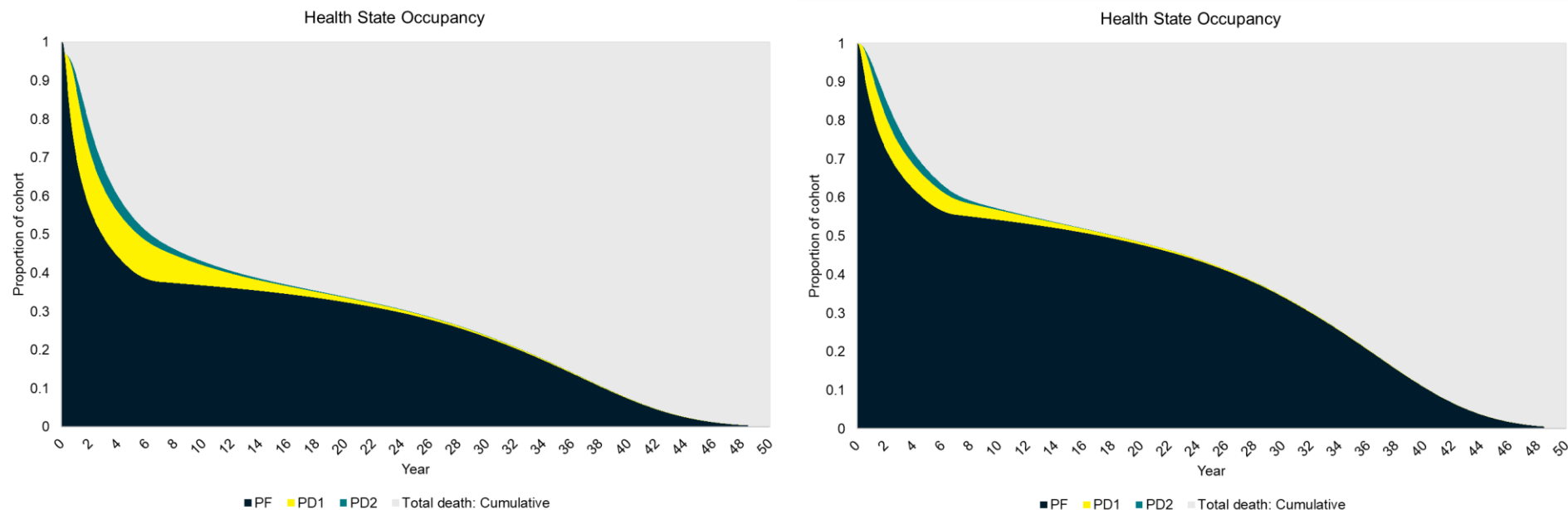
Figure 26 shows the state occupancy over time for both the CCRT and CCRT + pembrolizumab arms of the model, respectively.

Table 37: Summary of PFS, PPS, and TTD extrapolations selected for economic analysis

Arm	PFS model (A-18)	Justification	Arm	PFS model (KN826)	Justification	PPS model (KN826)	Justification	TTD	Justification
Pembrolizumab + CCRT	Generalised Gamma + cure from 5-7 years	Best statistical and visual fit, preferred fit of UK clinical experts. Same functional form between the arms.	Pembrolizumab + chemotherapy	3-knot hazard	Good statistical and visual fit, clinical plausible with landmark estimates in line with UK clinical experts. Validated in TA939	Generalised gamma	Good statistical and visual fit, clinical plausibility. Validated in TA939	KM	KM data complete up till end of pembrolizumab treatment period; further extrapolations not necessary
CCRT	Generalised Gamma + cure from 5-7 years	Best statistical and visual fit, preferred fit of UK clinical experts. Same functional form between the arms.	Chemotherapy	3-knot hazard	Good statistical and visual fit, clinical plausible with landmark estimates in line with UK clinical experts. Validated in TA939	Generalised gamma	Good statistical and visual fit, clinical plausibility. Validated in TA939	KM	KM data complete; further extrapolations not necessary

Key: CCRT; concurrent chemoradiotherapy; HR, hazard ratio; KM, Kaplan–Meier; PFS, progression-free survival; TTD, time to treatment discontinuation

Figure 26: State occupancy of the CCRT arm (left) and pembrolizumab + CCRT arm (right), over time



Key: CCRT, Concurrent chemoradiotherapy; PF, Progression free; PD1, progressed disease 1; PD2, progressed disease 2

3.4 Measurement and valuation of health effects

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

EQ-5D data was collected from the KEYNOTE-A18 trial. The total population FIGO stage III-IVA consisted of 553 patients, resulting in a combined total of 7,574 EQ-5D measurements. The population comprised patients who were randomised (n = 553), and completed at least one EQ-5D-5L questionnaire (n = 545). The EQ-5D-5L data from KEYNOTE-A18 were mapped onto the 3L scale using the algorithm developed by Hernandez-Alava et al. (2022). (78)

3.4.2 Mapping

Consistent with the current NICE position statement on the use of EQ-5D measurements in technology appraisals, EQ-5D-5L data from KEYNOTE-A18 was analysed and mapped to EQ-5D-3L using the algorithm developed by Hernandez-Alava et al. (2022). (78) All utilities within the model have age adjustment applied based on UK population data. (79)

Various analyses of the KEYNOTE-A18 utility data were conducted; naïve means by PF and PD health states and a series of linear mixed effects regression models that investigated whether certain variables were statistically significantly associated with utility. Two sets of regression models were investigated, one set included progression status and investigated the other included time-to-death as the hypothesised primary predictor of utility. For each set of models, several additional variables were investigated iteratively. These variables were the presence of ongoing grade 3+ AEs, treatment arm and age. The statistical significance of each variable was assessed and the goodness of fit of the models was compared using AIC and BIC values. A full report is available in Appendix L.

For models based on progression status, treatment arm, ongoing AEs and progression status were all statistically significant. However, this model sacrificed some goodness of fit, with an AIC 5 points higher and BIC 10 points higher than the regression model based on progression status and AEs alone. The recommended model therefore only features progression status and ongoing AEs as explanatory variables.

For the models based on time-to-death, treatment arm and age were not statistically significant and the best fitting model by AIC and BIC included only time-intervals to death and ongoing grade 3+ AEs. The time intervals were the same as those investigated in TA939. During the original CDF entry appraisal for TA939 (TA885), the NICE committee said that they felt time-

to-death utilities had uncertain validity and preferred not to consider them. We therefore do not discuss them in any more detail but have provided them for completeness.

For sensitivity analyses in the model, we selected the best fitting regressions based on progression status or time-to-death along with the naïve means from the trial. The company's view is that the naïve means method, which weights by observation, better captures utility compared to the linear mixed effects model, which effectively down-weights repeated observations in patients who have long survival. Since the vast majority of the progression free life years in the model are accrued by patients with long progression-free survival in the trial, it does not make conceptual sense to down-weight the contribution of observations from these patients, since they are more generalisable to the PF health state over the whole time horizon of the economic model. It is important to note that the majority of observations of PF utility values come from the first year of the trial, which includes a population of more mixed prognosis. The PF utility estimates of whichever method, but especially those drawn from linear mixed effects regression models should be considered conservative.

When comparing the progressed disease state utility values from the naïve means, the value of ■■■ is highly concordant with the progression free utility value taken from TA939 of ■■■, which provides some external validity to the estimates.

Table 38: Summary of utility values for scenario analyses

Source	State	Utility value: mean	Utility value: SE	Source
KEYNOTE-A18, Naïve means	Progression free	■■■	■■■	KEYNOTE-A18
	Progressed disease	■■■	■■■	
KEYNOTE-A18, progression-based regression analysis	Progression-free	■■■	■■■	
	Progression	■■■	■■■	
	Disutility due to Grade 3+ AE	■■■	■■■	
KEYNOTE-A18, time to death	360+ Days	■■■	■■■	
	270 - 359 Days	■■■	■■■	
	180 - 269 Days	■■■	■■■	
	90 - 179 Days	■■■	■■■	
	30 - 89 Days	■■■	■■■	
	0 - 29 Days	■■■	■■■	

Key: SE, standard error; AE, adverse event

* Assumed that 180-269 days is the same as 270-359 days

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify evidence for utility and HRQoL in LACC. Searches were run in Oct 2021, and updated in Aug 2023. Full details of the review are provided in Appendix Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

G. In total, 56 unique studies were identified as appropriate to provide evidence for utility and HRQoL in LACC. Only one study identified directly reported health state utility values based on EQ-5D and was based in Thailand, the rest only reported HRQoL measures. No studies used were UK based.

Katanyoo (2022) explored multiple different EQ-5D models in LACC (Thailand value set). All the approaches were significantly differentiated for disease status (i.e., treatment, disease-free, and progression) and presence of symptoms (i.e., no symptoms, one symptom, and >1 symptoms). (80)

3.4.4 Adverse reactions

The impact of AEs on HRQoL is incorporated into the model using incidences of treatment-related AEs reported from KEYNOTE-A18. Adverse events (Grade 3+) that occurred in at least 5% of patients in either arm of KEYNOTE-A18 were included in the model, in accordance with other oncology appraisals. As an exception, diarrhoea (grades 2 or higher) is also included based on the high expected cost of managing these AEs even for events that are below grade 3. The frequencies of Grade 3+ AEs that occurred in at least 5% of patients in either arm, are presented in Table 39. The duration of AEs presented in Table 40 were derived from the patient-level data from KEYNOTE-A18. AEs were split between those that occurred in year 1 and year 2 as to ensure utility decrements and costs are more appropriately applied into the correct year. We made the simplifying assumption that no AEs would persist beyond year 2, which we considered reasonable as no patients are on treatment after this point and AE rates were already very low in the second year of the trial.

For each AE, the probability of experiencing the AE in a given cycle is calculated by dividing the pre or post 12 month AE probability by the number of cycles in a year. A QALY decrement was calculated as the product of the incidence rate, disutility associated with the AE, and the duration of AE. The total QALY decrement due to AEs was then applied per cycle. The coefficient from the regression model is used to model the disutility of grade 3+ AE (Table 38).

Table 39: Grade 3+ AE occurring in ≥5% of patients

Adverse event	Months 0-12		12-24 months	
	Pembrolizumab + CCRT	CCRT	Pembrolizumab + CCRT	CCRT
Anaemia	■	■	■	■
White blood cell count decreased	■	■	■	■
Neutrophil count decreased	■	■	■	■
Lymphocyte count decreased	■	■	■	■

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Leukopenia		■		■		■		■
Neutropenia		■		■		■		■
Lymphopenia		■		■		■		■
Hypokalemia		■		■		■		■
Diarrhea (includes grade 2)		■		■		■		■

Key: AE, Adverse event; CCRT, Concurrent chemoradiotherapy;

Table 40: Duration of adverse events

AEs	Duration, weeks (SE)	Source
Anaemia	■	KEYNOTE-A18 HECON
White blood cell count decreased	■	
Neutrophil count decreased	■	
Lymphocyte count decreased	■	
Leukopenia	■	
Neutropenia	■	
Lymphopenia	■	
Hypokalaemia	■	
Diarrhoea	■	
Key: AE, adverse event; SE, standard error		

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

Within the base-case the naïve means method has been implemented due to the limitations of the linear mixed effects regression models discussed in the mapping section. However, since it seemed appropriate to account for AEs separately within the model, the beta coefficient from the linear mixed effects model was used in addition to the naïve means to estimate AE disutility.

The PD2 utility value was derived from KEYNOTE-826 as there was limited information from KEYNOTE-A18 on patients who had undergone a second progression. Given that the A18 PD utility estimate and the PF utility estimate from KEYNOTE-826 were almost the same (■ versus ■) and applied to the same population, we used the PD utility decrement from KEYNOTE-826 (■) to calculate the PD2 utility value in the model. A scenario analysis where only the A18 data were used and PD1 and PD2 were modelled to have the same utility as a simplifying assumption (Table 41), along with scenario analysis exploring regression derived progression based utilities and time to death utilities are also presented.

Since the PF utility value was already quite close to the general population utility in this cohort (0.849), we made the conservative assumption not to adjust the PF utility upwards to the Company evidence submission template for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

general population utility after the cure point. This accounts for some ongoing disutility from having had the disease and having successful treatment.

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

State	Utility value: mean (standard error)	SE	Justification
Progression free	■	■	Taken directly from KEYNOTE-A18
Progressed disease 1 (PD1 and PD2)	■	■	Taken directly from KEYNOTE-A18
Progressed disease 2	■	■	Disutility decrement of progression from KEYNOTE-826 applied to observed KEYNOTE-A18 progressed disease
Disutility from grade 3+ AE	■	■	Taken directly from KEYNOTE-A18

Key: AE, Adverse event; PD1, Progressed disease 1; PD2, Progressed disease 2; SE, Standard Error

3.5 Cost and healthcare resource use identification, measurement and valuation

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs for pembrolizumab + CCRT and CCRT alone are calculated for patients who were on treatment in each arm of the model. These costs were calculated per component with the planned dosing and administration of the regimen (Table 42) multiplied by the acquisition cost (Table 43). The proportion of patients receiving; EBRT, cisplatin and pembrolizumab are dictated by the corresponding TTD curve for each observed in KEYNOTE-A18.

The dosing schedules are implemented for each treatment as outlined in Table 42. Pembrolizumab + CCRT is implemented in the economic model according to the anticipated MHRA marketing authorisation and the KEYNOTE-A18 trial protocol. Cisplatin is included as per their licensed dose.

Table 42: Dosing schedules used in the analysis

Drug	Dose	Route	Frequency
Concurrent radiotherapy			
EBRT	45 Gy	N/A	25 fractions
Brachytherapy	40-45 Gy	N/A	4 fractions
Combination phase			
Pembrolizumab	200 mg	IV	Once every 3 weeks for a maximum of 5 cycles
Cisplatin	40mg/m ²	IV	Once every week for a maximum of 5 cycles
Maintenance phase			
Pembrolizumab	400 mg	IV	Once every 6 weeks for a maximum of 15 cycles

Key: EBRT, External beam radiotherapy; Gy, Gray; IV, Intravenous ; mg, milligram; m, metre

The list price for pembrolizumab is sourced from the British National Formulary (BNF) database. (81) Cisplatin is available in generic formulation with unit costs relevant to the NHS England setting sourced from the electronic market information tool (eMIT) (Table 50).(82) A commercial access agreement (CAA) is in place for pembrolizumab which makes it available to the NHS at a confidential discount (see Appendix J for details).

Table 43: List price unit costs for each treatment included in the model

Treatment	Mg per unit	Units per pack	Cost per pack (£)	Source
Pembrolizumab	100	1	2,630	BNF (81)
Cisplatin	10	1	3.67	eMIT (82)
	50	1	19.69	eMIT (82)
	100	1	37.34	eMIT (82)

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

Drug acquisition costs are applied as the cost per acquisition to the time on treatment curve for each intervention. Relative dose intensity (RDI) is assumed 100% as the model applies a stopping rule at 15 cycles of Q6W such that no more than 20 cycles of pembrolizumab can be used. The total costs per cycle of each treatment are summarised in Table 44.

Table 44: Drug acquisition costs per treatment per model cycle

Treatment arm	Phase	Drug	Total cost per cycle (£)
Pembrolizumab + CCRT	Combination	Pembrolizumab (up to 5 cycles)	5,288.13
		Cisplatin	
	Maintenance	Pembrolizumab (cycles 6-20)	10,520
CCRT	Combination	Cisplatin	28.13

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Key: CCRT, Concurrent chemoradiotherapy; RDI, relative dose intensity.

Drug administration costs are accrued for the duration of treatment in each treatment arm and applied in line with the planned administration schedule. The study treatments included in the model are administered intravenously in an outpatient setting. The unit costs of treatment administration are sourced from NHS reference costs 2023-2024 (Table 45). (83) In the case where a patient needs to receive a treatment infusion more than once a day, it is assumed that costs are assigned only once for those treatments. The complex chemotherapy administration cost is used for combination therapies (pembrolizumab + cisplatin), and the simple chemotherapy administration cost is used for maintenance monotherapy with pembrolizumab or cisplatin only. This is in line with the approach advised by the Cancer Drugs Fund lead in a recent pembrolizumab submission (TA983). (84)

Table 45: Drug administration unit costs

Administration type	Cost per administration (£)	Drug	Source
Complex chemotherapy	201.66	Pembrolizumab + Cisplatin,	NHS Reference costs 2023/24 (SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance, outpatient)
Simple chemotherapy	152.12	Cisplatin	NHS Reference costs 2023/24 (SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance, outpatient)
		Pembrolizumab monotherapy	

Key: NHS, National Health Service

The cost of administering the radiotherapy element of treatment has been calculated using the unit costs of treatment administration are sourced from NHS reference costs 2023-2024. (83) The number of radiotherapy sessions (fractions) used within the model has been sourced from the BGCS guidelines. (36) The total costs of EBRT and Brachytherapy are averaged across the first 8 weeks of the model and applied in each of those weeks. The weekly per cycle cost is then applied to the TTD curve linked to EBRT.

Table 46: Radiotherapy administration unit costs, per fraction

Radiotherapy type	Administration type	Cost per administration (£)	Number	Source
EBRT	Preparation	1,194	1	NHS Reference costs 2023/24 SC51Z/SC52Z (weighted average): Preparation for Complex Conformal Radiotherapy; Preparation for Complex

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Radiotherapy type	Administration type	Cost per administration (£)	Number	Source
				Conformal Radiotherapy, with Technical Support, Outpatient
	Fraction delivery	266	25	NHS Reference costs 2023/24 SC23Z: Deliver a Fraction of Complex Treatment on a Megavoltage Machine, Outpatient
	Total cost	7,840		
Brachytherapy	Preparation	1,435	1	NHS Reference costs 2023/24 SC54Z/SC55Z (Weighted average, elective inpatient): Preparation for Intracavitary Brachytherapy, Preparation for Interstitial Brachytherapy
	Fraction delivery	3,564	4	NHS Reference costs 2023/24 SC26Z, SC27Z, SC28Z (weighted average, elective inpatient): Deliver a Fraction of Intracavitary Radiotherapy without General Anaesthetic, Deliver a Fraction of Intracavitary Radiotherapy with General Anaesthetic, Deliver a Fraction of Interstitial Radiotherapy
	Total cost	15,692		

Key: EBRT, External beam radiotherapy

3.5.2 Health-state unit costs and resource use

Progression based health care resource use

Costs associated with disease management, monitoring and patient follow-up are included in the economic model, in line with the NICE reference case. Separate resource use was assumed for the PFS, PD1, and PD2 states as resource utilisation may differ between the 3 health states. In addition, resource use also differs depending on how long a patient has been in the PFS state, according to UK clinical experts and BGCS guidelines. (36, 61) Costs were applied to each resource, summed across all resources, and accrued according to time spent in each health state.

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All relevant unit costs were sourced from either PSSRU or NHS reference cost 2023/24, in line with the NICE reference case. (71, 83, 85)

Resource use items and frequency of use were obtained via a clinical expert opinion via an advisory board and 1:1 consultancy for resource use for both PFS and PD states (61, 72).

On feedback from clinicians and in line with the BCGS guidelines, it is assumed that progression free patients are discharged from care at 5 years, and as such accrue no further follow up health care cost from this point. 6 monthly GP visits for these patients has been explored in scenario analysis (61, 86)

A one off progression based cost has also been implemented that captures both the need to test patients for PD-L1 positively (as required for treatment of TA939), and the need for imaging.

Table 47: Resource use and costs associated with model health states

Health state	Resource	Frequen cy (every x weeks)	Source	Cost (£)	Note	Source
PFS 0 - 2 years	CT scan	(50%) 52	Advisory board	£142.33	CT or PET scan to be done yearly	NHS Reference Costs 2023/24 - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast (83)
	PET scan	(50%) 52	Advisory board	£629.70		NHS Reference Costs 2023/24 - RN01A - PET/CT scan of one area (Positron Emission Tomography with Computed Tomography) 19 years and over
	Outpatient visit	(50%) 12	Advisory board	£193.89	Either an in person outpatient visit or consultant led phone call once every 12 weeks	NHS Reference Costs 2023/24 - 370 - Total Outpatient Attendance, Consultant Led
	Consultant led phone call	(50%) 12	Advisory board	£173.01		NHS Reference Costs 2023/24 - 503 - Gynaecological Oncology Service, Consultant Led, Non Admitted, Non-face-to-face (HRG WF01C)
	MRI scan	One at 20 weeks	Advisory board/B GCS	£171.23	One off MRI 3 months post radiotherapy (86)	NHS Reference Costs 2023/24 - RD01A, RD02A - Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over; With contrast (weighted average)
PFS on treatment (Pembrolizuma b arm only)	Blood test	On treatmen t cycle	Advisory board	£8.04	Blood tests are only applied to patients in the pembrolizumab arm, linked to treatment cycle	NHS Reference Costs 2023/24 - DAPS05, 370 - Medical Oncology Service, Haematology

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Health state	Resource	Frequency (every x weeks)	Source	Cost (£)	Note	Source
	CT Scan	12 weekly while on treatment	Advisory board	£142.33	While scans are currently only conducted every year, it is expected that more regular CT scans would be needed while patients were on pembrolizumab to ensure progression has not occurred and patients were still eligible for continued treatment. A 3 monthly frequency is common in other settings.	NHS Reference Costs 2023/24 - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
PFS 2 - 5 years	CT scan	24	Advisory board	£142.33		NHS Reference Costs 2023/24 - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
	Outpatient visit	(50%) 24	Advisory board	£193.89	Either an in person outpatient visit or consultant led phone call once every 24 weeks	NHS Reference Costs 2023/24 - 370 - Total Outpatient Attendance, Consultant Led
	Consultant led phone call	(50%) 24	Advisory board	£173.01		NHS Reference Costs 2023/24 - 503 - Gynaecological Oncology Service, Consultant Led, Non

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Health state	Resource	Frequen cy (every x weeks)	Source	Cost (£)	Note	Source
						Admitted, Non-face-to-face (HRG WF01C)
PD1	CT scan	(50%) 52	Advisory board	£142.33	CT or PET scan to be done yearly	NHS Reference Costs 2023/24 - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
	PET scan	(50%) 52	Advisory board	£629.70		NHS Reference Costs 2023/24 - RN01A - PET/CT scan of one area (Positron Emission Tomography with Computed Tomography) 19 years and over
	Outpatient visit	3	Advisory board	£193.89		NHS Reference Costs 2023/24 - 370 - Total Outpatient Attendance, Consultant Led
	Blood test	3	Advisory board	£8.04		NHS Reference Costs 2023/24 - DAPS05, 370 - Medical Oncology Service, Haematology
PD2	CT scan	8	Advisory board	£142.33		NHS Reference Costs 2023/24 - RD22Z - Computerised Tomography Scan of One Area, with Pre- and Post-Contrast
	Outpatient visit	8	Advisory board	£193.89		NHS Reference Costs 2023/24 - 370 - Total Outpatient Attendance, Consultant Led
	Blood test	8	Advisory board	£8.04		NHS Reference Costs 2023/24 - DAPS05, 370 - Medical Oncology Service, Haematology

Health state	Resource	Frequency (every x weeks)	Source	Cost (£)	Note	Source
One off progression cost	One of scan on progression	On progression	Advisory board	£276.01	Applied on progression both from PF-PD1 and PD1-PD2	Average of: NHS Reference Costs 2023/24 - RD22Z, RD01A, RD02A, RD04Z, RD05Z, RN01A
	PD-L1 test	On progression	Advisory board	£36.20	Only applied on progression from PF-PD1	NHS Reference Costs 2023/24 - DAPS02 - Histopathology and histology

Key: CT scan, computerised tomography scan; NHS, National Health Service; PF, Progression free; PFS, progression-free survival; PD1, progressed disease1; PD2, progressed disease2; PD-L1, Programmed death ligand 1; PET, Positron emission tomography

Subsequent treatment

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

Because down stream efficacy and cost of subsequent treatment in the PD1 state are directly modelled using KEYNOTE-826 data, reliance on the observed subsequent treatment being comparable to the UK treatment is not needed. To understand the proportion of patients receiving various subsequent treatments, clinicians at the advisory board were asked to confirm the main treatment options used in current clinical practice and what proportion get each treatment.

Clinicians during the advisory board confirmed that: (61)

- The 2 treatment regimens used in the UK after progression on CCRT are;
 - Chemotherapy ± bevacizumab
 - Pembrolizumab + chemotherapy ± bevacizumab
- An estimated 20% of patients do receive any further anti-cancer therapy
- Currently, of those that go on to get subsequent treatment after CCRT, 80% are thought to be PD-L1 positive in UK clinical practice, and of these a further 80% are likely to receive pembrolizumab + chemotherapy ± bevacizumab (i.e. 64% of patients that get treatment)
- All remaining patients receive treatment receive chemotherapy ± bevacizumab (remaining 36%)
- Clinicians agreed that the proportion of patient that have the optional bevacizumab observed within KEYNOTE-826, 63%, reflected what they see in clinical practice.

The specific mix of carboplatin and cisplatin used as part of the chemotherapy regimen is taken directly from each arm of the KN-826 trial.

To model subsequent treatment in the pembrolizumab + CCRT arm, it was assumed that for the first 2.5 years, of those that get subsequent treatment, 100% get chemotherapy ± bevacizumab. This is due to the fact the NHS does not currently commission immunotherapy rechallenge if patients progression while on immunotherapy or for 6 months after successful

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completion of a course of immunotherapy. After 2.5 years, it is assumed that subsequent treatment in the pembrolizumab arm is equivalent to the CCRT arm. The time point and treatment mix can both be altered in sensitivity analysis.

In both arms of the model, clinicians advised that 20% of patients that progress will get no treatment due to lack of fitness or personal choice.

The duration of subsequent therapy was also derived from KEYNOTE-826 (Table 48). Inputs relating to the cost of drug acquisition for subsequent therapy are listed in Table 56, and are sourced from the BNF, eMIT and the respective SmPCs. (81, 82) Note that list prices are used for all therapies; confidential discounts, which may be in place for some agents, are unknown to MSD. However, all medicines have generic/biosimilar versions available and none are expensive.

Patients are also able to receive a further line of treatment after progression from the PD1 state to the post progression survival state. Again clinicians were asked about the treatments available to these patients and what proportion of patients get each.

The key feedback regarding 3rd line treatment from the advisory board was:

- The patient population is highly heterogeneous making it hard to comment on the exact treatments used in 3rd line
- Clinicians typically try and get patients onto trials if they are fit enough (it was noted this is out of scope for the NICE process)
- A simplifying assumption was suggested that all patients get low dose weekly paclitaxel, in line with BGCS guidance

This has been implemented in the model, with 100% of patients in the PD2 state receiving weekly paclitaxel. The median time on treatment has been taken from the protocol of the UK based COPELIA trial. (87).

Table 48: Distribution of subsequent therapies in patient that get receive treatment base case analysis

case analysis

Subsequent treatment		Initial treatment					
		Pembrolizumab + CCRT			CCRT		
		%	Mean Duration, months (SE)		%	Mean Duration, months (SE)	
2 nd line treatment							
Pembrolizumab + chemotherapy ± bevacizumab	Pembrolizumab	0.00%*	■	■	64.00%	■	■
	Paclitaxel	■	■	■	■	■	■
	Carboplatin	■	■	■	■	■	■

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Subsequent treatment		Initial treatment					
		Pembrolizumab + CCRT			CCRT		
		%	Mean Duration, months (SE)		%	Mean Duration, months (SE)	
2 nd line treatment							
	Bevacizumab	63.00%	■	■	63.00%	■	■
	Cisplatin	■	■	■	■	■	■
3 rd line treatment							
Paclitaxel (low dose)		100%	1.4	N/A		1.4	N/A

Key:CCRT, Concurrent chemoradiotherapy; SE, Standard error

Note: The denominator for these proportions is “people that get treatment”, within the base case 20% of patients don’t receive any further treatment.

* Pembrolizumab use post pembrolizumab + CCRT goes to 64% at 2.5 years in the base-case

Table 49: Subsequent therapy - drug formulation, dose, and total drug acquisition cost per month

	Drug	Dosing regimen	Cost per vial/pack	Vial/ tablet strength	Total acquisition cost per month	Source
Chemotherapy ± bevacizumab ± pembrolizumab	Pembrolizumab	200mg Q3W	£2,630.00	100 mg	£7,624	BNF(81)
	Paclitaxel	175mg/m ² Q3W	£4.79	30 mg	£46	eMIT(82)
		175mg/m ² Q3W	£12.89	100 mg		
		175mg/m ² Q3W	£22.37	150 mg		
		175mg/m ² Q3W	£31.89	300 mg		
	Carboplatin	750 Q3W	£6.71	50 mg	£56	eMIT
		750 Q3W	£12.18	150 mg		
		750 Q3W	£23.18	450 mg		
		750 Q3W	£38.93	600 mg		
	Bevacizumab	15mg/kg Q3W	£242.66	100 mg	£3,170	BNF
		15mg/kg Q3W	£924.40	400 mg		
		15mg/kg Q3W	£205.55*	100 mg		
		15mg/kg Q3W	£810.10*	400 mg		
	Cisplatin	40mg/m ² Day 1 and 8 Q1W	£19.69	50 mg	£110	eMIT
		40mg/m ² Day 1 and 8 Q1W	£37.34	100 mg		
Paclitaxel (3 rd line)		80mg/m ² Q1W	£4.79	30 mg	£63	eMIT
			£12.89	100 mg		
			£22.37	150 mg		
			£31.89	300 mg		

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

Note: * Bevacizumab biosimilar. The drug costs provided in this table are list prices, and pembrolizumab and bevacizumab are expected to have a confidential discount

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3.5.3 Adverse reaction unit costs and resource use

The costs associated with Grade 3+ AEs occurring in more than 5% of patients in either arm are included in the economic model. The unit costs associated with managing these AEs are based on the most relevant cost databases for the UK setting (NHS reference costs 2023/2024). (83) A summary is presented in Table 50. Costs of adverse event management are modelled by multiplying the AE cost to the probability of AE onset, split by year 1 and year 2. This is then applied per cycle to each arm of the model.

Table 50: Adverse event costs applied in the model

Event	Cost per episode (£)	Description	Source
Anaemia	£620	Weighted 2023/24 NHS Reference Cost (SA03G, SA03H, SA04G, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J), Non-elective short stay	2023/24 NHS Reference Costs
White blood cell count decreased	£561	Weighted 2023/24 NHS Reference Cost (SA08G, SA08H, SA08J), Non-elective short stay	2023/24 NHS Reference Costs
Neutrophil count decreased	£561	Weighted 2023/24 NHS Reference Cost (SA08G, SA08H, SA08J), Non-elective short stay	2023/24 NHS Reference Costs
Lymphocyte count decreased	£561	Weighted 2023/24 NHS Reference Cost (SA08G, SA08H, SA08J), Non-elective short stay	2023/24 NHS Reference Costs
Leukopenia	£696	Weighted 2023/24 NHS Reference Cost (SA35A-E), Non-elective short stay	2023/24 NHS Reference Costs
Neutropenia	£696	Weighted 2023/24 NHS Reference Cost (SA35A-E), Non-elective short stay	2023/24 NHS Reference Costs
Lymphopenia	£696	Weighted 2023/24 NHS Reference Cost (SA35A-E), Non-elective short stay	2023/24 NHS Reference Costs
Hypokalaemia	£584	Weighted 2023/24 NHS Reference Cost (KC05G-N), Non-elective short stay	2023/24 NHS Reference Costs
Diarrhoea	£567	Weighted 2023/24 NHS Reference Cost (FD04A, FD04B, FD04C, FD04D, FD04E, FD10A, FD10B, FD10C, FD10D, FD10E, FD10F, FD10G, FD10H, FD10J, FD10K, FD10L, FD10M), Non-elective short stay	2023/24 NHS Reference Costs

Key: NHS, National Health Service

3.5.4 Miscellaneous unit costs and resource use

Cost of testing

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On progression patients are routinely tested for PD-L1 status to test for eligibility for pembrolizumab (TA939). Within the model 100% of progressors are tested, at a cost of £36.20 (NHS Reference Costs 2023/24 -DAPS02 - Histopathology and histology)

End-of-life cost

A one-time terminal care cost is applied on movement to death (£7,429). This is inflated to the current cost year from the original value of £6,207. (85) This was sourced from the Georgiou and Bardsley (2014) study and has been used and accepted in a number of pembrolizumab appraisals (TA766, TA801, TA830, TA837, TA904) which have been accepted by NICE Committees.(88)

3.6 Severity

MSD consider that pembrolizumab does not qualify for a severity modifier in this indication as the expected QALY loss for standard of care versus the general population does not meet any severity modifier threshold.

3.7 Uncertainty

The evidence underpinning the economic model came from two large well-conducted RCTs that are directly relevant to UK clinical practice; KEYNOTE-A18 and KEYNOTE-826. Mature Final Analysis data were available from the latter. The control arm of KEYNOTE-A18 represents the standard of care for this patient group, making the addition of indirect treatment comparisons unnecessary. Parametric survival curves fit the data from the trials well. There was only one obvious set of best-fitting survival curves for the KEYNOTE-A18 PFS and TTP data, which substantially limits uncertainty in the extrapolations. The model had the capability to capture time dependent transition probabilities in all health states, which was key for accurately estimating the cost-effectiveness of pembrolizumab in the PD1 health state. EQ-5D data were directly available from the trials and were concordant between them. Resource uses were estimated by a panel of UK clinicians treating LACC. Nevertheless, there were some key uncertainties with the model. Due to the comparatively good outcomes in the KEYNOTE-A18 setting (e.g. versus the KEYNOTE-826 setting), PFS and OS were both relatively immature. Observed OS could not be used directly in the model due to its immaturity. The model controlled the PFS extrapolations by the use of a cure point. While it is acknowledged that this is a curative setting and the substantial majority of patients who are PFS at 5 years are cured, there was no data available on the incidence of long term recurrence that would enable the calculation of cure proportion so the 95% used in the model is semi-arbitrary, being based on precedent from other NICE appraisals.

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3.8 Managed access proposal

The Company regards the improvement in PFS and OS observed in KEYNOTE-A18, and the results of the economic analysis as solid evidence that pembrolizumab + CCRT should enter routine commissioning in this setting. However, MSD prioritises access for patients and will therefore consider all available access routes.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 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 Table 51.

Table 51. Summary of variables applied in the economic model

Table 31. Summary of variables applied in the economic model				
Variable	Value	SE	Distribution for PSA	Section in submission
Cycle length	1 week	-	Not varied	3.2.3Error! Reference source not found.
Time horizon, years	50 years	-	Not varied	
Discount rate: Costs	3.5%	-	Not varied	
Discount rate: Outcomes	3.5%	-	Not varied	
Starting age, years	51.5	-	Not varied	3.2.2
Female, %	100%	-	Not varied	
Body surface area, m2	1.7	(0.01)	Normal	
Weight, kg	63.1	(0.6)	Normal	
KEYNOTE-A18 transitions				
Parameter estimates for pembrolizumab PFS	Generalised gamma		Multivariate normal	3.3.2.1
mu	████	████	Multivariate normal	
sigma	████	████	Multivariate normal	
Q	████	████	Multivariate normal	
Parameter estimates for pembrolizumab TTP	Generalised gamma		Multivariate normal	
mu	████	████	Multivariate normal	
sigma	████	████	Multivariate normal	
Q	████	████	Multivariate normal	
Parameter estimates for CCRT PFS	Generalised gamma		Multivariate normal	

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mu	■	■	Multivariate normal
sigma	■	■	Multivariate normal
Q	■	■	Multivariate normal
Parameter estimates for CCRT TTP	Generalised gamma		
mu	■	■	Multivariate normal
sigma	■	■	Multivariate normal
Q	■	■	Multivariate normal
KEYNOTE-826 transitions			
Parameter estimates for pembrolizumab PFS	3 knot hazard		Multivariate normal
gamma0	■	■	Multivariate normal
gamma1	■	■	Multivariate normal
gamma2	■	■	Multivariate normal
gamma3	■	■	Multivariate normal
gamma4	■	■	Multivariate normal
Parameter estimates for pembrolizumab TTP	3 knot hazard		Multivariate normal
gamma0	■	■	Multivariate normal
gamma1	■	■	Multivariate normal
gamma2	■	■	Multivariate normal
gamma3	■	■	Multivariate normal
gamma4	■	■	Multivariate normal
Parameter estimates for pembrolizumab PPS	Generalised gamma		
mu	■	■	Multivariate normal
sigma	■	■	Multivariate normal

3.3.2.2

Q				Multivariate normal	
Parameter estimates for chemotherapy PFS		3 knot hazard		Multivariate normal	
gamma0				Multivariate normal	
gamma1				Multivariate normal	
gamma2				Multivariate normal	
gamma3				Multivariate normal	
gamma4				Multivariate normal	
Parameter estimates for chemotherapy TTP		3 knot hazard			
gamma0				Multivariate normal	
gamma1				Multivariate normal	
gamma2				Multivariate normal	
gamma3				Multivariate normal	
gamma4				Multivariate normal	
Hazard applied to chemotherapy PFS for no treatment		2		Varied in scenario analyses	
Parameter estimates for chemotherapy PPS		Generalised gamma			3.3.2.3
mu				Multivariate normal	
sigma				Multivariate normal	
Q				Multivariate normal	
Parameters for cure point					
Start of cure period, year		5	-	Not varied	3.3.2.1
End of cure period, year		7	-	Not varied	
Cure proportion		95%	-	Not varied	
Subsequent treatment market shares – second line					
CCRT arm	Pembrolizumab	51%	-	Not varied	3.5.2
	Paclitaxel		-		
	Carboplatin		-		
	Bevacizumab		-		
	Cisplatin		-		
	No treatment	20%	-		

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Pembrolizumab arm	Pembrolizumab	0%	-	Not varied	
	Paclitaxel	■	-		
	Carboplatin	■	-		
	Bevacizumab	■	-		
	Cisplatin	■	-		
	No treatment	20%			
Subsequent treatment market shares – third line					
Both arms	Paclitaxel (low dose)	100%	-		3.5.2
Medical management costs by health state					
Medical management costs in PF state per week, up to year 2		£23	N/A	Gamma	3.5.2
Medical management costs in PF state per week, years 2 - 5		£13	N/A	Gamma	
Medical management costs in PD1 state per week		£78	N/A	Gamma	
Medical management costs in PD2 state per week		£43	N/A	Gamma	
Terminal care cost (one-time cost)		£7,429	£743	Gamma	3.5.4
Drug administration costs					
IV (simple)		£152	(£15)	Gamma	3.5.1
IV (complex)		£201	(£20)	Gamma	
AE costs					
Pembrolizumab 0-12 months, per week		£22	N/A	Gamma	3.5.3
Pembrolizumab 12-24 months, per week		£1	N/A	Gamma	
CCRT 0-12 months, per week		£29	N/A	Gamma	
CCRT 12-24 months, per week		<£1	N/A	Gamma	
Utilities					
Utility of PF		■	■	Beta	3.4.5
Utility of PD1		■	■	Beta	
Utility of PD2		■	■	Beta	
Disutility from AEs		■	■	Normal	

3.9.2 Assumptions

Table 52: List of assumptions made in the submission

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. (71)
Population	All patients with FIGO 2014 stage III-IVA	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

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Topic	Assumption	Justification/Reason
		the population of KN-A18 were on average 51 years old.
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 3.2.3
Definition of progression	Investigator assessed progression based on RECIST 1.1.	This is the primary outcome of KN-A18 and most in line with expected UK clinical practice.
Subsequent treatments	Based on expected UK clinical practice.	Subsequent treatments given in KN-A18 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-A18 are included.	Commonly accepted approach in previous health technology appraisals.
Utilities	Progression base utilities applied based on KN-A18 stage III-IVa 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-A18.	Full detail provided in section 3.4
Dosing and maximum treatment duration	Actual received dose as per KN-A18. Pembrolizumab is given up to 20 treatment cycles (~2 years).	Based on trial protocol and expected SmPC
Cure point	95% of progression free patients cured starting at 5 years and finishing at 7 years	Clinical feedback and curative intent of treatment
Testing costs	Included on progression	CPS≥1 testing is required for eligibility for TA939.

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

Table 53 shows the cost-effectiveness results for pembrolizumab + CCRT versus CCRT using the list prices of all treatments and the CAA price for pembrolizumab. The results show that pembrolizumab + CCRT is estimated to offer greater health benefits compared to CCRT alone, with an additional [REDACTED] LYs and 2.05 QALYs gained per patient lifetime. Treatment with pembrolizumab + CCRT is associated with incremental costs of [REDACTED], resulting in an ICER of [REDACTED] per QALY gained. The ICER is lower than the NICE cost-effectiveness threshold of £30,000/QALY gained. This supports the addition of pembrolizumab + CCRT to the LACC treatment pathway. Disaggregated results of the base case analysis are presented in Appendix I.

Table 53: Base case results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER
CRT	■	9.39	■	-	-	-	-
Pembrolizumab + CRT	■	11.97	■	■	2.57	2.05	■

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

3.11 Exploring uncertainty

We conducted a range of sensitivity and scenario analyses on the model.

3.11.1 Probabilistic sensitivity analysis

Key parameters were varied within appropriate probability distributions to examine the effect of joint uncertainty on the model's results, the PSA was run for 1,000 iterations. The incremental costs and QALYs were similar to the deterministic base-case. Pembrolizumab + CCRT was cost effective at a WTP of £30,000/QALY in [REDACTED] of iterations.

Table 54: Probabilistic sensitivity analysis results

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER
CCRT	[REDACTED]	9.41	[REDACTED]	=	=	=	=
Pembrolizumab + CCRT	[REDACTED]	11.92	[REDACTED]	[REDACTED]	[REDACTED]	2.00	[REDACTED]

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

Table 55: PSA iterations plotted on the cost-effective plane



Table 56: Cost-effectiveness acceptability curve



3.11.2 Deterministic sensitivity analysis

Figure 27 shows a tornado diagram in which key input parameters are varied to extreme values to examine their effect on the results. The varying of no single parameter affected the cost effectiveness decision at a threshold of £30,000/QALY gained.

Figure 27: Tornado diagram (DSA results)



3.11.3 Scenario analysis

Results from the scenario analysis can be found in Table 57

Table 57: Results of scenario analyses explored in the cost effectiveness analysis

Scenario	Base case value	Scenario value	Rationale	ICER	% change
Base case				■	■
35 year time horizon	50	35	Estimating impact if a shorter time-horizon is selected	■	■
0% discounting	3.5%	0%	As per NICE guidance	■	■
Exclude end of life cost	£7,429	0		■	■
Utilities based on time until death	Naïve means	Time to death analysis	Explores differing utility calculation methods	■	■
Utilities based on multivariate regression	Naïve means	Regression analysis		■	■
Exclude adverse event disutilities	■	0	Remove potential double counting of impact of AEs	■	■
PD and PD2 utility are equal	Decrement from KN-826	Same PD1 and PD2 as observed in KN-A18	Explores differing utility calculation methods	■	■
Exclude utility adjustment based on age	N/A	N/A		■	■
Exclude treatment waning	Starts 3-5 year from treatment completion	No waning	Explore long term effectiveness assumptions	■	■
Pembrolizumab PFS/TTP distribution = Gompertz	Generalised Gamma	Gompertz	Explore alternative PFS/TTP curves	■	■

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Scenario	Base case value	Scenario value	Rationale	ICER	% change
CRT PFS/TTP distribution = Gompertz	Generalised Gamma	Gompertz	Explore alternative PFS/TTP curves	■	■
Both PFS/TTP distributions = Gompertz	Generalised Gamma	Gompertz	Explore alternative A-18 PFS/TTP curves	■	■
KN-826 PFS/TTP using 2knot hazard (both arms)	3 knot hazard	2 knot hazard	Explore alternative 826 PFS/TTP curves	■	■
KN-826 PFS/TTP using 1knot hazard (both arms)	3 knot hazard	1 knot hazard	Explore alternative 826 PFS/TTP curves	■	■
Pembrolizumab arm PPS weighted to account for pre and post 2.5 year rechallenge	0%	■	Explore PPS assumptions	■	■
Cure proportion of 50%	95%	50%	Explore varying cure assumptions	■	■
Cure starting at 3 finishing at 5 years	Cure from 5-7 years	Cure from 3-5 years	Explore long term effectiveness assumptions	■	■
Cure starting at 7 finishing at 9 years	Cure from 5-7 years	Cure from 7-9 years		■	■
Remove cure assumption	95% cure from years 5 - 7	No cure		■	■
Remove cure and waning assumption				■	■
6 monthly GP visit post 5 years PFS	0	£45	Explore HCRU post 5 year discharge	■	■
No treatment hazard ratio = 3	HR = 2	HR = 3	Explore no treatment assumptions	■	■
No treatment hazard ratio = 1.5	HR = 2	HR = 1.5		■	■

Scenario	Base case value	Scenario value	Rationale	ICER	% change
10% get no further treatment after progressing	20% no treatment	10% no treatment		■	■
Remove the background mortality SMR	SMR = 1.19	SMR = 1	Explore long term survival estimates	■	■

3.12 Subgroup analysis

No subgroup analyses were conducted.

3.13 Benefits not captured in the QALY calculation

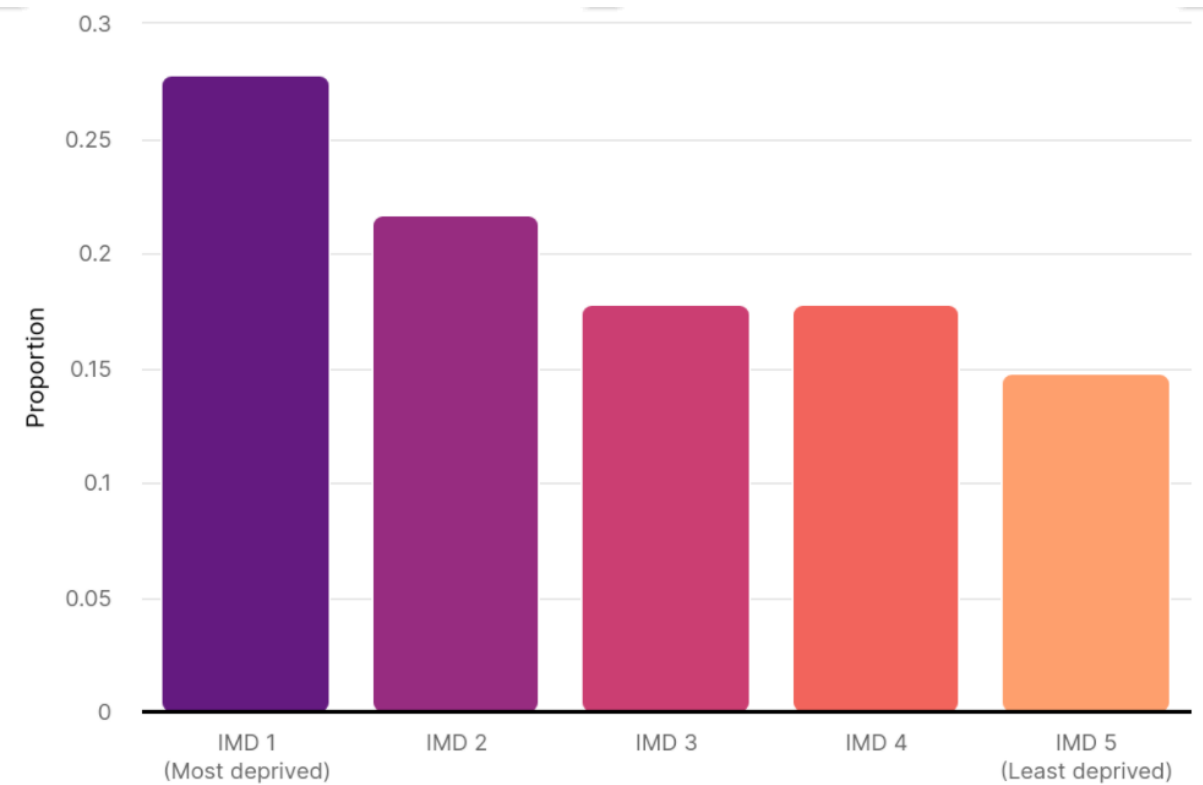
LACC primarily affects working age women. Clinicians have informed us it is common for those women to still have children at home and that LACC can have a significant negative effect on family life. This is supported by evidence from a Survey conducted by Jo's Cervical Trust (discussed earlier in section 1.3.4). The evidence suggests that adding pembrolizumab to standard care would result in a substantial improvement in the proportion of those women who are cured from an otherwise life threatening disease.

As highlighted in section 1.3.3 of the clinical section of this dossier, LACC is associated with substantial health inequalities, not only in incidence but in outcome as well. The primary reason for this appears to be differences in engagement with the NHS cervical screening programme across deprivation quantiles. Advice to the company is that patients from lower socio-economic groups, patients with low health literacy, migrant women and those without English as a first language are all groups that are disproportionately represented in LACC. Clinicians commented that the more advanced the disease, the steeper the gradient of incidence would be across deprivation quantiles.(61, 72)

For these reasons, the company has produced a Distributional Cost-effectiveness Analysis using the outputs of the economic model along with the York DCEA online calculator. (89) We selected ICD10 Code C53 ("malignant neoplasm of the cervix uteri") as the most appropriate. A substantial gradient in incidence across the deprivation quintiles can be seen. It should be noted that this ICD10 code relates to all neoplasms of the cervix, even those that would be detected at earlier stages via the cervical screening programme. It is likely that stage III-IVa LACC has an even steeper social gradient in incidence. There is evidence of this in Figure 2,

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which shows that 5 year survival is 9.5% lower in the most deprived quintile versus the least deprived as well as in the clinician commentary discussed above.



The results of the analysis show a net health benefit of [REDACTED], assuming a WTP of £30,000/QALY, and a flat opportunity cost gradient. Table 58 highlights that for all opportunity cost gradients, pembrolizumab + CCRT would result in the reduction of the inequality gap, with those from the most deprived areas of the country benefiting the most from the intervention. It is important to bear in mind that the population for this indication is substantially smaller than the total ICD C53 population but also that the gradient is likely to be much steeper, due to the strong association between later stage presentations and deprivation. The overall effect on the net health inequality benefit is hard to quantify but it would certainly remain net positive.

Table 58: Net health benefit (QALYs) by IMD quintile

Net health benefit (QALYs)	IMD 1 (most deprived)	IMD 2	IMD 3	IMD 4	IMD 5	Total	Net health inequality benefit
Health opportunity cost gradient							
Flat	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Moderate	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Steep	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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Key: IMD, Indices of multiple deprivation; QALY, Quality adjusted life year

MSD therefore believes it is important that the NICE committee take into account the extent to which adding pembrolizumab to standard care in this setting improves health inequalities when deciding the most appropriate threshold ICER for decision-making.

MSD also believe it is important NICE take into account the effect on family members and dependents. The evidence suggests that pembrolizumab will improve the proportion of women with LACC who are cured by their treatment plan and can therefore return to normal life, which has substantial spillover effects on the quality of life of family members and carers as well as enabling them to return to work.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

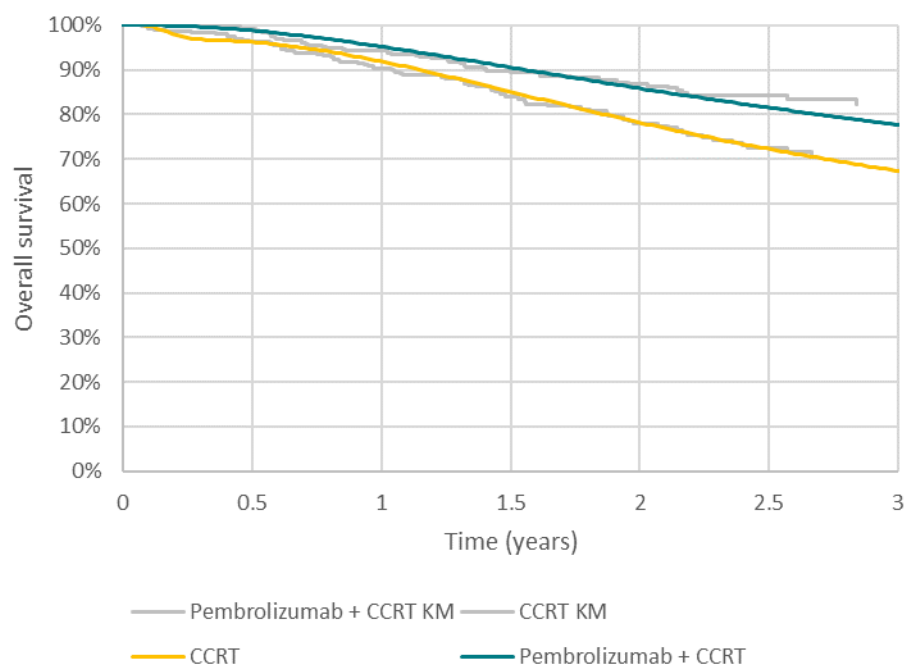
The internal validity and technical accuracy of the model were also checked by an independent health economist using an extensive quality check list derived from the Drummond, Philips and the TECH-VER checklists.(90-92)

OS from KEYNOTE-A18 was not used directly within the economic model but the observed OS was compared to the modelled OS and a close visual fit was demonstrated, suggesting the model has good internal validity.

Various PFS projections were shown to a group of UK clinicians treating LACC at the company's UK advisory board and they confirmed that the base case generalised gamma models provided plausible estimates for both arms. The cure point in the model is set equal to what is considered to be the benchmark in clinical practice.(61) The downstream part of the model is based on mature RCT data already critiqued by a NICE EAG and validated by a NICE committee during TA885 and TA939.

Resource uses were elicited from UK clinicians treating LACC.

Figure 28: Modelled OS compared against observed OS from KEYNOTE-A18



3.15 Interpretation and conclusions of economic evidence

An economic SLR was conducted and retrieved no relevant published cost-effectiveness analyses in LACC so a *de novo* economic model was developed. The economic model was based on data from two high quality RCTs that were directly relevant to the decision problem; KEYNOTE-A18 provided data on the treatment effects of pembrolizumab in this setting, along with data on treatment use, HRQoL and adverse events and KEYNOTE-826 provided data on outcomes on the standard treatment options after progression.

The model had several strengths; as well as being based on directly relevant RCTs, it was capable of handling time-dependent transition probabilities in all states and therefore accurately handling a number of different scenario analyses and adjustments, such as the inclusion of outcomes for patients who are not treated on progression. The structure, data and outputs of the model were all validated at a UK advisory board as being reflective of the natural history and treatment pathway of LACC as it is treated in UK clinical practice.

Although observed OS from the trial was not directly used in the model, the model replicated the observed data well, suggesting that it had good internal validity.

The ICER produced by the model was largely insensitive to sensitivity and scenario analyses, with all scenarios examined producing ICERs less than £30,000/QALY gained. [REDACTED]. The probabilistic sensitivity analysis suggested that pembrolizumab was cost-effective in [REDACTED] of iterations versus a threshold of £30,000/QALY gained. The most influential parameters were

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those related to the PFS extrapolations; the PFS and TTP survival curves and the assumptions related to cure and treatment effect waning. While the use of gompertz curves for PFS and TTP increases the ICER, the company notes that the base case generalised gamma curve provides a substantially better visual and statistical fit to the observed data and produces projections deemed reasonable by clinicians at the UK advisory board. The timing and magnitude of the cure proportion are uncertain in this setting but the scenarios examined show that the inherent uncertainty in this assumption does not lead to large changes in the ICER. This is because the plateauing nature of the PFS curves in both arms of A18 suggest a long term separation between the arms regardless of what time point the projected hazards are adjusted to reflect the expectation of cure.

Stage III-IV LACC has a pronounced social gradient due primarily to lack of engagement with the UK cervical screening programme among certain groups. The company's Distributional Cost-Effectiveness Analysis suggests that the introduction of pembrolizumab in this setting would improve health inequalities in the UK as greater QALY benefits are gained by those in lower socioeconomic groups while opportunity costs are potentially incurred by all groups equally. The inequality benefit for pembrolizumab remained when sensitivity analyses on the social gradient in opportunity costs were undertaken. The company suggests that this is an important modifier for decision-making and should be taken into account along with the clinical and cost-effectiveness estimates. The company would also like to highlight the substantial burden of LACC on a cohort of primarily working age women. The addition of pembrolizumab to chemoradiotherapy is likely to improve the probability that their treatment plan will be genuinely curative and therefore enable more women to return to normal work and family life. Taken together, the evidence suggests that pembrolizumab is highly likely to be a cost-effective addition to standard care in this setting within the NHS.

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5 Appendices

Please see separate Appendices document

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Summary of Information for Patients (SIP)



March 2025

File name	Version	Contains confidential information	Date
ID6138 pembrolizumab SIP [No CON].docx	1	Yes	19 September 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Pembrolizumab (KEYTRUDA®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with FIGO 2014 Stage III-IVA locally advanced cervical cancer in adults who have not received prior definitive therapy

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is pending. See section 1.2 in the company submission for more details.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Organisation	Financial transaction 2024/5	Have met with MSD	Relationship
Black Health Agency for Equality	N	N	None

Cancer Black Care	N	N	None
Cancer 52	Y	Y	Corporate Member 2024
Eve Appeal	Y	Y	Contracted with MSD for the provision of paid for services including participation in MSD policy and educational campaigns centred on the implementation of the World Health Organization and NHS' cervical cancer elimination aspiration. Eve Appeal further received a grant to support their information provision services.
Go Girls	N	N	Email correspondence to understand if they had received invitation documentation from NICE
Helen Rollason Cancer Charity	N	N	N
Independent Cancer Patients Voice	N	N	N
Macmillan Cancer Support	N	Y	Meeting to discuss annual plans and policy landscape. Macmillan contributed a forward to a MSD report on NHS best practise in tackling health inequalities
Maggie's Centres	N	Y	Meeting to discuss annual plans and sponsorship opportunities. No sponsorship was taken forward.
Marie Curie	N	N	N
South Asian Health Foundation	N	N	N
Specialised Healthcare Alliance	N	N	N
Tenovus Cancer Care	N	Y	Meetings to discuss annual plans and policy landscape.
Wellbeing of Women	N	N	N
Women's Health Concern	N	N	N

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Cervical cancer starts in the cells lining the cervix, which is the opening between the vagina and the womb (uterus)

In 2022, 2,641 new cervical cancer cases were registered in England, corresponding to an incidence rate of 9.3 per 100,000 population. (1) Over half of cases, 54.1%, were in women aged 15–49 years. (1)

Cervical cancer diagnosis age standardised rates per 100,000 population in 2022 are nearly twice as high for people who live in the most deprived England quintile compared with the least deprived, 12.1 vs. 7.3 (1) The higher rate is attributed to multiple factors including lower uptake of cervical screening, higher prevalence of smoking and earlier onset of sexual activity. (2)

Jo's Cervical Trust conducted a survey in 2016 with 35 women who had been diagnosed with cervical cancer in the previous two years to understand their experience of cervical cancer and what they valued throughout the treatment pathway. (3) Throughout treatment women found life to be challenging due to the side effects, the time required to attend appointments and recover and changes to their lives. The women also considered the impact on the wider family unit such as disruptions to their children's routine, lack of energy to play, becoming closer to their partners emotionally but, in majority of cases, intimate relationships were negatively affected.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The British Gynaecological Cancer Society (BGCS) guidelines recommend women with abnormal vagina bleeding 'should receive an abdominal, speculum and pelvic examination.' (4) NICE guidelines state a patient should be referred to a specialist via the urgent suspected cancer pathway if 'the appearance of the cervix is consistent with cervical cancer'. (5)

Cervical screening is also another route of diagnosis that can lead to a cervical cancer diagnosis.

A colposcopy is undertaken to obtain biopsies which are then used to make a diagnosis. (4)

2c) Current treatment options:

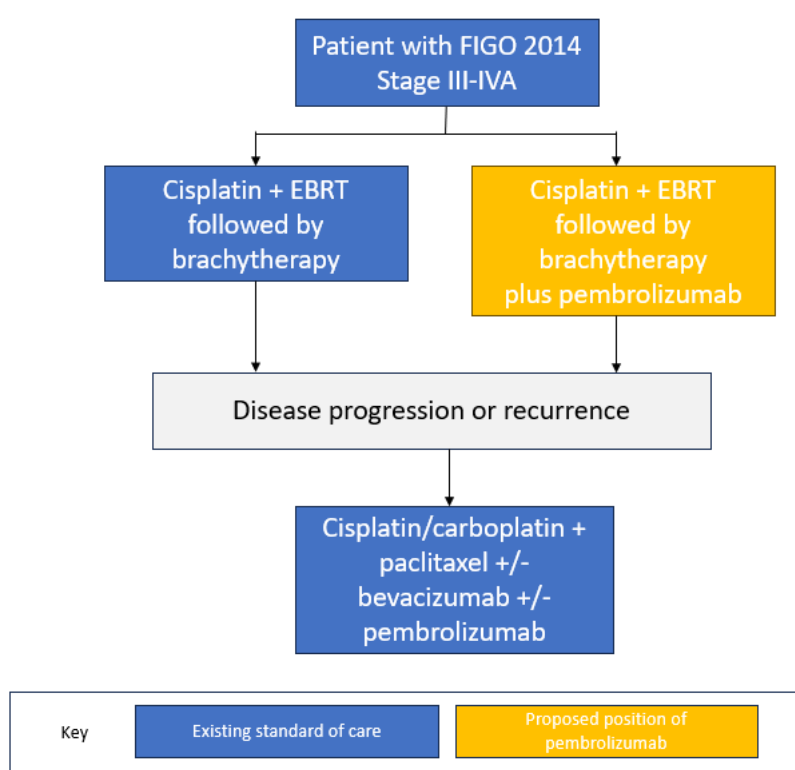
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The current standard of care is chemoradiotherapy as recommended by the British Gynaecological Cancer Society. (4) Chemoradiation consists of external beam radiotherapy, intracavitary brachytherapy and concomitant chemotherapy with cisplatin. Figure 1 shows the current standard of care and the proposed position of pembrolizumab.

Figure 1: Clinical pathway of care for patients with FIGO Stage III-IVA cervical cancer and the proposed placement of pembrolizumab



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Jo's Cervical Trust conducted a survey in 2016 with 35 women who had been diagnosed with cervical cancer in the previous two years to understand their experience of cervical cancer and what they valued throughout the treatment pathway. (3) After diagnosis, a range of emotions and experiences were reported including, feeling isolated in decision making, being concerned about

future fertility, trust in clinicians, and being comfortable with the treatment plan proposed. Women reported being given lots of information, mainly in the form of paper leaflets and being directed to patient group websites. Many of the respondents, who received chemotherapy, experienced physical and psychological side effects of treatment such as nausea, anxiety and feeling lonely. Radiotherapy was also considered to be a challenging treatment. Throughout treatment women found life to be challenging due to the side effects, the time required to attend appointments and recover and changes to their lives. The women also considered the impact on the wider family unit such as disruptions to their children's routine, lack of energy to play, becoming closer to their partners emotionally but, in majority of cases, intimate relationships were negatively affected. Finally, for those who were employed, some were able to use sick leave whilst others had to take early retirement.

A 2014 report found the cost to a woman of having cervical cancer was £5,844 over the course of a year due to increase living costs (car parking, energy bills, childcare) and loss of income. (6)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

An important role of the immune system is the ability to be able to tell the difference between healthy and unhealthy cells. The level of activity of immune cells, such as T cells, is crucial to maintaining a balanced immune response.

Under normal conditions, a protein called programmed death-ligand 1 (PD-L1) which naturally occurs on cells, plays an important role in maintaining this balanced immune response. PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This ensures that normal cells are protected from excessive damage. However, PD-L1 is produced in larger amounts on cancerous cells than normal cells. As a result, when binding to PD-1 on immune T cells, this interaction tricks the immune system thereby protecting the tumour from being attacked by the body's immune system.

PD-1 inhibitors, such as pembrolizumab, act to block the interaction between PD-1 and PD-L1 and by doing so, boost the immune response which helps the person's own immune cells to attack the cancer cells.

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link:

[KEYTRUDA](#)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

In combination with cisplatin, external beam radiotherapy followed by brachytherapy. Chemoradiotherapy appears to make the tumor microenvironment favourably for immuno-oncology, such as pembrolizumab as shown in the PACIFIC study. (7)

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Pembrolizumab comes in a 25mg/mL concentrate solution for infusion. One 4mL vial of concentrate contains 100 mg of pembrolizumab. (8)

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an infusion into the vein (intravenous infusion) over 30 minutes.

The regimen in the KEYNOTE-A18 trial is pembrolizumab is given in combination with cisplatin and EBRT followed by brachytherapy. The pembrolizumab is given every 3 weeks for 5 cycles. This is followed by pembrolizumab only every 6 weeks for up to 15 cycles as long as it is working (i.e. as long as the cancer does not progress) and side effects are tolerable.

For brevity the treatment arms will be referenced as pembrolizumab/placebo + CCRT (cisplatin based radiotherapy) in the remainder of the document.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Study Title	NCT Number	Study Status	Phases	Enrollment
Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)	NCT02628067	Recruiting	Phase 2	1,609
Study of Pembrolizumab, Radiation and Immune Modulatory Cocktail in Cervical/Uterine Cancer	NCT03192059	Completed	Phase 2	43
QUILT-3.055: A Study of Combination Immunotherapies in Patients Who Have Previously Received Treatment With Immune Checkpoint Inhibitors	NCT03228667	Recruiting	Phase 2	40

The Combination of GX-188E Vaccination and Pembrolizumab in Patients With HPV 16 and/or 18+ Advanced Cervical Cancer	NCT03444376	Completed	Phase 1 Phase 2	65
CPI-006 Alone and in Combination With Ciforadenant and With Pembrolizumab for Patients With Advanced Cancers	NCT03454451	Completed	Phase 1	117
Study of NEO-201 in Solid Tumors Expansion Cohorts	NCT03476681	Recruiting	Phase 1 Phase 2	121
NBTXR3 Activated by Radiotherapy for Patients with Advanced Cancers Treated with an Anti-PD-1 Therapy	NCT03589339	Recruiting	Phase 1	145
Efficacy and Safety Study of First-line Treatment With Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Women With Persistent, Recurrent, or Metastatic Cervical Cancer (MK-3475-826/KEYNOTE-826)	NCT03635567	Completed	Phase 3	617
Trans-Artery/Intra-Tumor Infusion of Checkpoint Inhibitors Plus Chemodrug for Immunotherapy of Advanced Solid Tumors	NCT03755739	Recruiting	Phase 2 Phase 3	200
Safety and Efficacy of Tisotumab Vedotin Monotherapy & in Combination With Other Cancer Agents in Subjects With Cervical Cancer	NCT03786081	Active - Not recruiting	Phase 1 Phase 2	214
FT500 as Monotherapy and in Combination With Immune Checkpoint Inhibitors in Subjects With Advanced Solid Tumors	NCT03841110	Completed	Phase 1	37
A Study of XmAb®22841 Monotherapy & in Combination w/ Pembrolizumab in Subjects w/ Selected Advanced Solid Tumors	NCT03849469	Completed	Phase 1	78
GEN1046 Safety Trial in Patients With Malignant Solid Tumors	NCT03917381	Active - Not recruiting	Phase 1 Phase 2	429
Focused Ultrasound Ablation and PD-1 Antibody Blockade in Advanced Solid Tumors	NCT04116320	Active - Not recruiting	Phase 1	5
Safety, PK and Efficacy of ONC-392 in Monotherapy and in Combination of Anti-PD-1 in Advanced Solid Tumors and NSCLC	NCT04140526	Recruiting	Phase 1 Phase 2	733
Evaluating Length of Treatment With PD-1/PD-L1 Inhibitor in Advanced Solid Tumors	NCT04157985	Recruiting	Phase 3	578
Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer (MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047)	NCT04221945	Active - Not recruiting	Phase 3	1,060
Efficacy of Immunotherapy Plus a Drug in Patients With Progressive Advanced Mucosal Cancer of Different Locations	NCT04357873	Active - Not recruiting	Phase 2	112
A Study of SGN-B6A in Advanced Solid Tumors	NCT04389632	Recruiting	Phase 1	824
AN0025 and Pembrolizumab Combination in Advanced Solid Tumors	NCT04432857	Active - Not recruiting	Phase 1	63
Pembrolizumab and Olaparib in Cervical Cancer Patients	NCT04483544	Active - Not recruiting	Phase 2	8
GYNecological Cancers Treated with NETrin MAbs in Combination with Chemotherapy and /or Pembrolizumab	NCT04652076	Active - Not recruiting	Phase 1 Phase 2	240
Pembrolizumab for the Treatment of Cervical Intraepithelial Neoplasia	NCT04712851	Recruiting	Phase 2	25
Pembrolizumab and Lenvatinib in Advanced Cervical Cancer	NCT04865887	Recruiting	Phase 2	35
Study of NGM707 As Monotherapy and in Combination with Pembrolizumab in Advanced or Metastatic Solid Tumor Malignancies	NCT04913337	Active - Not recruiting	Phase 1 Phase 2	179

GI-101 As a Single Agent or in Combination with Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors	NCT04977453	Recruiting	Phase 1 Phase 2	430
MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005) (KEYVIBE-005)	NCT05007106	Active - Not recruiting	Phase 2	604
A Study to Investigate Safety and Tolerability of TransCon IL-2 $\hat{I}^2/\hat{I}^3$ Alone or in Combination With Pembrolizumab and/or TransCon TLR7/8 Agonist or Other Anticancer Therapies in Adult Participants With Locally Advanced or Metastatic Solid Tumor Malignancies	NCT05081609	Recruiting	Phase 1 Phase 2	473
ASTEROID: A Trial of ASTX660 in Combination With Pembrolizumab	NCT05082259	Recruiting	Phase 1	48
A Beta-only IL-2 ImmunoTherapY Study	NCT05086692	Recruiting	Phase 1 Phase 2	115
STK-012 Monotherapy and in Combination Therapy in Patients with Solid Tumors	NCT05098132	Recruiting	Phase 1	202
Triplex Checkpoint Inhibitors Therapy for Advanced Solid Tumors	NCT05187338	Recruiting	Phase 1 Phase 2	100
Study of NGM831 as Monotherapy and in Combination With Pembrolizumab or Pembrolizumab and NGM438 in Advanced or Metastatic Solid Tumors	NCT05215574	Active - Not recruiting	Phase 1	130
Personalized Neoantigen Peptide-Based Vaccine in Combination With Pembrolizumab for Treatment of Advanced Solid Tumors	NCT05269381	Recruiting	Phase 1 Phase 2	36
Study of NGM438 as Monotherapy and in Combination With Pembrolizumab in Advanced or Metastatic Solid Tumors	NCT05311618	Active - Not recruiting	Phase 1	71
Oral Axl/Mer/CSF1R Selective Tyrosine Kinase Inhibitor Q702 in Combination With Pembrolizumab in Patients With Selected Advanced Solid Tumors	NCT05438420	Recruiting	Phase 1 Phase 2	120
A Safety, Tolerability and Efficacy Study of NC410 Plus Pembrolizumab in Participants with Advanced Unresectable or Metastatic Solid Tumors	NCT05572684	Active - Not recruiting	Phase 1 Phase 2	97
A Study to Evaluate the Safety, Pharmacokinetics, and Activity of RO7502175 as a Single Agent and in Combination With Checkpoint Inhibitor in Participants With Locally Advanced or Metastatic Solid Tumors	NCT05581004	Recruiting	Phase 1	450
Study of TNG260 and an Anti-PD Antibody in STK11 Mutated Solid Tumors	NCT05887492	Recruiting	Phase 1 Phase 2	126
Study of XNW5004 Tablet in Combination With KEYTRUDA® (Pembrolizumab) in Subjects With Advanced Solid Tumors Who Failed Standard Treatments (KEYNOTE F19)	NCT06022757	Recruiting	Phase 1 Phase 2	204
Safety and Efficacy of NEO212 in Patients with Astrocytoma IDH-mutant, Glioblastoma IDH-wildtype or Brain Metastasis	NCT06047379	Recruiting	Phase 1 Phase 2	134
PRGN-2009 in Combination with Pembrolizumab Versus Pembrolizumab in Patients with Recurrent or Metastatic Cervical Cancer	NCT06157151	Recruiting	Phase 2	46
GM103 Intratumoral Injection in Patients With Locally Advanced, Unresectable, Refractory and/or Metastatic Solid Tumors	NCT06265025	Recruiting	Phase 1 Phase 2	125
Study of Pembrolizumab and Lenvatinib in Metastatic and Recurrent Cervix Cancer (LenPem Cervix)	NCT06266338	Recruiting	Phase 2	30

A Study of VET3-TGI in Patients With Solid Tumors	NCT06444815	Recruiting	Phase 1	60
Accelerated Brachytherapy Forward Chemo Radiation Therapy (ABC-RT) for Locally-advanced Cervical Cancer	NCT06529809	Recruiting	Phase 1 Phase 2	50

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Two primary endpoints were used to assessment the effectiveness of pembrolizumab in the indication under review.

1. Overall Survival (OS) is defined as the 'length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.' (9) Taking the median OS in a trial can be a useful measure of how long a patient may expect to live after starting to take the medicine in the trial.
2. Progression Free Survival (PFS) is defined as the 'length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.' (10) PFS is considered an indication of disease control and stabilisation.

The hazard ratio (HR) is a summary statistic for PFS and OS which compares the probability of events in one treatment arm (pembrolizumab + CCRT), with the probability of events in another treatment arm (placebo + CCRT). It is used to see if patients receiving one treatment experience the outcome faster (or slower) than another treatment. A HR of 1 indicates that there is no difference between the treatments. Here, a HR of less than 1 indicates that pembrolizumab + CCRT decreases the chance of the outcome and a HR exceeding 1 indicates that the pembrolizumab + CCT increases the chance of the outcome. For information that we can share at the time of writing:

OS Results:

- The OS HR was 0.57 (95% CI: 0.39, 0.83), in favour of pembrolizumab + CCRT
- This represents a 43% reduction in the risk of death when treated with pembrolizumab + CCRT compared placebo + CCRT
- The median OS was not reached in either group.

PFS Results:

- The PFS HR was 0.57 (95% CI: 0.43,0.76) in favour of pembrolizumab + CCRT, representing a 43% reduction in the risk of progression.
- Median PFS was not reached in either group.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used

does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The KEYNOTE-A18 trial used three types of questionnaires to measure the QoL of patients: EORTC QLQ-C30, EORTC QLQ-CX24 that looks specifically at the quality of life of cancer patients, and the EQ-5D, that looks at the general health status of a patient, and EQ-5D-5L.

The EQ-5D is of most relevance to a NICE appraisal and consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system has five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). Results from these questions can then be combined and scaled to produce a single score with a maximum score of 1. Scores can vary from 0, which represents death, to 1 which represents the best possible health state. The EORTC uses different questions, however it also produces a score that is meant to represent a patient's quality of life. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. From this we can gather three scores (from the EQ-5D questionnaire, the EQ-5D VAS and the EORTC questionnaires) that can assess how a patient feels throughout their treatment.

The findings from the questionnaires cannot be reported as the data are commercially sensitive.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The grading system for adverse reactions, or side effects, referred to above is explained in section 4a.

The side effects that were reported in KEYNOTE-A18 are consistent with the common side effects listed in the pembrolizumab SmPC. The ten most common were anaemia, nausea, diarrhoea, white blood cell count decreased, neutrophil count decreased, vomiting, urinary tract infection, platelet count decreased, hypomagnesaemia and hypokalaemia.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Pembrolizumab reduces the risk of the cancer coming back. This means that it may stop the cancer from progressing to stages where treatments aiming to cure the disease are not available.
- Most of the side effects that patients can experience while on treatment or after treatment are of mild or moderate severity. Overall, the benefit-risk ratio for pembrolizumab in this indication is considered positive.
- While treatment requires infusion every three or six weeks for up to a year, resulting in more frequent visits to hospital compared to active monitoring, pembrolizumab does not negatively affect quality of life.
- The infusion time of pembrolizumab is short and there is the potential for pembrolizumab to be given every 6 weeks, which could result in short and infrequent visits to a hospital for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients are at an increased risk of developing immune related side effects, some of which may last beyond the patient stopping pembrolizumab. Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects.

Pembrolizumab, like any other medicine, does not work the same in every patient. Not all patients' cancer will respond to treatment and it may not result in an extended life expectancy.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

MSD has developed a cost-effectiveness model to assess the value and economic considerations of using pembrolizumab plus chemoradiotherapy compared with chemoradiotherapy alone. Currently, chemoradiotherapy (consisting of external beam radiotherapy + brachytherapy + concurrent cisplatin) is regarded as the first-line therapy in patients with LACC. The model accounts for resources, costs, survival, and quality of life of patients receiving either pembrolizumab plus chemoradiotherapy, or chemoradiotherapy alone.

The model simulates patients' progression through a set of distinct health states over their entire lifetime. These health states are relevant to patients with LACC, and each health state is associated with a certain amount of costs and a certain quality of life.

The following health states were used in this cost-effectiveness model:

- Progression-free: a patient's disease is responding to treatment or is stable and not actively progressing. Costs in this health state are associated with treatment received, treatment administration costs, management of disease, and adverse events, with costs varying over time. Quality of life is higher compared with patients with progressed disease and is also affected by treatment-related adverse events.
- Progressed disease 1: a patient's disease is assumed to have progressed. Costs in this health state are associated with treatment received, treatment administration costs, and management of disease. Quality of life is lower compared with patients with progression-free disease.
- Progressed disease 2: a patient's disease is assumed to have progressed again. Costs in this health state are associated with treatment received, treatment administration costs, and management of disease. Quality of life is lower compared with patients with only 1 disease progression.
- Death: This state includes costs associated with provision of care towards the end of life

The model uses the clinical data available for pembrolizumab plus chemoradiotherapy and chemoradiotherapy alone to estimate how fast a patient progresses through these different health states. More specifically, it uses the data on progression-free survival from the KEYNOTE-A18 trial to estimate how long patients spend in the progression-free state(11). Data on the time to second progression and death is taken from the KEYNOTE-826 trial(12). The time spent in each health state is then adjusted for the quality of life of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient as a result of the treatment received. This is then compared with the total costs associated with that treatment (consisting of treatment costs, subsequent treatment costs, adverse event costs, and general costs associated with management of LACC such as routine visits and testing). This comparison allows for an assessment of whether the costs associated with using pembrolizumab plus chemoradiotherapy are justifiable based on the additional QALYs patients gain.

Clinical benefits included in the model

The model predicted that treatment with pembrolizumab plus chemoradiotherapy would lead to more clinical benefit (i.e. more QALYs) gained than treatment with chemoradiotherapy alone (please note that the exact QALY results are confidential). This benefit was mainly driven by the progression-free survival and in turn overall survival benefit that pembrolizumab plus chemoradiotherapy has over chemoradiotherapy alone. This resulted in a longer time spent in the progression-free health state (compared with chemoradiotherapy alone), which was associated

with a better overall quality of life, and a longer survival overall. The model suggested that pembrolizumab improved the probability that a patient would be cured by their treatment plan.

Costs included in the model

Pembrolizumab is subject to confidential price agreements with the NHS, so full cost information cannot be presented. However, broadly, treatment with pembrolizumab plus chemoradiotherapy was associated with higher costs than treatment with chemoradiotherapy alone. This was mostly driven by higher treatment costs of pembrolizumab, and as patients live for longer, more disease management costs are accrued. However, patients receiving chemoradiotherapy were expected to incur higher subsequent treatment costs.

Model results

Overall, the company's model determined that treatment with pembrolizumab plus chemoradiotherapy was associated with additional benefit to patients (QALYs).

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The addition of pembrolizumab to current standard of care represents a step change in the management of patients with certain stages of LACC (i.e. FIGO 2014 stage III-IVA) and should be considered innovative in its potential to make a significant and substantial impact on health-related benefits. If approved, pembrolizumab in combination with chemoradiotherapy (followed by pembrolizumab maintenance) will be the first advanced treatment that can be used to treat patients in the first line with certain stages of LACC in line with the anticipated licence (i.e. FIGO 2014 stage III-IVA).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Cervical cancer diagnosis rates per 100,000 population in 2022 were nearly twice as high for people who live in the most deprived quintile in England compared with the least deprived, with rates of 12.1 versus 7.3, respectively. (1)

Survival at various timepoints is also poorer for those falling into the most deprived category compared with the least deprived, with 5-year survival being 56.2% for the most deprived compared with 65.7% for the least deprived (see Figure 2). (13)

If approved, the company's analyses suggest that pembrolizumab would improve health inequalities.

For further details please see section 1.3.3 and section 3.13 in the company submission document.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

In oncology clinical trials, the severity of adverse events are usually graded according to US National Cancer Institute's AE Severity Grading Scale - Common Terminology Criteria for Adverse Events (CTCAE). (14) CTCAE can also be used to grade the AE for non-oncology studies, but generally not appropriate for studies using healthy volunteers.

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing or feeding).
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- Brachytherapy: 'A type of internal radiation therapy in which seeds, ribbons, or capsules that contain a radiation source are placed in your body, in or near the tumor. Brachytherapy is a local treatment and treats only a specific part of your body.' (15)
- Chemoradiotherapy: A combined treatment of having 'chemotherapy and at the same time as radiation.' (16)
- Colposcopy: 'A procedure in which a lighted, magnifying instrument called a colposcope is used to examine the cervix, vagina, and vulva.' (17)
- Concomitant chemoradiotherapy: 'When chemotherapy is given on the same or another day during a course of radiotherapy.' (18)
- External Beam Radiotherapy (EBRT): This type of radiotherapy 'comes from a machine that aims radiation at your cancer. It is a local treatment, which means it treats a specific part of your body.' (19)
- Locally advanced: 'Cancer that has spread from where it started to nearby tissue or lymph nodes.' (20)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. NHS Digital. Cancer Registration Statistics, England, 2022 2024 [Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2022>].
2. Cancer Research UK. Deprivation doubles cervical cancer risk 2008 [Available from: <https://news.cancerresearchuk.org/2008/12/02/deprivation-doubles-cervical-cancer-risk/>].
3. Jo's Cervical Cancer Trust. Cervical cancer stories: diagnosis, care, treatment and life beyond 2016 [Available from: https://web.archive.org/web/20220127201019/https://www.jostrust.org.uk/sites/default/files/jcct_cervical_cancer_stories_full_report_v1.0.pdf].
4. British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) Cervical Cancer Guidelines: Recommendations for Practice 2020 [Available from: <https://www.bgcs.org.uk/wp-content/uploads/2021/07/FINAL-Cx-Ca-Version-for-submission-2.pdf>].
5. NICE. Suspected cancer: recognition and referral NG12 - 1.5 Gynaecological cancers 2023 [Available from: <https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer#gynaecological-cancers>].
6. Salter J. Behind the Screen 2014 [Available from: https://demos.co.uk/wp-content/uploads/2014/06/Behind_the_screen_-_web.pdf].
7. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.
8. Medicines & Healthcare products Regulatory Agency. KEYTRUDA 25 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION 2025 [Available from: <https://products.mhra.gov.uk/product/?product=KEYTRUDA+25+MG%2FML+CONCENTRATE+FOR+SOLUTION+FOR+INFUSION&page=1&doc=Spc>].
9. National Cancer Institute. OS 2025 [Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/os>].
10. National Cancer Institute. Progression-free survival 2025 [Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/progression-free-survival>].

11. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;404(10460):1321-32.
12. Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, et al. First-Line Pembrolizumab + Chemotherapy Versus Placebo + Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Final Overall Survival Results of KEYNOTE-826. *J Clin Oncol*. 2023;41(36):5505-11.
13. NHS Digital. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021 2023 [Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021>].
14. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 2017 [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf].
15. National Cancer Institute. Brachytherapy to Treat Cancer 2019 [Available from: <https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/brachytherapy>].
16. Macmillan Cancer Support. Chemoradiation 2022 [Available from: <https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/chemoradiation>].
17. National Cancer Institute. Colposcopy 2025 [Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/colposcopy>].
18. NottsHNCS. Concomitant 2025 [Available from: <https://nottshncs.nhs.uk/glossary/concomitant-treatment>].
19. National Cancer Institute. External Beam Radiation Therapy for Cancer 2018 [Available from: <https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/external-beam>].
20. National Cancer Institute. Locally advanced cancer 2025 [Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/locally-advanced-cancer>].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID6138 Pembrolizumab cervical cancer CQ response [CON]		Yes	19 September 2025

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Systematic literature review (SLR) methods

A1. Company's submission (CS) Appendix B, page 23. The literature searches included the trials registry clinicaltrials.gov; however, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart (Figure 1, page 23 of the CS appendices) reports that 143 records were excluded prior to screening "marked as trial registry." Please explain the reasoning behind searching a source if its contents were ineligible for inclusion.

MSD response:

A separate search of ClinicalTrials.gov, conducted outside of Ovid, was performed to identify recent relevant trials with available results not yet published/indexed in the literature. The 143 records excluded at the initial screening stage were retrieved from the Cochrane Central Register of Controlled Trials (CENTRAL) via the Ovid platform. To avoid duplication between CENTRAL and ClinicalTrials.gov, these 143 CENTRAL records were excluded, as ClinicalTrials.gov is more up to date.

A2. CS Appendix B, page 8. The text states that the Scottish Intercollegiate Guidelines Network (SIGN) search filters were used to retrieve trials. What source was used for the terms to retrieve observational studies of adverse effects, and how were systematic reviews/meta-analyses identified (which the CS appendices state were hand-searched for relevant references)?

MSD response:

Adverse effects as an outcome were captured within the PICOTS criteria for the SLR of clinical effectiveness, as detailed in Section B.1.2 of the Appendices that were submitted as part of the evidence dossier for the project. The adverse effect outcomes collected were:

- Treatment-emergent adverse events (any and grade ≥ 3)
- Treatment-related adverse events (any and grade ≥ 3)
- Serious adverse events (any and treatment-related)
- Discontinuation due to adverse events (overall and treatment-related)
- Death due to adverse events (overall and treatment-related)

Eligible study types were:

- Randomized controlled trials.
- Non-randomized trials
- Single-arm trials

Thus, MSD consider that the search strategies and inclusion criteria applied would have led to the inclusion of relevant studies focusing on adverse effects of relevant interventions and comparators.

No dedicated search for SLRs/NMAs was conducted, and SLRs and NMAs were an excluded study type. However, during abstract and full-text screening, potentially relevant SLRs/NMAs were identified and hand-searched for relevant references. See Table 1 for a list of searched SLRs/NMAs.

Table 1: References reporting SLRs and NMAs that were hand searched

Author	Year	Title	DOI
Cheng et al	2021	Effectiveness comparisons of various therapies for figo stage ib2/iiia2 cervical cancer: A bayesian network meta-analysis	https://dx.doi.org/10.1186/s12885-021-08685-9
Datta et al	2019	Efficacy and safety evaluation of the various therapeutic options in locally advanced cervix cancer: A systematic review and network meta-analysis of randomized clinical trials	https://dx.doi.org/10.1016/j.ijrobp.2018.09.037
Datta et al	2017	Concurrent chemoradiotherapy vs. Radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis	https://dx.doi.org/10.1016/j.ygyno.2017.01.033
Hu et al	2016	Meta-analysis of cisplatin-based chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma	
Liu et al	2022	Concurrent chemoradiotherapy followed by adjuvant chemotherapy versus concurrent chemoradiotherapy alone in locally advanced cervical cancer: A systematic review and meta-analysis	https://dx.doi.org/10.3389/fonc.2022.997030
Lu et al	2021	Chemoradiotherapy alone vs. Chemoradiotherapy and hysterectomy for locally advanced cervical cancer: A systematic review and updated meta-analysis	https://dx.doi.org/10.3892/ol.2020.12421
Ma et al	2019	Platinum single-agent vs. Platinum-based doublet agent concurrent chemoradiotherapy for locally advanced cervical cancer: A meta-analysis of randomized controlled trials	https://dx.doi.org/10.1016/j.ygyno.2019.04.013
Meng et al	2016	Concurrent cisplatin-based chemoradiotherapy versus exclusive radiotherapy in high-risk cervical cancer: A meta-analysis	https://dx.doi.org/10.2147/OTT.S97436
Petrelli et al	2014	Radiotherapy with concurrent cisplatin-based doublet or weekly cisplatin for cervical cancer: A systematic review and meta-analysis	https://dx.doi.org/10.1016/j.ygyno.2014.04.049
Qi et al	2022	Efficacy and safety of pembrolizumab on cervical cancer: A systematic review and single-arm meta-analysis	https://dx.doi.org/10.3389/fonc.2022.910486
Schmidt et al	2022	Efficacy and safety of immunotherapy for cervical cancer-a systematic review of clinical trials	https://dx.doi.org/10.3390/cancers14020441
Wang et al	2021	Survival outcomes of neoadjuvant chemotherapy-related strategies compared with concurrent	https://dx.doi.org/10.1007/s00404-020-05916-5

		chemoradiotherapy for locally advanced cervical cancer: A meta-analysis of randomized controlled trials	
Wang et al	2011	Radiochemotherapy versus radiotherapy in locally advanced cervical cancer: A meta-analysis	https://dx.doi.org/10.1007/s00404-010-1385-5
Xue et al	2018	The efficacy of concurrent weekly carboplatin with radiotherapy in the treatment of cervical cancer: A meta-analysis	https://dx.doi.org/10.1016/j.ygyno.2018.07.005
Zhu et al	2020	Weekly versus triweekly cisplatin-based concurrent chemoradiotherapy in the treatment of locally advanced cervical carcinoma: An updated meta-analysis based on randomized controlled trials	https://dx.doi.org/10.1097/MD.00000000000018663

A3. PRIORITY. CS, Section 2, pages 36 to 60. Please confirm that all clinical and safety data presented in the clinical section of the CS relate to Interim Analysis 2 (IA2) of KEYNOTE-A18. Please also confirm that the cut-off date for IA2 is January 2024.

MSD response:

MSD can confirm that all clinical data provided within the original CS related to the Jan 2024 data. As part of MSD's clarification question response, clinical outcomes for the final analysis (data cut Jan 2025) have been provided in an appendix. MSD's response also includes an updated model that includes relevant FA data.

A4. PRIORITY. CS, Section 2, page 19. The text states: *"Results from the final analysis are expected in [REDACTED]"* Please clarify whether the results of the final analysis are expected to be available within the timescales for this appraisal.

MSD response:

As per A3, FA data are available and MSD have provided the updated final analysis clinical outcomes and model in an addendum as part of the clarification response.

A5. CS, Section 1.3.2, Table 3, page 14 and CS, Section 2.6.1.1, Table 12, page 37. The 3-year overall survival (OS) in the placebo group KEYNOTE-826 is [REDACTED]; this is substantially [REDACTED] than the 3-year net survival in the 2015-2019 English population (Stage 3 = 53.2%, Stage 4 = 22.8%).

- (a) Please clarify which staging classification system was used for the data on stage in the English population shown in Table 3? Please map the data to the

International Federation of Gynecology and Obstetrics (FIGO) 2014 and FIGO 2018 staging systems if those classification systems were not used.

(b) If available, please provide landmark progression-free survival (PFS) estimates for the English population treated under current standard of care.

MSD response:

Information on FIGO staging tool and PFS estimates is not available from NHS Digital. The apparent difference in 3-year OS is likely a result of mismatches in the population. An appendix to the NHS Digital report indicates that approximately 55% (222/400) and 33% (173/526) of patients diagnosed at stages III and IV, respectively, received CRT.⁽¹⁾ Additionally, 26% and 36% of patients diagnosed with stage III and stage IV, respectively, received either palliative treatment or no treatment. The report does not provide information on performance status, comorbidities or radiotherapeutic technique. The company consider that section 1.3.2 of the CS relates to the generalities of the epidemiology of cervical cancer in England and that the specific percentages reported in Table 3 are not generalisable to the precise population covered by the marketing authorisation for pembrolizumab.

A6. PRIORITY. CS, Section 2. Please provide data on patient characteristics for the following subgroups *at progression* for KEYNOTE-A18 (amongst the subset of patients who progressed):

- Patients in the pembrolizumab group who received subsequent treatment
- Patients in the pembrolizumab group who did not receive any subsequent treatment
- Patients in the placebo group who received subsequent treatment
- Patients in the placebo group who did not receive any subsequent treatment.

Please compare these data with the Combined Positive Score (CPS) ≥ 1 KEYNOTE-826 *baseline* patient characteristics (pembrolizumab vs placebo group).

MSD response:

Patient baseline characteristics for the requested subgroups from KEYNOTE-A18 are presented in Table 2 and Table 3, together with baseline characteristics for the CPS ≥ 1 population of KEYNOTE-826 (Table 4) and the subgroup of patients from

KEYNOTE-826 with CPS ≥ 1 and who had received prior chemoradiotherapy at enrolment into the trial (Table 5). MSD note that, in KEYNOTE-A18, patient characteristics were not routinely collected at progression and only data on 'ECOG closest to progression' are available for the instance of disease progression. However, MSD consider that, at the moment of disease progression, most of the patient's characteristics, such as ethnicity, will not have changed from baseline measurement, and, for others, such as age, the change will be minimal and, thus, baseline characteristics are relevant the EAG's request.

Of note, ECOG closest to progression was defined as the ECOG measurement closest to progression among the measurements before or on the day of progression. For the participant characteristics at baseline and progression with and without subsequent therapy, subsequent therapy was defined as oncologic medications, radiation therapy or surgery.

After inspection of the forest plots from KEYNOTE-826, MSD considered that the only obviously relevant subgroup analysis to perform was on patients who had prior chemoradiotherapy and so we present a comparison with the baseline characteristics of these patients, as well as the CPS >1 population.

MSD provide a narrative overview of similarities and difference in patient characteristics across the groups but consider it important to highlight that the subgroups presented for KEYNOTE-A18 are *ad hoc* subgroups and are based on a characteristic that could not be accounted for as a strata at randomisation, and, as such, randomisation has been broken and imbalances may have been introduced.

For example, [REDACTED]
[REDACTED]
[REDACTED]. MSD
note that [REDACTED] from the two trials
(Table 2, Table 3, Table 4, Table 5). However, [REDACTED] of those in
KEYNOTE-A18 who progressed and received subsequent treatment [REDACTED]
[REDACTED]
[REDACTED] in KEYNOTE-826 ([REDACTED]
[REDACTED]
[REDACTED]). As noted earlier, [REDACTED]

[REDACTED]

[REDACTED]. MSD consider that the [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. MSD also note that, in line with the inclusion criteria

of the two studies, there is disparity between KEYNOTE-A18 and KEYNOTE-826 in the proportion of patients with FIGO stage III-IVA, with 100% of patients from KEYNOTE-A18 having cervical cancer of FIGO stage III-IVA compared with [REDACTED] of patients from KEYNOTE-826 with CPS ≥ 1 who had received prior chemoradiotherapy (Table 5). Theoretically it would have been possible to isolate the patients who received prior chemoradiotherapy *and* had FIGO stage III-IVA at diagnosis but the sample size would have been small, which would have added to the uncertainty given neither cohort is appropriately randomised.

Table 2: Patient characteristics (at baseline or at progression) by treatment group for FIGO III to IVA patients who progressed based on investigator assessment and received subsequent treatment (ITT population)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Sex						
Female	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Age (Years)						
< 65	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
≥ 65	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Mean	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
SD	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Range	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Race						
American Indian Or Alaska Native	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Asian	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Black Or African American	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Multiple	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
White	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Ethnicity						
Hispanic Or Latino	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Not Hispanic Or Latino						
Geographic Region						
Asia Pacific						
EMEA						
North America						
Latin America						
Geographic Region 2						
North America						
Western Europe						
Rest of the World						
Age Group (Years)						
< 65						
65 - 74						
Baseline ECOG						
0						
1						
ECOG at PD^a						
0						
1						
2						
FIGO 2014 Stage at Screening						
III to IVA						
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic						
No Positive Pelvic nor Para-Aortic						
Histology Subtype						
Non-squamous						
Squamous						
Planned Type of EBRT						
IMRT or VMAT						
non-IMRT and non-VMAT						
Planned Total Radiation therapy Dose per (EQD2)						
< 70 Gy						
>= 70 Gy						
PD-L1 Status						
CPS<1						
CPS>=1						
Missing						
SD=Standard deviation.						
a: ECOG at PD was defined as the ECOG measurement closest to progression among the measurements before or on the day of progression						

Subsequent Treatment includes oncologic medications, radiation therapy or surgery., EMEA = Europe, the Middle East and Africa, EBRT = External beam radiotherapy, IMRT = Intensity modulated radiotherapy, VMAT = Volumetric modulated arc therapy.

Database Cutoff Date: 07JAN2025

Table 3: Patient characteristics (at baseline or at progression) by treatment group for FIGO III to IVA patients who progressed based on investigator assessment and did not receive subsequent treatment (ITT population)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population						
Sex						
Female						
Age (Years)						
< 65						
>= 65						
Mean						
SD						
Median						
Range						
Race						
American Indian Or Alaska Native						
Asian						
Black Or African American						
Multiple						
White						
Ethnicity						
Hispanic Or Latino						
Not Hispanic Or Latino						
Not Reported						
Geographic Region						
Asia Pacific						
EMEA						
North America						
Latin America						
Geographic Region 2						
North America						
Western Europe						
Rest of the World						
Age Group (Years)						
< 65						
65 - 74						

75 - 84						
85+						
Baseline ECOG						
0						
1						
ECOG at PD^a						
0						
1						
2						
FIGO 2014 Stage at Screening						
III to IVA						
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic						
No Positive Pelvic nor Para-Aortic						
Histology Subtype						
Non-squamous						
Squamous						
Planned Type of EBRT						
IMRT or VMAT						
non-IMRT and non-VMAT						
Planned Total Radiation therapy Dose per (EQD2)						
< 70 Gy						
>= 70 Gy						
PD-L1 Status						
CPS<1						
CPS>=1						
SD=Standard deviation. a: ECOG at PD was defined as the ECOG measurement closest to progression among the measurements before or on the day of progression Subsequent Treatment includes oncologic medications, radiation therapy or surgery., EMEA = Europe, the Middle East and Africa, EBRT = External beam radiotherapy, IMRT = Intensity modulated radiotherapy, VMAT = Volumetric modulated arc therapy. Database Cutoff Date: 07JAN2025						

Table 4: KEYNOTE-826 baseline patient demographics and disease characteristics for those with CPS $\geq$ 1

	CPS $\geq$ 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)	██████	██████	██████
Race, n (%)			
White	153 (56.0)	172 (62.5)	325 (59.3)
Asian	██████	██████	██████
Ethnicity, n (%)			
Hispanic or Latino	██████	██████	██████
Non-Hispanic or Latino	██████	██████	██████
Geographic region, n (%)			
EU/EMEA	██████	██████	██████
Latin America	██████	██████	██████
North America	██████	██████	██████
Asia Pacific	██████	██████	██████
ECOG PS, n (%)			
0	160 (58.6)	148 (35.8)	308 (56.2)
1	111 (40.7)	127 (46.2)	238 (43.4)
2	██████	██████	██████
Missing	██████	██████	██████
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)
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	██████	██████	██████
Undifferentiated carcinoma	██████	██████	██████

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⁽²⁾; KEYNOTE-826 Clinical study report.⁽³⁾			

Table 5: KEYNOTE-826 baseline patient demographics and disease characteristics for the subgroup of patients with CPS ≥1 and who received prior chemoradiotherapy with or without surgery

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population						
Sex						
Female						
Age (Years)						
<50						
50 to 64						
65 to 74						
≥75						
Mean						
SD						
Median						
Range						
Race						
American Indian Or Alaska Native						
Asian						

Black Or African American						
American Indian Or Alaska Native And Black Or African American						
American Indian Or Alaska Native And White						
American Indian Or Alaska Native And White And Asian						
Black Or African American And White						
Multiple						
White						
Missing						
Ethnicity						
Hispanic Or Latino						
Not Hispanic Or Latino						
Not Reported						
Unknown						
Geographic Region						
Asia Pacific						
EU/EMEA						
North America						
Latin America						
ECOG Performance Scale						
0						
1						
2						
Stage at Initial Diagnosis^b						
I						
II						
III						
IIIA						
IIIB						
IVA						
IVB						
Disease Status at Study Entry						
Persistent or Recurrent with distant metastases at study entry						
Persistent or Recurrent without distant metastases at study entry						
Histology of Subtype of Cervical Cancer						
Adenocarcinoma						
Adenosquamous/Both - Squamous And Adenocarcinoma						
Squamous Cell/Squamous Cell Carcinoma						

PD-L1 Status						
1=<CPS<10						
CPS>=10						
Bevacizumab Use						
Yes						
No						
Prior Therapy						
Chemoradiation (CRT) and Surgery						
CRT Only						
a: Participants in France cannot report race by law. b: Stage at Initial Diagnosis determined using FIGO 2009/ NCCN 2017 criteria. c: Metastatic includes participants with para-aortic lymph node involvement. Table includes participants with CPS at baseline above or equal to 1 and with prior chemoradiation therapy, with or without surgery, reported at baseline. SD: Standard Deviation Database Cutoff Date: 03OCT2022						

A7. CS, Section 2.7, Table 18, pages 43 to 45. Please confirm that this table includes only the All Patients As Treated (APaT) population of patients who progressed. If not, please clarify what the denominator in each group relates to (pembrolizumab + CCRT N= ; CCRT N=).

MSD response:

Table 18 presents data for the APaT population of patients with FIGO stage III/IVA disease who received subsequent oncologic treatment.

A8. CS, Section 2.4, Figure 9, page 46. The hazard ratio (HR) for OS . Please comment on this finding.

MSD response:

The KEYNOTE-A18 trial was not powered to detect differences by subgroups, including based on age, and age was not a stratification factor in the trial. There are only approximately per arm among patients aged >65, the confidence intervals for the OS HR are wide and cross 1. The PFS HR . The company do not believe it is appropriate to draw conclusions about age group-specific treatment effects from these data.

A9. PRIORITY. CS, Section 2.9, pages 47 to 52. The CS states that the concurrent chemoradiotherapy (CCRT) regimen administered in KEYNOTE-A18 reflects that

used in current UK clinical practice. In light of this, please clarify why it was considered necessary to explore evidence synthesis using external studies of CCRT.

MSD response:

MSD did this for completeness as the NICE scope was vague about chemoradiotherapy regimen and some papers on alternative or historical regimens were identified within the SLR. No study was ultimately considered to provide relevant data.

A10. CS, Section 2.12.3, page 62. The text states: *“The baseline characteristics of enrolled patients and study design (including the modality of chemoradiotherapy) of KEYNOTE-A18 were discussed with UK clinicians treating LACC at an advisory board. The clinicians agreed the study design and participants reflect current UK clinical practice, and the evidence is therefore directly applicable.”* The EAG has read the minutes of the MSD 2024 advisory board meeting and could not find any reference to this discussion. Please provide any additional notes from this discussion, if available.

MSD response:

No additional meeting notes are available. However, the meeting summaries do present useful evidence in this regard. The clinicians confirmed that the staging presentation of the trial as a whole is more advanced than would be seen in UK clinical practice, where most patients are stage I and II because of the success of the UK screening programme. The company considers this is a minor limitation as it relates to the marketing authorisation for pembrolizumab since it is restricted to the stage III-IV patients. They confirmed that patients who present with stage III-IV disease are often migrant women or those from socioeconomic and cultural groups who do not engage with screening programmes. The extent to which this would be an effect modifier is uncertain. There is some discussion around PD-L1 proportions in locally advanced disease although this is not tested for currently in clinical practice so it is difficult to know how generalisable the trial is. They confirmed that the radiotherapy techniques used in clinical practice reflect the standard of care in the UK although some centres give higher doses than current BGCS guidelines. They also commented that the use of interstitial as an addition to standard intracavity brachytherapy appears low in both arms compared to UK practice. It is not obvious whether this would bias the treatment effect estimates as the proportions are similar between the arms. In the

summaries of the individual clinician consultancies it is confirmed that ethnicity is not a significant factor. Median age in KEYNOTE-A18 (49,50) is very similar to KEYNOTE-826 (51,50) and age was not raised as a concern in TA939.

A11. CS, Section 2.10.5, Table 25, page 58. The penultimate row in the table appears to report the cause of death as “death.” Please provide further details.

MSD response:

We can confirm that in the clinical trial database, deaths with unknown cause are coded as “death”.

Section B: Clarification on cost-effectiveness data

Literature searches

B1. CS Appendices F, G and H, pages 82 to 196. The table numbers quoted as reporting the searches for Appendices F, G and H appear to be incorrect. For example, in Section F1 of the CS appendices (page 82) it is stated that Tables 26 to 28 contain the search strategies, but these do not seem to match (should these instead refer to Tables 33 to 35?). The same problem exists in CS Appendices G and H. Please confirm the correct table numbers reporting the search strategies for each of these SLRs.

MSD response:

As far as MSD can tell, the search strategies for cost-effectiveness analyses SLR were tables 33-35. For health related quality of life studies, SLR tables 42-44 and for cost and resource use SLR tables 33-35.

These have now been superseded via the SLR updates in the appendices.

B2. CS, Section 3.1, page 65. The CS states that the most recent update searches were conducted on the 23rd August 2023. This search date is approximately two years ago. Please update the searches and provide details of any additional relevant economic studies of pembrolizumab plus CCRT in the target population for this appraisal.

MSD response

MSD apologise for this, please find the updated SLRs and their summaries in the appendices. No additional evidence was deemed relevant for inclusion in the updated economic model.

Survival analysis, extrapolation and cure

B3. PRIORITY. CS, Section 3.2.3, page 67. The economic model estimates the per-cycle risk of death in the 'Progression Free' and 'Progressed Disease 1' states as the difference between time to progression (TTP) (PFS censored for pre-progression death events) and PFS. The same approach is applied to the transition between the 'Progressed Disease 1' and 'Progressed Disease 2' states. Please explain why a competing risks approach was not used (for example, the approach described by Williams *et al.*, *Medical Decision Making*, 2017, 37[4]).

MSD response:

One described advantage of the method cited by Williams et al. is that the competing risks approach avoids bias that is caused by an imbalance in censoring (for reasons other than death) between the competing survival curves. KEYNOTE-A18 is a high quality RCT without imbalances in censoring between the arms so this advantage is unlikely to be relevant in this situation.

MSD note that the TTP and PFS method is conceptually similar to the competing risks approach in that the outcome of TTP is calculated by using PFS data and treating transitions directly to death as censor events. A weakness of using competing risks here would be that the transition to death would have to be calculated by censoring all progression events and only counting transitions directly to death as events. We note that there are very few transitions directly to death in this relatively young population and therefore the competing risks approach may have increased uncertainty due to the sparseness of the data. This is evidenced by the extreme closeness of the PFS and TTP curves and small resultant hazards for PF->Death transitions.

Further to this, the PFS and TTP approach was accepted by the NICE committee in TA939 and the validated data were available from that appraisal for use within this model.

B4. PRIORITY. CS, Section 3.2.1, page 70. The text states: “*The primary source of clinical data for the economic model is KEYNOTE-A18 (Jan 2023 datacut)...*” Please confirm that this is a typographical error and that the model uses data from the January 2024 data-cut (IA2). If this is not a typographical error, please update the model to use the most recent available data-cut.

MSD response:

MSD apologise for this typographical error; the data cut used for the CS was the Jan 2024 datacut (IA2). As part of the clarification response MSD have now provided updated outcomes and a model using the FA data cut.

B5. PRIORITY. CS, Section 3.3.2, page 71. The text states that model selection included “*Assessment of the underlying hazard functions.*” However, plots of the PFS and TTP hazards in KEYNOTE-A18 are not presented in the CS and the description of the parametric survival model selection process does not refer to consideration of the underlying empirical and/or modelled hazard functions. Please clarify how the empirical and modelled hazard functions were used to inform parametric model selection for the transitions out of the ‘Progression Free’ health state.

MSD response:

As part of MSD’s clarification response, updated KEYNOTE-A18 final analysis results and survival analysis for PFS, TTP and OS have been provided along with smoothed and empirical hazard plots. Please refer to the addendum for the updated survival analysis including discussion on how the underlying hazards informed curve selection.

B6. PRIORITY. CS, Section 3.2.4, pages 69 to 79. For PFS, TTP and OS in KEYNOTE-A18, please provide plots of the empirical/unsmoothed and smoothed hazard function for each end point and each treatment group. Please also plot the hazard function of each of the fitted parametric survival models on top of the empirical and smoothed hazard.

MSD response:

As part of MSD’s clarification response, updated KEYNOTE-A18 final analysis results and survival analysis for PFS, TTP and OS have been provided along with

smoothed and empirical hazard plots. Please refer to the addendum for the updated survival analysis including discussion on how the underlying hazards informed curve selection.

B7. PRIORITY. CS, Section 3.3.2.3, pages 90 to 93. For post-progression survival (PPS) in KEYNOTE-826, please provide plots of the empirical/unsmoothed and smoothed hazard function for each treatment group. Please also plot the hazard function of each of the fitted parametric survival models on top of the empirical and smoothed hazard.

MSD response:

The answer below relates to the full licensed population of KEYNOTE-826. The addendum also contains the relevant figures for the “prior-CRT” population.

Please see below the smoothed hazard plot for PPS in each arm of the KEYNOTE-826 trial, with the one-piece parametric fit hazard functions overlayed.

Figure 1 indicates that all parametric distributions provide a reasonable visual fit to the underlying smoothed PPS hazards in the pembrolizumab arm, although the generalised gamma fit best captures the curved shape from around 20 weeks to 100 weeks. This provides further support for the generalised gamma selection in the base, building on the rationale of lowest AIC and good visual fit to the KM data.

Figure 1: Plot of hazard function of parametric distributions used for long-term extrapolation for the group treated with pembrolizumab + chemotherapy

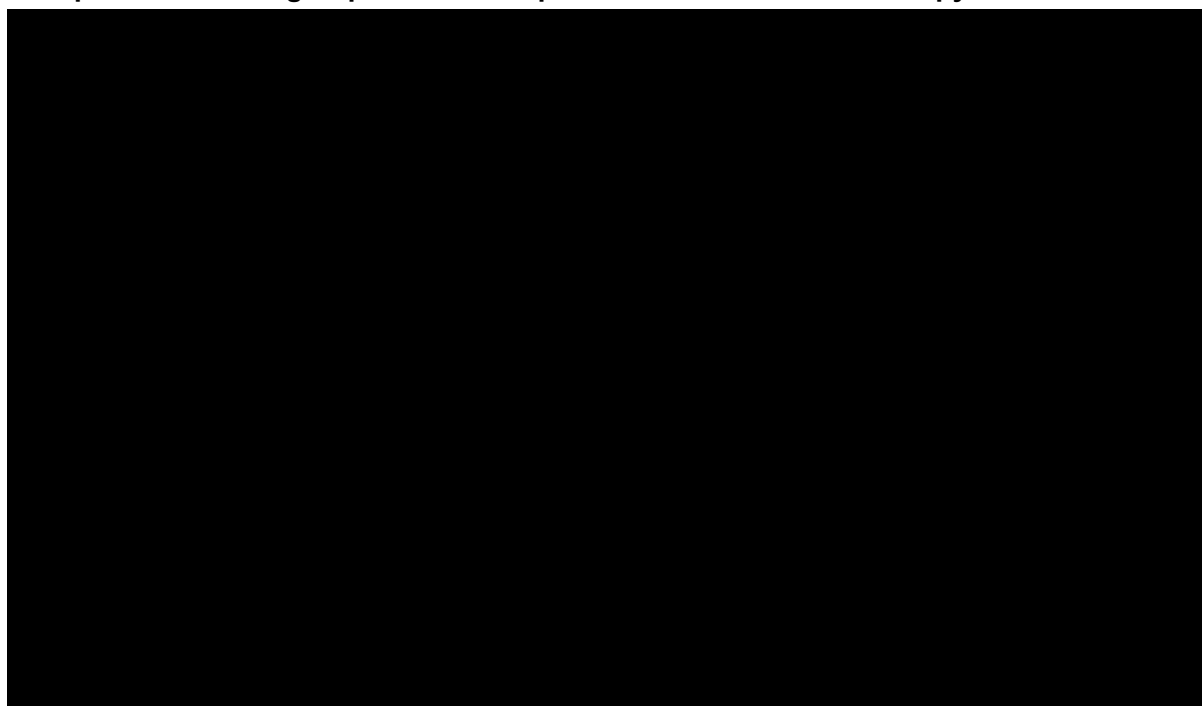
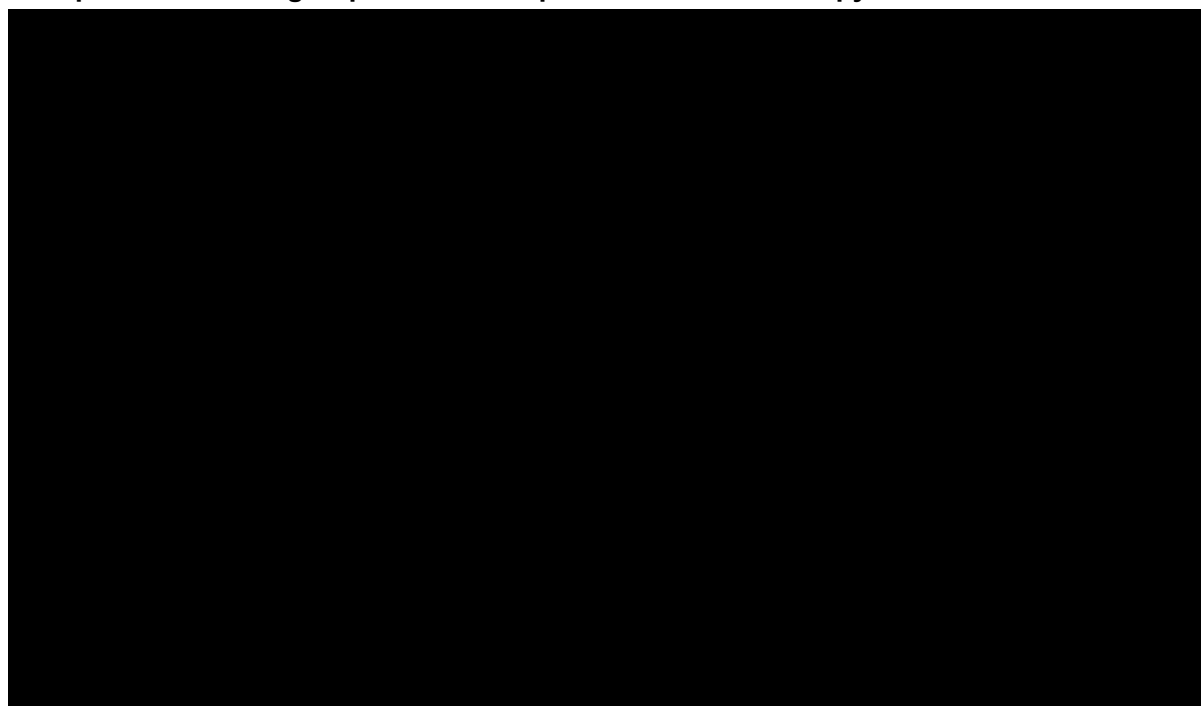


Figure 2 shows that past 50 weeks the generalised gamma distribution is the only curve fit that accurately captures the underlying smoothed hazard observed in the chemotherapy arm of KEYNOTE-826. As with the pembrolizumab arm this builds on rationale for picking the generalised gamma curve, with it having a good visual fit to the KM data and the lowest AIC. This combination of generalised gamma in both arm also satisfies clinical expectation from TA939 that the mean PPS in the pembrolizumab arm should be higher than the chemotherapy arm and the curves should not cross. The company note that KN-826 PPS life years make up a very small proportion of modelled life years and alternative assumptions have a very limited effect on the ICER.

Figure 2: Plot of hazard function of parametric distributions used for long-term extrapolation for the group treated with placebo + chemotherapy



B8. PRIORITY. CS, Section 3.3.2.1, pages 73 to 76. For PFS and TTP data from KEYNOTE-A18, the survival analysis presented in the CS includes standard parametric survival distributions only. The text on page 75 of the CS states: *“The generalised gamma and Gompertz curves were the only ones to fit the observed data well. This is clear for both CCRT and pembrolizumab + CCRT arms.”* However, these distributions do not appear to provide a good visual representation of the available PFS and TTP data. Please explore the use of more flexible parametric survival models (e.g., restricted cubic spline [RCS] models with 1-3 knots) in line with the models fitted to the PFS and TTD data from KEYNOTE-826. Please also incorporate these RCS distributions into the economic model.

MSD response:

As part of the updated survival analysis using final analysis, the appropriateness of spline fits to the new data-cut are discussed in the addendum.

B9. PRIORITY. CS, Section 3.2.3, page 66 and CS, Section 2.6.1.2, Figure 6, page 39. The CS justifies the cure assumptions applied in the economic model through reference to a *“plateauing of PFS data in the pembrolizumab arm”* of KEYNOTE-A18. The plot of observed PFS in KEYNOTE-A18 shown in CS Figure 6 does not appear

to feature a plateau, and PFS events continue in both groups up to the final observed time point in the trial. Through reference to CS Figure 6, please explain where the company believes a plateau occurs.

MSD response:

In the quotation from section 3.2.3, the company are explaining the reasons for a state transition structure being preferred over a partitioned survival model. In this case that, due to relative data maturity, a dramatic slowing down of events had already been observed for the PFS outcomes but not yet for OS. OS therefore needed to be some function of PFS in order for the modelled outcomes to be plausible.

The justifications for the cure assumptions are discussed more fully on pages 77 and 78 of the CS in Section 3.3.2.1. The basics of these are that the curves are extrapolated to 5 years, which is the point at which patients are no longer followed up routinely in UK clinical practice, the remaining extrapolated hazard is gradually reduced by 95% to allow for some recurrences after this over a tapering period from 5-7 years in both arms. These assumptions are consistent with NICE committee preferences in other appraisals of immunotherapies in curative oncology settings e.g. TA830, TA1017. Given the recent advances in radiotherapeutic techniques, no long-term epidemiological data were identified to enable a more exact calculation of the cure proportion.

In both the clinical advisory board and the company's one-to-one consultancies, clinicians confirmed that they expect the addition of pembrolizumab to increase the proportion of patients who are cured by their treatment plan.

B10. CS, Section 3.3.2.2, Figures 18 and 19, pages 83 and 84. The legends obscure parts of these plots. Please update the plots.

MSD Response:

New versions of these plots are provided below.

Figure 3: Update to Figure 18 from original submission: PFS visual fits of all 1, 2 and 3 knot models to the smooth spline hazards

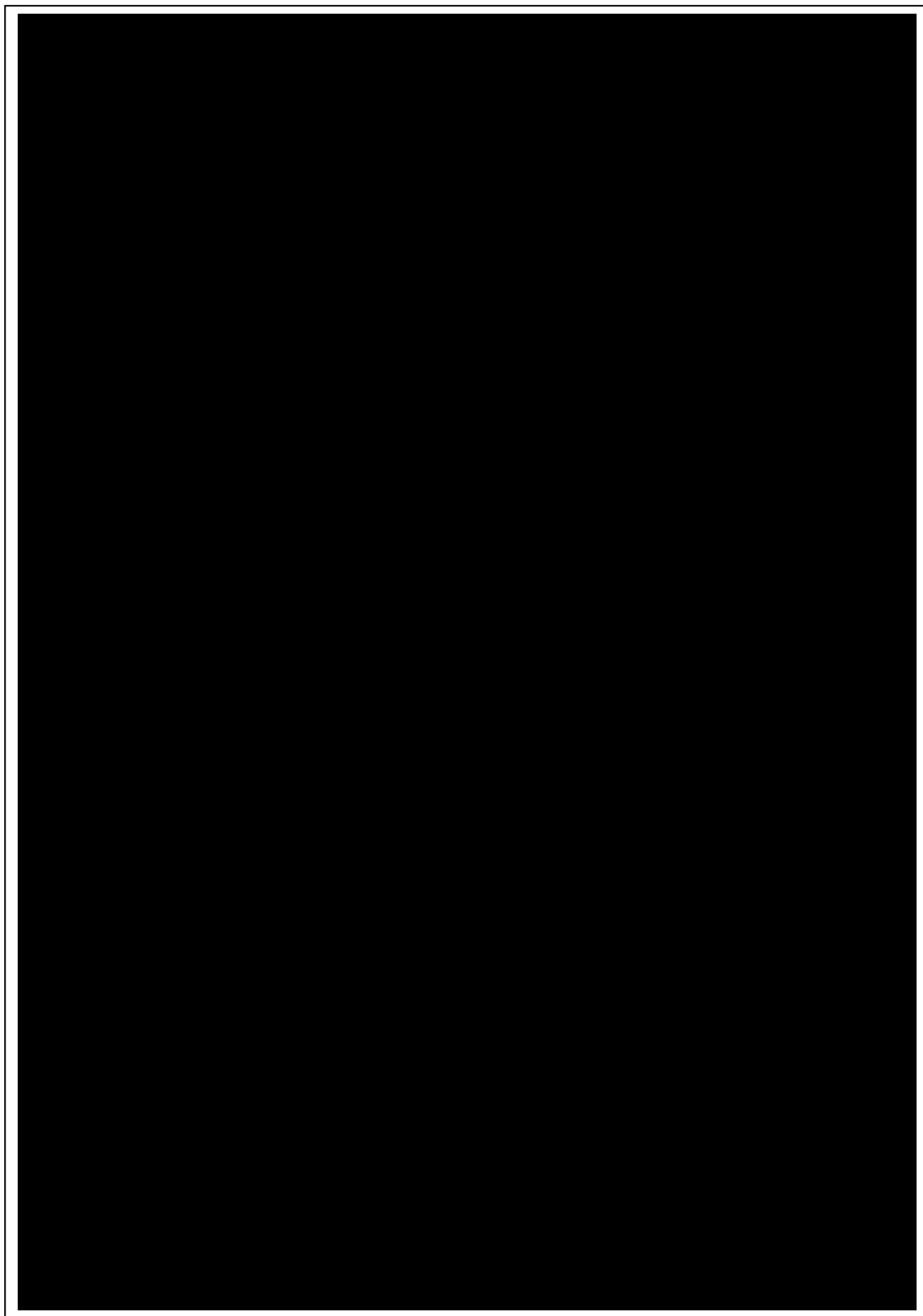
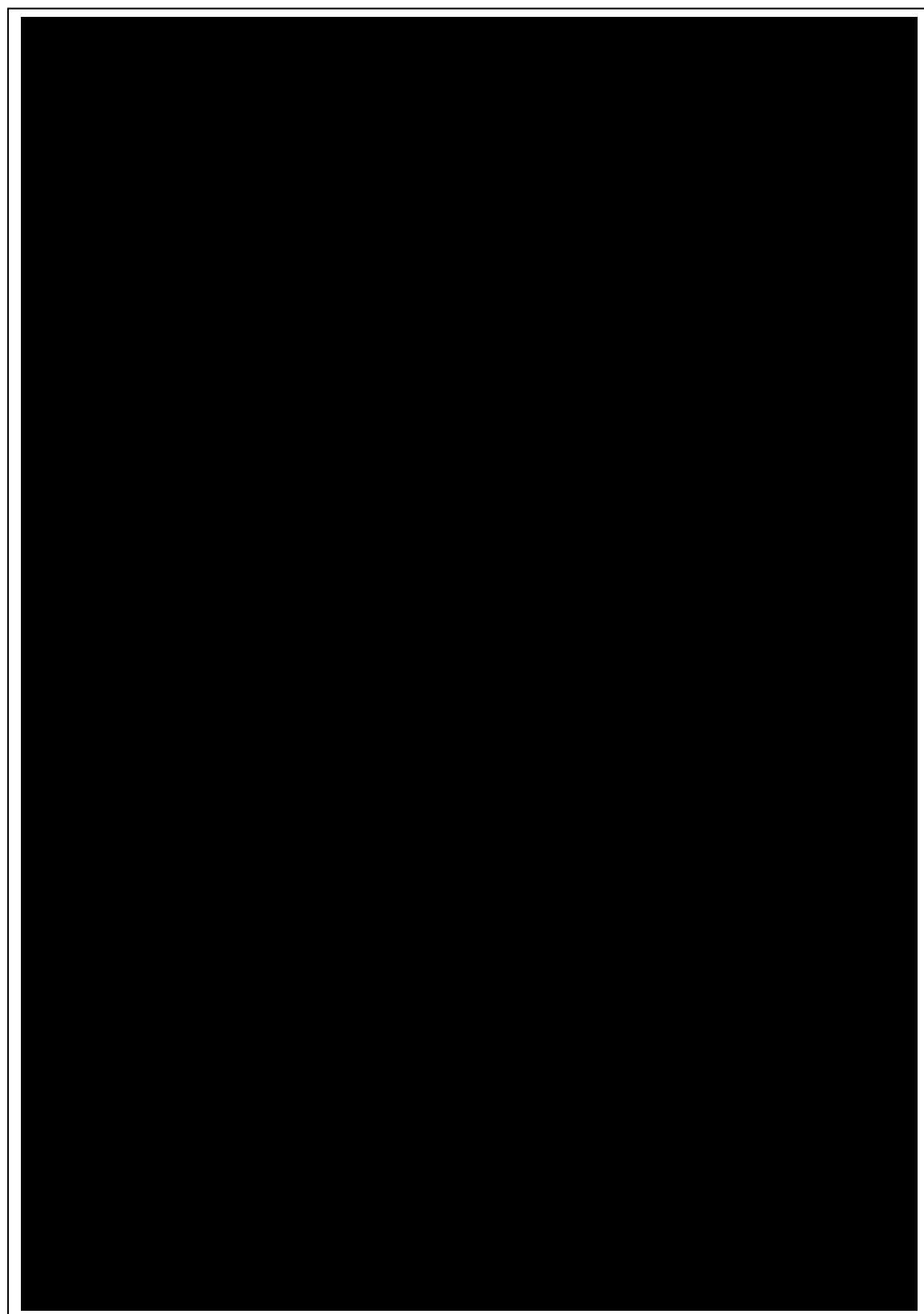


Figure 4. Update to Figure 19 from original submission: TTP visual fits of all 1, 2 and 3 knot models to the smooth spline hazards



B11. PRIORITY. CS, Section 3.3.2.1, pages 76 to 77. The model applies a structural assumption of cure beginning at 5 years. Please fit mixture-cure models (MCMs) to the available PFS and TTP data from KEYNOTE-A18 and present: (a) the resulting cure fractions and (b) plots of the observed and MCM-predicted survival. Please provide an interpretation of the results of this analysis.

MSD response:

Unfortunately, due to prioritising analyses that would be incorporated into the health economic model, we did not have time to produce these analyses.

B12. PRIORITY. CS, Section 3.3.2.1, page 77. The text states “*Clinical validation at the 2024 advisory board confirmed that the generalised gamma with 5-7 year cure point provided the most plausible long term PFS estimates.*” The economic model includes adjustment of the fitted PFS models to account for both cure and treatment effect waning. Please clarify whether the final PFS models presented to the clinical experts included both of these adjustments.

MSD response:

Clinicians at the 2024 advisory board were asked about the premise of cure in these patients. There was agreement that the intention of treatment is curative and recurrences are rare among those who are cancer free at 5 years. Clinicians considered that life expectancy might differ from the “average” UK citizen of their age, given the comorbidities related to LACC and relative social deprivation of a typical LACC patient and advised the company to investigate including an adjustment that elevated their mortality but were not able to supply any relevant data. The company’s approach to this is detailed in section 3.3.2.5 of the CS. Clinicians confirmed that patients are not routinely followed up in the NHS after 5 years without disease following CCRT.

Clinicians were presented a range of curves with different cure point assumptions applied, they validated the 5-7 year cure generalised gamma PFS curve as the most representative of their clinical experience and expectation but suggested it might be slightly lower if adjusted to reflect differences between this population and the general population in history and comorbidities.

Treatment waning had not been applied to these curves, although the additional effect of waning is small as cure assumptions are applied to both arms and the hazards for 95% of the populations are therefore already converged between 5-7 years.

B13. PRIORITY. CS, reference pack, MSD consultancy meeting slide deck and MSD advisory board meeting slide deck. These slide decks provide only limited details of the discussions held with clinical experts. Are more detailed minutes of these meetings available? If so, please provide these.

MSD response:

No more detailed minutes are available.

B14. CS, Section 3.3.2.3, Table 35, page 91. The CS refers to several criteria used to select parametric survival models for PPS based on the KEYNOTE-826 data. However, the use of expert clinical input is not included as a criterion. Please explain why clinical input was not sought.

MSD response:

This section of the dossier was reproduced from the CDF exit of pembrolizumab in the KEYNOTE-826 indication where the selected curves were agreed as appropriate by company, EAG and the NICE committee based on the selection criteria provided and the discussion at the original ACMs. The KM data are mature and therefore there is little consequential difference between the different parametric models as the extrapolation period is very short. The proportion of life years spent in the PD2 health state in the model is very low (~2%). Considering all these factors, the company therefore do not consider that seeking clinical opinion about these curves would have meaningfully aided decision-making in this appraisal.

B15. PRIORITY. CS, Section 3.3.2.2, pages 80 to 93. The company's model uses the CPS ≥ 1 population from KEYNOTE-826 (October 2022 data-cut) to estimate transition probabilities in patients with progressed disease:

- (a) Please comment on differences in stage at initial diagnosis between the intention-to-treat (ITT) CPS ≥ 1 population from KEYNOTE-826 and the FIGO 2014 Stage III–IVA patients in KEYNOTE-A18, and the potential impact of differences on the results of the economic model.

- (b) In KEYNOTE-826, around 55% of patients had received prior chemoradiation (with or without surgery). In the economic model, all patients who progress have received prior chemoradiation. Please comment on the extent to which the population of patients enrolled in KEYNOTE-826 reflects high-risk patients with LACC who have progressed on pembrolizumab plus CCRT or CCRT alone.
- (c) Please clarify whether any additional follow-up of KEYNOTE-826 data has become available since NICE Technology Appraisal (TA) 939.

MSD response:

- a) Please see our response to CQ A6. Upon inspection of the data, MSD have tried to address this uncertainty by providing data on the patients from KEYNOTE-826 who had prior CRT and implementing their projected outcomes in the economic model.
- b) We have examined modelling the PD1 and PD2 health states using data from only those who had prior CRT and the effect is moderately large. There is a pronounced plateau in the pembrolizumab arm of KEYNOTE-826 in this population and, as a result, pembrolizumab use appears more cost-effective in this population. It should be noted that prior chemo-radiation was not a stratification factor in KEYNOTE-826 and differences in outcomes could be influenced by imbalances in baseline characteristics. Differences in baseline characteristics were not major (see addendum) between the arms but more people in the pembrolizumab arm received bevacizumab (66% versus 57%, for example), which might have biased the effectiveness in favour of pembrolizumab in the 826 setting and consequently against pembrolizumab in the A18 setting.
- c) No additional follow up is available from KEYNOTE-826. The Final Analysis from that trial was used in TA939.

B16. PRIORITY. CS, Section 3.14, Figure 28, page 133. The CS presents a comparison of model-predicted OS versus observed OS in KEYNOTE-A18. Please clarify whether clinical input was sought regarding the clinical plausibility of long-term model-predicted OS for each treatment group.

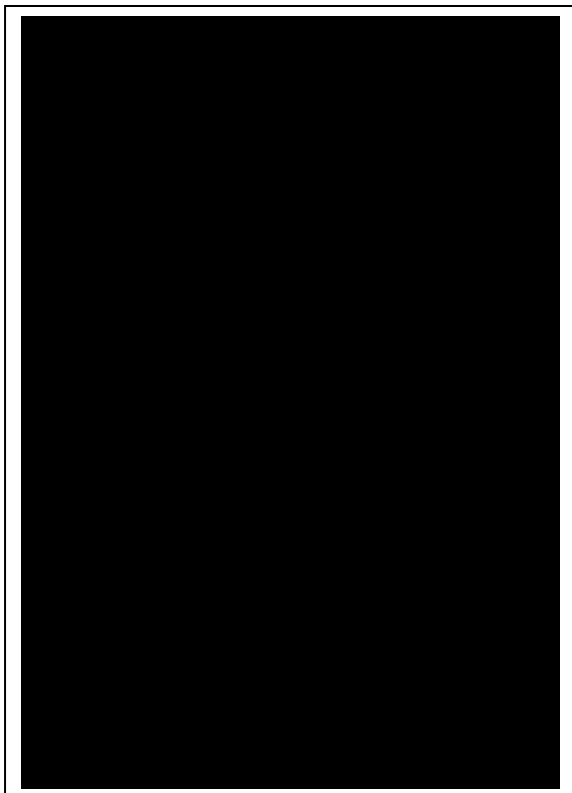
MSD response:

Clinical input was not sought on landmark OS percentages but, since clinical opinion was sought on long-term model-predicted PFS, which in turn predicts 90-95% of undiscounted life years in the model depending on assumptions, it is not clear what advantage this would have had. The natural history of the disease is that long term OS is determined by long term PFS, which is largely determined by the probability of cure. The model structure was confirmed as an appropriate way to model OS by clinicians at the ad board.

B17. PRIORITY. CS, Section 3.3.2.1, page 73 to 79. Please provide Kaplan-Meier curves and summary statistics for PPS in the pembrolizumab + CCRT and CCRT arms for stage III–IVA patients in KEYNOTE-A18, and compare these with the post-(first)-progression survival estimates predicted by the economic model.

MSD response:

Figure 5: Kaplan-Meier curve for post progression (investigator assessment) survival



Note: MK-3475 is pembrolizumab

Figure 6: Kaplan Meier curve for post progression survival (by BICR) in KEYNOTE-A18



The hazard ratios for both these curves are [REDACTED]

[REDACTED].

The updated economic model underestimates post-progression survival for the pembrolizumab arm compared to what was observed in KEYNOTE-A18. Please see the addendum for discussion on the new post-progression calibration functionality, which has been implemented into the company's base case analyses.

Health-related quality of life (HRQoL)

B18. CS, Section 3.4.3, page 100. The CS states that the most recent update searches were conducted on the 23rd August 2023. This search date is approximately two years ago. Please update the searches and provide details of any additional HRQoL studies relevant to the target population for this appraisal.

MSD response:

As per question B2, updated SLRs can be found in the appendices.

B19. CS, Section 3.4.4, page 101. The model applies the same disutility to all Grade 3/4 adverse events (AEs). This assumption may be considered unconventional, as many economic models of anticancer therapies apply event-specific disutility values. Please provide further justification for the adopted approach and explain why individual AE-specific disutility values were not used in the economic model.

MSD response:

AE disutility has been taken directly for the EQ-5D data collected in KEYNOTE-A18. This presents the most direct evidence source for AE related disutility for the population in under review. This method has been adopted in multiple other appraisals such as TA1037 and TA1017. Pembrolizumab has a well established safety profile and AE disutility has never been an influential model parameter in any of the 30+ NICE appraisals of this drug to date.

B20. CS, Section 3.4.4, page 101. The model includes disutility values applied to Grade 3/4 AEs occurring in the pembrolizumab + CCRT and CCRT arms of KEYNOTE-A18. However, the model assumes that most patients who progress go on to receive further subsequent treatments, but no further quality-adjusted life year (QALY) losses are applied to AEs arising from these treatments. Please explore the inclusion of AEs resulting from treatments for progressed disease in the economic model.

MSD response:

MSD agree the EAG's suggestion is appropriate, however, given time constraints we have not been able to incorporate this in the economic model. In the TA885/939 appraisal, the one-off QALY losses per weekly cycle were [REDACTED] in the pembrolizumab arm and [REDACTED] in the SoC arm. Alternatively, there were one-off total QALY losses of [REDACTED] in the pembrolizumab arm and [REDACTED] in the SoC arm. Given the small absolute magnitude of these numbers, the similarity between them and the fact that there are similar proportions of progressing patients getting subsequent treatment in each model arm, the company considers that including subsequent treatment AEs would have only a tiny effect on the outcomes of the model. Given there are more progressors in the CCRT arm, this limitation biases the model very slightly against pembrolizumab.

B21. CS, Appendix L, pages 203 to 210. Please comment on the completeness of the data for the utility models described in CS Appendix L. In addition, page 204 of Appendix L states that the analysis was conducted using data from 553 subjects in the Full Analysis Set (FAS) population; why were the data for the remaining 48 patients in the FAS population not included in this analysis?

MSD response:

601 patients are included in the mITT population, 599 are included in the APaT and 553 in the PRO FAS (for EQ-5D).

Of the 601 FIGO stage III-IVA that entered the trial, 2 did not receive the study treatment, this accounts for the 599 APaT. A further 46 did not have at least one completed EQ-5D questionnaire and therefore could not be included in the utility analysis. The remaining 553 make up the PRO FAS.

Costs

B22. CS, Section 3.3.2.4, Figure 25, page 94 and executable model, worksheet “Trace (1)”, column Cl. The figure shows that a small proportion of patients in KEYNOTE-A18 remained on treatment beyond 2 years; however, the model includes a stopping rule which forces the time to treatment discontinuation (TTD) function to drop to zero at 2 years. Please justify this assumption and consider revising this aspect of the model.

MSD response:

Within the trial, the stopping rule is dictated by number of cycles and is not strictly time based. Within the KEYNOTE-A18 trial, pembrolizumab has a maximum of 20 allowed cycles. 5 cycles at Q3W and 15 at Q6W. This equates to a time frame of roughly 2 years (theoretically a final cycle on pembrolizumab at week 99). Due to factors such as missed/delayed appointments and treatment holidays this can mean that patients remain on treatment past 2 years. We can confirm that no patient had more than 20 cycles of treatment in the trial. To appropriately model time on treatment within the model we assume that 100% of patients still on the TOT curve will receive pembrolizumab on their set cycle, assuming no delays or holidays. Given the fact patients could die or progress during a treatment delay or holiday this approach is a strict upper bound of the true pembrolizumab use in the trial. The model could

theoretically be set to use the whole TOT KM curve while using some sort of adjustment to account for patients who were still “on treatment” but skipped cycles. This would slightly reduce the ICER because the same total amount of pembrolizumab would be used but a very small number of patients would have treatment after 104 cycles and therefore have their costs slightly reduced by economic discounting. It is important to note that the mean number of treatment doses actually received in the trial was [REDACTED] and this is what is modelled (this can be derived in columns DX:DY of the Trace (1) sheet by dividing the total undiscounted acquisition costs for pembrolizumab by the per-cycle cost of pembrolizumab). Since the assumptions in the model combine to estimate the actual mean cycles of pembrolizumab received by patients in the trial, the company believes the approach is appropriate and that any alternative approach should also produce a mean of [REDACTED]

[REDACTED]		Table 6
[REDACTED]		

Table 6: Mean cycles of pembrolizumab among those beginning the initial and those beginning maintenance phases in KEYNOTE-A18

	All Cycles	Cycles 1-5	Cycles 6+
Participants in population	295	295	264
Actual Number of Dose Administrations^a			
Participants with data	[REDACTED]	[REDACTED]	[REDACTED]
Mean	[REDACTED]	[REDACTED]	[REDACTED]
SD	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]
Range	[REDACTED]	[REDACTED]	[REDACTED]
Expected Number of Dose Administrations^b			
Participants with data	[REDACTED]	[REDACTED]	[REDACTED]
Mean	[REDACTED]	[REDACTED]	[REDACTED]
SD	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]
Range	[REDACTED]	[REDACTED]	[REDACTED]
Percentage of Actual vs Expected Number of Dose Administrations^c			
Participants with data	[REDACTED]	[REDACTED]	[REDACTED]
Mean	[REDACTED]	[REDACTED]	[REDACTED]
SD	[REDACTED]	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]	[REDACTED]
Range	[REDACTED]	[REDACTED]	[REDACTED]
a: Refers to the actual number of doses received			
b: Refers to the expected number of doses that participants would have received up to the database			

cutoff date based on the protocol specified interval for administering each treatment component, given that the participant is remaining on treatment. It is limited to the maximum number of doses that a participant may receive as per study protocol. Expected number of dose administrations per participant for All Cycles was calculated as a sum of expected number of dose administrations in Cycles 1-5 and Cycles 6+.

c: Defined as the actual number of doses divided by the expected number of doses and then multiplied by 100.

Pembrolizumab was administered Q3W for 5 infusions (5 cycles) followed by Q6W for 15 infusions (15 cycles).

Q3W=dosing every 3 weeks; Q6W=dosing every 6 weeks

Database Cutoff Date: 07JAN2025

B23. CS, Section 3.5.1, Table 43, page 104 and Table 49, page 115. The current release of the electronic Market Information Tool (eMIT) indicates lower prices for all preparations of cisplatin, paclitaxel and carboplatin. Please update the model using current prices.

MSD response:

A new release of eMIT prices was published after the original submission. Not all prices are lower in the new release of eMIT prices, some are higher. The difference between prices used in the submitted model and in the recent eMIT release are produced in Table 7 for reference. As requested, an updated model is provided using current prices for cisplatin, paclitaxel and carboplatin. These costs are also applied in the revised base case.

Table 7: Comparison of the prices current release of the eMIT (01 Jan – 31 Dec 2024) and those used in the economic model

Name and pack size	NPC code	Pharmex data for the period 1 January 2024 to 31 December 2024, weighted average price	CEM	% change
Cisplatin 100mg/100ml solution for infusion vials/pack size 1	DHA010	£43.86	£37.34	17.5%
Cisplatin 10mg/10ml solution for infusion vials/pack size 1	DHA013	£3.68	£3.67	0.3%
Cisplatin 50mg/50ml solution for infusion vials/pack size 1	DHA011	£24.33	£19.69	23.6%
Carboplatin 150mg/15ml solution for infusion vials/pack size 1	DHE001	£6.60	£12.18	-45.8%
Carboplatin 450mg/45ml solution for infusion vials/pack size 1	DHE002	£22.92	£23.18	-1.1%
Carboplatin 50mg/5ml solution for infusion vials/pack size 1	DHE003	£5.07	£6.71	-24.4%
Carboplatin 600mg/60ml solution for infusion vials/pack size 1	DHA162	£19.75	£38.93	-49.3%

Paclitaxel 100mg/16.7ml solution for infusion vials/pack size 1	DHA145	£9.89	£12.89	-23.3%
Paclitaxel 150mg/25ml solution for infusion vials/pack size 1	DHA297	£19.46	£22.37	-13.0%
Paclitaxel 300mg/50ml solution for injection vials/pack size 1	DHA210	£18.75	£31.89	-41.2%
Paclitaxel 30mg/5ml solution for infusion vials/pack size 1	DHA144	£6.94	£4.79	44.9%

B24. CS, Section 3.3.2.4, page 94 and CS, Section 3.5.1, page 104. The model applies a relative dose intensity (RDI) of 100% for all treatment components used in the intervention and control arms of KEYNOTE-A18 (pembrolizumab, cisplatin-based chemotherapy and radiotherapy).

- Was an RDI of 100% observed for all treatment components in KEYNOTE-A18? If not, please clarify why this assumption was made.
- Please clarify whether the cost calculations assume that an RDI of 100% applies to all subsequent-line therapies. If so, please clarify why the RDI from KEYNOTE-826 was not used in the model?
- Please amend the model to include RDI for all therapies, if appropriate

MSD response:

- An RDI of 100% was not observed in KEYNOTE-A18. The percentage of actual vs expected number of doses was (
- Table 8):
 - For pembrolizumab [REDACTED]
 - For cisplatin in the pembrolizumab arm [REDACTED]
 - For cisplatin in the control arm [REDACTED]

Please refer to MSD's rationale in B22 as to why the company believes a 100% RDI approach is appropriate. Briefly, the model's assumptions already combine to estimate the mean number of cycles actually received in KEYNOTE-A18.

Table 8. Summary of treatment compliance whilst on therapy (APaT)

	Pembrolizumab	Cisplatin for those also receiving pembrolizumab	Cisplatin for those not receiving pembrolizumab
Participants in population	295	295	304
Actual Number of Dose Administrations^a			
Participants with data	[REDACTED]	[REDACTED]	[REDACTED]
Mean	[REDACTED]	[REDACTED]	[REDACTED]

SD				
Median				
Range				
Expected Number of Dose Administrations^b				
Participants with data				
Mean				
SD				
Median				
Range				
Percentage of Actual vs Expected Number of Dose Administrations^c				
Participants with data				
Mean				
SD				
Median				
Range				
a: Refers to the actual number of doses received b: Refers to the expected number of doses that participants would have received up to the database cutoff date based on the protocol specified interval for administering each treatment component, given that the participant is remaining on treatment. It is limited to the maximum number of doses that a participant may receive as per study protocol. c: Defined as the actual number of doses divided by the expected number of doses and then multiplied by 100. Pembrolizumab was administered Q3W for 5 infusions (5 cycles) followed by Q6W for 15 infusions (15 cycles). Cisplatin (5 infusions) was given weekly (an optional, sixth infusion of cisplatin may have been administered according to local practice). Maximum expected dose is limited to 5 infusions. Q3W=dosing every 3 weeks; Q6W=dosing every 6 weeks Database Cutoff Date: 07JAN2025				

- c) We have modified the approach to costing subsequent treatments to make it more intuitive. We have now included the actual number of cycles of subsequent treatments received in KEYNOTE-826 and so a relative dose intensity adjustment is not needed.
- d) MSD believe the current approach is the most appropriate due to matching the mean cycles of treatment actually received by the relevant patients in the datasets.

B25. CS, Section 3.5.1, page 105. The text states that *“The number of radiotherapy sessions (fractions) used within the model has been sourced from the BGCS guidelines.”* Please clarify why the number of radiotherapy fractions was not taken from KEYNOTE-A18.

MSD response:

Some study sites in KEYNOTE-A18 follow different international guidelines e.g. Japan. Both radiotherapy type and number of grays were stratification factors in KEYNOTE-A18 and the median grays did not differ between the arms (median total cervix EQD2 dose of 87.47 and 87.30 for pembrolizumab plus CCRT and placebo plus CCRT, respectively). Since the EBRT ToT curve is nearly identical between the arms (SoC Area Under the ToT curve is 99.5% of the pembro arm) we do not believe costing different regimens could influence the results of the model.

B26. PRIORITY. CS, Section B.3.5.1, page B.3.5.1, pages 105 to 106 and executable model, worksheet “Trace (1)”, columns Cl:CM and worksheet “Trace (2)”, columns BX:CA. Whilst not explained in the CS, the executable model applies the same TTD function for cisplatin and radiotherapy in both treatment groups. Please explain whether this was an intentional assumption or if it reflects an error. If it was an intentional assumption, please clarify which data have been used (one trial arm or pooled data for both arms) and provide a justification for the approach. Please amend the model if appropriate.

MSD response:

The data for the CCRT arm were used for both arms for simplicity given the KM curves for non-pembrolizumab treatment components are almost identical between the arms. The data have now been separated out in the model to be more technically correct. The influence this has on the ICER is very small as would be expected.

B27. CS, Section 3.5.3, page 116. The model includes costs associated with the management of Grade 3/4 AEs occurring in KEYNOTE-A18. However, the model assumes that most patients who progress go on to receive further treatments but no further costs are applied to AEs arising from these treatments. Please explore the inclusion of AEs resulting from treatments for progressed disease in the economic model.

MSD response:

MSD agree the EAG’s suggestion is appropriate, however, given time constraints we have not been able to incorporate this in the economic model. In the TA885/939 appraisal (2019/2020 prices), the one-off costs losses per weekly cycle were █████ in the pembrolizumab arm and █████ in the SoC arm. Alternatively, there were one-off total

costs of [REDACTED] in the pembrolizumab arm and [REDACTED] in the SoC arm. Given the small absolute magnitude of these numbers, the similarity between them and the fact that there are similar proportions of progressing patients getting subsequent treatment in each model arm, the company considers that including subsequent treatment AEs would have only a tiny effect on the outcomes of the model. Given there are more progressors in the CCRT arm, this limitation biases the model very slightly against pembrolizumab.

B28. CS, Section 3.5.2, pages 106 to 111. The model includes costs associated with disease management, monitoring and patient follow-up for the 'Progression-free', 'Progressed disease 1' and 'Progressed disease 2' health states. As 80% of patients in the 'Progressed disease 1' state are assumed to receive active subsequent treatments, the EAG considered that the costs should reflect the corresponding monitoring requirements for pembrolizumab where it is used. Please update the costs accordingly.

MSD response:

MSD consider that the treatment-specific monitoring costs over and above the monitoring costs that are already accounted for in each health state would be negligible so we have not amended the model. The level of subsequent treatment is higher in the CCRT arm so this may mean the model is slightly biased against pembrolizumab if there are any monitoring costs unaccounted for.

B29. CS, Section 3.5.2, Table 48, pages 113 to 114, and executable model, worksheet "Subsequent Tx Costs", cells E10:E11. The late progressors in the pembrolizumab plus CCRT arm and progressors from the CCRT arm receive equivalent weighted survival benefits from KEYNOTE-826. However, the model applies different one-off acquisition costs for these groups. Please provide a justification for this difference and comment on the face validity of this assumption.

MSD response:

The carboplatin/cisplatin/paclitaxel mix in the two arms have been modelled slightly differently as per what was observed in the KEYNOTE-826 trial. Currently when an early progressor becomes a late progressor the only change is addition of pembrolizumab (with no change to the chemotherapy mix). This is the reason for the

difference. The difference is very minimal between the arms and changes to this assumption will not affect the ICER.

B30. CS, Section 3.5.2, Table 48, page 113. The economic model assumes that 100% of patients who experience a second progression will go on to receive paclitaxel:

- (a) Please clarify why 100% of patients who experience a second progression receive third-line therapy (which contrasts with the assumption that 20% of patients who experience a first progression receive no active second-line therapy)
- (b) Please clarify why the mix of subsequent-line therapies after the second progression event is not informed by KEYNOTE-826 and comment on the face validity of this aspect of the model.

MSD response:

LYs and cost in the PD2 state account for less than 1% of LYs and costs in the pembrolizumab arm and 2% of the CCRT arm, therefore pragmatic choices were made when modelling this population.

This population can be highly heterogeneous given varying combinations of 2 previous lines of treatment will have already been used. A simplifying conclusion that these patients would receive low dose cisplatin.

While the company consider the EAG's points that these data could have been modelled with <100% getting any sort of treatment and/or in line with KEYNOTE-826 are reasonable, it is also likely that some patients receive more than one line of chemotherapy following transition to PD2.

B31. CS, Section 3.5.1, Table 44, pages 104 to 105. The total drug acquisition costs per model cycle for pembrolizumab plus CCRT in both combination and maintenance phases in CS Table 44 are different from the costs used in the executable model. Please confirm that Table 44 contains typographical errors and provide a corrected version.

MSD response:

In this section of the CS the text is describing a *treatment* cycle (every 3 or 6 week), not a model cycle (one week). The company believes that table 44 correctly represents the *treatment* cycle cost being used in the model.

B32. CS, Section 3.5.2, Table 47, page 108. The NHS Cost Collection 2023/24 reports different prices for some resource use items included in the economic model. Please update the unit costs for PET-CT scans, consultant-led oncology appointments (non-admitted face-to-face appointment) and consultant-led phone call (non-admitted non-face-to-face appointment) in the economic model.

MSD response:

MSD has cross-checked the National Cost Collection Data Publication: National Schedule 2023/24 against the economic model and identified discrepancies only in relation to rounding to the nearest pound. Therefore, the model's unit costs remain unchanged.

For clarification, the PET-CT scan cost in the model (£629.70) is a weighted average of currency codes for a 'Directly Accessed' test (RN01A: 2,132 examinations of £354) and 'Nuclear Medicine' test (RN01A: 70,645 examinations of £638).

B33. CS, Section 3.5.4, page 117. Please confirm that the end-of-life care cost is incurred by all patients including those who are assumed to be cured after year 7. If so, please comment on the rationale of this assumption.

MSD response:

Within the CS end-of-life costs were applied to everyone entering the death state. MSD accepts that when applying a cure this is likely inappropriate as this cost is specific to cancer related deaths. In line with NICE's position to exclude "Future Unrelated Costs" (e.g. section 4.4.11 of the manual but also discussed in position statements over the years), this now presents the company's base-case and within the new model we have added the functionality to remove the end of life cost for all patients that move from the PFS state to death after the cure point. The company considers that end of life care costs for patients who are cured of cancer are Future Unrelated Costs in the same way that any other care they might receive for non-cancer conditions would be considered a Future Unrelated Cost and excluded.

Executable model

B34. Executable model, worksheet “KN-826 PPS”, column AG and CS, Section 3.11.3, Table 57, page 129. Post-progression survival 2 (PPS2) is underestimated in the pembrolizumab plus CCRT group (i.e., the probability of transitioning from ‘Progressed Disease 2’ to ‘Death’ is overestimated). As the parameter called ‘p_PD2_pembro_hist_int’ (contained in worksheet “Controls”, cell I171) is set to zero, the weighted PPS2 survival model for pembrolizumab plus CCRT group is underestimated as it ignores the effect of pembrolizumab in the late progressor group. The text in worksheet “Controls” cell D168 states *“In the pembrolizumab + CRT arm, the base case is assumed to be the value for early progressors. A scenario was run on the weighted average of early and late progressors.”* Please justify this approach. In addition, please explain how the proportion of [REDACTED] was derived in the scenario analysis presented in Table 57 (scenario labelled *“Pembrolizumab arm PPS weighted to account for pre and post 2.5 year rechallenge”*).

MSD response:

As stated in B30, the LYs and costs accrued in the PD2 account for less than 2% of the total LYs and costs in the model, as such simplifying assumptions were made to reduce complexity in the model, especially where it was unlikely to make a material difference to the ICER.

MSD agrees with the EAG that PPS2 was underestimated in the pembrolizumab + CCRT arm where rechallenge was modelled after 2.5 years, and that as such the ICER is biased against pembrolizumab as a result (especially given treatment costs are assumed equal in the PD2 state). This bias is expected to be small.

To explore this bias we ran a scenario in which we used a weighted average hazard of PPS from both KEYNOTE-826 arms, applied across all time point from t=0. While the company cannot exactly replicate the [REDACTED] figure, the methodology was to calculate the proportion of patients that enter the PD2 state (‘Trace (1)’!BI:BI) after the rechallenge time point (2.5 years), in the CS this was [REDACTED]. The next step was to apply the proportion of late progressors receiving pembrolizumab, 52%. This results in a value of [REDACTED]. While the cause of this discrepancy is unclear, the scenario itself was to demonstrate that this aspect of structural uncertainty had been considered and

had little to no impact on the ICER, which was shown when the ICER decreased just [REDACTED].

MSD agree that further, more technically sound methods could have been explored but this would have required the introduction of further time dependent tunnel states to account for the fact that only late progressors from the PD1 state receive this benefit.

The above scenario analysis highlights that the lack of this functionality biases the model very slightly against pembrolizumab.

B35. Executable model. worksheet “Life Tables”, column O. The EAG believes that there is a one-cycle lag in the calculations of the general population mortality risks. Please confirm that this is an error and correct it in a revised version of the economic model.

MSD response:

MSD apologise for the error. It has been corrected in the new model and the effect on the ICER is very small.

B36. Executable model, worksheet “Life Tables”, cells D16:E98. The model uses life tables for the UK. Please amend the economic model to use life tables for England.

MSD response:

The model has been updated to include only the England lifetables, 2021-2023 edition.

B37. Executable model, worksheet “KN-826 PPS Data”, cells O30:O41 and R30:R41. For all other worksheets which contain the survival model coefficients except for that listed above, the coefficients are contained in the column with the row heading ‘Coefficient.’ However, for PPS in the comparator group, the values contained in column O (‘Coefficient’) appear to be redundant and instead the correct coefficients have been pasted as values to column R (‘MultiNormInv’). These coefficients are then not sampled using the MultiNormInv function. Please clarify if this is an error and correct the model, if necessary.

MSD response:

MSD apologise for the error. This has been corrected in the new model.

B38. Executable model, worksheet “KN-826 PPS”, columns O and AB. Starting from model cycle 2,087, there are programming errors in the calculation of per-cycle transition probabilities. Please confirm that these are errors and correct the model.

MSD response

MSD apologise for the error. This has been corrected and the effect on the ICER is very small.

B39. Executable model, worksheet “KN-826 PFS Splines”, column AO. The model multiplies the chemotherapy group PFS transition probabilities by an HR of 2.0 to estimate mortality risks for patients receiving no treatment. Should this HR instead be applied to the underlying hazard (rate) rather than the per-cycle probability? Please correct the model, if necessary.

MSD response:

The company has improperly described this as a “hazard ratio” when in fact the original curves that were shown to clinicians were calculated using multipliers to the per cycle probability of death, just as they are in the economic model. The company considers that both methods would produce similar curves and that “hazard ratio” is a useful shorthand description of what is occurring. The ideal situation would have been that we would have calculated the original curves based on applying the multipliers to the per cycle hazard so that the terminology matched the calculations exactly, however, what is most important is that the curve clinicians looked at and felt most appropriate is what is used in the model. The *true* HR is inherently uncertain and itself is unlikely to be exactly 2. For this reason we presented scenario values of 1.5 and 3 to explore a plausible range of no treatment survival curves. These affected the ICER by ~0.2%.

B40. Executable model, worksheets “Trace (1)” and “Trace (2)”, transition probability adjustments. The model uses a semi-Markov approach which includes tunnel states:

- (a) Please confirm that the user-defined Visual Basic for Applications (VBA) function named “*multiplyreverseVector*” was used in the model to implement the tunnel states.
- (b) The transition probabilities for risks of progression and death from the ‘Progressed Disease 1’ and ‘Progressed Disease 2’ state appear to be adjusted by general population mortality risks conditional on patient age, assuming that

patients enter the PD1 and PD2 sub-models in the first model cycle. This approach is incorrect because the risks of progression and death should be constrained using the general population mortality risk relevant to the age at which patients enter each sub-model. Please correct the model, if necessary.

MSD response:

MSD apologise for this error and were unable to correct it in the time available. However, the effect to of this on the model's results is expected to be very minor for two reasons. Firstly, very few patients enter the tunnel states after the first few years of the model (90% of cumulative incidence by year 3 and 95% by year 5 in the CCRT arm) and secondly, transitions to death and progression after a PD1 event are high compared to general population mortality and it is unlikely the cap would kick in for decades of model time, given the young age of the population.

B41. Executable model, worksheets "Trace (1)" and "Trace (2)", cell P19. The base case model does not include half-cycle correction, and the calculations in the trace ignore life years gained (LYGs) and QALYs accrued in the first model cycle; this is incorrect. Given that the model already includes functionality to account for half-cycle correction, why has this not been included in the company's base case model?

MSD response:

Given the one-week cycle length we did not think there would be any advantage in switching on half-cycle correction. In the updated model, half-cycle correction has now been applied and the error in P19 has been rectified.

B42. Executable model, worksheets "Trace (1)", cell EA7 and "Trace (2)", cell DP7. The model includes a once-only cost of brachytherapy of £15,692; this cost is applied to patients who discontinue external beam radiotherapy (EBRT). When the cost of EBRT is set equal to £0 and the discount rates are set equal to 0%, the expected costs of radiotherapy in the model are estimated to be approximately £12,000. Why is this cost not £15,692 (i.e., why is the cost of brachytherapy not applied to all patients)? Please correct the model, if necessary.

MSD response:

We have updated the model to ensure this does not happen and all alive patients incur the cost of brachytherapy on discontinuing RT in both arms.

B43. Executable model, worksheet “Trace (1)”, column DK and worksheet “Trace (2)”, column CZ. The model calculates the per-cycle QALY loss associated with AEs based on the overall frequency of events in the ITT population of KEYNOTE-A18 in the first and second years. However, in the model trace, the per-cycle QALY loss is applied only to those patients who remain progression-free in each model cycle. The same issue also applies to the AE management costs. Please confirm that this approach underestimates the overall incidence of AEs observed in the trial and address this issue in a revised version of the model.

MSD response:

MSD can confirm the EAGs assessment is correct, and as a result AEs disutility may be underestimated in both arms of the model. Given that the risk of PFS in the first 2 year is higher in the CCRT arm this may bias against pembrolizumab. In prioritizing adaptations to the model as part of the clarifying questions this has not been changed although a scenario analysis exploring the complete removal of AE disutility indicates that AEs have a small impact on the ICER (0.2% difference vs basecase).

B44. Executable model, worksheet “Trace (1)”, column AV, and worksheet “Trace (2)”, column AN. Please explain why the transition probability from health states ‘Progressed Disease 2’ to ‘Death’ becomes 1.0 from model cycle 2,245 onwards for the pembrolizumab plus CCRT group, and from model cycle 2,464 onwards for the CCRT group. If this is a programming error, please update the model accordingly.

MSD response:

This is now been fixed so that all patients are assumed to die at age 100 (cycle 2,531 in the base case) in both arms.

B45. Executable model, worksheet “Trace (1)”, column ET, and worksheet “Trace (2)”, column EI. At the first progression, 100% of patients are assumed to incur Programmed Death Ligand 1 (PD-L1) testing costs (including those who were early progressors from the pembrolizumab plus CCRT arm and the 20% of patients who

would not receive any treatment). Please confirm whether this assumption was intentional and, if so, please provide the clinical rationale of providing PD-L1 testing for patients who cannot receive pembrolizumab treatment following progression.

MSD response:

This was an error. The model has been updated so that only patients who are potentially candidates for PD-L1 testing receive it. In the base case, no patients within the first 2.5 years in the pembrolizumab arm receive testing. For all other patients, the calculation is the proportion progressing patients divided by the assumed probability of PD-L1 positivity from the advisory board (80%). This equals 64% of progressors getting a test in the base case.

B46. Executable model, worksheet “Trace (1)”, columns AB and AG. Please explain why the approach used to apply a constraint to the adjusted per-cycle probability of TTP2 is different between early progressors and late progressors. Please confirm that this is a programming error and correct the model.

MSD response:

This was a programming error which has been corrected with minimal effect on the model's results.

B47. Executable model, worksheet “Subsequent Tx Costs”. With respect to the subsequent treatment costs:

- (a) Please explain why the price of biosimilars were not used to calculate bevacizumab acquisition costs.
- (b) Please justify why, except for pembrolizumab, drug wastage costs were not included for subsequent-line treatments.

MSD response:

- a) Following the recent loss of exclusivity for Avastin®, bevacizumab is now available through biosimilar alternatives. However, clinical experts participating in the UK advisory board for the TA939 appraisal indicated that Avastin® is still the drug of choice. Pricing between originator and biosimilars is similar. Consequently, the base case analysis in both submissions applies the cost of

Avastin®. A scenario analysis was conducted using the price of biosimilars, but the impact on the ICER was minimal.

- b) Due to time constraints, MSD was unable to fully adapt the model to account for drug wastage for drug doses based on bodyweight or BSA. Instead, subsequent drug acquisition costs were inflated using a single inflation factor. This inflation factor was informed by the TA939 appraisal, which found the cost of bevacizumab including wastage (no vial sharing, £2,375.11) to be 6% higher than bevacizumab excluding wastage (with vial sharing, £2,242.83). This percentage is modifiable in the model. This adjustment is not applied to pembrolizumab or carboplatin as these have fixed dose regimens in which the vial sizes are a divisor of the fixed dose and therefore wastage can never occur

B48. Executable model, worksheet “Controls”, cells J216 and K216. The MSD 2024 advisory board meeting minutes (page 14) state that: *“In current practice, advisors felt that 80% of progressors from CCRT would be PD-L1 positive, and that of these, a further 80% would receive pembrolizumab + chemotherapy +/- bevacizumab (e.g. 64% of those that get treatment). Remaining progressors would get chemotherapy +/- bevacizumab.”* However, the economic model assumes that amongst the 80% of patients who receive subsequent-line treatment, 64% receive pembrolizumab plus chemotherapy +/- bevacizumab treatment (i.e., 51.2% receive pembrolizumab plus chemotherapy +/- bevacizumab, 28.8% receive chemotherapy +/- bevacizumab and 20% receive no treatment). Please confirm whether this is intentional, and if not, please correct the error.

MSD response:

MSD apologise for any confusion, the figures within the model are correct, but the write up may have been unclear. The 80% pembrolizumab figure relates to *those that get treatment*. The calculation is as follows:

- 100 progressors
- 80% get treatment (20% get no treatment) = 80 patients
- 80% of the 80 that get treatment would be eligible for treatment with pembrolizumab = 64 patients

- 80% of the 64 patients theoretically eligible for pembrolizumab assumed to test PD-L1+ = 51.2 patients

B49. Executable model, worksheet “Parameters”, column V. Please justify why (i) the distribution and mean treatment duration of subsequent treatments (except pembrolizumab and bevacizumab), (ii) RDI, and (iii) utility decrements related to AEs were not included in the PSA. In addition, please explain why the distributions of bevacizumab (and pembrolizumab) for early/late progressors from pembrolizumab plus CCRT group and progressors from CCRT alone group were sampled independently in the probabilistic sensitivity analysis (PSA).

MSD response:

- Mean treatment duration for paclitaxel, carboplatin and cisplatin were not explored in the PSA as the number of cycles, and therefore time on treatment is strictly capped at 6 cycles, with the mean being very close to this (i.e. most patients finish a full course of treatment). This means the distribution of mean TOT is both capped and unlikely to follow any “typical” distribution used within a PSA
- As per B22 and B24, MSD believes it is most appropriate to model RDI at 100% when using mean cycles of treatment.
- MSD apologise for this omission, this is now included in the PSA
- MSD apologise for this error, this has now been corrected by applying the same random number used for the PSA across the 3 populations. Note that the random number is equal across populations but different for % receiving pembrolizumab vs % receiving bevacizumab.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Addendum to company evidence submission



September 2025

File name	Version	Contains confidential information	Date
ID6138 Pembrolizumab for high risk LACC_addendum	1	No	19 September 2025

Company response to clarification questions for pembrolizumab with chemoradiation for
untreated high-risk locally advanced cervical cancer [ID6138]

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1 Clinical effectiveness

Please find below figures and tables update to reflect data from the final analysis, with a cutoff date of 7 January 2025.

1.1 Patient characteristics and status

Table 1: Update of Table 8 from company submission: Baseline characteristics of FIGO 2014 Stage III-IVA participants in KEYNOTE-A18

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	296		305		601	
Sex						
Female	296	100	305	100	601	100
Age (Years)						
< 65						
>= 65						
Mean						
SD						
Median						
Range						
Race						
American Indian Or Alaska Native						
Asian						
Black Or African American						
Multiple						
Native Hawaiian Or Other Pacific Islander						
White						
Ethnicity						
Hispanic Or Latino						
Not Hispanic Or Latino						
Not Reported						
Geographic Region						
Asia Pacific						
EMEA						
North America						
Latin America						
Geographic Region 2						
North America						
Western Europe						

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Rest of the World						
Age Group (Years)						
< 65						
65 - 74						
75 - 84						
85+						
Baseline ECOG						
0						
1						
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic						
No Positive Pelvic nor Para-Aortic						
Histology Subtype						
Non-squamous						
Squamous						
Planned Type of EBRT						
IMRT or VMAT						
non-IMRT and non-VMAT						
Planned Total Radiation Therapy Dose per (EQD2)						
< 70 Gy						
>= 70 Gy						
PD-L1 Status						
CPS <1						
CPS >=1						
Missing						
Key: EMEA, Europe, the Middle East and Africa; EBRT, External beam radiotherapy; IMRT, Intensity modulated radiotherapy; VMAT, Volumetric modulated arc therapy.						
Database Cutoff Date: 07 Jan 2025						
Source: KEYNOTE-A18 IA2 TLF						

Table 2: Update to Table 11 of company submission: Patient flow - FIGO 2014 stage III-IVA participants

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	296		305		601	
Status for Trial						
Discontinued						
Death						
Lost To Follow-Up						
Withdrawal By Subject						
Participants Ongoing						

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Status for Study Medication in Trial						
Started						
Completed						
Discontinued						
Adverse Event						
Clinical Progression						
Excluded Medication						
Lost To Follow-Up						
Non-Compliance With Study Drug						
Non-Study Anti-Cancer Therapy						
Physician Decision						
Progressive Disease						
Radiographic Progression						
Withdrawal By Subject						
Participants Ongoing						
If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.						
Database Cutoff Date 7 Jan 2025						

1.2 Estimates of clinical effectiveness

Table 3: Update to Table 12 of company submission: Analysis of Overall Survival (ITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)		
Kaplan–Meier Estimates (months) ^a Median (95% CI)		
Hazard Ratio (95% CI) ^b		
p-value ^c		
OS Rate at month 6 (%) (95% CI)		
OS Rate at month 12 (%) (95% CI)		
OS Rate at month 18 (%) (95% CI)		
OS Rate at month 24 (%) (95% CI)		
OS Rate at month 30 (%) (95% CI)		
OS Rate at month 36 (%) (95% CI)		
OS Rate at month 48 (%) (95% CI)		
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.		
c One-sided p-value based on log-rank test.		

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Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; OS, overall survival.
Database Cutoff Date: 7 Jan 2025

Figure 1: Update to Figure 5 of company submission: Kaplan–Meier Estimates of Overall Survival (mITT Population)

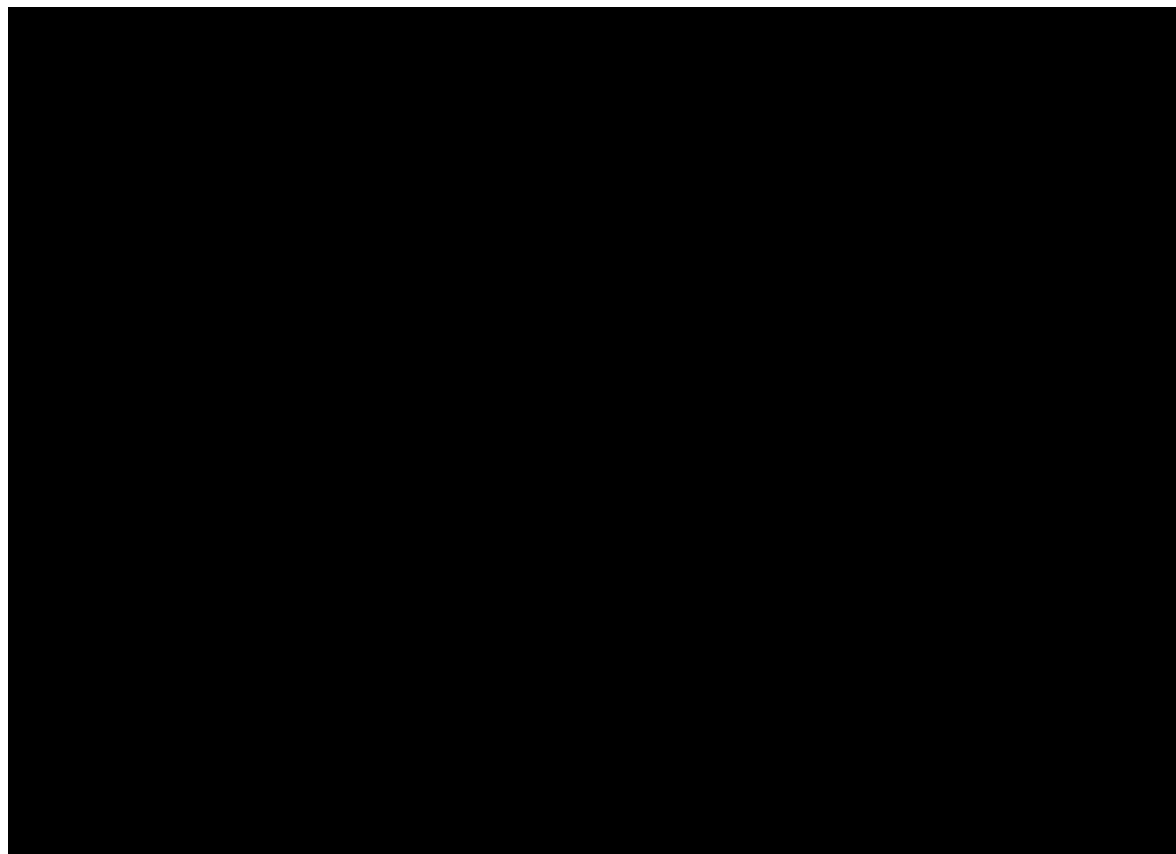


Table 4: Update to Table 13 of company submission. Analysis of Progression Free Survival (Primary Censoring Rule) Based on Investigator Assessment (mITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)	██████	██████
Death	██████	██████
Documented progression	██████	██████
Kaplan–Meier Estimates (months) ^a Median (95% CI)	██████	██████
Hazard Ratio (95% CI) ^b	██████	
p-value ^c	██████	
PFS Rate at month 6 (%) (95% CI)	██████	██████
PFS Rate at month 12 (%) (95% CI)	██████	██████
PFS Rate at month 18 (%) (95% CI)	██████	██████
PFS Rate at month 24 (%) (95% CI)	██████	██████

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PFS Rate at month 30 (%) (95% CI)		
PFS Rate at month 36 (%) (95% CI)		
^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. ^c One-sided p-value based on log-rank test. Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; PFS, progression-free survival. Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) Database Cutoff Date: 7 Jan 2025		

Figure 2: Update to Figure 6 of company submission: Kaplan–Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (mITT Population)



Table 5: Update to Table 14 of the company submission: Objective Response Based on investigator assessment per RECIST 1.1 (Participants With Measurable Disease at Baseline)

	Pembrolizumab + CCRT (n = 292)	Placebo + CCRT (n = 300)
Number of objective responses		
ORR, % (95% CI)		
Difference (pembrolizumab + CCRT versus placebo + CCRT), %		
Estimate (95% CI) ^a		
Nominal p-value ^b		
^a Based on unstratified Miettinen & Nurminen method. ^b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached; ORR, objective response rate. Database Cutoff Date: 7 Jan 2025		

Table 6: Update to Table 15 of the company submission: Summary of Best Objective Response based on Investigator Assessment per RECIST 1.1 (Participants with measurable disease at baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	%	95% CI ^a	n	%	95% CI ^a
Number of Participant in Population	292			300		
Complete Response (CR)						
Partial Response (PR)						
Overall Response (CR+PR)						
Stable Disease (SD)						
Disease Control (CR+PR+SD)						
Progressive Disease (PD)						
Not Evaluable (NE)						
No Assessment						
^a Based on binomial exact confidence interval method. Investigator assessed responses per RECIST 1.1 are included in this table. Database Cutoff Date: 7 Jan 2025						

Table 7: Update to Table 16 of company submission: Analysis of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=296)	(N=305)
Number of Events (%)		
Kaplan–Meier Estimates (months) ^a Median (95% CI)		
vs Placebo + CCRT		
Hazard Ratio (95% CI) ^b		

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p-value ^c		
^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. ^c One-sided p-value based on log-rank test Key: CCRT, concurrent chemoradiotherapy; CI, confidence interval; NR, Not reached. Database Cutoff Date: 7 Jan 2025		

Figure 3: Update to Figure 7 of company submission: Kaplan–Meier Estimates of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (mITT Population)

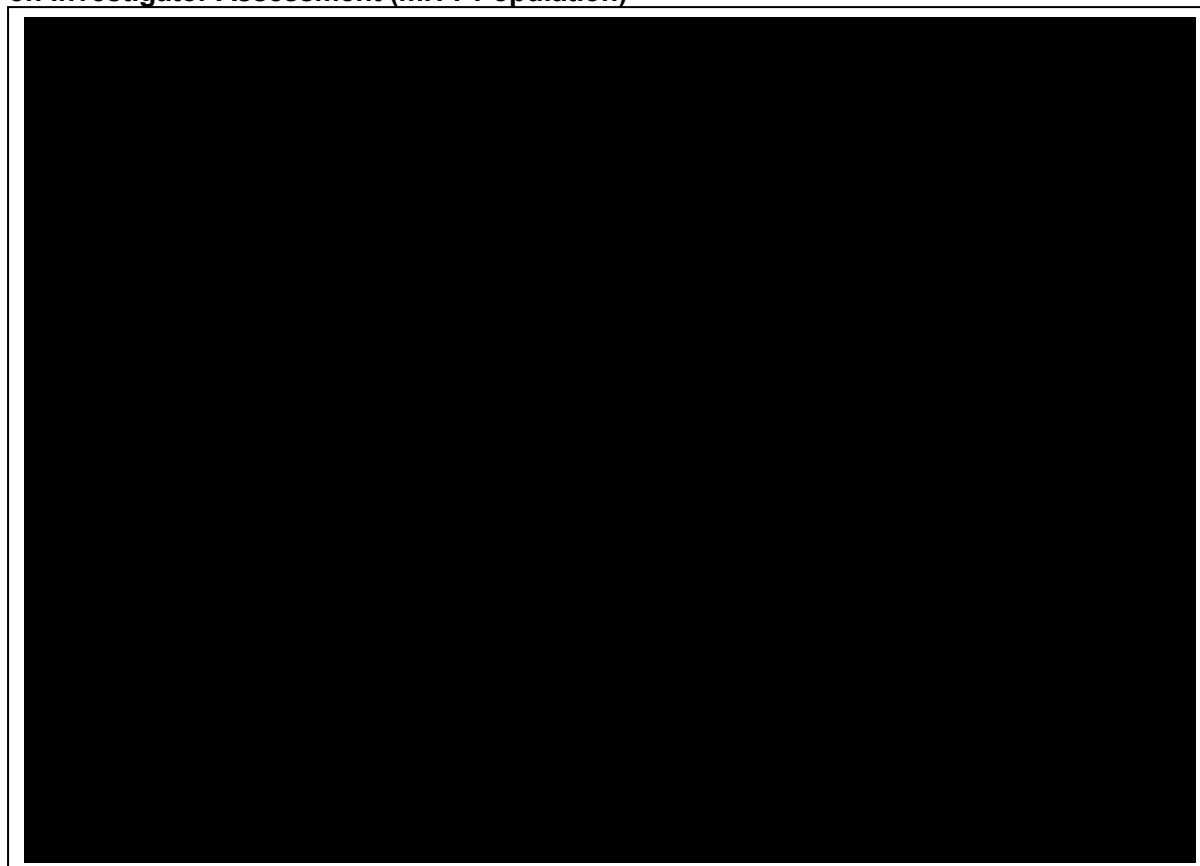


Table 8: Update to Table 17 of the company submission: Analysis of Change from Baseline in EQ-5D-5L VAS Score to Week 36 FAS population

	Baseline		Week 36		Change from Baseline to Week 36	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) ^a
Pembrolizumab + CCRT						
Placebo + CCRT						
Pairwise Comparison					Difference in LS Means ^a	p-Value ^a
					(95% CI)	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Pembrolizumab + CCRT vs. Placebo + CCRT		
^a Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction. For baseline and Week 36, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group. Database Cutoff Date: 7 Jan 2025		

Figure 4: Update to Figure 8 of company submission: Line Plot of Empirical Mean Change from Baseline and 95% CI for the EQ-5D-5L Over Time by Treatment Group FAS population



1.3 Subsequent therapies and adverse effects

Table 9: Update to Table 18 of company submission: Subsequent oncologic therapies APaT

	Pembrolizumab + CCRT (n=80) n (%)	Placebo + CCRT (n=117) n (%)
Participants who did not receive subsequent oncologic therapies		
Participants who died		
Participants who are alive		
Participants who received subsequent oncologic therapies		
1 st subsequent line		
carboplatin + paclitaxel		
bevacizumab + carboplatin + paclitaxel		
cisplatin + paclitaxel		

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bevacizumab + carboplatin + paclitaxel + pembrolizumab		
bevacizumab + cisplatin + paclitaxel		
carboplatin + paclitaxel + pembrolizumab		
cisplatin		
paclitaxel		
paclitaxel nanoparticle albumin-bound		
bevacizumab + carboplatin + cisplatin + paclitaxel		
bevacizumab + carboplatin + paclitaxel nanoparticle albumin-bound		
pembrolizumab		
bevacizumab + cadonilimab + capecitabine + catequentinib + cisplatin + paclitaxel		
bevacizumab + cisplatin + paclitaxel + paclitaxel nanoparticle albumin-bound		
bevacizumab + cisplatin + paclitaxel + pembrolizumab		
bevacizumab + denosumab + paclitaxel + topotecan		
bevacizumab + paclitaxel + pembrolizumab + topotecan		
bevacizumab + paclitaxel nanoparticle albumin-bound		
bevacizumab + zimberelimab		
cadonilimab		
carboplatin		
carboplatin + catequentinib + docetaxel		
carboplatin + gemcitabine + paclitaxel + pembrolizumab		
carboplatin + paclitaxel + paclitaxel nanoparticle albumin-bound		
carboplatin + paclitaxel nanoparticle albumin-bound		
cisplatin + gemcitabine + paclitaxel		
cisplatin + paclitaxel + zoledronic acid		
cisplatin + paclitaxel nanoparticle albumin-bound		
cyclophosphamide + doxorubicin + vincristine		
paclitaxel + topotecan		
2 nd subsequent line		
bevacizumab + carboplatin + paclitaxel		
bevacizumab		

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bevacizumab + cisplatin + paclitaxel		
bevacizumab + paclitaxel		
bevacizumab + pembrolizumab		
gemcitabine		
topotecan		
carboplatin + paclitaxel + pembrolizumab		
cadonilimab		
carboplatin + paclitaxel		
cemiplimab		
cisplatin + gemcitabine		
cisplatin + paclitaxel		
doxorubicin		
gemcitabine + pemetrexed		
marsdenia tenacissima stem		
paclitaxel nanoparticle albumin-bound + zimberelimab		
pembrolizumab		
tisotumab vedotin		
vinorelbine		
3 rd subsequent line		
angelica sinensis + paeonia lactiflora + poria cocos + rehmannia glutinosa + reynoutria multiflora		
bevacizumab + carboplatin + paclitaxel		
bevacizumab + cisplatin + paclitaxel + pembrolizumab		
cisplatin + gemcitabine		
irinotecan		
pembrolizumab		
cemiplimab		
4 th subsequent line		
bevacizumab + carboplatin		
cemiplimab		
5 th subsequent line		
carboplatin + paclitaxel		
doxorubicin		
Number of participants: all-participants-as-treated population Every participant is counted once for each applicable row and column. Percentages are based on the number of participants who progressed based on Investigator Review. If a treatment reflects a combination of regimens, the duration is derived using the first initiation date of any treatment within the regimen and the last date at which any treatment within the regimen is observed.		

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

To be included in this summary, start date of individual component must be on or after date of progression based on Investigator Review.

Database Cutoff Date: 7 Jan 2025

Table 10: Update to Table 20 of company submission: Summary of drug exposure – APaT

	Pembrolizumab + CCRT	Placebo + CCRT
	(N=295)	(N=304)
Duration on Therapy (Months)		
n	295	304
Mean (SD)		
Median		
Range		
Number of Cycles		
n	295	304
Mean (SD)		
Median		
Range		
Number of cycles of Pembro/Placebo refer to Q3W cycles from C1 to C5 and Q6W from C6 onward. Database Cutoff Date: 7 Jan 2025		

Table 11: Update to Table 21 of company submission: - Exposure by duration APaT

	Pembrolizumab + CCRT			Placebo + CCRT		
	(N=295)			(N=304)		
	n	(%)	Person-months	n	(%)	Person-months
Duration of Exposure						
>0 m						
≥1 m						
≥3 m						
≥6 m						
≥12 m						
≥18 m						
≥24 m						
Each participant is counted once on each applicable duration category row.						
Duration of exposure is the time from the first dose date to the last dose date.						
Database Cutoff Date: 07 Jan 2025						

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Table 12: Update to Table 22 of company submission: – Adverse event summary APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events				
with no adverse event				
with drug-related ^a adverse events				
with toxicity grade 3-5 adverse events				
with toxicity grade 3-5 drug-related adverse events				
with serious adverse events				
with serious drug-related adverse events				
who died				
who died due to a drug-related adverse event				
discontinued any drug due to an adverse event				
discontinued PEMBROLIZUMAB/ PLACEBO				
discontinued CISPLATIN				
discontinued EBRT				
discontinued BRACHYTHERAPY				
discontinued All Drugs				
discontinued any drug due to a drug-related adverse event				
discontinued PEMBROLIZUMAB/PLACEBO				
discontinued CISPLATIN				
discontinued EBRT				
discontinued BRACHYTHERAPY				
discontinued All Drugs				
discontinued any drug due to a serious adverse event				
discontinued PEMBROLIZUMAB/ PLACEBO				
discontinued CISPLATIN				
discontinued EBRT				
discontinued BRACHYTHERAPY				
discontinued All Drugs				
discontinued any drug due to a serious drug-related adverse event				
discontinued PEMBROLIZUMAB/ PLACEBO				
discontinued CISPLATIN				
discontinued EBRT				
discontinued BRACHYTHERAPY				

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Discontinued All Drugs				
^a Determined by the investigator to be related to the drug. Grades are based on NCI CTCAE version 5.0. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 07 Jan 2025				

Table 13: Update to Table 23 of company submission: Adverse events ≥10% APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events				
with no adverse events				
Anaemia				
Nausea				
Diarrhoea				
White blood cell count decreased				
Neutrophil count decreased				
Vomiting				
Urinary tract infection				
Platelet count decreased				
Hypomagnesaemia				
Hypokalaemia				
Hypothyroidism				
Alanine aminotransferase increased				
Aspartate aminotransferase increased				
Constipation				
Neutropenia				
Weight decreased				
Fatigue				
Decreased appetite				
Leukopenia				
Blood creatinine increased				
Lymphocyte count decreased				
Pyrexia				
Hyponatraemia				
Abdominal pain				
Hyperthyroidism				
Dysuria				
Thrombocytopenia				
Pelvic pain				

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COVID-19				
Back pain				
Hyperglycaemia				
Asthenia				
Arthralgia				
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 7 Jan 2025				

Table 14: Update to Table 24 of company submission: Grade 3-5 Adverse events ≥1% APaT

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more grade 3-5 adverse events				
with no adverse events				
Anaemia				
White blood cell count decreased				
Neutrophil count decreased				
Lymphocyte count decreased				
Neutropenia				
Lymphopenia				
Leukopenia				
Hypokalaemia				
Platelet count decreased				
Diarrhoea				
Urinary tract infection				
Hypertension				
Hypomagnesaemia				
Weight decreased				
Alanine aminotransferase increased				
Hydronephrosis				
Sepsis				
Thrombocytopenia				
Hypocalcaemia				
Hyponatraemia				
Abdominal pain				
Acute kidney injury				
Febrile neutropenia				
Pleural effusion				

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Pyelonephritis				
Urosepsis				
Pelvic pain				
Radiation proctitis				
Urogenital fistula				
Vomiting				
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 5.0. Database Cutoff Date: 7 Jan 2025				

Table 15: Update to Table 26 of company submission: Participants With AEOSI (Incidence > 0% in One or More Treatment Groups) (All-Participants-as-Treated Population)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	295		304	
with one or more adverse events				
with no adverse events				
Hypothyroidism				
Hyperthyroidism				
Gastritis				
Colitis				
Pneumonitis				
Hypersensitivity				
Autoimmune thyroiditis				
Drug hypersensitivity				
Enterocolitis				
Erythema multiforme				
Infusion related reaction				
Dermatitis bullous				
Nephritis				
Pancreatitis				
Thyroiditis				
Autoimmune colitis				
Autoimmune hepatitis				
Autoimmune hypothyroidism				
Autoimmune nephritis				
Diabetic ketoacidosis				
Encephalitis				
Gastritis erosive				

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Graves' disease				
Guillain-Barre syndrome				
Haemolytic anaemia				
Immune-mediated thyroiditis				
Interstitial lung disease				
Myocarditis				
Nephrotic syndrome				
Sarcoidosis				
Secondary adrenocortical insufficiency				
Silent thyroiditis				
Thyroid disorder				
Type 1 diabetes mellitus				
Uveitis				
Vasculitis				
Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Database Cutoff Date: 7 Jan 2025				

2 Cost effectiveness

2.1 KEYNOTE-A18 Final analysis update

This section includes updated survival analysis and utility values derived from the final analysis data-cut (Jan 2025). All analysis relates this data-cut unless stated otherwise.

All endpoints used are the same as those defined in the CS.

2.1.1 PFS-INV

The transition probabilities starting from the progression-free state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-A18 trial, in accordance with best practice methods and guidance from NICE DSU TSD 14. ⁽¹⁾ Parametric models were fitted to both PFS and TTP.

Parametric models fitted to TTP were used to determine the time dependant transition probability of progressing, while difference between the weekly hazard of PFS and TTP determines the transition from the progression free state, straight to death.

Progression-free survival was defined via investigator assessment per RECIST.

Figure 5: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-A18 PFS – pembrolizumab + CCRT versus CCRT



Key: MK-3475, Pembrolizumab; PFS-INV, investigator assessed progression free survival

Figure 6: Cumulative hazard plot – PFS – pembrolizumab + CCRT versus CCRT



Key: MK-3475, Pembrolizumab

2.1.1.1 Standard parametric models

The standard parametric models along with the observed PFS KM data from KEYNOTE-A18 are shown in Figure 8. Five of the seven standard parametric curves provided poor visual fit to the observed KMs and underestimated PFS from week 120 onwards for both arms (**Error! Not a valid bookmark self-reference.** and Figure 8); The generalised gamma and Gompertz curves were the best fits to both arms. Although for the CCRT arm these curves didn't not fit closely to the KM from 50-120 weeks.

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

- Of these two, the generalised gamma outperformed the Gompertz in terms of average of AIC and BIC. No curves are within 5 points of the generalised gamma model in the CCRT arm, and only the log-normal is within 5 in the pembrolizumab + CCRT in the pembrolizumab arm but it is not within 3 points.
- While the fits may have been sufficient, especially for the pembrolizumab+ CCRT arm, spline models have been explored for both arms.

Figure 7 and Figure 8 for CCRT and pembrolizumab + CCRT respectively. Table 16 summarises goodness-of-fit for the parametric models to the observed data as assessed by the AIC and BIC statistics. The following conclusions were drawn:

- Five of the seven standard parametric curves provided poor visual fit to the observed KMs and underestimated PFS from week 120 onwards for both arms (**Error! Not a valid bookmark self-reference.** and Figure 8); The generalised gamma and Gompertz curves were the best fits to both arms. Although for the CCRT arm these curves didn't not fit closely to the KM from 50-120 weeks.
- Of these two, the generalised gamma outperformed the Gompertz in terms of average of AIC and BIC. No curves are within 5 points of the generalised gamma model in the CCRT arm, and only the log-normal is within 5 in the pembrolizumab + CCRT in the pembrolizumab arm but it is not within 3 points.
- While the fits may have been sufficient, especially for the pembrolizumab+ CCRT arm, spline models have been explored for both arms.

Figure 7: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PFS – CCRT



Key: PFS-INV, Investigator assessed progression free survival

Figure 8: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PFS - Pembrolizumab + CCRT



Key: MK-3475, Pembrolizumab, PFS-INV, Investigator assessed progression free survival

Table 16: Summary of parametric fitting performances of KEYNOTE-A18 PFS for pembrolizumab + CCRT and CCRT

Treatment	Pembrolizumab + CCRT			CCRT		
	AIC	BIC	Average	AIC	BIC	Average
Extrapolation						
Exponential						
Weibull						
Log-normal						
Log-logistic						

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Gompertz									
Gamma									
Generalized Gamma									

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

Figure 9: Empirical and smoothed hazards for KN-A18 PFS - Pembrolizumab + CCRT



Figure 10: Smoothed hazard plot and standard parametric model hazards - PFS CCRT



Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Figure 11: Empirical and smoothed hazards for KN-A18 PFS - CCRT



Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer
[ID6138]

Figure 12: Smoothed hazard plot and standard parametric model hazards - PFS pembrolizumab + CCRT



2.1.1.2 Spline models

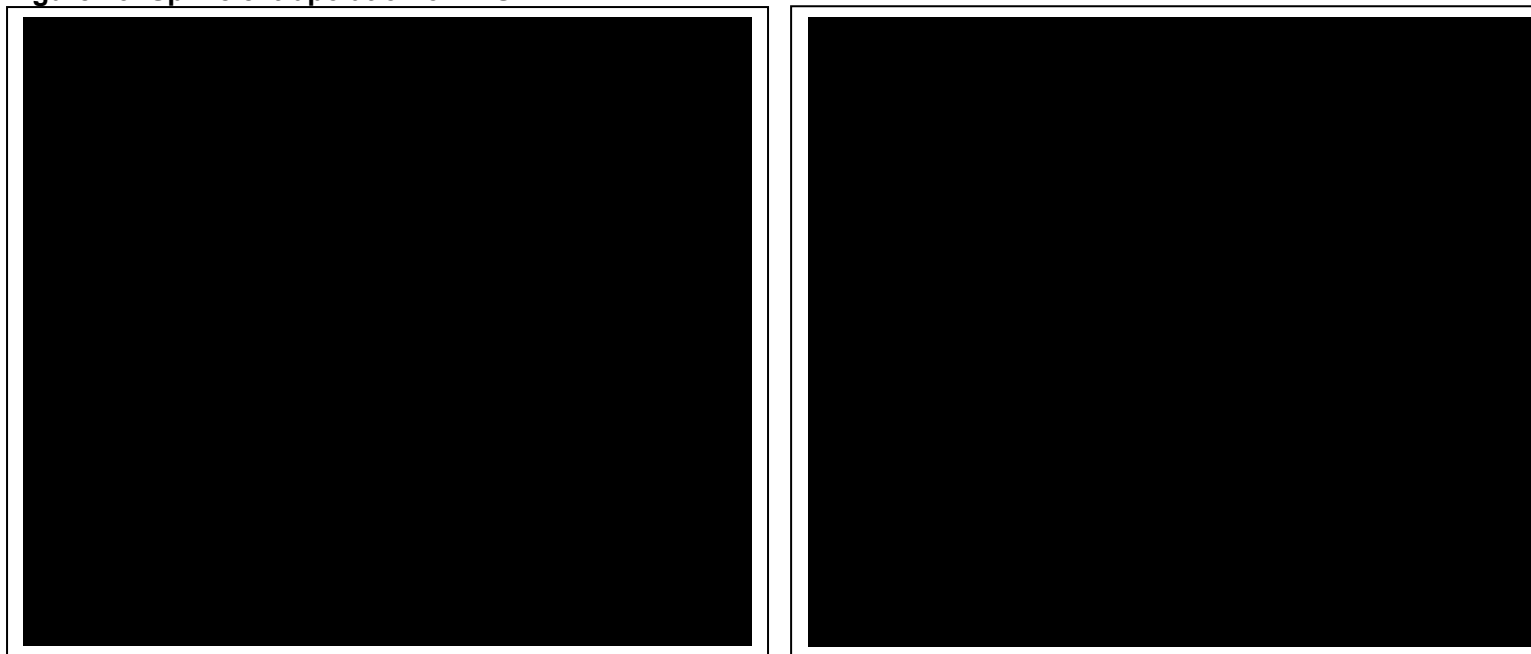
Analyses were conducted for 1, 2, and 3 knot spline models, using normal, odds, and hazard scales. Knots were placed uniformly along the distribution of uncensored log event times. Overlays of the spline models with the observed KM data are shown in Figure 13 and

Figure 15.

The use of splines provided options that numerically improved the AIC and BIC in both arms compared with the standard models (Table 17 and Table 18), also providing suitable fit to both observed KM and hazard for CCRT (Figure 13 and Figure 14).

However, for pembrolizumab + CCRT, the spline models either had relatively poor fit or did not provide any improvement in the visual fit to the smoothed hazard plots compared to standard models described above. There were no meaningful improvements in visual fit or in AIC/BIC versus the generalised gamma model with the best fitting spline models being within 1 or 2 points versus the generalised gamma.

Figure 13: Spline extrapolation of PFS – CCRT



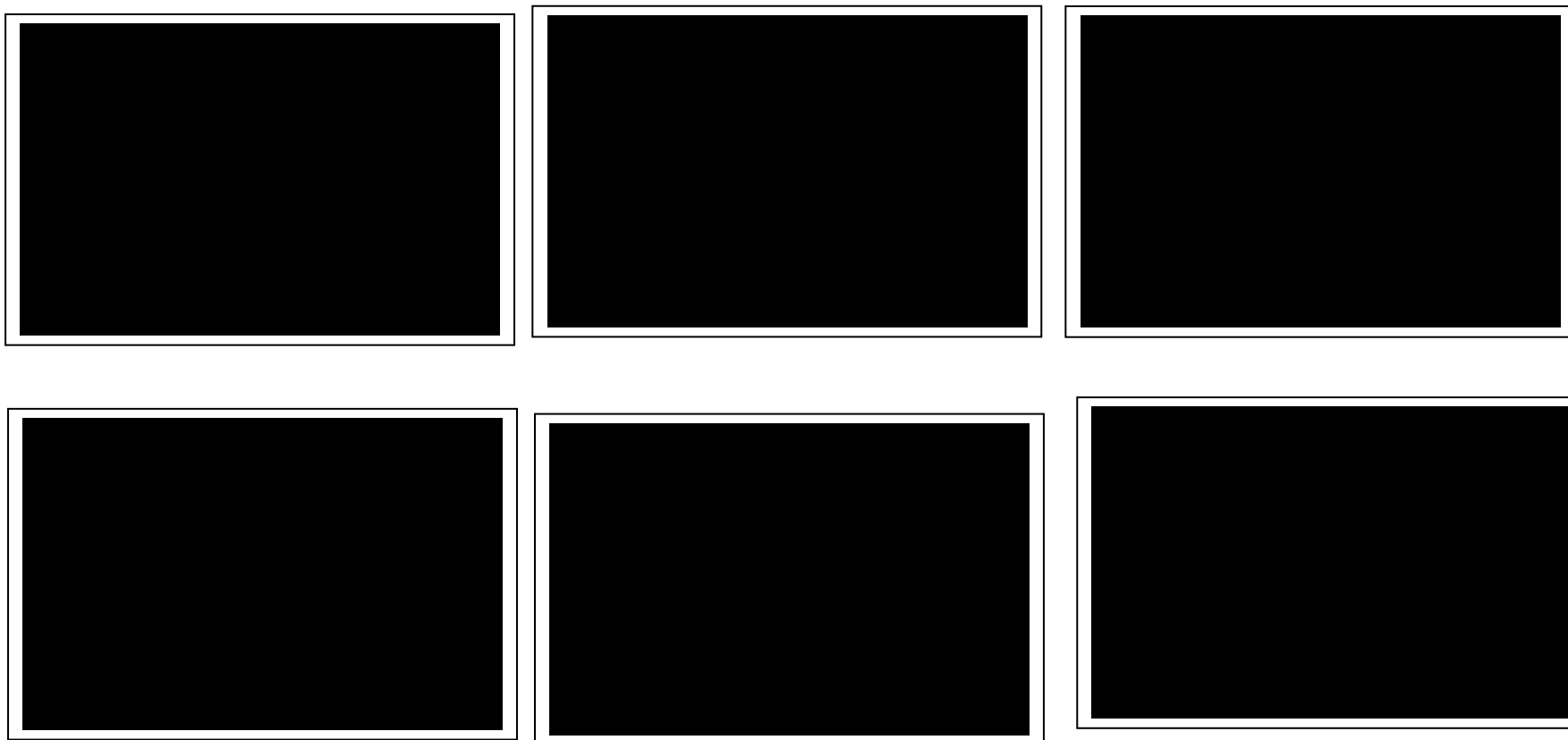
Key: CT, paclitaxel + carboplatin; k, knot; KM, Kaplan-Meier; PFS, progression-free survival

Table 17: Summary of parametric fitting performances of spline models of PFS for CCRT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	████	████	████	████	████	████	████	████	████
Odds	████	████	████	████	████	████	████	████	████
Normal	████	████	████	████	████	████	████	████	████

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

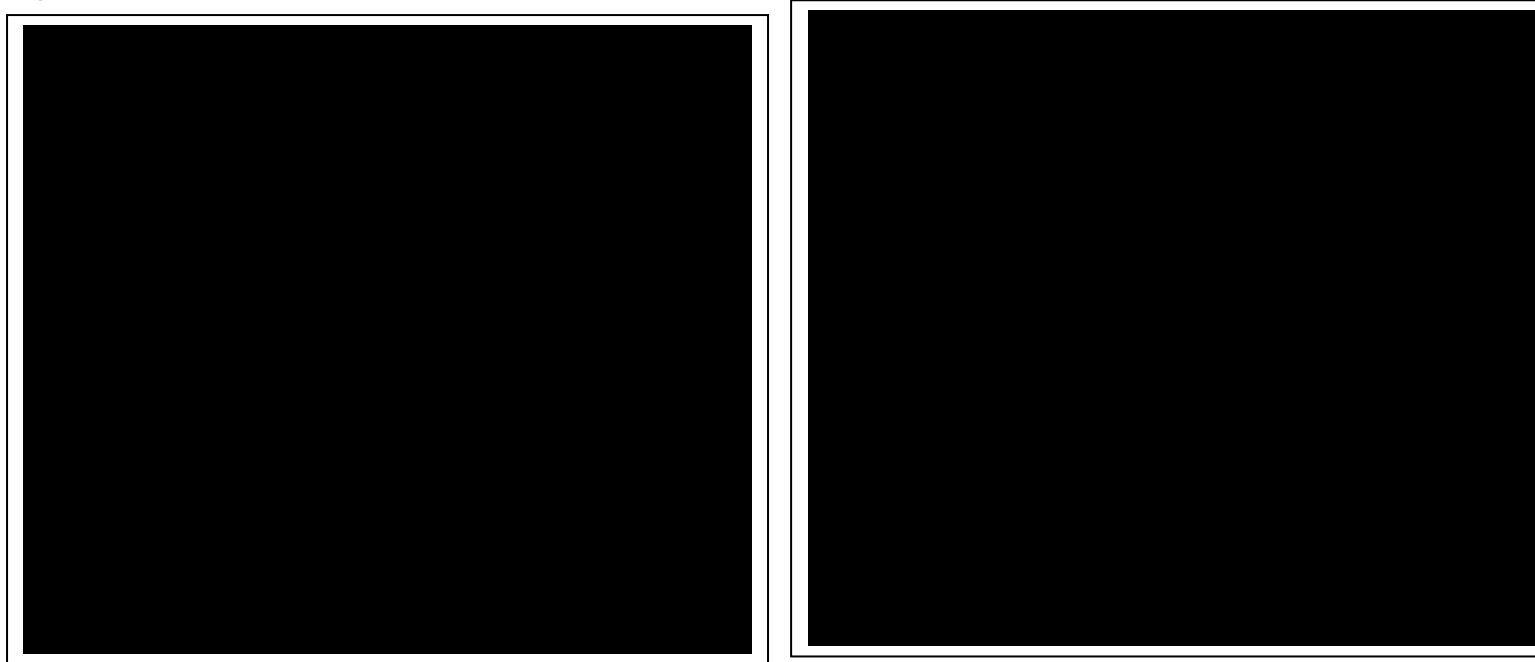
Figure 14: CCRT spline hazard fits - PFS





Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer
[ID6138]

Figure 15: Spline extrapolation of PFS – pembrolizumab + CCRT



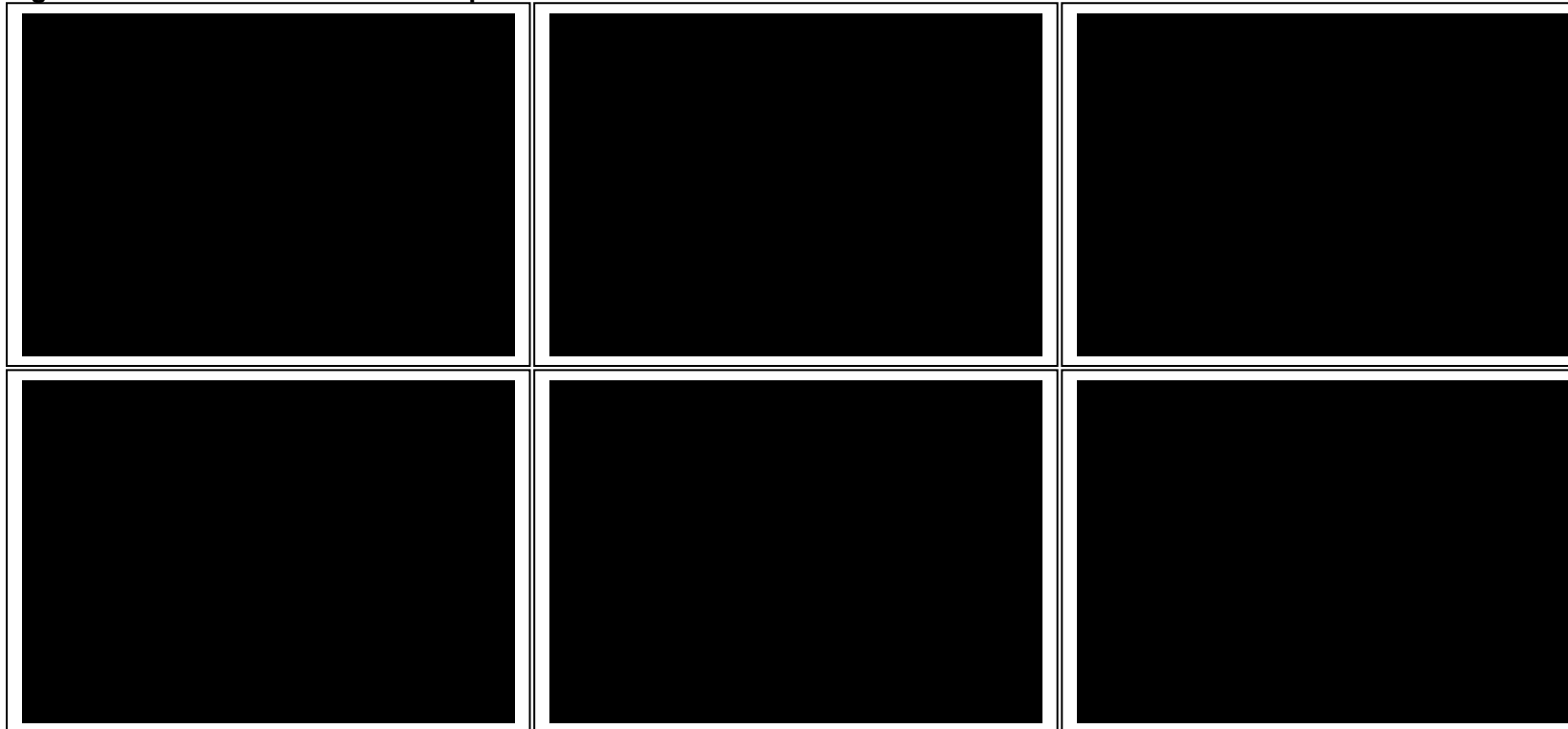
Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer
[ID6138]

Table 18: Summary of parametric fitting performances of spline models of PFS for pembrolizumab + CCRT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard									
Odds									
Normal									

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

Figure 16: Pembrolizumab + CCRT spline hazard fits - PFS





Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer
[ID6138]

2.1.1.3 Validation and selection

During the advisory board conducted as part of the original CS, landmark estimates were not provided by the clinical advisors, instead a selection of PFS curves for both arms of trial were presented, with cure assumptions were presented, of the options the generalised gamma curves with cure of 95% between 5-7 years were selected. Table 19 and Table 20 present the landmark PFS estimates of these original curves alongside the modelled estimates for the FA analysis curves (again with 95% cure between 5-7 years applied).

CCRT

1. Due to poor visual fit to observed data, all models apart from the generalised gamma and Gompertz were rejected.
2. Spline fits were further considered to assess if fit could be improved, as generalised gamma and Gompertz, while being the best fitting, struggled to capture the shape of the curve.
3. AIC of the best fitting splines was over 10 points lower than the best fitting standard curve, suggests a meaningfully better statistical fit The 1-knot odds had the lowest AIC with 1 and 2-knot hazard splines being within 2 AIC.
4. All 1 and 2-knot splines had good fit to the smoothed hazards.

As such the 1-knot odds curve with a cure assumption on 95% patients between 5-7 is used within the base-case modelling. The 1-knot hazard and generalised gamma, along with the cure assumption are further explored in the sensitivity analysis.

The long term PFS curves suggested by the splines are morphologically similar to the generalised gamma estimates validated by the clinical advisers, the key difference is that the implied proportion cured is about 8% higher.

Table 19: PFS landmark estimates for CCRT (INV)

Data cut	Model	Year								
		1	2	3	5	10	15	20	25	30
IA2	Generalised gamma	71.9%	57.4%	49.5%	41.0%	37.1%	35.3%	32.8%	29.3%	23.9%
FA	Generalised gamma (scenario)	████	████	████	████	████	████	████	████	████
	1kH (scenario)	████	████	████	████	████	████	████	████	████
	2kH	████	████	████	████	████	████	████	████	████
	3kH	████	████	████	████	████	████	████	████	████
	1kO (base case)	████	████	████	████	████	████	████	████	████
	2kO	████	████	████	████	████	████	████	████	████
	3kO	████	████	████	████	████	████	████	████	████
	1kN	████	████	████	████	████	████	████	████	████
	2kN	████	████	████	████	████	████	████	████	████
	3kN	████	████	████	████	████	████	████	████	████
Abbreviations: FA, final analysis; IA, interim analysis; INV, investigator; k, knot; H, hazards; O, odds; N, normal										

Pembrolizumab +CCRT

1. The generalised gamma had the best AIC and BIC. The log-normal model had the closest fit but this had 7 AIC and 4 greater BIC.
2. All bar the generalised gamma provided poor visual fit to the KM curve
3. The gompertz had the best visual fit to the smoothed hazard, with the generalised gamma also providing a suitable visual fit.
4. While the generalised gamma appeared to provide a close fit the to KM curve, splines were explored.
5. All nine splines provided similar AIC to the generalised gamma, all being within 3 AIC. All of the splines provided similar visual fit to the KM when compared to the generalised gamma.
6. Due to all the splines have hazard 0 and time 0, none could capture the shape of the smoothed observed hazard up to week 15-20. From weeks 50-60 all 1-knot and 2-knot splines have a similar, suitable fit to the hazards
7. Clinical validation at the 2024 advisory board confirmed that the generalised gamma with 5-7 cure point provided the most plausible long term outcomes. ⁽²⁾ All models produce similar landmark estimates.

NICE TSD14 recommends using the same parametric form in both arms when there is not a strong rationale to do otherwise. ⁽¹⁾.

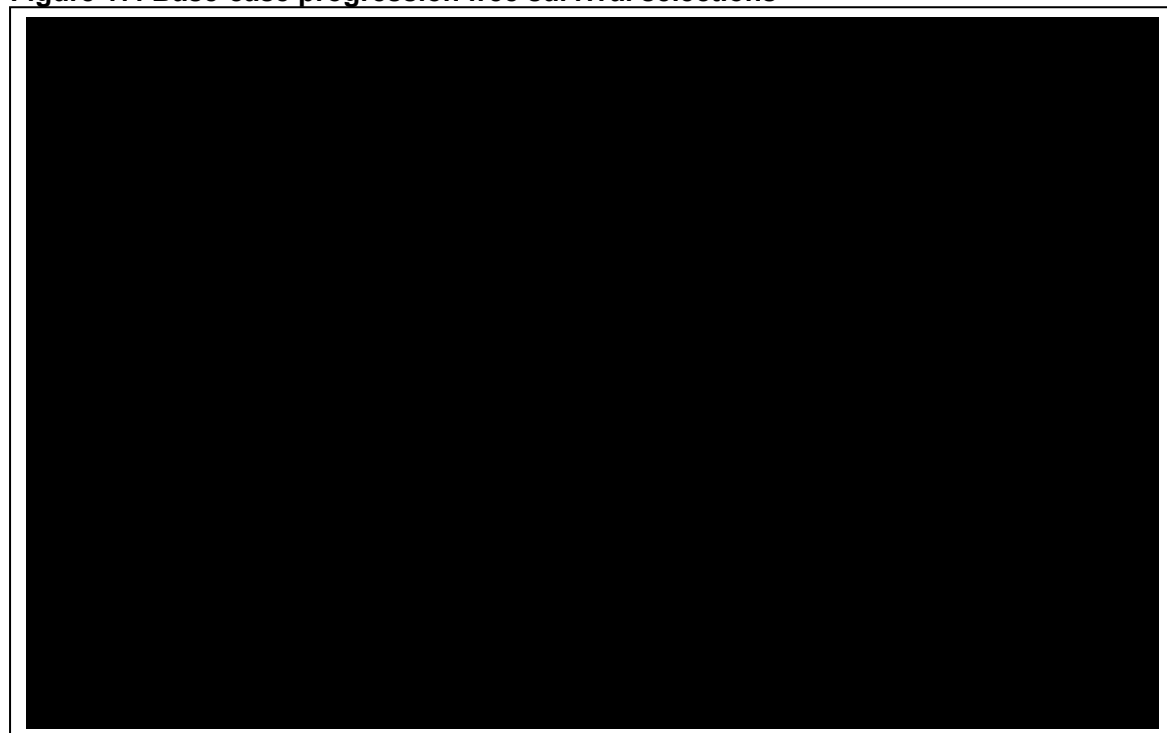
Therefore in the base-case the 1-knot odds has been explored as to match the CCRT pick. Its projections are almost identical to the original generalised gamma. The generalised gamma and 1-knot hazard have also been explored in scenarios to match those presented in the CCRT arm.

It can be seen from the landmark table that all models produce results similar to the original generalised gamma curves that were validated by the advisers at IA2.

Table 20: PFS landmark estimates for pembrolizumab + CCRT (INV)

Data cut	Model	Year								
		1	2	3	5	10	15	20	25	30
IA2	Generalised gamma	83.5%	72.9%	66.6%	59.0%	54.2%	51.5%	47.9%	42.8%	34.9%
FA	Generalised gamma (scenario)									
	1kH (scenario)									
	2kH									
	3kH									
	1kO (base case)									
	2kO									
	3kO									
	1kN									
	2kN									
	3kN									
Abbreviations: FA, final analysis; IA, interim analysis; INV, investigator; k, knot; H, hazards; O, odds; N, normal										

Figure 17: Base-case progression free survival selections



Key: CCRT, concurrent chemoradiotherapy; KM, Kaplan-Meier

2.1.2 PFS-BICR

In order to explore uncertainty in the extrapolations, the company are also incorporating PFS as assessed by Independent Central Review (also RECIST criteria) since this was the original primary endpoint of the trial before being switched to IA. There is a notable difference in the shape of the CCRT KM curve between PFS as assessed by the investigator and by the central review, while the pembrolizumab curve appears similar. Table and Table present the landmark PFS estimates of these original curves alongside the modelled estimates for the FA analysis curves (again with 95% cure between 5-7 years applied).

Figure 18: Kaplan-Meier curves and Schoenfeld residuals for PFS-BICR



Figure 19: Comparison of cumulative hazard in PFS-BICR

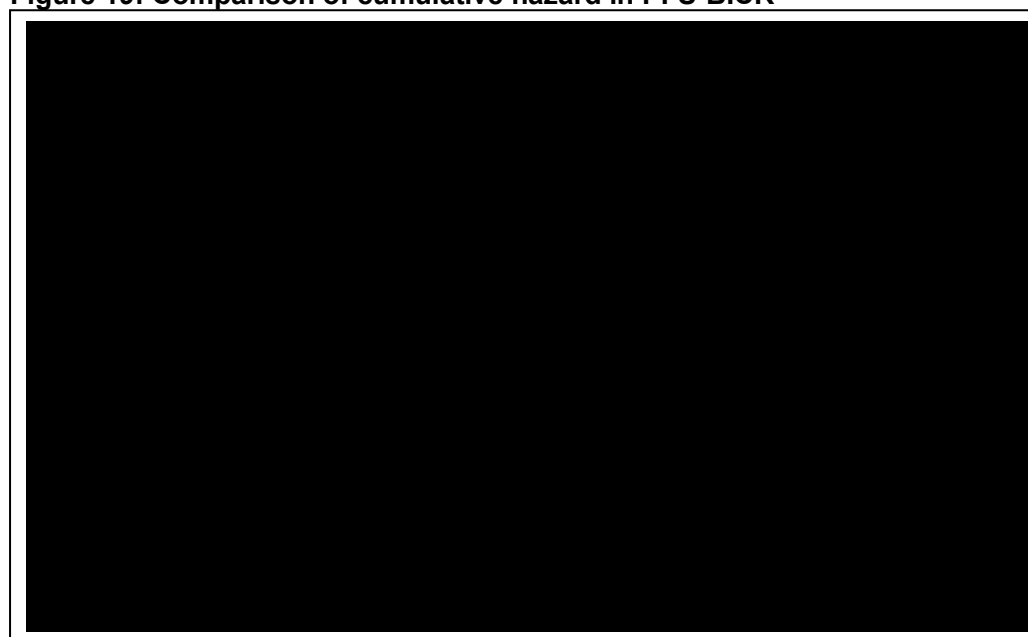


Figure 20: One-piece parametric survival models for pembrolizumab+CCRT PFS-BICR

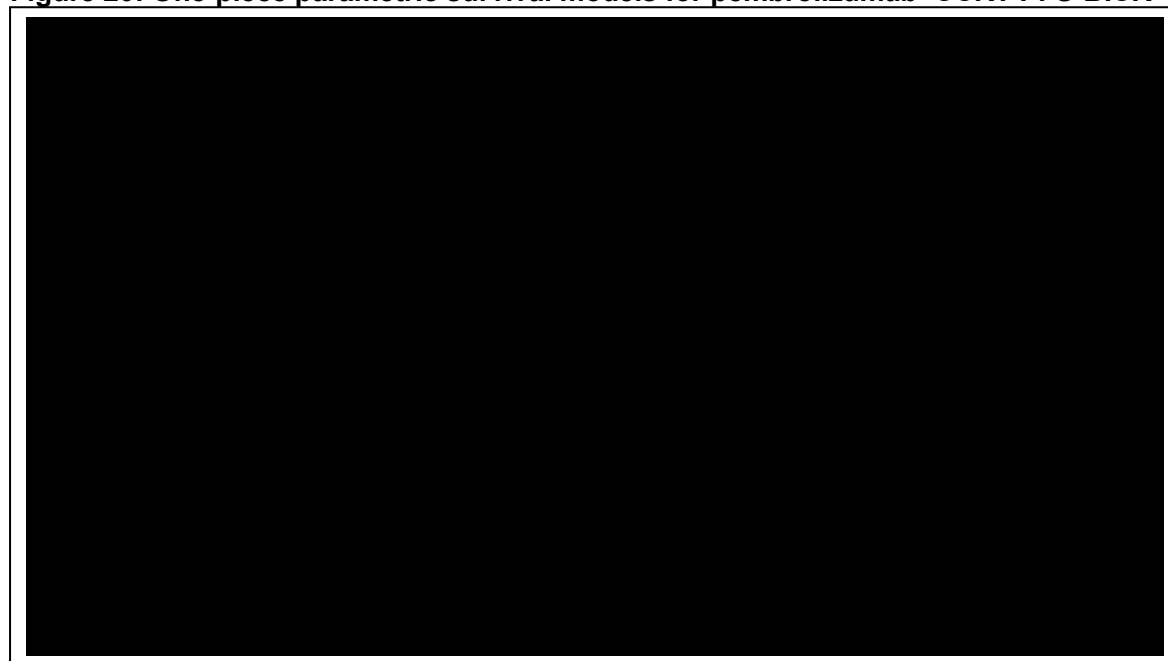


Table 21: AIC and BIC statistics for one-piece parametric models for pembrolizumab+CCRT PFS-BICR

Model	AIC	BIC	Average
Exponential	████	████	████
Weibull	████	████	████
Log-normal	████	████	████
Log-logistic	████	████	████
Gompertz	████	████	████
Gamma	████	████	████
Generalized Gamma	████	████	████

Figure 21: One-piece parametric survival models for CCRT PFS-BICR



Table 22: AIC and BIC statistics for one-piece models for CCRT PFS-BICR

Model	AIC	BIC	Average
Exponential			
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Gamma			
Generalized Gamma			

The generalised gamma models provide the best fit by both AIC and BIC for both arms. There are no other curves within 5 points of AIC. Visual inspection suggests the generalised gamma models provide a close fit to the KM curves for both arms. The company believes that spline models are not needed due to the closeness of this fit. The generalised gamma models were selected for use within the economic model. Notably, the delta between the long term survival estimates in the generalised gamma models is more similar to that validated by clinicians at the advisory board (i.e. the IA2 generalised gamma estimates) than the delta in the extrapolations based on PFS-INV.

Table 23: PFS landmark estimates for CCRT (BICR)

Data cut	Model	Year								
		1	2	3	5	10	15	20	25	30
IA2 using INV*	Generalised gamma									
FA using BICR	Generalised gamma									
	Exponential									
	Weibull									
	Log-normal									
	Log-logistic									
	Gompertz									
	Gamma									
Abbreviations: BICR, blinded independent central review; FA, final analysis; IA, interim analysis; PFS, progression free survival; INV, investigator * The option of BIRC assessment is only included for the FA data cut in the FIGO III-IVA population.										

Table 24: PFS landmark estimates for pembrolizumab + CCRT (BICR)

Data cut	Model	Year								
		1	2	3	5	10	15	20	25	30
IA2 using INV*	Generalised gamma									
	Generalised gamma									

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FA using BICR	Exponential									
	Weibull									
	Log-normal									
	Log-logistic									
	Gompertz									
	Gamma									
Abbreviations: BICR, blinded independent central review; FA, final analysis; IA, interim analysis; PFS, progression free survival; INV, investigator * The option of BIRC assessment is only included for the FA data cut in the FIGO III-IVA population.										

2.1.3 TTP-INV

As with the original CS, the same models have been chosen for the TTP curves as the PFS curves. Assessing the various fits below there is no obvious statistical or clinical reason for implementing different types/families of PFS and TTP curve selections within each arm. All analyses have been run using the same type of model between PFS and TTP e.g. 1-knot odds.

Figure 22: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-A18 TTP – pembrolizumab + CCRT versus CCRT



Figure 23: Cumulative hazard plot – TTP – pembrolizumab + CCRT versus CCRT



2.1.3.1 *Standard parametric models*

Figure 24: Parametric fitting and extrapolation of long-term KEYNOTE-A18 TTP – Pembrolizumab + CCRT



Figure 25: Parametric fitting and extrapolation of long-term KEYNOTE-A18 TTP - CCRT



Table 25: Summary of parametric fitting performances of KEYNOTE-A18 TTP for pembrolizumab + CCRT and CCRT

Treatment	Pembrolizumab + CCRT			CCRT		
	AIC	BIC	Average	AIC	BIC	Average
Extrapolation						
Exponential						
Weibull						
Log-normal						
Log-logistic						
Gompertz						
Gamma						
Generalized Gamma						

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

Figure 26: Empirical and smoothed hazards for KN-A18 TTP - Pembrolizumab + CCRT



Figure 27: Smoothed hazard plot and standard parametric model hazards – TTP- Pembrolizumab + CCRT



Figure 28: Empirical and smoothed hazards for KN-A18 TTP - CCRT

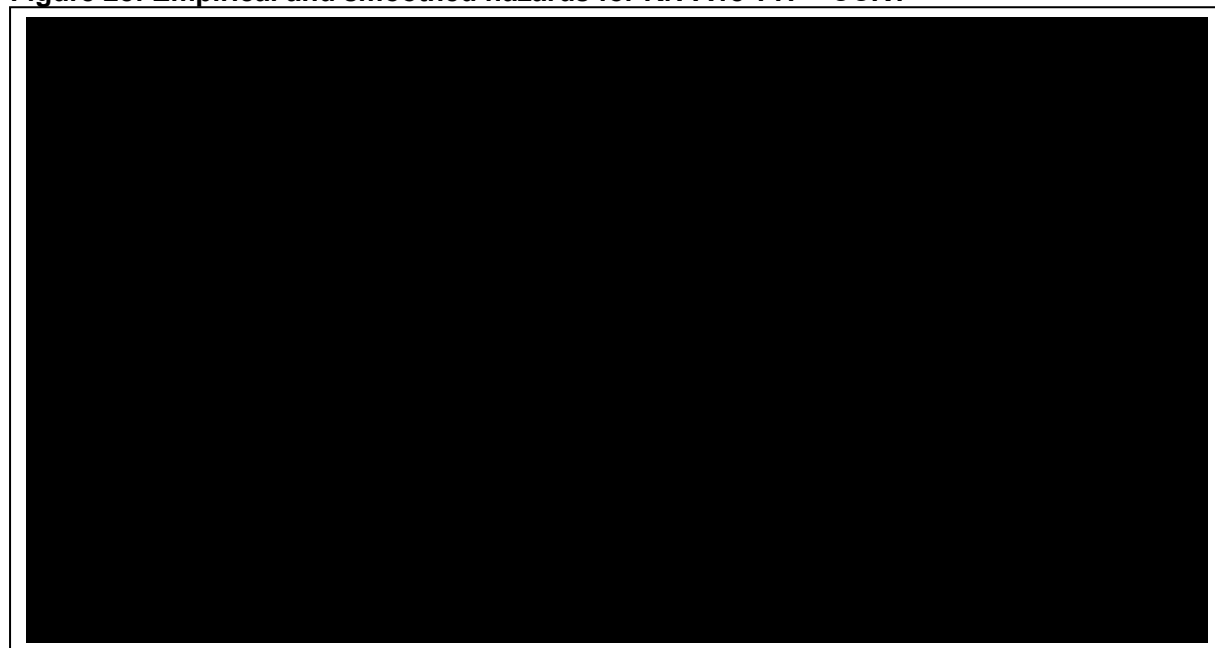
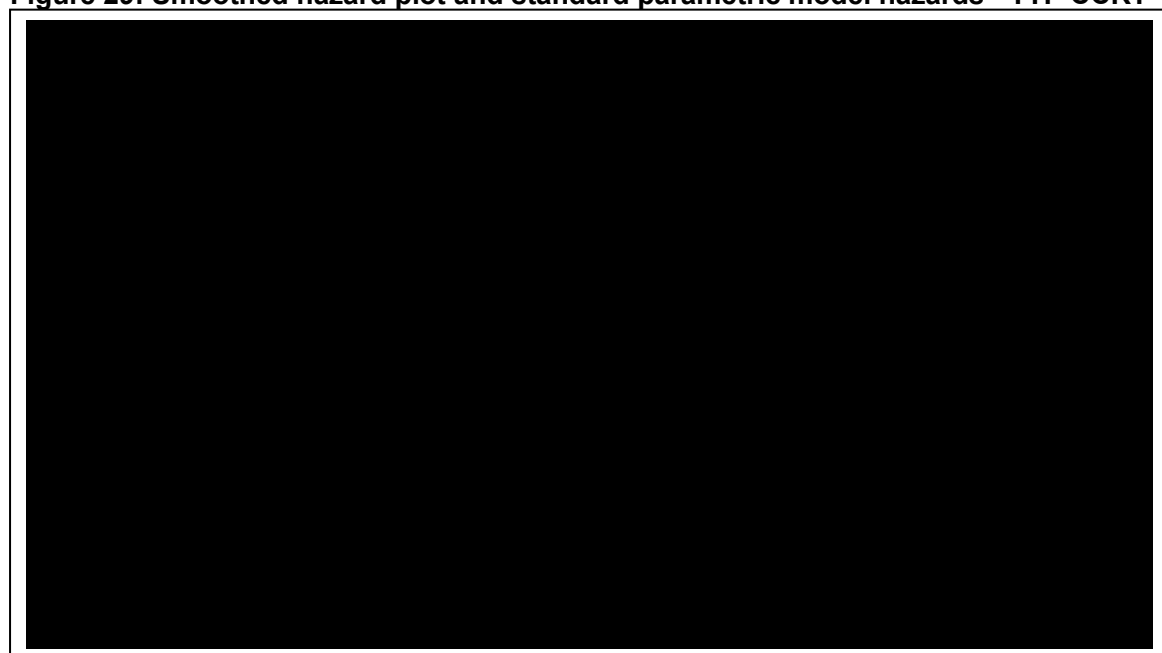
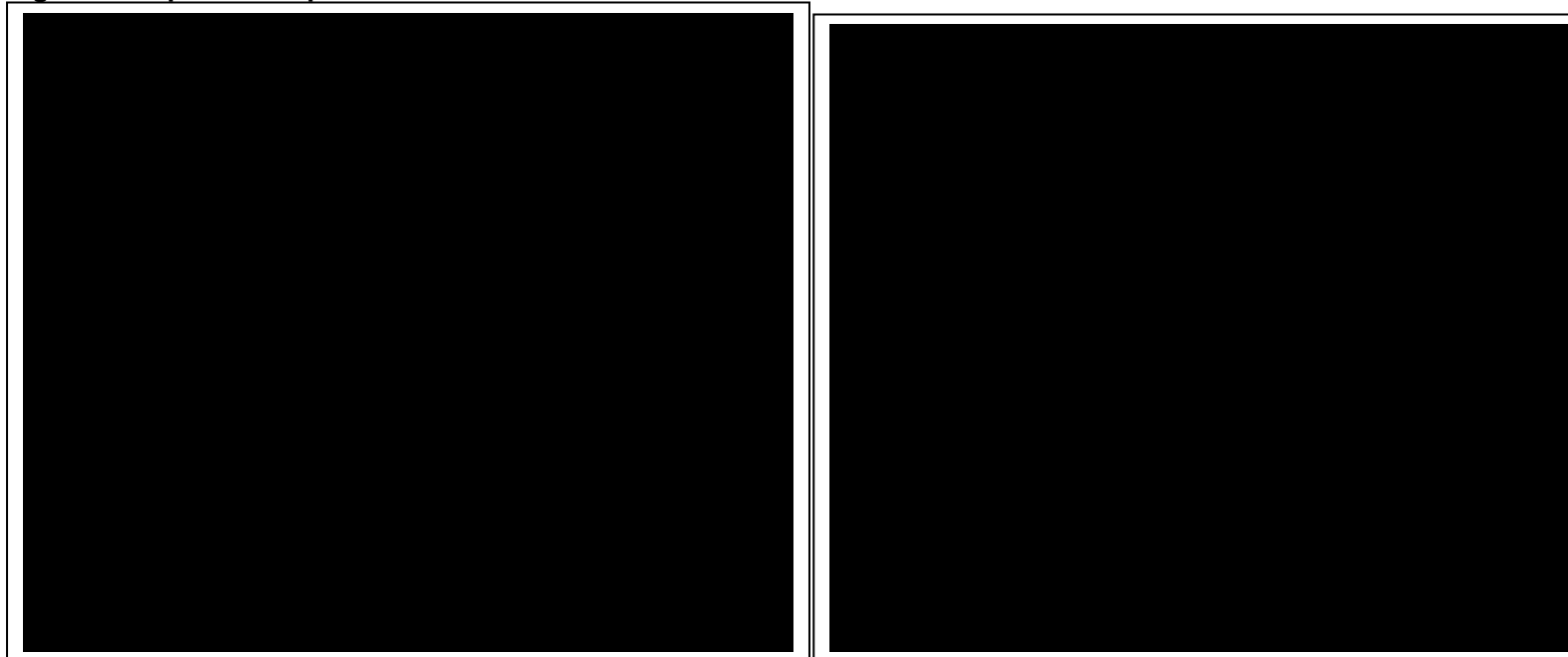


Figure 29: Smoothed hazard plot and standard parametric model hazards - TTP CCRT



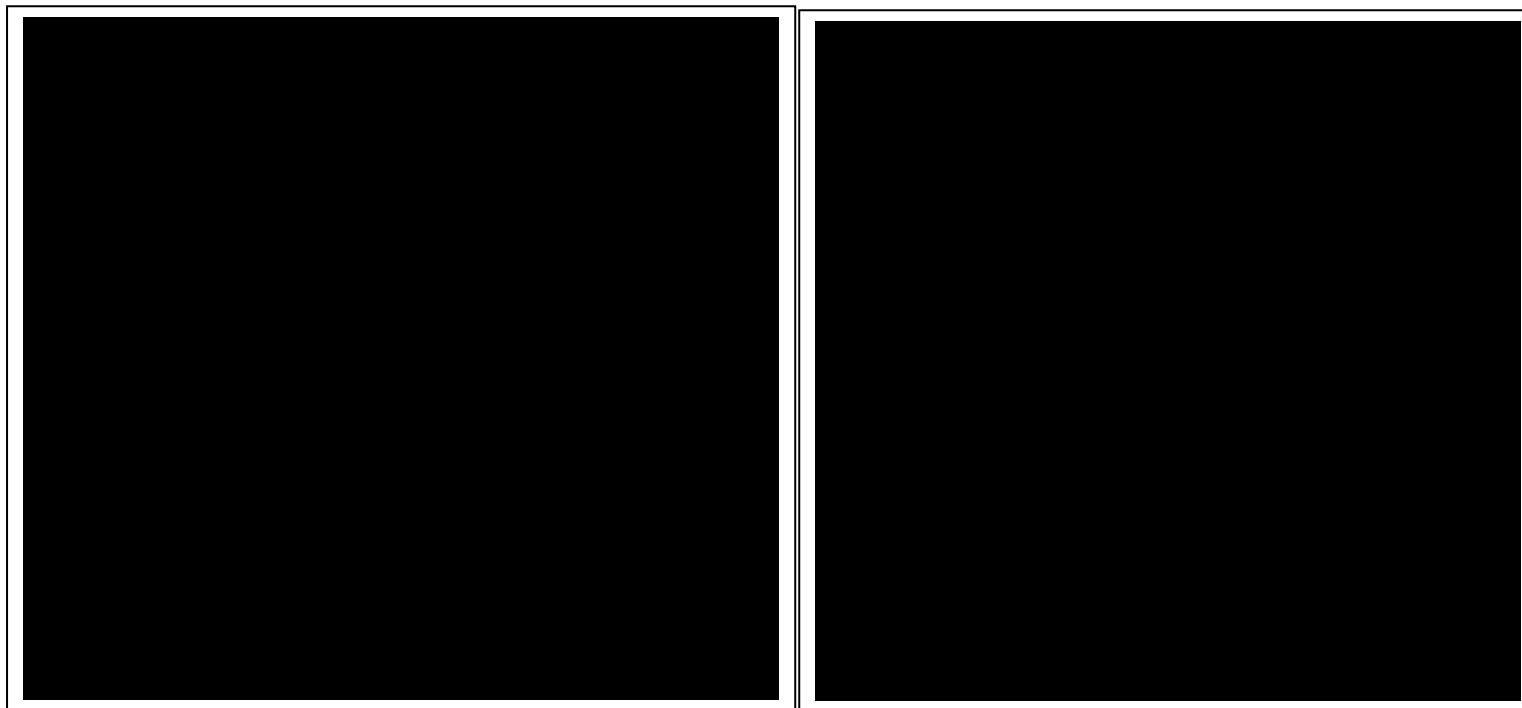
2.1.3.2 Spline models

Figure 30: Spline extrapolation of TTP – Pembrolizumab + CCRT



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Figure 31: Spline extrapolation of TTP –Pembrolizumab + CCRT



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Figure 32: CCRT + Pembrolizumab spline hazard fits - TTP

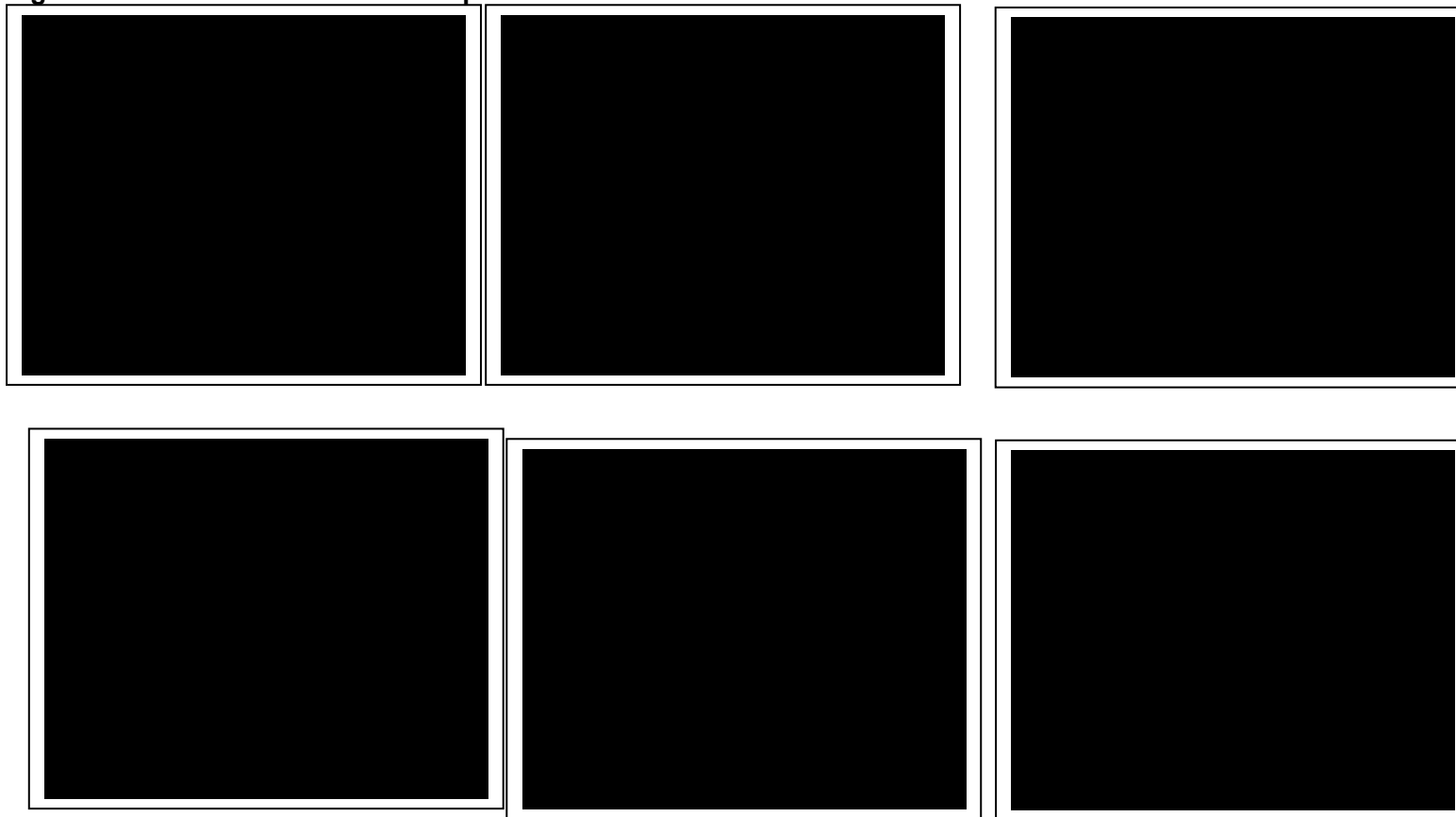




Table 26: Summary of parametric fitting performances of spline models of TTP for Pembrolizumab CCRT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	████	████	████	████	████	████	████	████	████
Odds	████	████	████	████	████	████	████	████	████
Normal	████	████	████	████	████	████	████	████	████

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

Figure 33: CCRT spline hazard fits

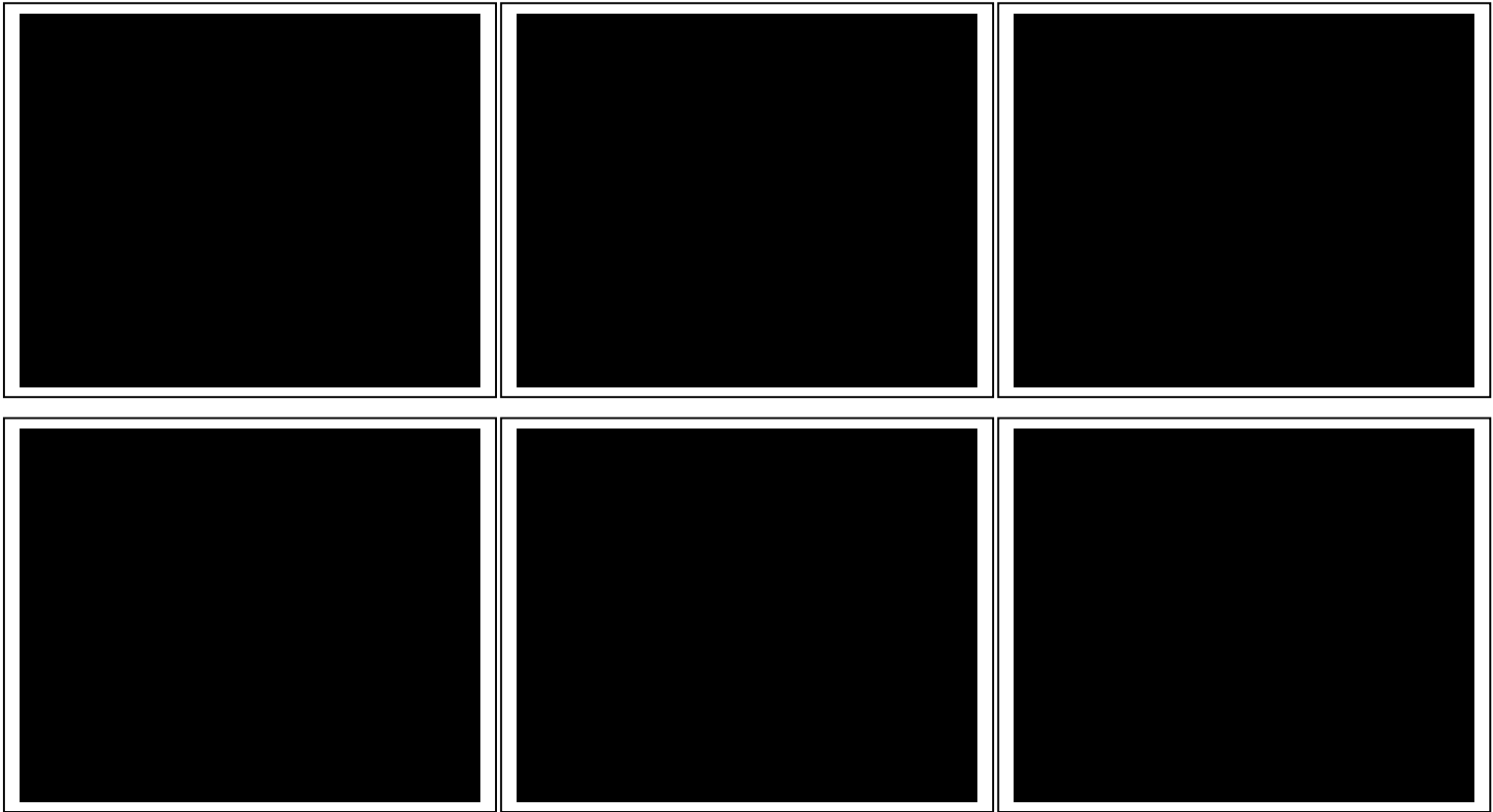




Table 27: Summary of parametric fitting performances of spline models of TTP for CCRT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard									
Odds									
Normal									

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

2.1.4 TTP-BICR

This section provides the outputs for TTP based on blinded independent central review. The same pattern is seen as was seen in PFS-BICR with the generalised gamma model again being the best fitting in both arms.

Figure 34: TTP-BICR and Parametric fits - Pembrolizumab+CCRT arm

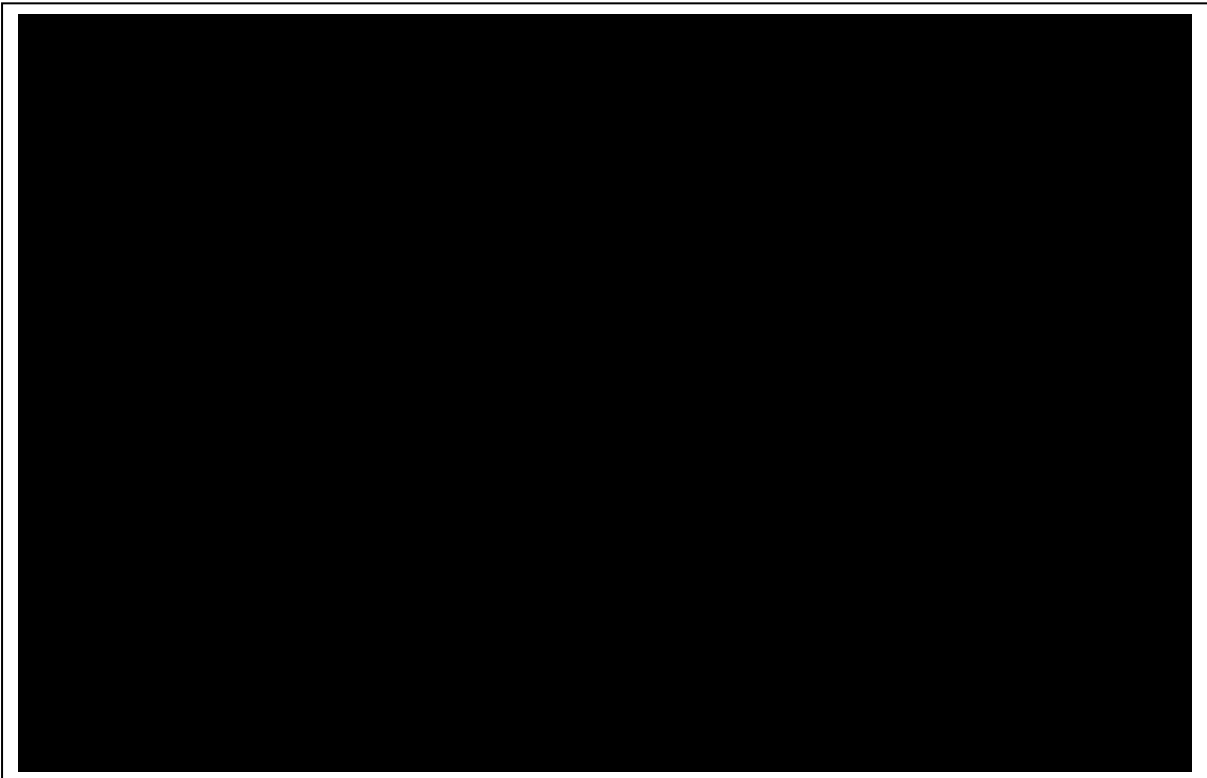


Figure 35: TTP-BICR and Parametric fits - CCRT arm

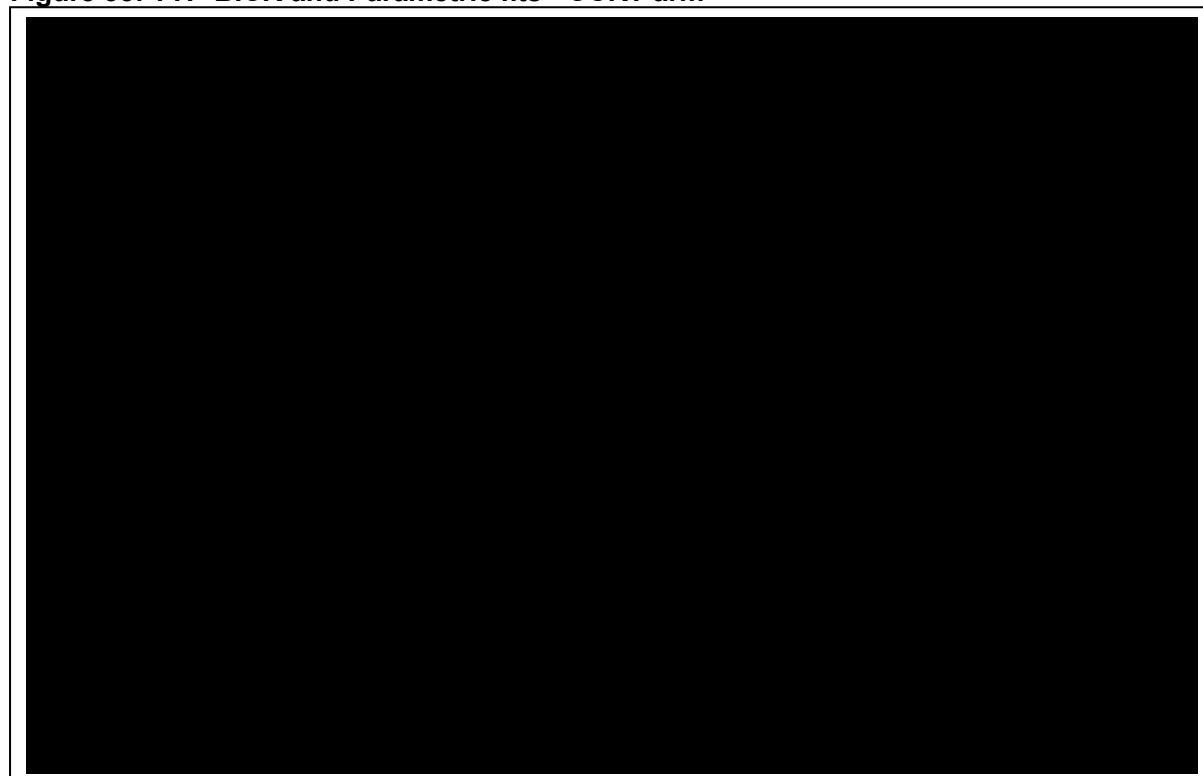


Table 28: AIC/BIC for parametric fits for TTP-BICR

Pembro+CCRT - Goodness of fit statistics									
Model	AIC		BIC		Rank AIC		Rank BIC		
Exponential									
Gamma									
Gen. Gamma									
Gompertz									
Log-Logistic									
Log-Normal									
Weibull (AFT)									

CCRT - Goodness of fit statistics									
Model	AIC		BIC		Rank AIC		Rank BIC		
Exponential									
Gamma									
Gen. Gamma									
Gompertz									
Log-Logistic									
Log-Normal									
Weibull (AFT)									

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2.1.5 OS

This section provides the curve fitting outputs for the KEYNOTE-A18 overall survival. These are not used to directly model OS in the model engine but have been used to validate and calibrate modelled OS over the observed follow up period.

No formal validation or selection process of the fits has been performed, but all curves bar exponential provide similar fits to the KM across the observed follow up period. Based on AIC and visual fit to the KM curves the generalised gamma was chosen to calculate the mean squared error values that were used to calibrate the pembrolizumab arm post progression survival (see section 2.4 below).

Figure 36: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-A18 OS – pembrolizumab + CCRT versus CCRT



Figure 37: Cumulative hazard plot – OS – pembrolizumab + CCRT versus CCRT

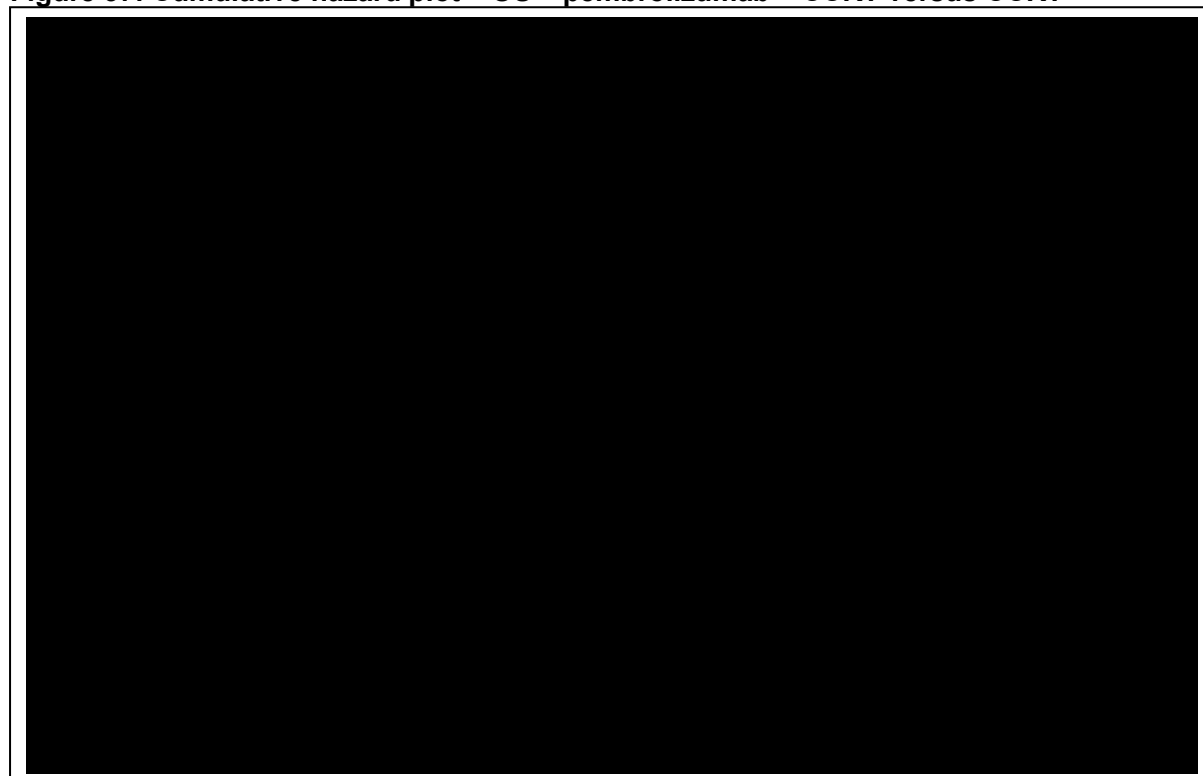


Figure 38: Parametric fitting and extrapolation of long-term KEYNOTE-A18 OS – Pembrolizumab + CCRT

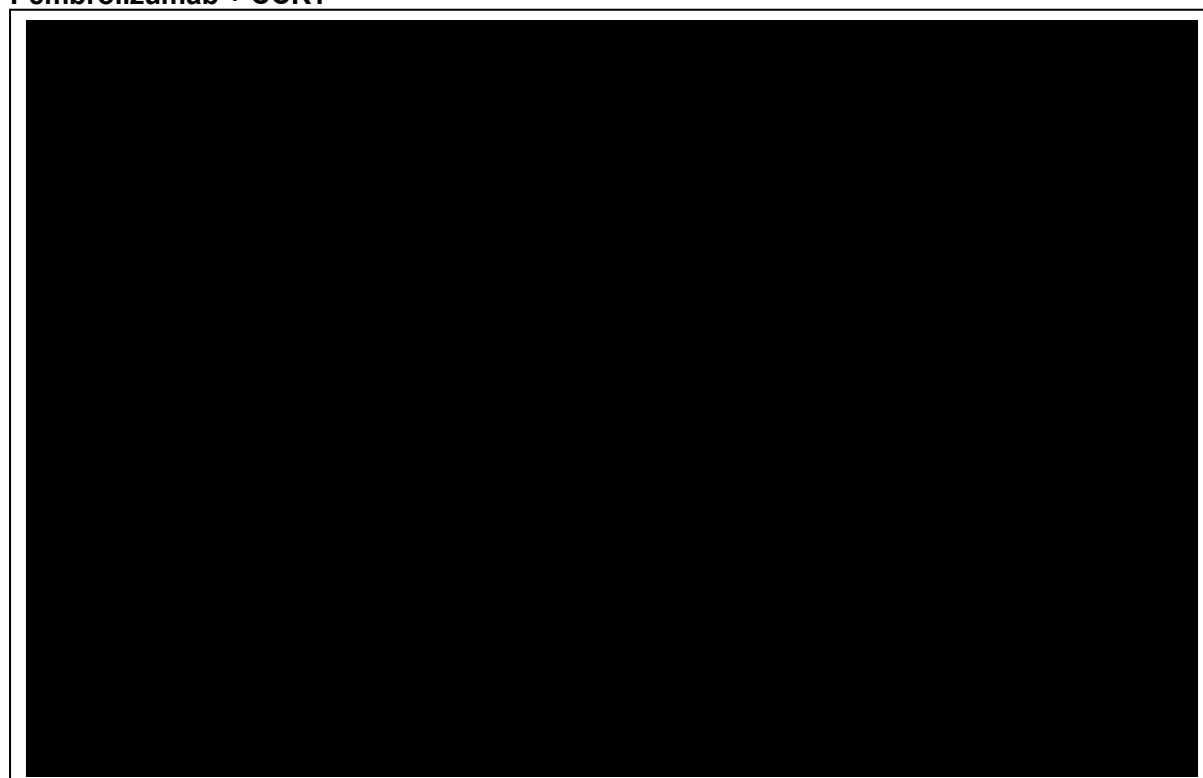


Figure 39: Parametric fitting and extrapolation of long-term KEYNOTE-A18 OS - CCRT

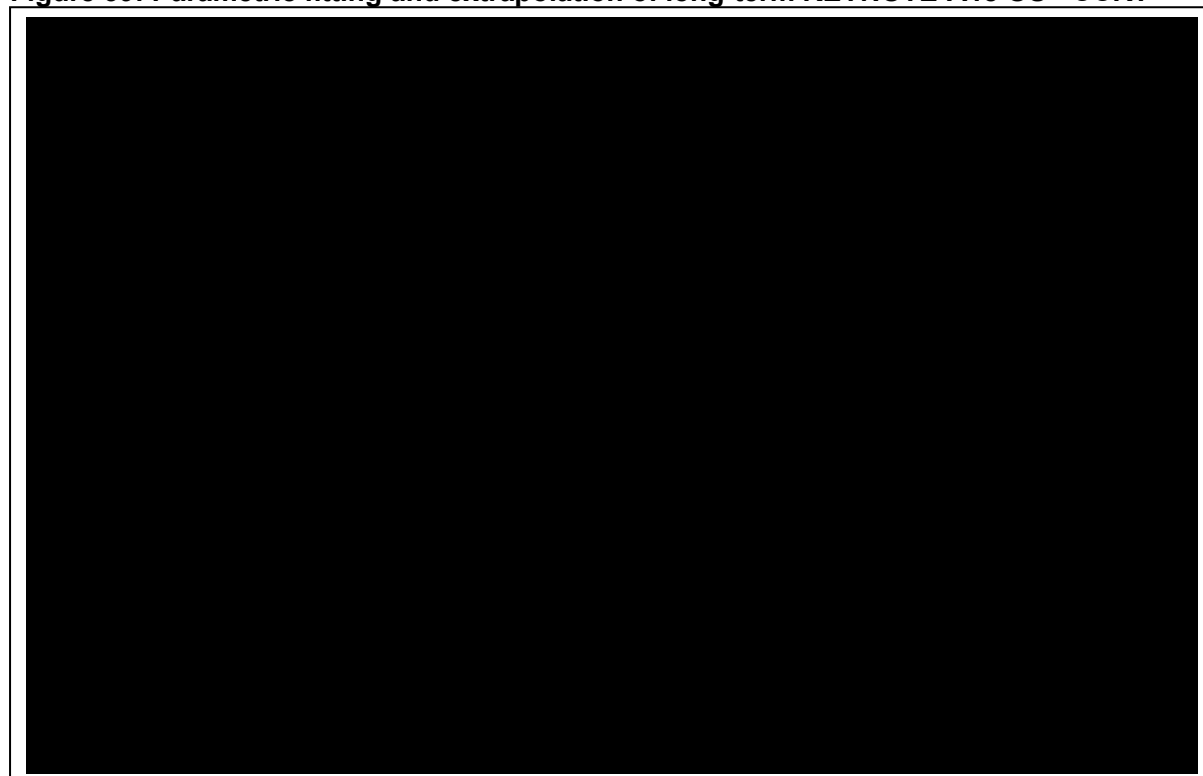


Table 29: Summary of parametric fitting performances of KEYNOTE-A18 OS for pembrolizumab + CCRT and CCRT

Treatment	Pembrolizumab + CCRT			CCRT		
	AIC	BIC	Average	AIC	BIC	Average
Exponential	████	████	████	████	████	████
Weibull	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████
Gamma	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████

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

Figure 40: Empirical and smoothed hazards for KN-A18 OS - Pembrolizumab + CCRT

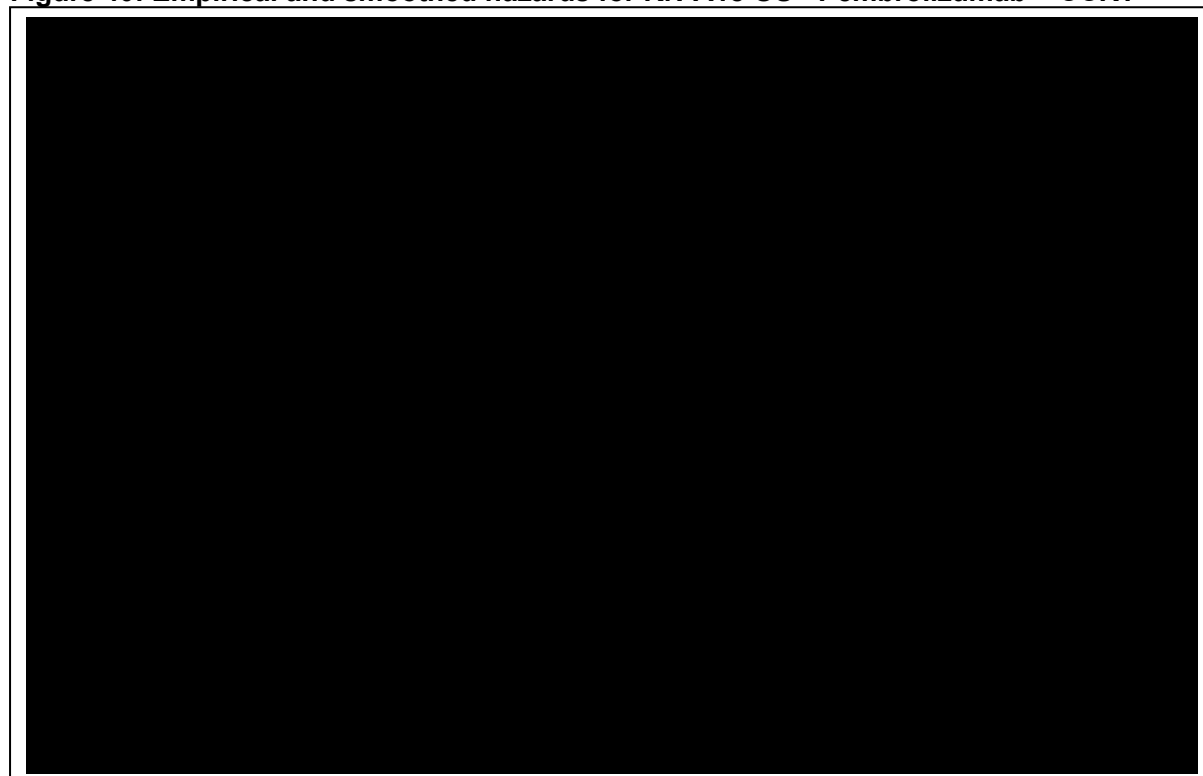


Figure 41: Smoothed hazard plot and standard parametric model hazards – OS - Pembrolizumab + CCRT

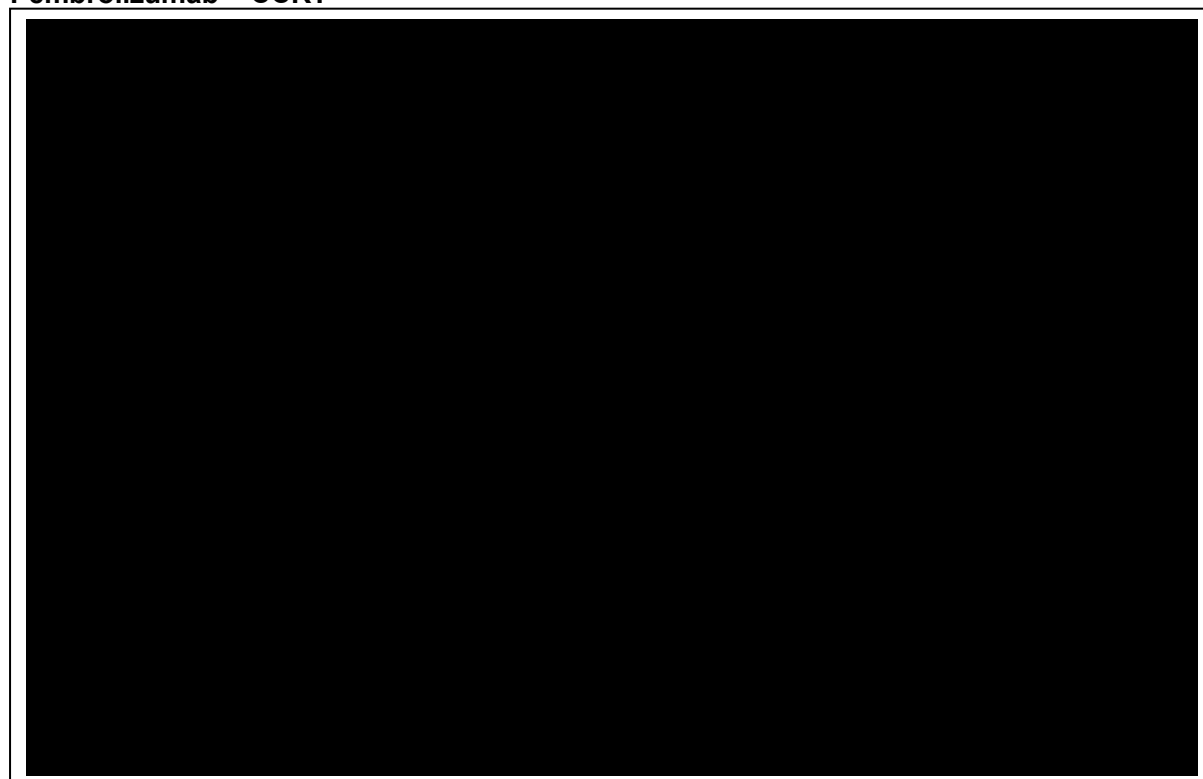


Figure 42: Empirical and smoothed hazards for KN-A18 OS - CCRT

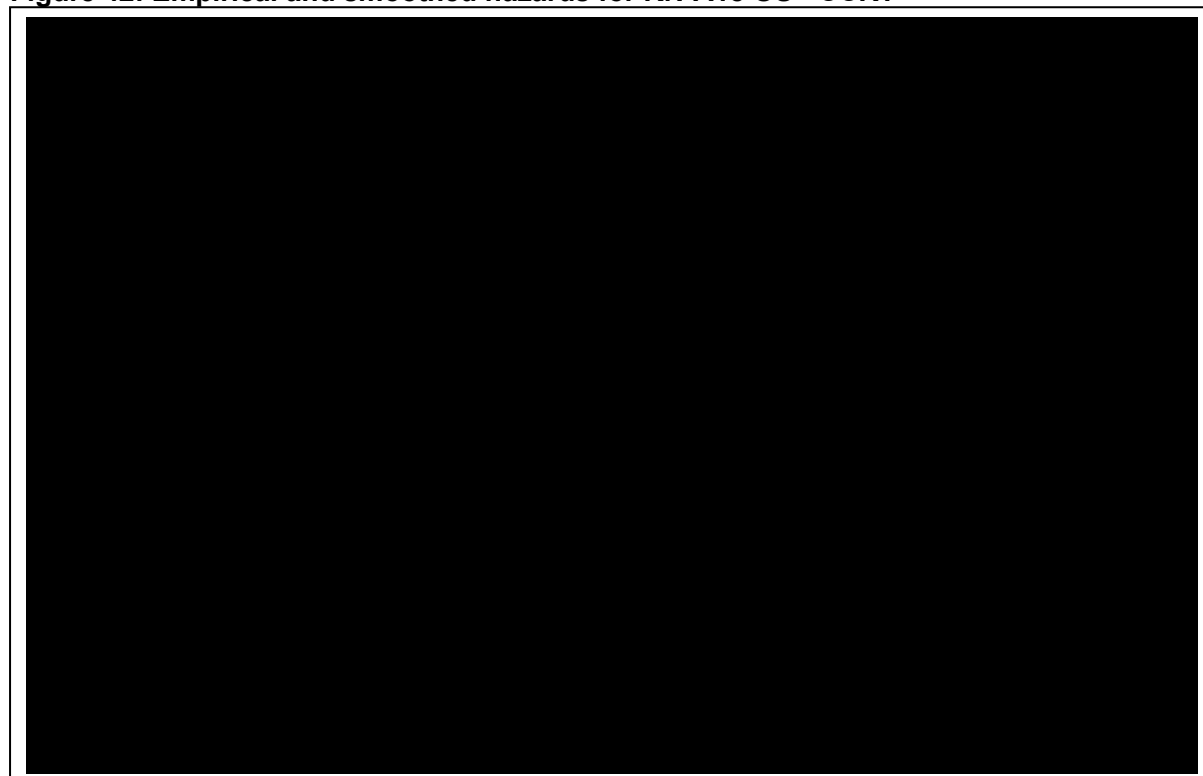
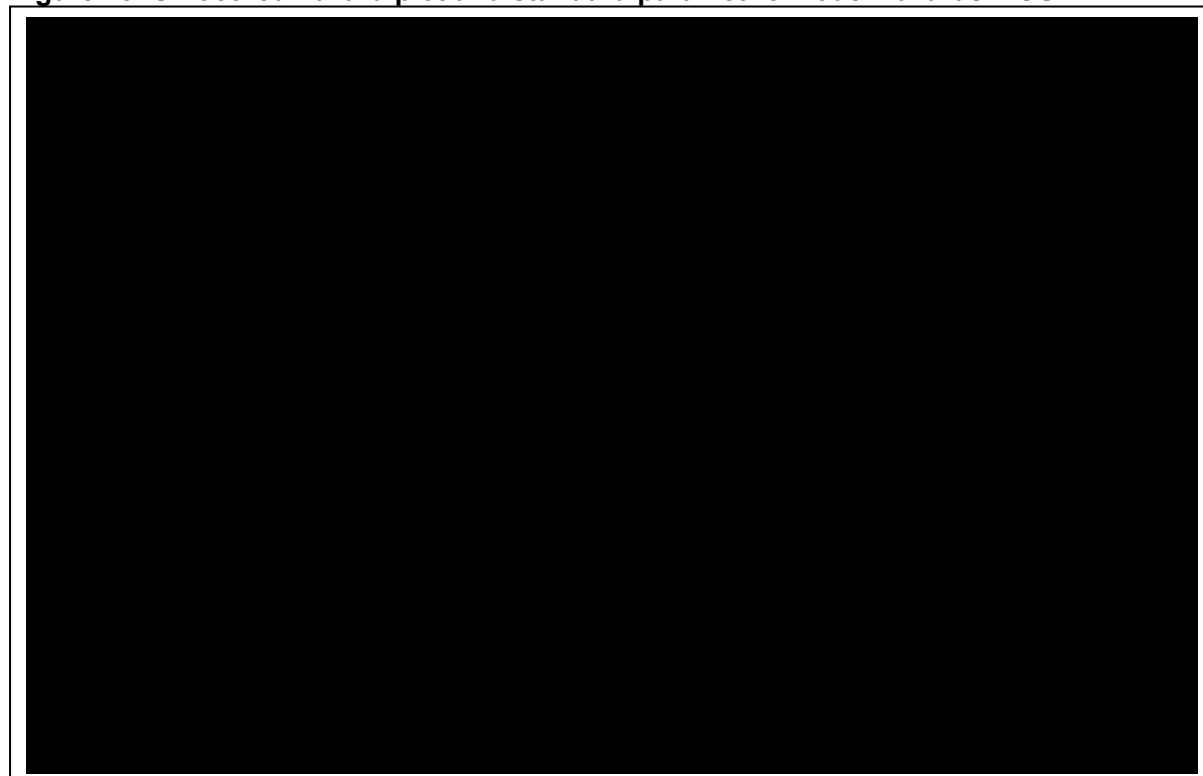


Figure 43: Smoothed hazard plot and standard parametric model hazards – OS - CCRT



2.2 Utility values

2.2.1 Naïve means

Table 30 details the updated mean utility values observed at final analysis within KEYNOTE-A18. Methods of calculation are consistent with those in the original submission

Progression based

Table 30: Summary of progression based utility values (naive means) from KEYNOTE-A18 final analysis

	Total (N=554)				
	n	m	Mean	SE	95% CI
Progression-Free					
Progressive Disease					
Hernández Alava et al. (2023). n = Number of participants with non-missing EQ-5D score. m = Number of records with non-missing EQ-5D score. Health state based on investigator review. EQ-5D score during baseline is excluded. Observations that occur after a censored first progression (i.e. health state is unknown) are excluded from the table. Summary statistics are computed based on several records per participant treated as independent observations, except for baseline where there is a single record per participant. Database Cutoff Date: 07JAN2025					

Table 31: Summary of time to death based utility values (naive means) from KEYNOTE-A18 final analysis

Time until death	Mean	SE	N	Source
360+ Days				KN-A18
270 - 359 Days				KN-A18
180 - 269 Days				Assume same as 270-359 days
90 - 179 Days				KN-A18
30 - 89 Days				KN-A18
0 - 29 Days				KN-A18

2.2.2 Regression analysis

Table 32: Summary of progression based utility values (regression analysis) from KEYNOTE-A18 final analysis

State	Utility value: mean	Utility value: SE	Source
Progression free			KN-A18
Progressed disease			
During Grade 3+ AE			

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2.2.3 Base-case utilities

The updated model still uses the disutility decrement of progression from KEYNOTE-826 applied to observed KEYNOTE-A18 progressed disease to estimate the PD2 utility. Table 33 details the new base-case utility values used within the updated model

Table 33: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	SE	Justification
Progression free			Taken directly from KEYNOTE-A18
Progressed disease 1 (PD1 and PD2)			Taken directly from KEYNOTE-A18
Progressed disease 2			Disutility decrement of progression from KEYNOTE-826 applied to observed KEYNOTE-A18 progressed disease
Disutility from grade 3+ AE			Taken directly from KEYNOTE-A18

Key: AE, Adverse event; PD1, Progressed disease 1; PD2, Progressed disease 2; SE, Standard Error

2.3 Survival analysis of KEYNOTE-826 prior chemoradiotherapy population

In response to question B15 the company has included a restricted population from KEYNOTE-826 in the model, which may represent the post progression patients better than the full marketing authorisation population that was used in the CS.

The survival analysis below is conduct on only the CPS>1 and had prior chemoradiotherapy population from KEYNOTE-826.

Within the sections relating to KEYNOTE-826 the abbreviation CT is used to denote chemotherapy.

All endpoints used are the same as those defined in the CS.

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Table 34: KEYNOTE-826 baseline characteristics for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (ITT population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	155		151		306	
Sex						
Female	155	(100.0)	151	(100.0)	306	(100.0)
Age (Years)						
<50						
50 to 64						
65 to 74						
≥ 75						
Mean						
SD						
Median						
Range						
Race						
American Indian Or Alaska Native						
Asian						
Black Or African American						
American Indian Or Alaska Native And Black Or African American						
American Indian Or Alaska Native And White						
American Indian Or Alaska Native And White And Asian						
Black Or African American And White						
Multiple						
White						
Missing						
Ethnicity						
Hispanic Or Latino						
Not Hispanic Or Latino						
Not Reported						
Unknown						
Geographic Region						
Asia Pacific						
EU/EMEA						
North America						
Latin America						
ECOG Performance Scale						

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0						
1						
2						
Stage at Initial Diagnosis^b						
I						
II						
III						
IIIA						
IIIB						
IVA						
IVB						
Disease Status at Study Entry						
Persistent or Recurrent with distant metastases at study entry						
Persistent or Recurrent without distant metastases at study entry						
Histology of Subtype of Cervical Cancer						
Adenocarcinoma						
Adenosquamous/Both - Squamous And Adenocarcinoma						
Squamous Cell/Squamous Cell Carcinoma						
PD-L1 Status						
1= $\leq$ CPS $\leq$ 10						
CPS $\geq$ 10						
Bevacizumab Use						
Yes						
No						
Prior Therapy						
Chemoradiation (CRT) and Surgery						
CRT Only						
a: Participants in France cannot report race by law. b: Stage at Initial Diagnosis determined using FIGO 2009/ NCCN 2017 criteria. c: Metastatic includes participants with para-aortic lymph node involvement. Table includes participants with CPS at baseline above or equal to 1 and with prior chemoradiation therapy, with or without surgery, reported at baseline. SD: Standard Deviation Database Cutoff Date: 03OCT2022						

2.3.1 Mean cycles of treatment received data

Actual vs Expected Number of Cycles per Participants

Pembrolizumab

Table 35: Percentage of actual vs expected number of cycles of pembrolizumab per participant for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (APaT)

	Pembro Combo
Participants in population	155
Actual Number of Dose Administrations	
Participants with data	██████
Mean	██████
SD	██████
Median	██████
Range	██████
Expected Number of Dose Administrations	
Participants with data	██████
Mean	██████
SD	██████
Median	██████
Range	██████
Percentage of Actual vs Expected Number of Dose Administrations	
Participants with data	██████
Mean	██████
SD	██████
Median	██████
Range	██████
Expected number of dose administrations is based on the total number of administrations the participant could have received from start to end of study treatment administration. Database Cutoff Date: 03OCT2022	

Cisplatin

Table 36: Percentage of actual vs expected number of cycles of cisplatin per participant for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (APaT)

	Pembro Combo	Control
Participants in population	25	13
Actual Number of Dose Administrations		
Participants with data	██████	██████
Mean	██████	██████
SD	██████	██████

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Median		
Range		
Expected Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
Percentage of Actual vs Expected Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
The expected doses for cisplatin, carboplatin and paclitaxel is based on a planned number of 6 cycles of treatment. Participants with data for 'Expected Number of Dose Administrations' are participants with data who received at least one dose of that treatment. Database Cutoff Date: 03OCT2022		

Carboplatin

Table 37: Percentage of actual vs expected number of cycles of carboplatin per participant for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (APaT)

	Pembro Combo	Control
Participants in population	134	142
Actual Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
Expected Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
Percentage of Actual vs Expected Number of Dose Administrations		
Participants with data		
Mean		

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SD		
Median		
Range		
The expected doses for cisplatin, carboplatin and paclitaxel is based on a planned number of 6 cycles of treatment. Participants with data for 'Expected Number of Dose Administrations' are participants with data who received at least one dose of that treatment. Database Cutoff Date: 03OCT2022		

Paclitaxel

Table 38: Percentage of actual vs expected number of cycles of paclitaxel per participant for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (APaT)

	Pembro Combo	Control
Participants in population	155	151
Actual Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
Expected Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
Percentage of Actual vs Expected Number of Dose Administrations		
Participants with data		
Mean		
SD		
Median		
Range		
The expected doses for cisplatin, carboplatin and paclitaxel is based on a planned number of 6 cycles of treatment. Participants with data for 'Expected Number of Dose Administrations' are participants with data who received at least one dose of that treatment. Database Cutoff Date: 03OCT2022		

Bevacizumab

Table 39: Percentage of actual vs expected number of cycles of bevacizumab per participant for participants with CPS ≥ 1 and prior chemoradiation therapy with or without surgery (APaT)

	Pembro Combo	Control
Participants in population	102	86
Actual Number of Dose Administrations		
Participants with data	████	████
Mean	████	████
SD	████	████
Median	████	████
Range	████	████
Expected Number of Dose Administrations		
Participants with data	████	████
Mean	████	████
SD	████	████
Median	████	████
Range	████	████
Percentage of Actual vs Expected Number of Dose Administrations		
Participants with data	████	████
Mean	████	████
SD	████	████
Median	████	████
Range	████	████
Expected number of dose administrations is based on the total number of administrations the participant could have received from start to end of study treatment administration. Database Cutoff Date: 03OCT2022		

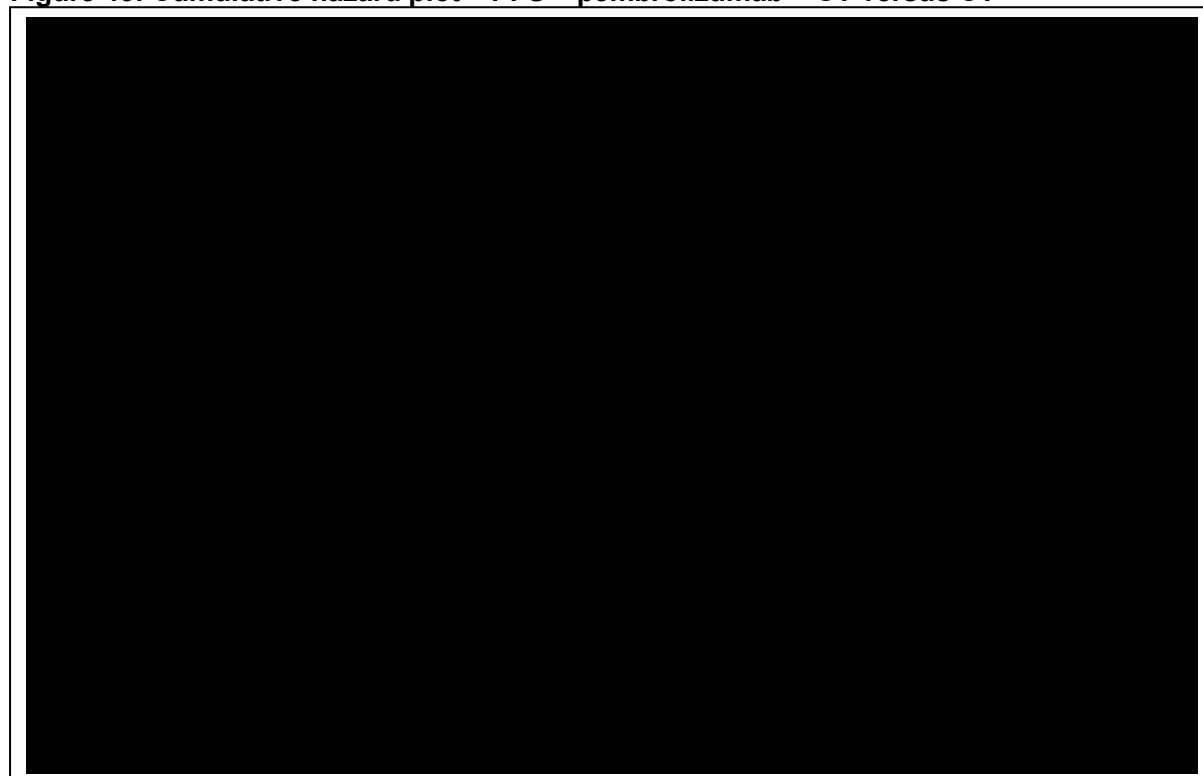
2.3.2 PFS

Progression-free survival was defined via investigator assessment per RECIST, this was a primary endpoint of the KEYNOTE-826 trial.

Figure 44: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-826 PFS – pembrolizumab + CT versus CT

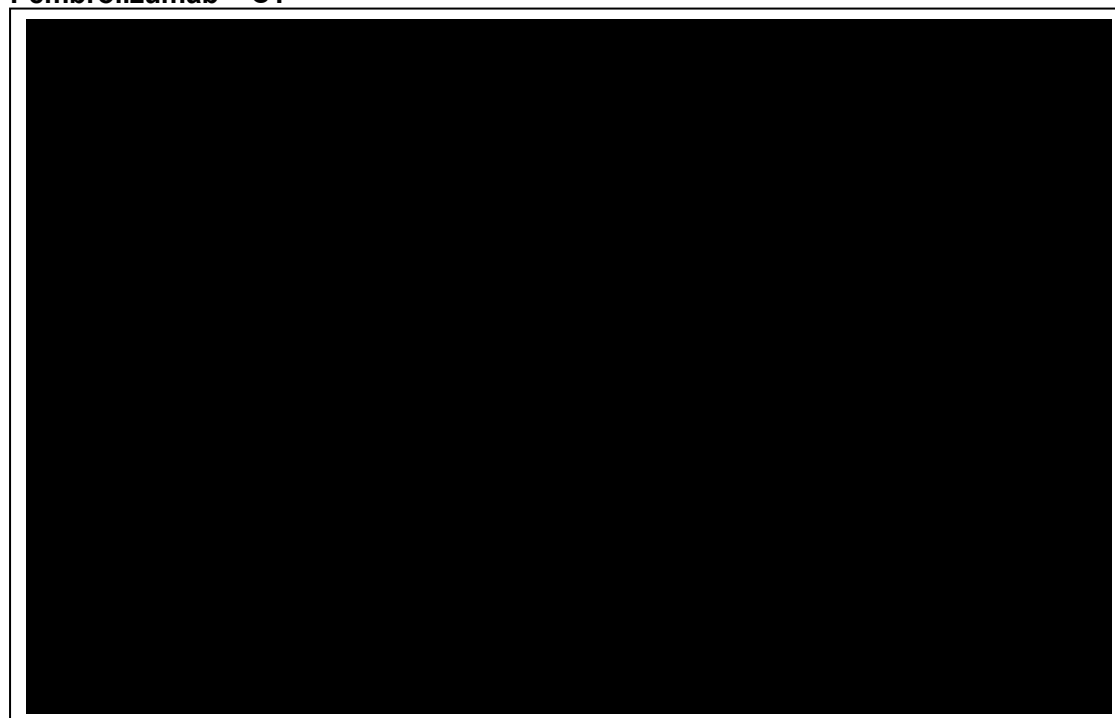


Figure 45: Cumulative hazard plot – PFS – pembrolizumab + CT versus CT



2.3.2.1 Standard parametric models

Figure 46: Parametric fitting and extrapolation of long-term KEYNOTE-826 PFS - Pembrolizumab + CT



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Figure 47: Parametric fitting and extrapolation of long-term KEYNOTE-826 PFS - CT

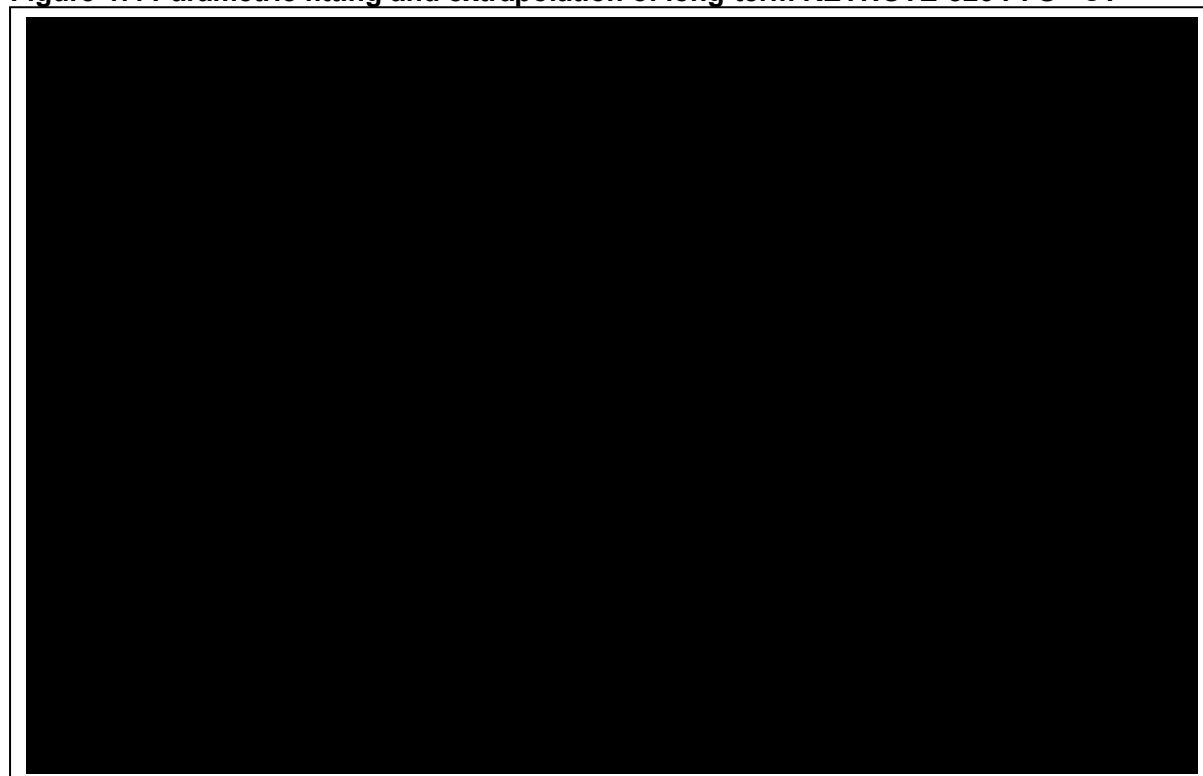


Table 40: Summary of parametric fitting performances of KEYNOTE-826 PFS for pembrolizumab + CT and CT

Treatment	Pembrolizumab + CT			CT		
	AIC	BIC	Average	AIC	BIC	Average
Extrapolation						
Exponential						
Weibull						
Log-normal						
Log-logistic						
Gompertz						
Generalized Gamma						

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

Figure 48: Smoothed hazard plot and standard parametric model hazards – PFS Pembrolizumab + CT

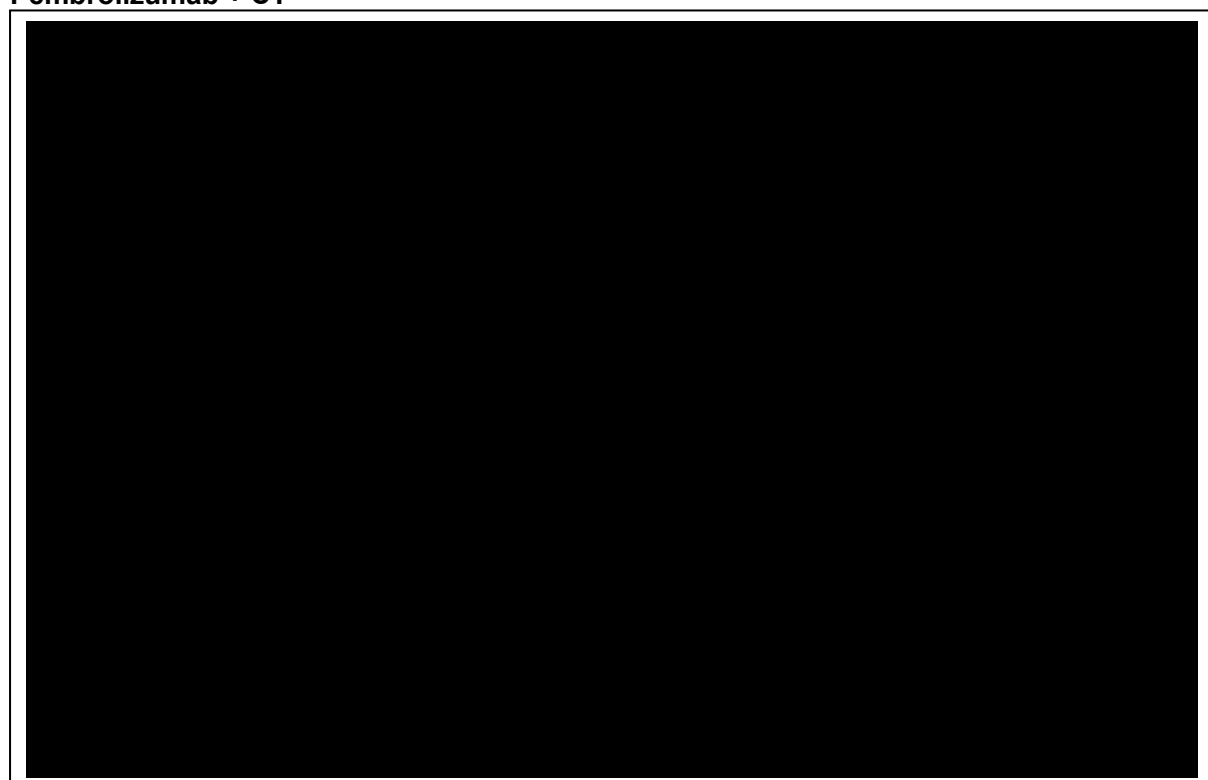
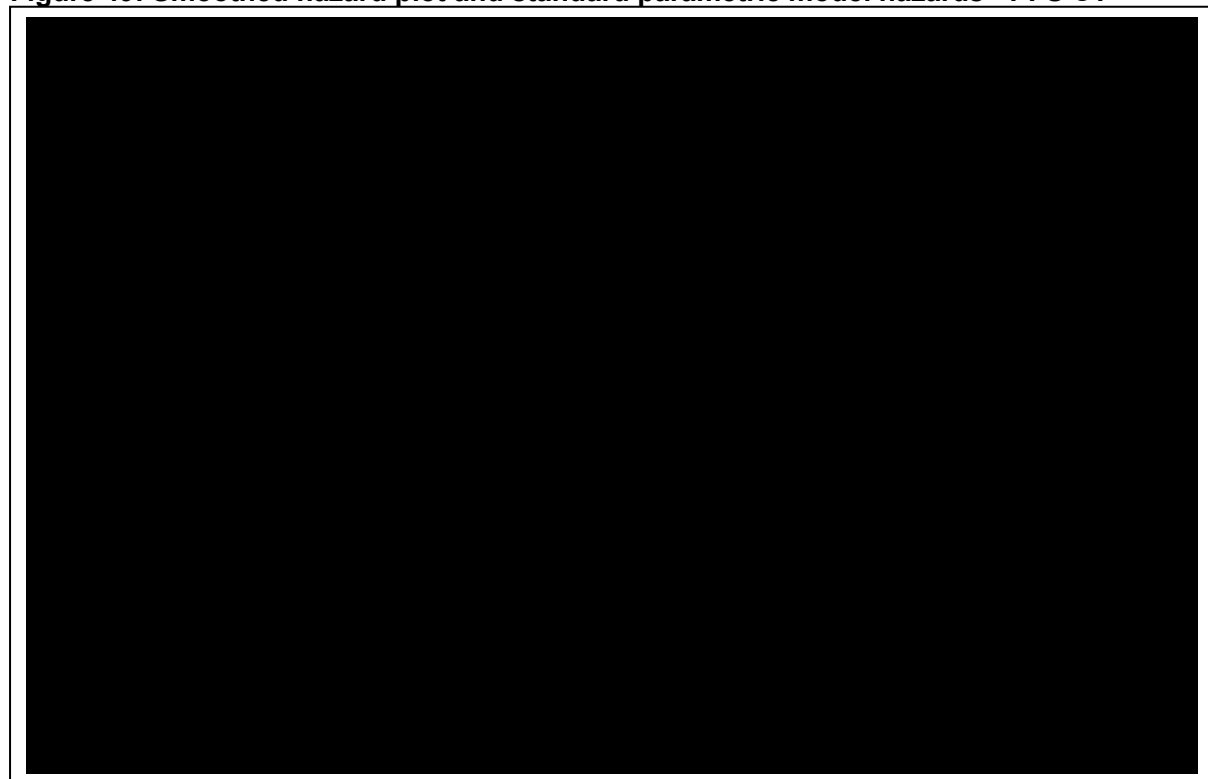


Figure 49: Smoothed hazard plot and standard parametric model hazards - PFS CT



2.3.2.2 *Spline models*

Due to time constraints clinical validation was unable to be sought on the estimated outcomes of this subgroup of the KEYNOTE-826 trial. As such selections have been based on statistical fit. We note that the implied plateaus are morphologically similar to those validated in TA939.

Figure 50: Long term unadjusted spline models fitted to PFS KM data for the prior-CRT population of KN-826 receiving pembrolizumab

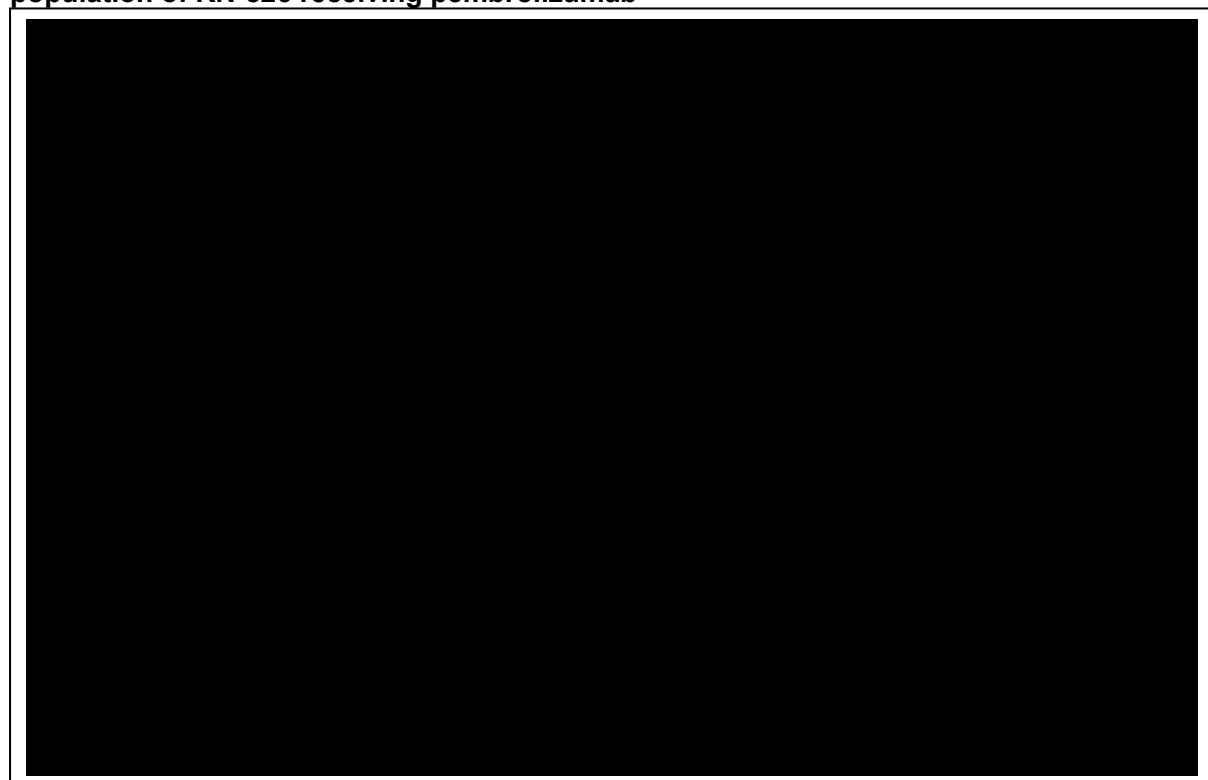
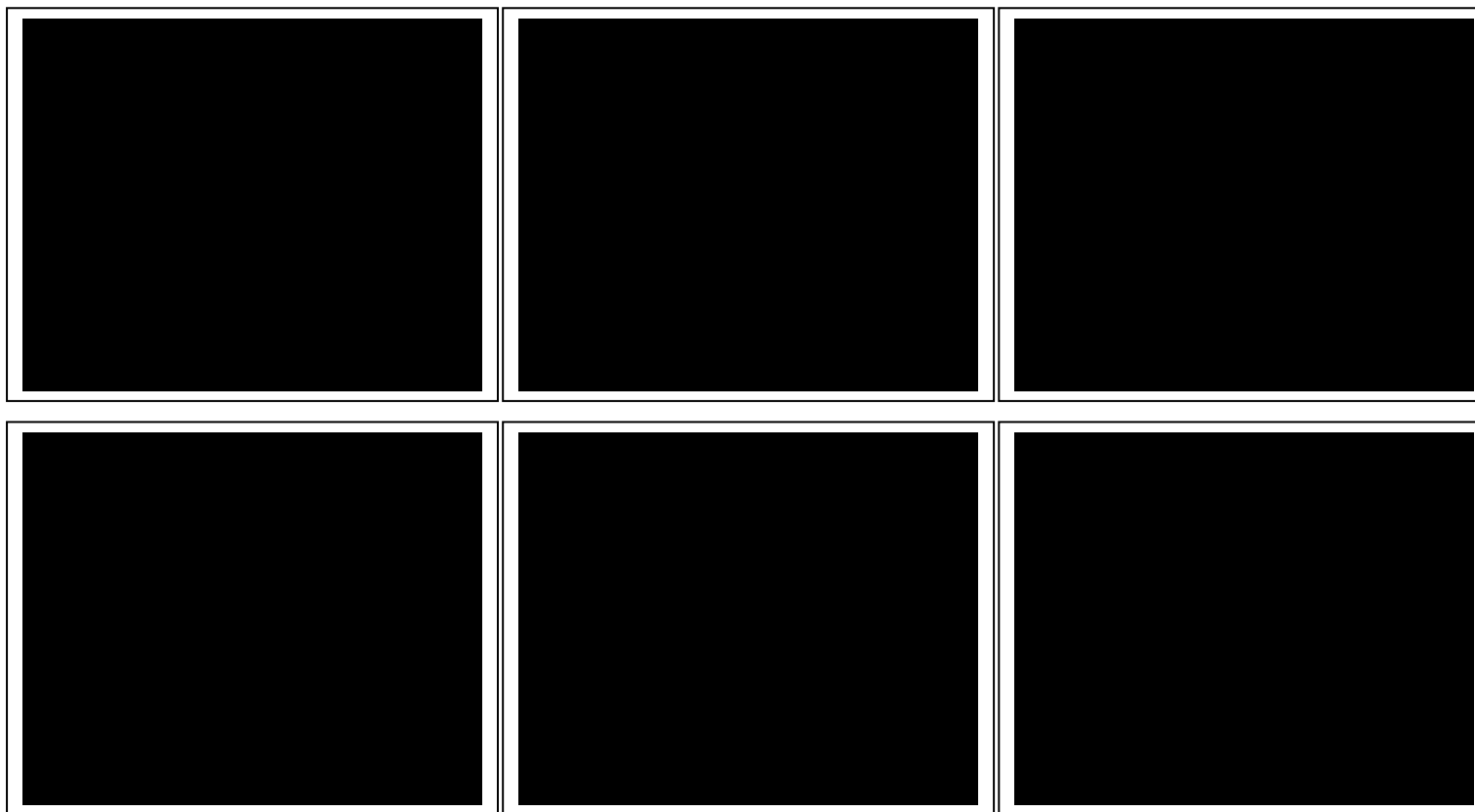


Figure 51: Pembrolizumab + CT spline hazard fits - PFS



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Table 41: Summary of parametric fitting performances of spline models of PFS for pembrolizumab + CT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard									
Odds									
Normal									

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

Figure 52: Spline models fitted to placebo arm, prior CRT patients from KN-826

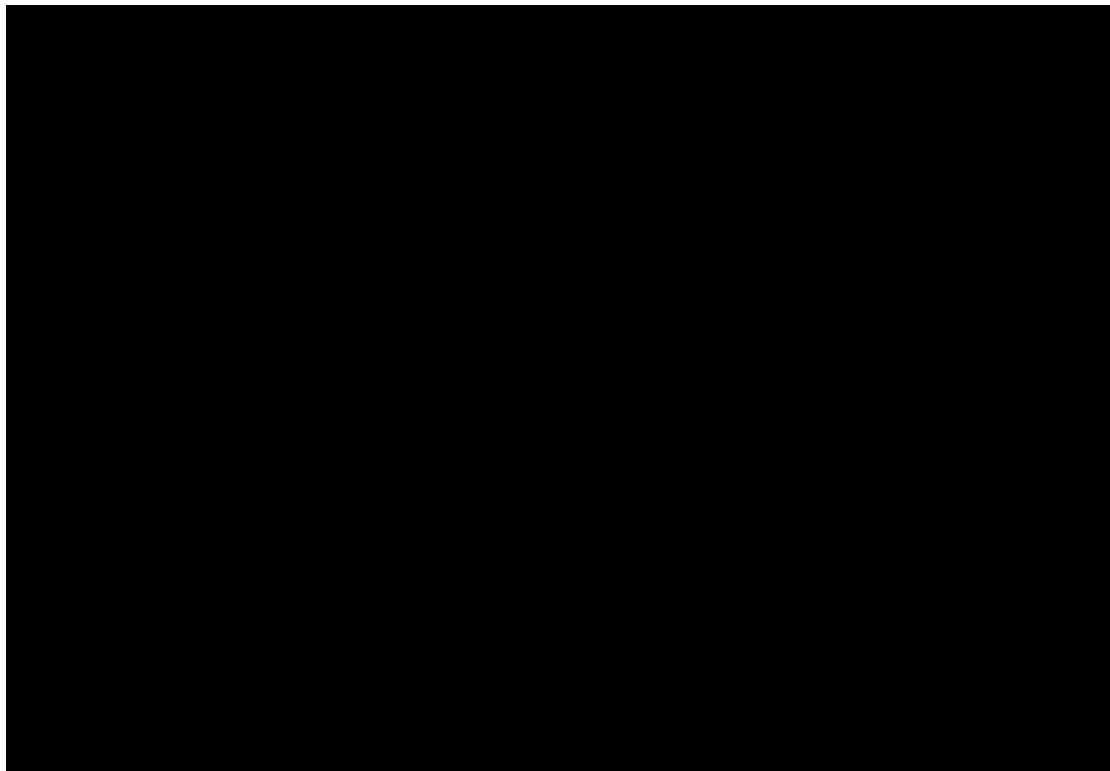


Figure 53: CT spline hazard fits - PFS

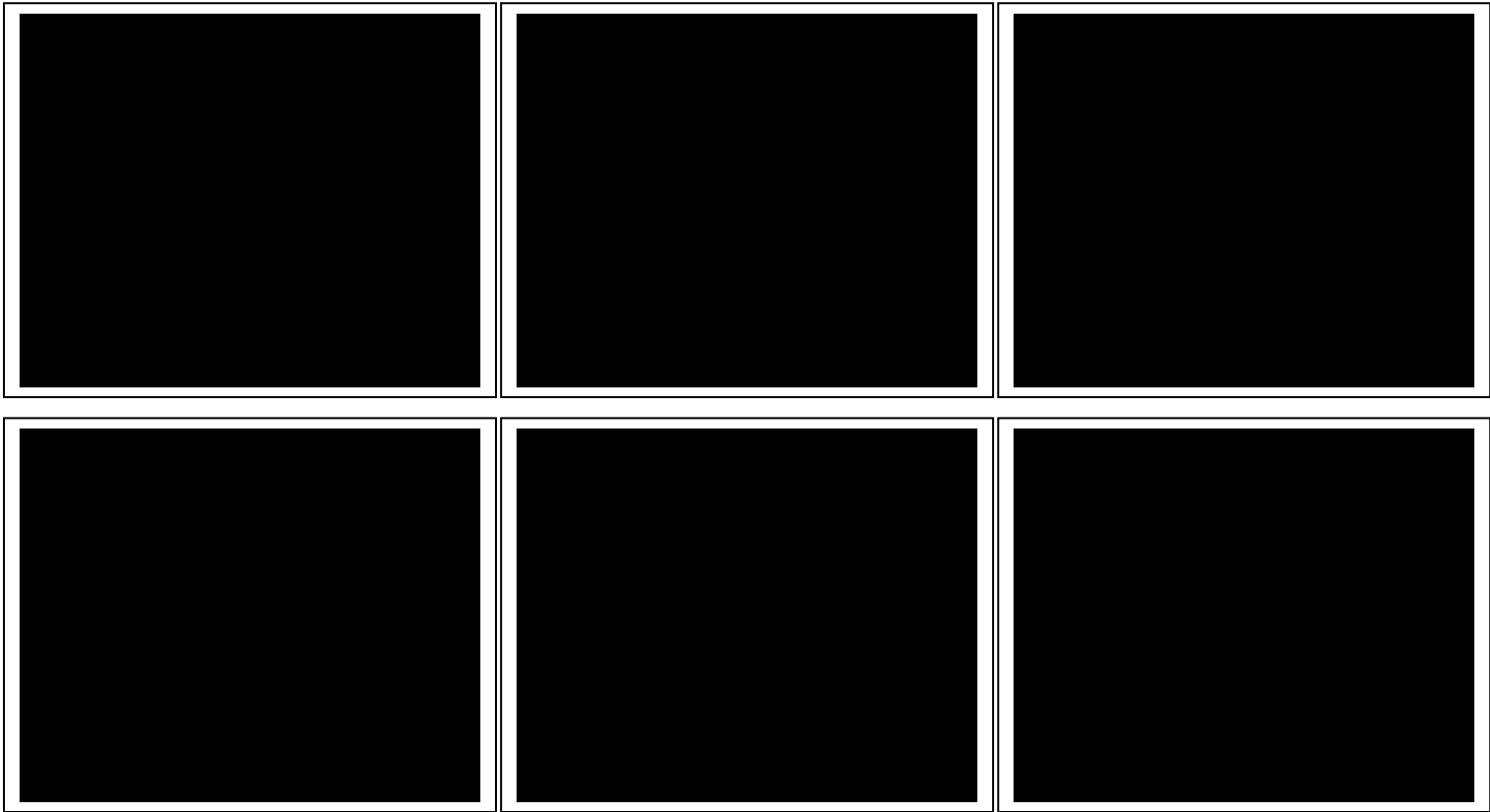




Table 42: Summary of parametric fitting performances of spline models of PFS for CT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard									
Odds									
Normal									

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

2.3.2.3 Validation and selection

Pembrolizumab + CT

- Due to the poor visual fit no one-piece models were considered appropriate and only splines were considered appropriate
- For the splines, visual inspection of the hazard plots show that all 2 and 3 knot splines have similar fit and 1 knot models do not fit the KM data well
- AIC and BIC showed a slight preference for the 2-knot models but the 3-knot hazard and odds splines being within 2 AIC of the 2-knot splines

CT

- Due to the poor visual fit no one-piece were considered and only splines were considered
- For the splines AIC/BIC and visual inspection of the hazard plots show that all bar the 1-knot normal curve have similar fit.
- Overall the extrapolations were similar for all curves.

Overall assessment

- We selected the spline model with 2-knot odds model as the base case in both arms as this appeared to be the joint best fitting along with the 2-knot hazard model.
- The best fitting curves produce a substantial plateau in the pembrolizumab arm, which suggests around 40% of patients would be cured by pembrolizumab in this setting. This is controlled to some degree by the treatment waning assumptions within the economic model. This suggests that pembrolizumab is more effective in this subgroup than among the whole KN-826 population, which may be clinically reasonable given the exclusion of *de novo* metastatic patients from the analysis.

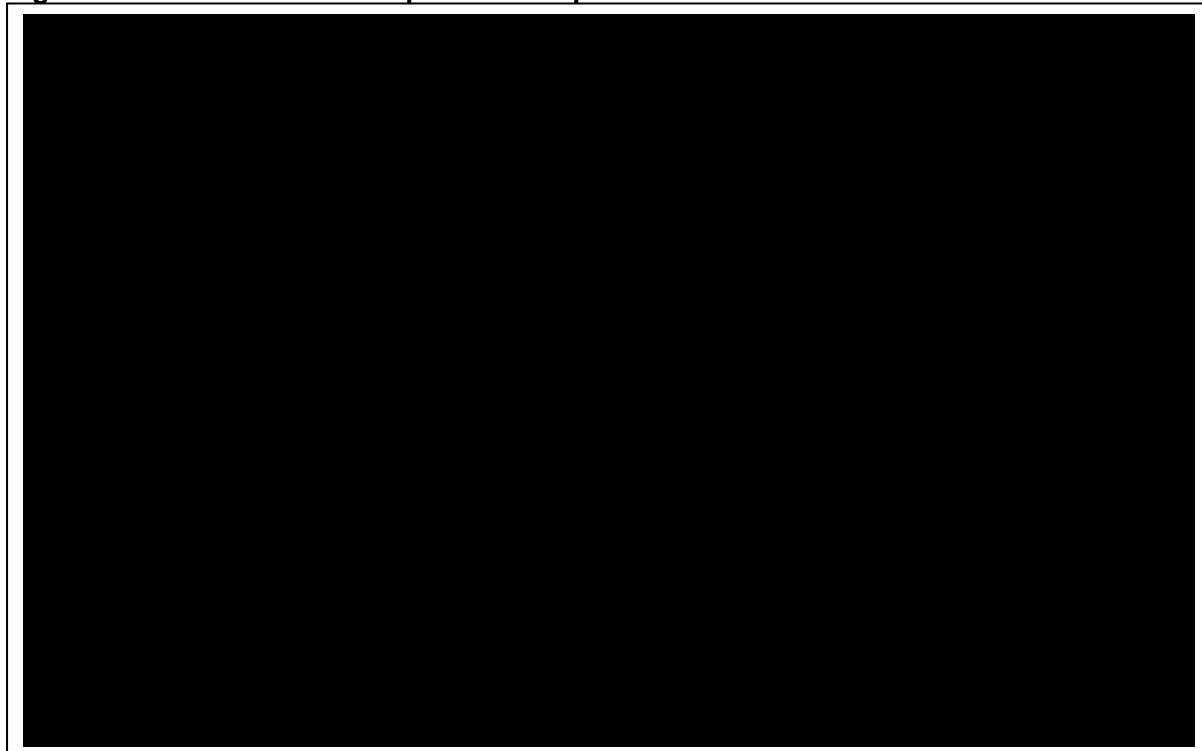
2.3.3 TTP

As with the curve selection in section 2.1 the models selected for PFS were used for TTP. The 2-knot odds is also the joint best fitting by AIC for both arms.

Figure 54: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-826 TTP – pembrolizumab + CT versus CT



Figure 55: Cumulative hazard plot – TTP – pembrolizumab + CT versus CT



2.3.3.1 *Standard parametric models*

Figure 56: Parametric fitting and extrapolation of long-term KEYNOTE-826 TTP - Pembrolizumab + CT



Figure 57: Parametric fitting and extrapolation of long-term KEYNOTE-826 TTP - CT



Table 43: Summary of parametric fitting performances of KEYNOTE-826 TTP for pembrolizumab + CT and CT

Treatment	Pembrolizumab + CT			CT		
	AIC	BIC	Average	AIC	BIC	Average
Exponential	████	████	████	████	████	████
Weibull	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, paclitaxel + carboplatin; TTP, Time to progression.

Figure 58: Smoothed hazard plot and standard parametric model hazards – TTP Pembrolizumab + CT

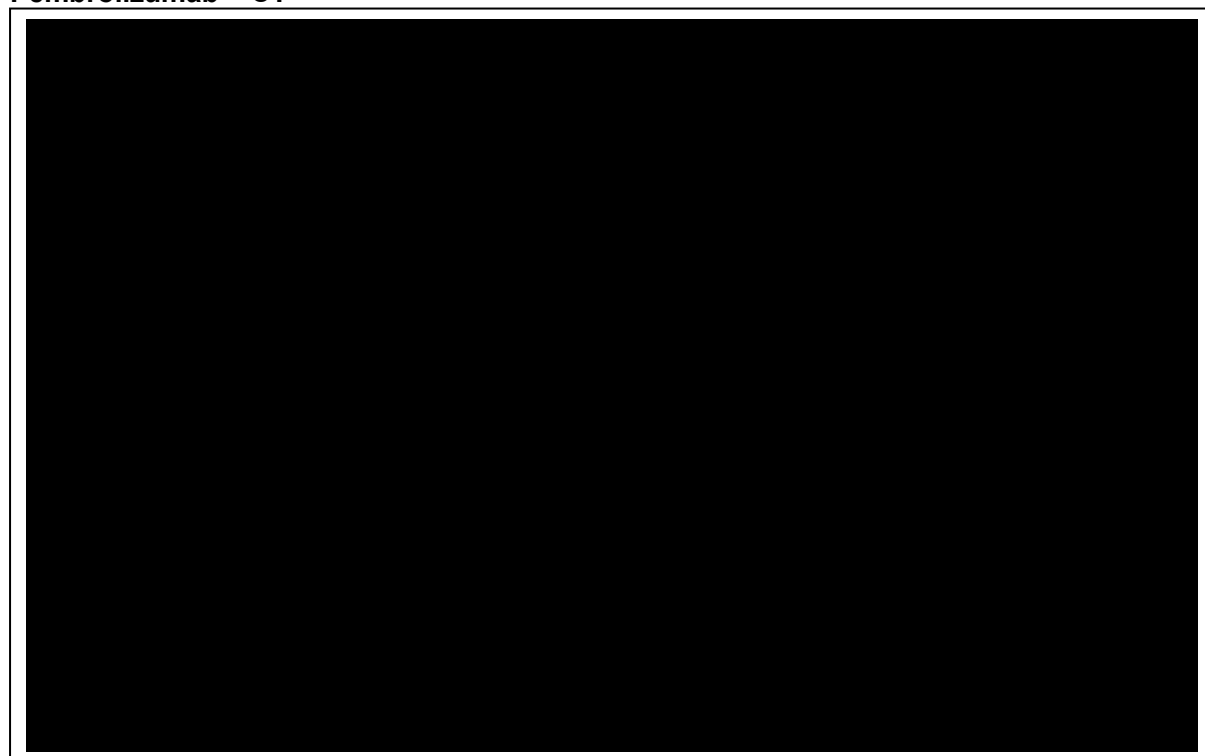
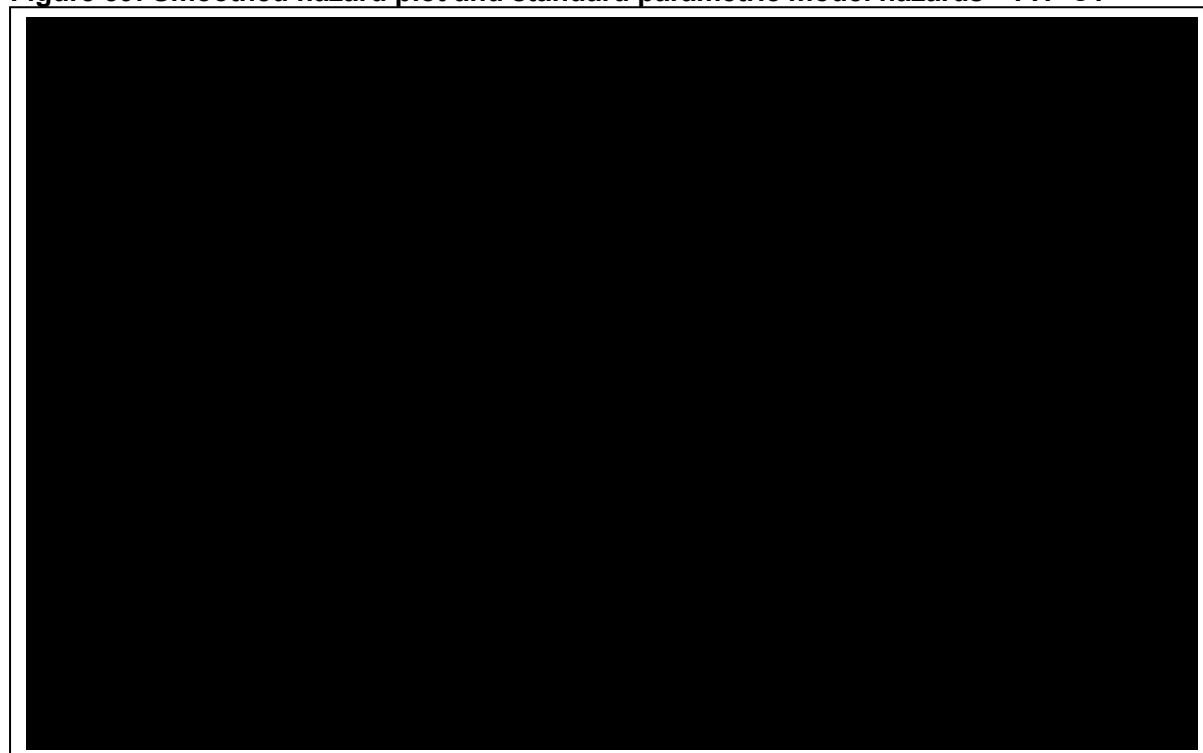


Figure 59: Smoothed hazard plot and standard parametric model hazards - TTP CT



2.3.3.2 *Spline models*

Figure 60: KN-826 prior-CRT population receiving pembrolizumab - spline fits



Figure 61: Pembrolizumab + CT spline hazard fits - TTP

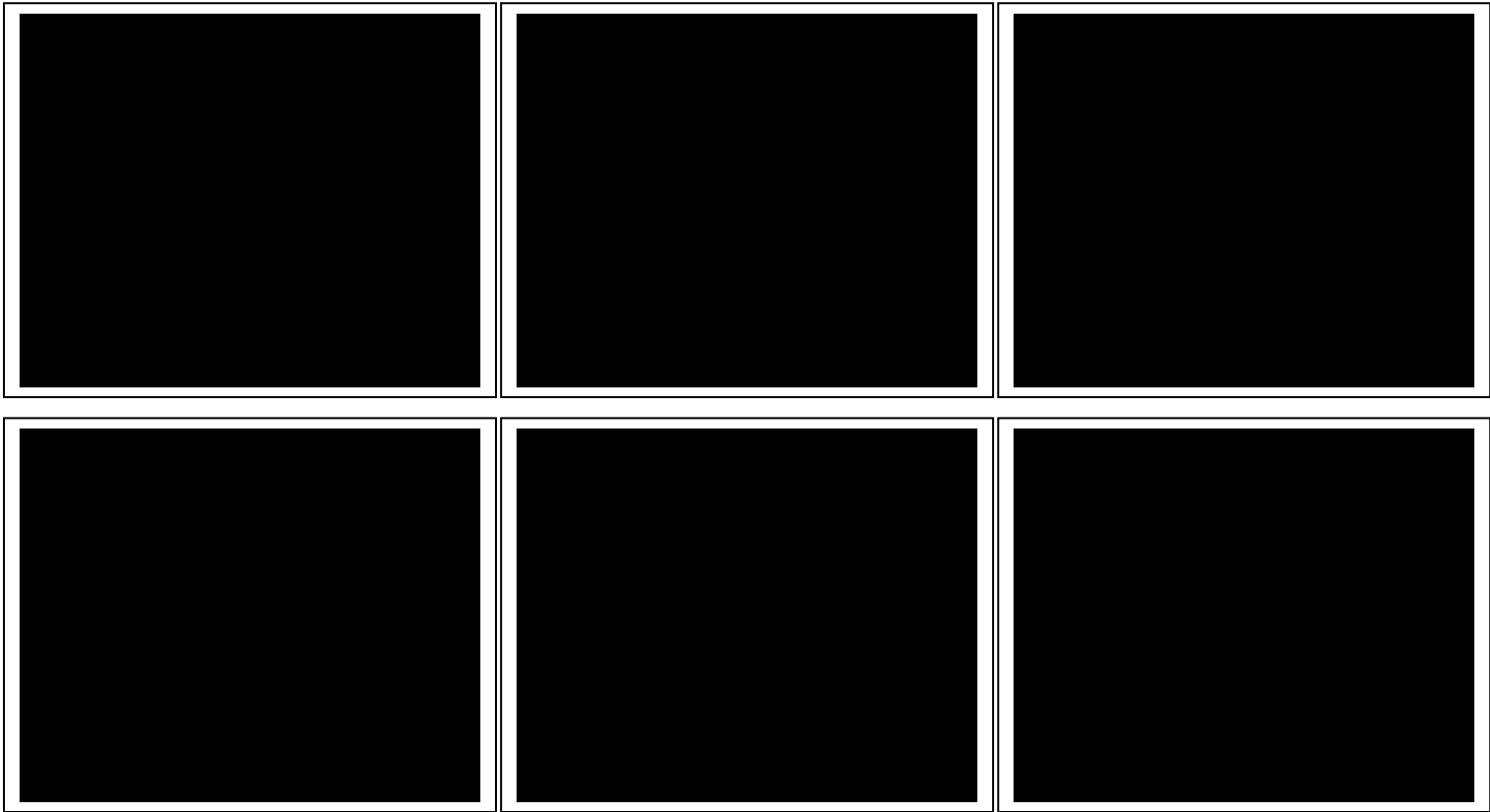




Table 44: Summary of parametric fitting performances of spline models of TTP for Pembrolizumab + CT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard	████	████	████	████	████	████	████	████	████
Odds	████	████	████	████	████	████	████	████	████
Normal	████	████	████	████	████	████	████	████	████

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

Figure 62: Spline fits for TTP in KN-826 for those with prior CRT

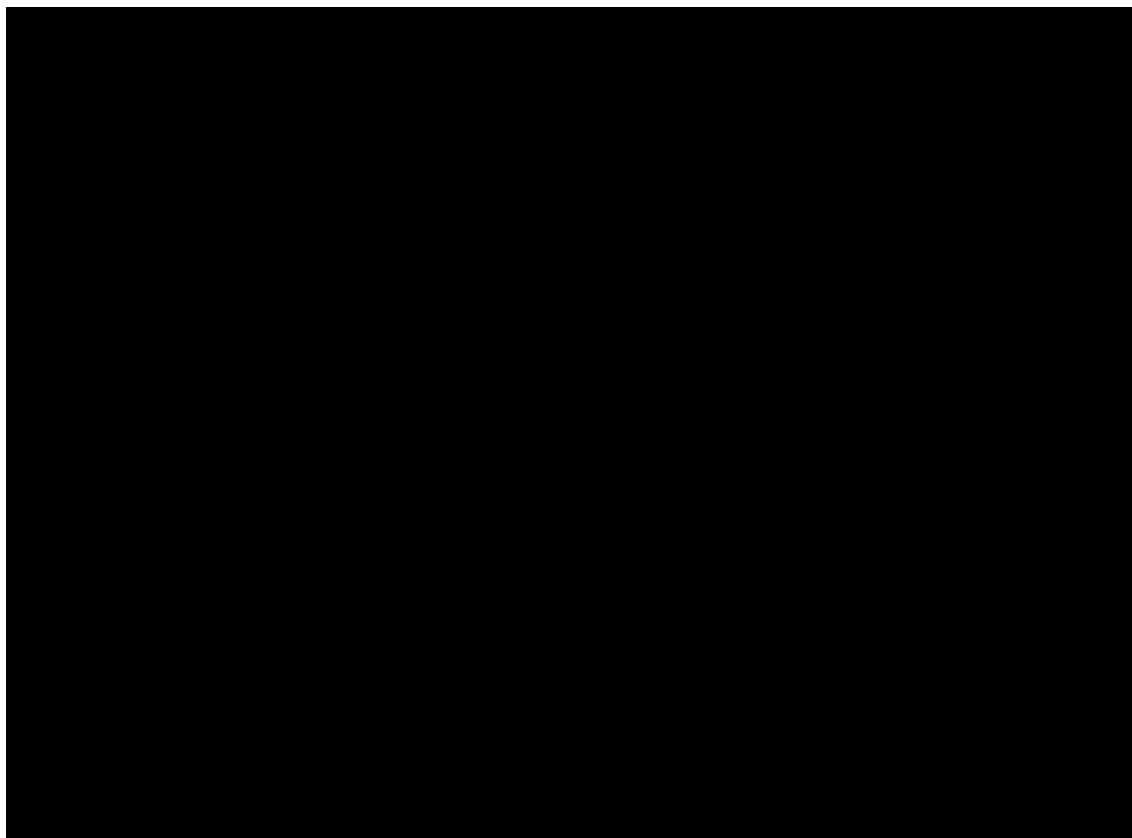


Figure 63: CT spline hazard fits - TTP

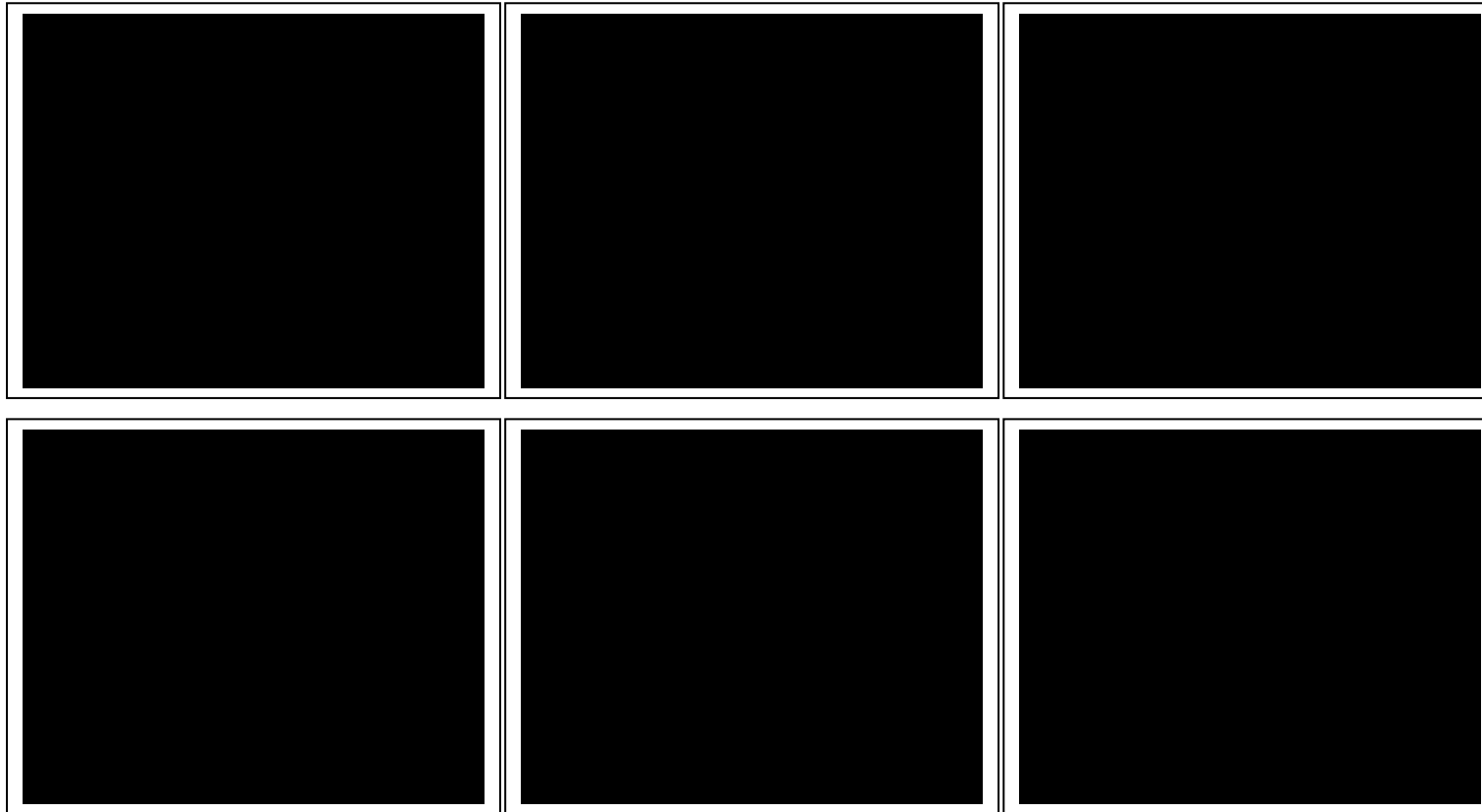




Table 45: Summary of parametric fitting performances of spline models of TTP for CT

	AIC			BIC			Average		
k =	1	2	3	1	2	3	1	2	3
Hazard									
Odds									
Normal									

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

2.3.4 PPS

Figure 64: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-826 PPS – pembrolizumab + CT versus CT



Figure 65: Cumulative hazard plot – PPS – pembrolizumab + CT versus CT



2.3.4.1 *Standard parametric models*

Figure 66: Parametric fitting and extrapolation of long-term KEYNOTE-826 PPS – Pembrolizumab + CT



Figure 67: Parametric fitting and extrapolation of long-term KEYNOTE-826 PPS - CT

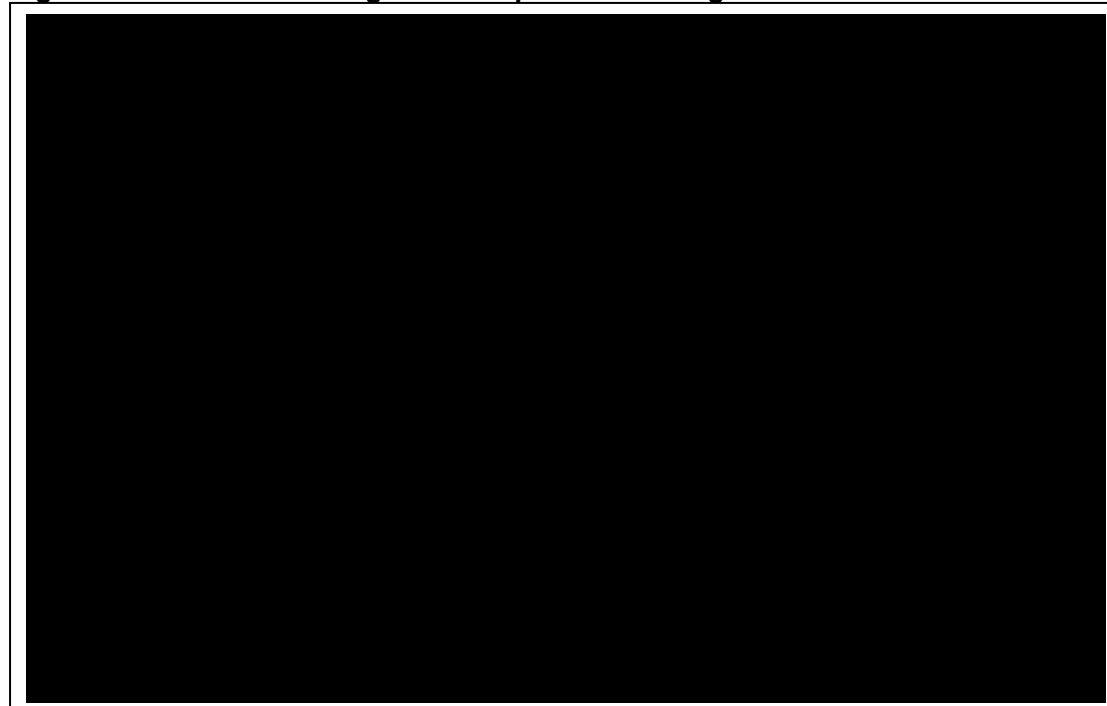


Table 46: Summary of parametric fitting performances of KEYNOTE-826 PPS for pembrolizumab + CT and CT

Treatment	Pembrolizumab + CT			CT		
	AIC	BIC	Average	AIC	BIC	Average
Exponential	████	████	████	████	████	████
Weibull	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████

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

Figure 68: Smoothed hazard plot and standard parametric model hazards - PPS Pembrolizumab + CT

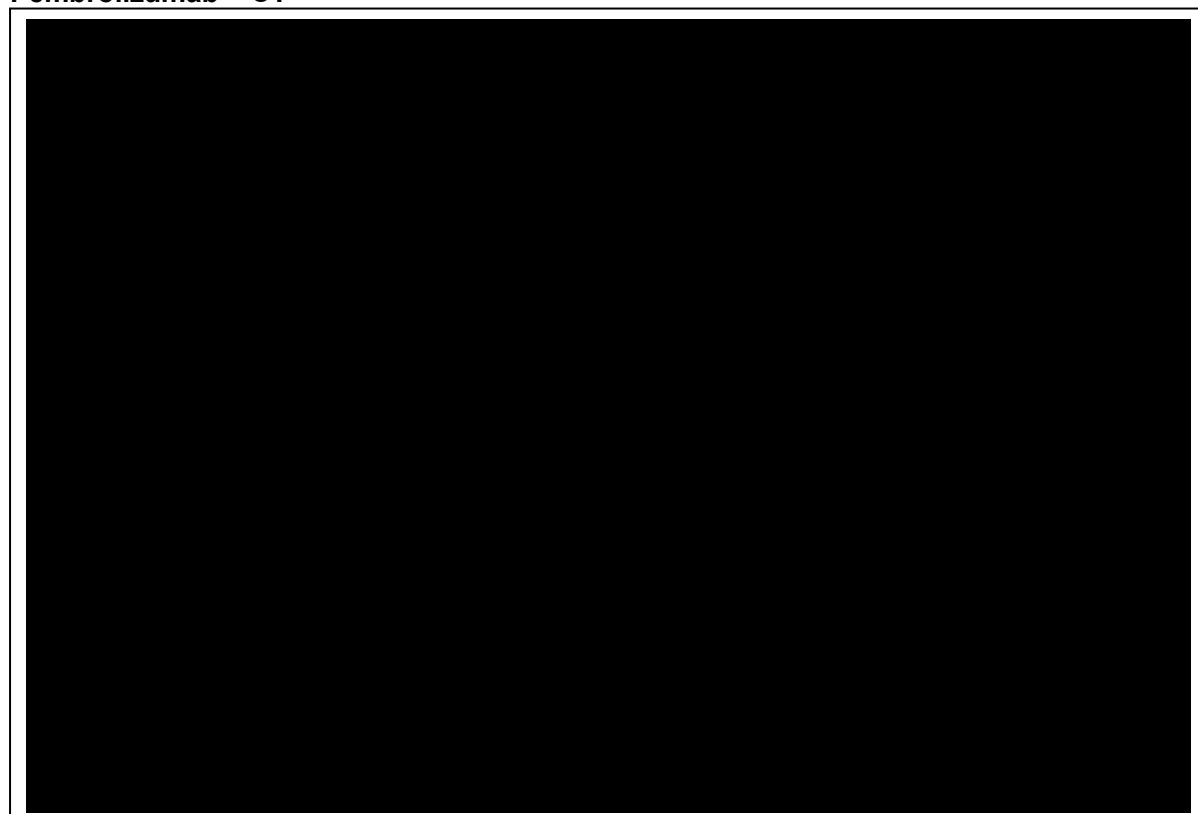


Figure 69: Smoothed hazard plot and standard parametric model hazards - PPS CT



2.3.4.2 Validation and selection

CT

- All of the fits provided similar extrapolations across the observed follow up period
- Based on AIC/BIC and visual fit to the hazard plot the generalised gamma, log-logistic and log-normal are the three best fitting curves

Chemotherapy

- The best visual fits to the KM were the generalised gamma, log-logistic and log-normal curves. All other curves did not accurately capture the KM between 20-100 weeks
- Based on AIC/BIC the generalised gamma, log-logistic and log-normal were again the three best fitting curves
- In terms of fit to hazards, the generalised gamma matched the shape the best across the whole observed time horizon, although both the log-logistic and log normal curves captures the rise in hazards between week 0 and 40 followed by a negative gradient thereafter.

Overall

- Overall we selected the log-normal curves as they were joint best fitting, had the lowest combined AIC and BIC across the arms and preserved the slight PPS advantage that

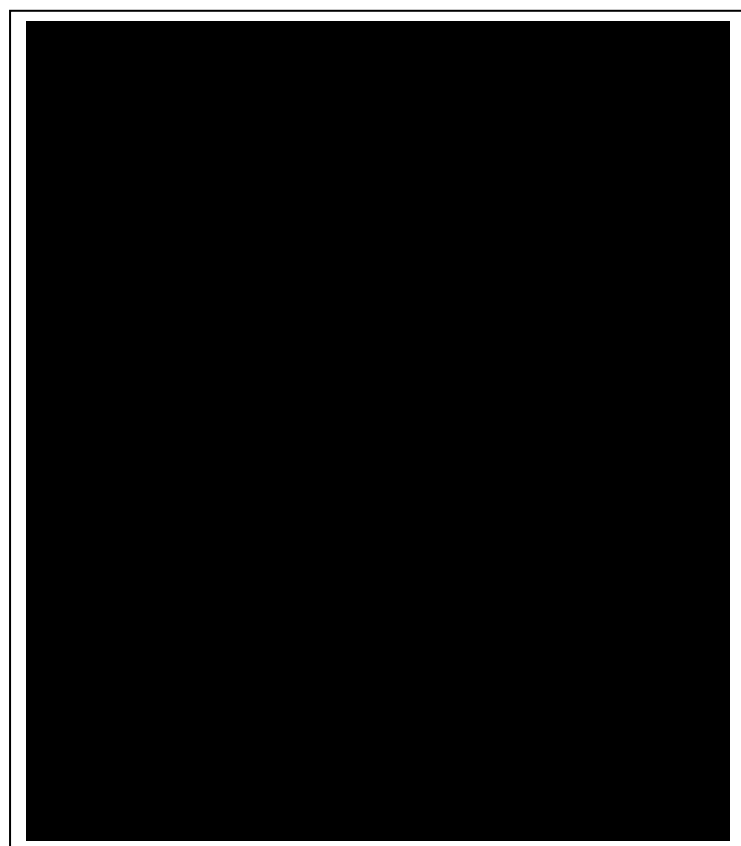
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the TA939 committee had preferred. The generalised gamma model fit the hazards well but had quite a long tail in the pembrolizumab arm.

2.4 Calibration of OS

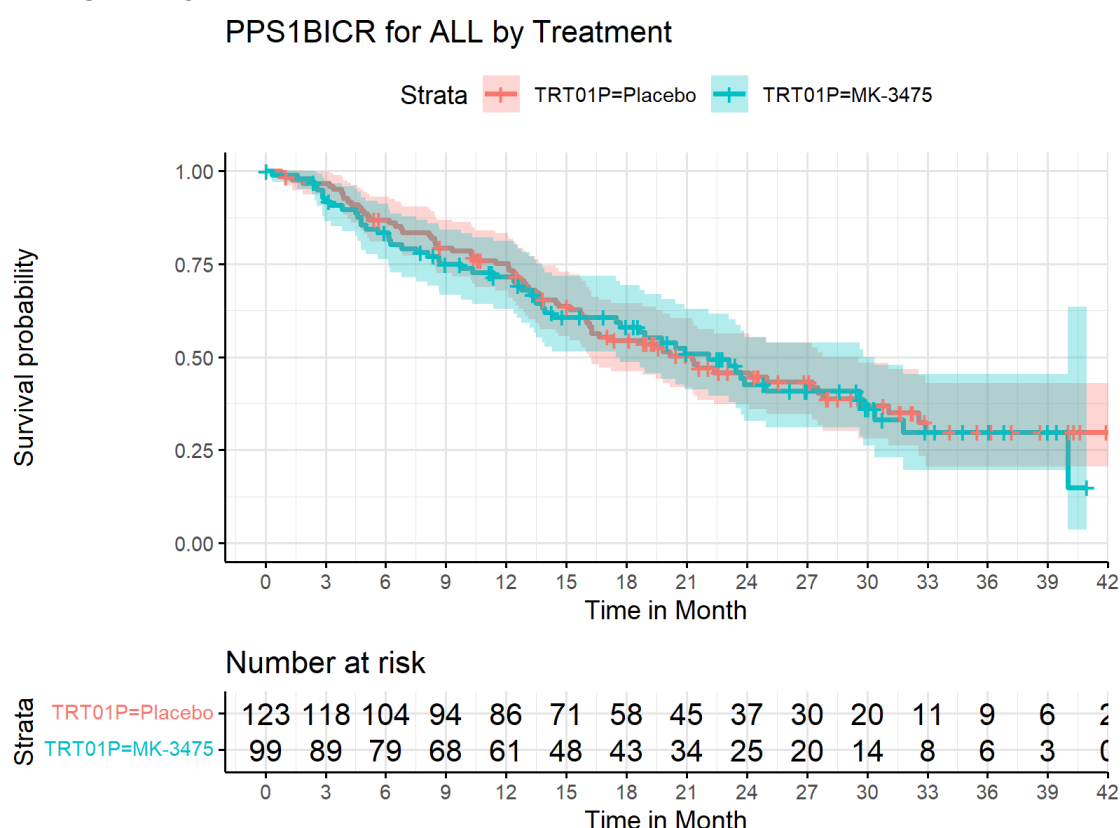
While the company's model predicted the observed OS in both KEYNOTE-A18 trial arms well at submission, this was no longer true after the integration of the final analysis. The model continued to reasonably accurately predict observed OS in the CCRT arm but substantially under-predicted OS in the CCRT+pembrolizumab arm. This is principally because, although patients in the CCRT arm have access to more effective treatments and theoretically should have longer post-progression survival, the observed PPS within the trial is in fact roughly equal whether PFS is based on Investigator Assessment or on BICR.

Figure 70: Kaplan-Meier curve for time from first progression (investigator assessment) to death form KEYNOTE-A18



Note: MK-3475 is pembrolizumab

Figure 71: KM curve from time of first progression (assessed by BICR) to death from KEYNOTE-A18



This is not the first time that this phenomenon has been observed in attempting to model OS based on an earlier endpoint and a treatment pathway; in NICE TA1037, the model had to be recalibrated to provide a temporary post-progression survival advantage to pembrolizumab in order to replicate the observed trial outcomes. In that appraisal, the calibration was applied up to 5 years because there was 5 years of data and thereafter the downstream transition probabilities continued in line with the therapy mix and downstream trial data within the Markov structure. This approach was agreed as appropriate by both the EAG and NICE committee during that appraisal. In that appraisal we used an algorithm to select the most appropriate calibration factor but, due to time constraints in this appraisal there is a user-specified multiplier and time-cap. In the base case we have chosen a time-cap of 4 years due to having 4 years of data and we have performed manual goal-seeking to determine the calibration factors, which temporarily slow down all downstream transition probabilities in both arms of the model so that the N at risk weighted sum

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of squared errors between the Markov model's estimates and the directly extrapolated OS parametric survival curves was minimised. Under the base case assumptions calibration factors of 0.44 and 0.54 for PFS BICR and 0.45 and 0.85 for PFS INV were needed for the pembrolizumab and CCRT alone arms respectively.

Figure 72: Modelled OS versus directly extrapolated and observed OS (PFS-INV base case settings)

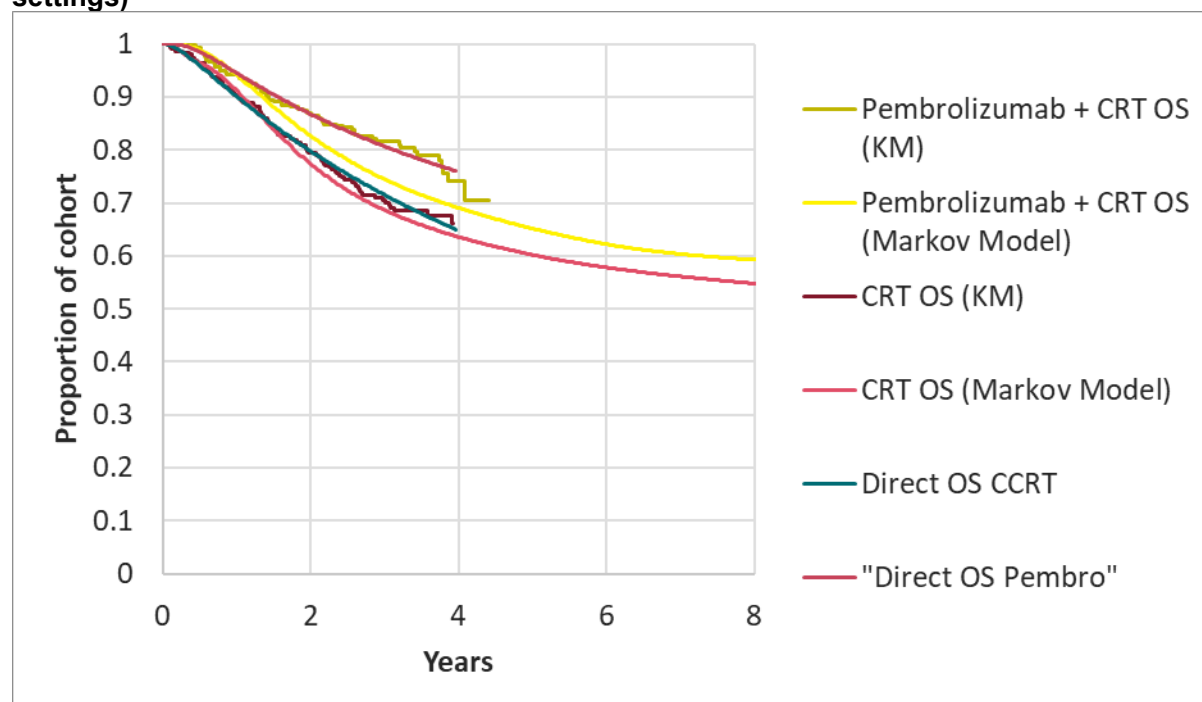


Figure 73: Modelled OS versus directly extrapolated and observed OS prior to calibration (PFS-BICR base case settings)

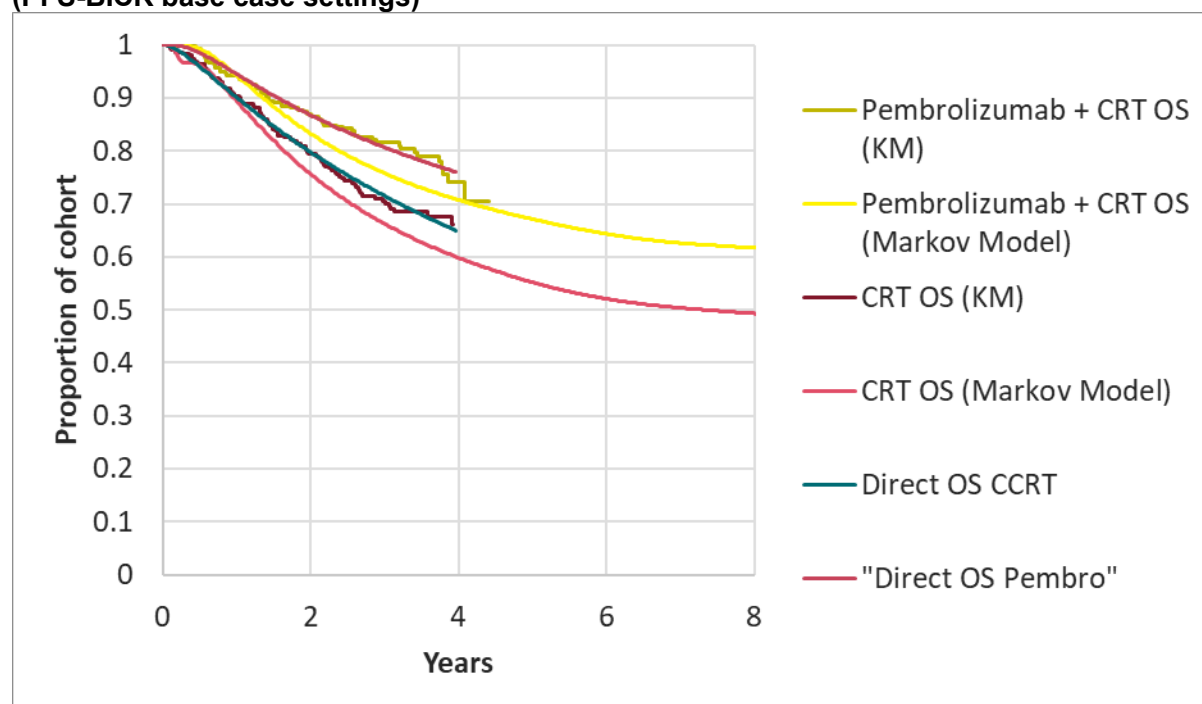


Figure 74: Modelled OS versus directly extrapolated and observed OS after calibration (PFS-INV base case settings)

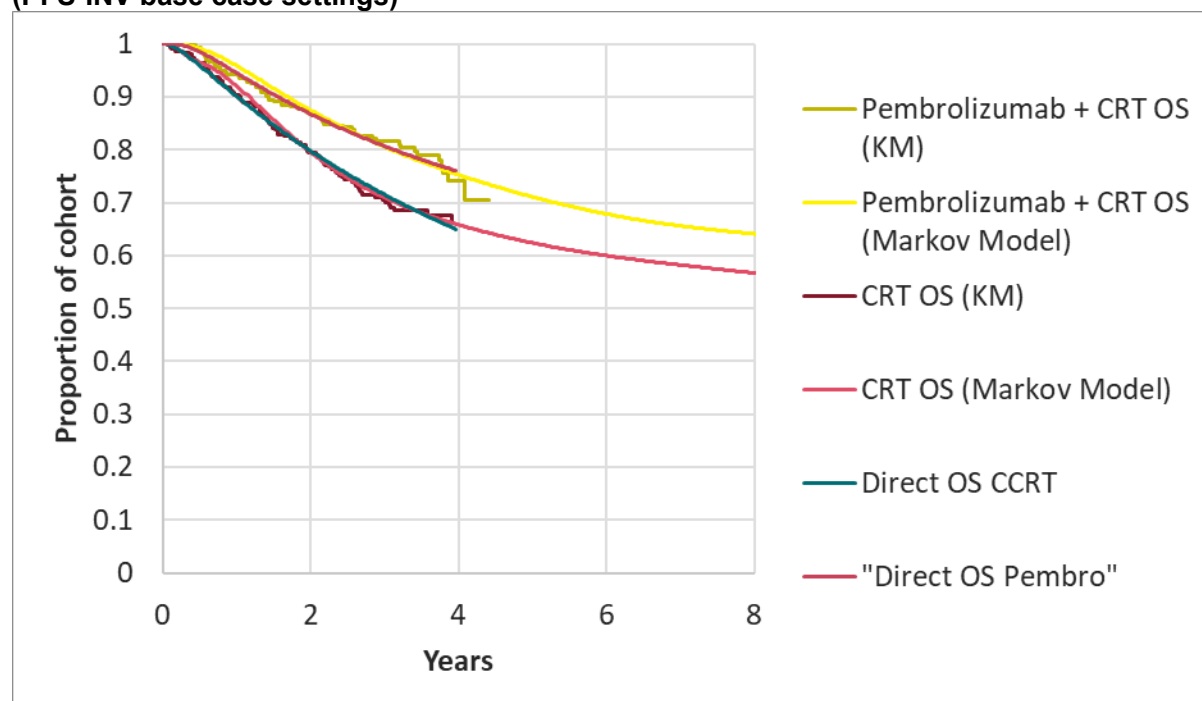
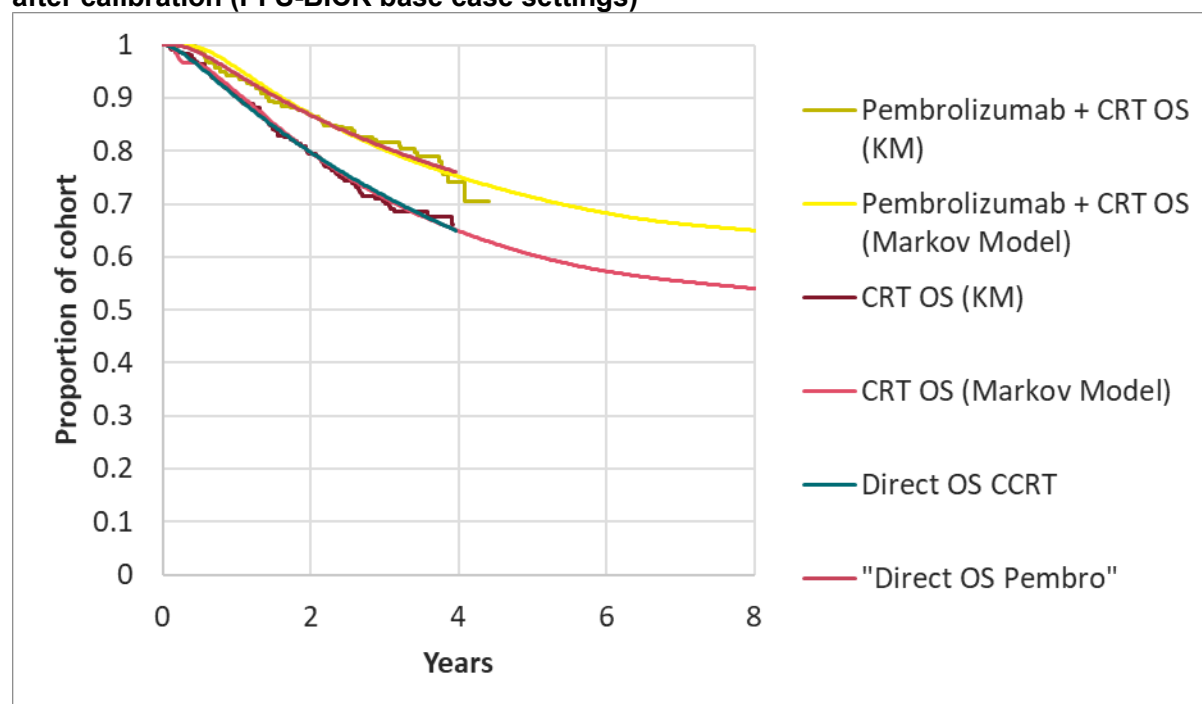


Figure 75: Markov model OS compared with directly extrapolated OS and observed OS after calibration (PFS-BICR base case settings)



There were several biological justifications for why there might be a post-progression treatment effect for pembrolizumab discussed during TA1037. The company's considerations, drawn from clinician suggestions and targeted review of relevant papers, were outlined in the section beginning on page 106 of the committee papers for ACM1 of that appraisal.⁽³⁾ The overarching explanations are that a) 'progressions' are not equal between the arms such that the cohort exposed to pembrolizumab may be entering PD1 with relatively less disease than those who have not been exposed to pembrolizumab (trials define progression from maximal point of response rather than from baseline level of disease) and b) that pembrolizumab 'sensitises' patients to downstream treatments (the synergistic effects of immunotherapy and chemotherapy, whether used together or in sequence are well reported in the literature). It can be seen from the distribution of subsequent treatments between the arms that the equal PPS is not explained by the treatments received. A higher percentage of patients in the CCRT arm received subsequent treatments (93/117 versus 52/80) and a higher proportion of these treatments were pembrolizumab (26.4% of patients in CCRT received pembrolizumab as a subsequent treatment versus 8.3% in the pembrolizumab arm. We were unable to determine whether these patients received this before or after 2.5 years from initiation in the pembrolizumab

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arm.). A higher proportion of treatments for second and third progressions were also reported in the CCRT arm, perhaps supporting the theory that progressors in the CCRT arm had relatively more advanced disease at progression.

The matching of modelled OS to the observed data in this way is akin to setting the model up to be a Partitioned Survival Analysis for its first 4 years and then setting it to a Markov structure after that to ensure the relationship between the key projected outcomes remains clinically plausible.

2.5 Updated results of the cost-effectiveness analysis

2.5.1 Updated base case settings and key changes

Table 48 contains a list of changes to the company's base case following the arrival of the FA data and in response to questions from the EAG with an indication of their effect on the ICER.

Table 47: Key base case settings

Base case based on INV	
A18 PFS/TTP survival curves	1-knot odds
826 PFS/TTP survival curves	2-knot odds
Calibration Factor Pembro+CCRT	0.45
KN826 PPS	Log-normal
Calibration Factor CCRT	0.85
Proportion of eligible patients receiving subs pembro	64%
Base case based on BICR	
A18 PFS/TTP survival curves	Gen Gamma
826 PFS/TTP survival curves	2-knot odds
KN826 PPS	Log-normal
Calibration Factor Pembro+CCRT	0.44
Calibration Factor CCRT	0.54
Proportion of eligible patients receiving subs pembro	64%

Table 48: List of changes to the company's base case

CQ	Change	Effect on ICER
A4	PFS and TTP data from FA	Large
-	PPS calibrated so model matches observed OS	Large
B15	KN826 data based on prior CRT population	Moderate
A4	Utility data from FA	Small
B23	eMIT prices for chemotherapy regimens updated	Small

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B36	Life tables updated to reflect England	Small
B41	Half cycle correction switched on and corrected	Small
B42	Brachytherapy costs corrected	Small
B45	Only eligible patients receive PD-L1 tests on progression	Small
B47	Subs treatment wastage included	Small
B33	Exclusion of EoL costs after cure	Small
B35, B37, B38, B44, B46	Minor programming errors corrected	Small
B26	Separation of ToT components by arm	Small
Abbreviations: CQ, clarification question; CRT, chemoradiotherapy; eMIT, electronic market information tool; FA, final analysis; ICER, incremental cost effectiveness ratio; OC, overall survival; PFS, progression free survival; TTP, time to progression		

2.5.2 Base case results

Table 49 contains the updated deterministic base case results, inclusive of the PAS for pembrolizumab.

Table 49: Base case results (deterministic)

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
INV – primary base case							
CRT				-	-	-	-
Pembrolizumab + CRT						1.209	
BIRC – secondary base case							
CRT				-	-	-	-
Pembrolizumab + CRT						1.715	
Average of base cases							
CRT							
Pembrolizumab + CRT						1.462	
Abbreviations: BICR, blinded independent central review; INV, investigator; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

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Table 50 contains the updated PSA results based on 1,000 iterations, inclusive of the PAS for pembrolizumab. The difference between the deterministic and probabilistic ICER using the BICR assessment of PFS is [REDACTED]. Using the INV assessment of PFS, the difference is [REDACTED].

Table 50: Base case results (probabilistic)

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
INV – primary base case							
CRT				-	-	-	-
Pembrolizumab + CRT						1.235	
BIRC – secondary base case							
CRT				-	-	-	-
Pembrolizumab + CRT						1.556	
Average of base cases							
CRT							
Pembrolizumab + CRT						1.396	
Abbreviations: BICR, blinded independent central review; INV, investigator; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

The PSA iterations are illustrated on the cost-effectiveness plane for pembrolizumab + CRT versus CRT in Figure 76 and Figure. The probability of pembrolizumab + CRT being cost-effective versus CRT at various willingness-to-pay (WTP) thresholds is given in Figure 77.

Figure 76: Cost-effectiveness plane (INV)

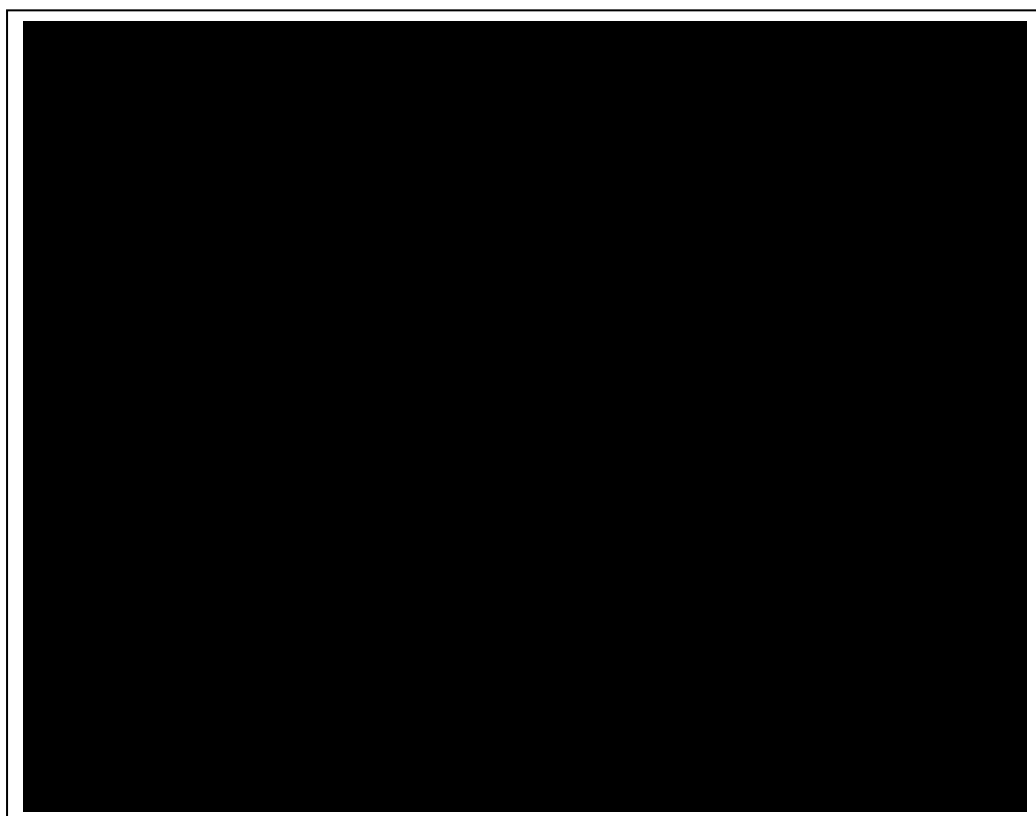


Figure 77: CEAC (INV)



Figure 78: Cost-effectiveness plane (BICR)

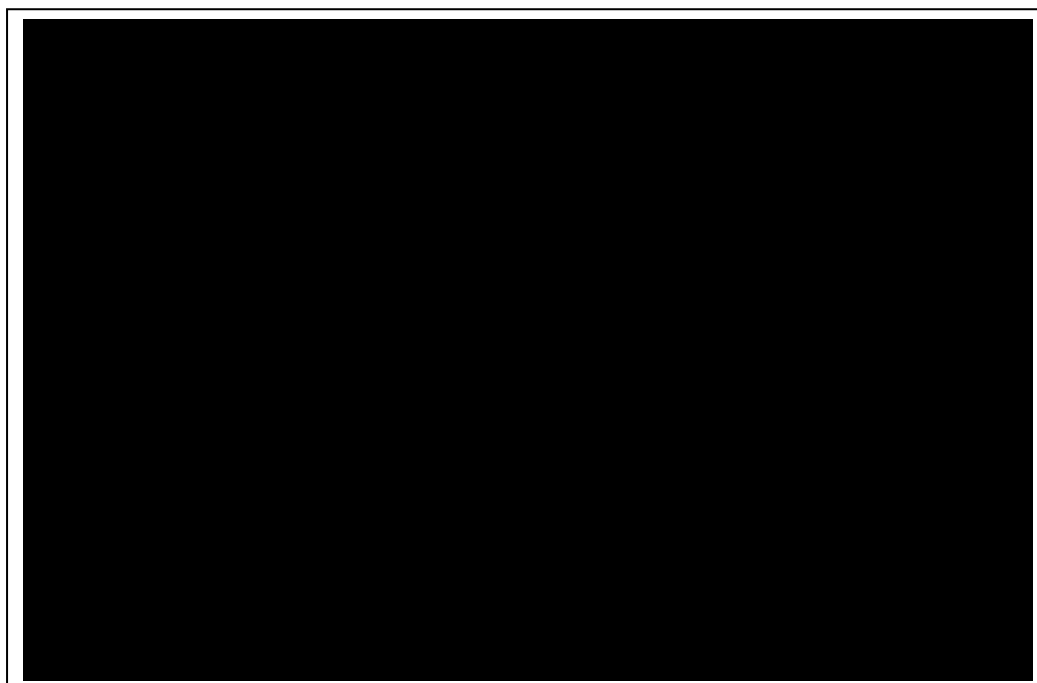
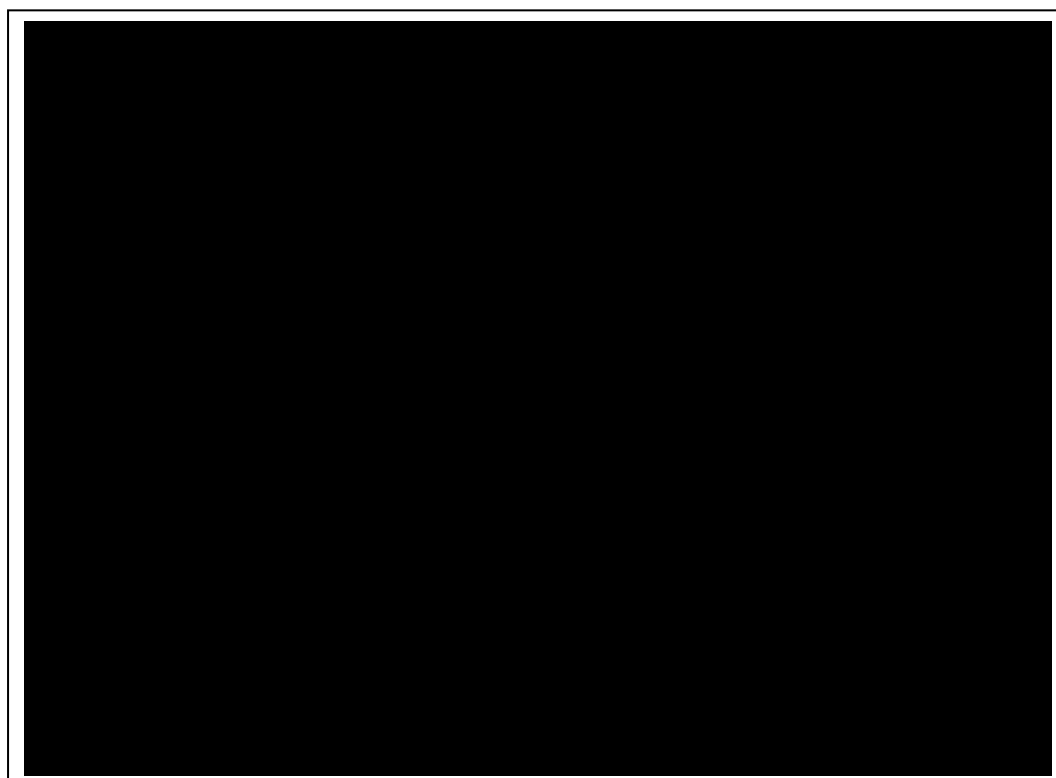


Figure 79: CEAC (BICR)



2.5.3 Sensitivity and Scenario Analyses

Table 51 contains results of one-way sensitivity analysis (OWSA) for the top 10 parameters using the INV assessment of PFS. Results are most sensitive to the proportion of patients receiving subsequent pembrolizumab or bevacizumab and the duration of subsequent pembrolizumab or bevacizumab. These results are also illustrated in a tornado plot.

Table 51: Results of OWSA (INV)

Rank	Parameter name	Lower bound ICER	Upper bound ICER	ICER delta
1	% receiving Pembrolizumab after CRT (54.4% - 73.1%)			
2	Subs treatment duration in pembro + chemo (treatment cycles) - Pembrolizumab (17.07 - 21.33)			
3	Subs treatment duration in pembro + chemo (treatment cycles) - Bevacizumab (14.47 - 20.73)			
4	% receiving Bevacizumab after CRT (59.2% - 66.8%)			

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5	Utility based on KNA18: Progressive disease (PD1) (0.705 - 0.771)			
6	Subs treatment duration in chemo regimen (treatment cycles) - Bevacizumab (11.06 - 16.94)			
7	% receiving Pembrolizumab after Pembrolizumab + CRT (54.4% - 73.1%)			
8	Utility based on KNA18: Progression-free (0.836 - 0.844)			
9	% receiving Bevacizumab after Pembrolizumab + CRT (59.2% - 66.8%)			
10	Cost per resource: Oncology Appointment (£153.30 - £228.04)			

Figure 80: OWSA tornado plot (INV)



Table 54 contains the results of key scenario analysis using the INV assessment of PFS. Assumptions which have the largest impact on the ICER include those related to cure, treatment effect waning and the survival model applied to PFS and TTP.

Table 52: Results of scenario analysis (INV)

Scenario	Inc. Costs	Inc. LYs	Inc. QALYs	ICER	Difference to base case
Remove cure and waning assumption			0.836		
Both arm A18 PFS/TTP is generalised gamma			1.528		
Exclude pembro treatment waning			0.956		
0% discounting			1.606		

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Both arm A18 PFS/TTP is 1-knot hazard			1.115		
Cure starting at 3 finishing at 5 years			1.283		
Exclude utility adjustment based on age			1.304		
Remove cure assumption			1.180		
10% get no further treatment after progressing			1.111		
35 year time horizon			1.172		
Cure starting at 7 finishing at 9 years			1.184		
Utilities based on time until death			1.177		
Cure proportion of 50%			1.195		
Utilities based on multivariate regression			1.180		
Remove the background mortality SMR			1.236		
Exclude end of life cost			1.209		
No treatment hazard ratio = 1.5			1.200		
PD and PD2 utility are equal			1.202		
Replacing the cost of Avastin with biosimilars			1.209		
No treatment hazard ratio = 3			1.216		
Weighting PPS curve by the implied weighted average of pre and post 2.5 year progressers in the pembro arm			1.215		
Exclude adverse event disutilities			1.213		
6 monthly GP visit post 5 years PFS			1.209		
Subs pembro use set equal to trial (8.3% in pembro arm, 26.4% in CCRT arm). Calibration factors 0.51 and 0.70.			1.26		

Table 53 contains results of OWSA for the top 10 parameters using the BICR assessment of PFS. Results are most sensitive to the duration of subsequent pembrolizumab and the PD utility value. These results are also illustrated in a tornado plot (Figure 81).

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Table 53: Results of OWSA (BICR)

Rank	Parameter name	Lower bound ICER	Upper bound ICER	ICER delta
1	Subs treatment duration in pembro + chemo (treatment cycles) - Pembrolizumab (17.07 - 21.33)			
2	Utility based on KNA18: Progressive disease (PD1) (0.705 - 0.771)			
3	Subs treatment duration in pembro + chemo (treatment cycles) - Bevacizumab (14.47 - 20.73)			
4	% receiving Pembrolizumab after CRT (54.4% - 73.1%)			
5	Cost per resource: Oncology Appointment (£153.30 - £228.04)			
6	% receiving Bevacizumab after CRT (59.2% - 66.8%)			
7	Utility based on KNA18: Progression-free (0.836 - 0.844)			
8	Subs treatment duration in chemo regimen (treatment cycles) - Bevacizumab (11.06 - 16.94)			
9	% receiving Bevacizumab after Pembrolizumab + CRT (59.2% - 66.8%)			
10	EOL Cost: EOL cost - Georghiou and Bardsley 2014, inflated (£5,972.92 - £8,885.08)			

Figure 81: OWSA tornado plot (BICR)

Table 54 contains the results of key scenario analysis using the BICR assessment of PFS. Assumptions which have the largest impact on the ICER include the survival model applied to PFS and TTP, the discount rate and the cure assumption.

Table 54: Results of scenario analysis (BICR)

Scenario	Inc. Costs	Inc. LYs	Inc. QALYs	ICER	Difference to base case
0% discounting			2.327		
Remove cure assumption			1.466		
Cure proportion of 50%			1.589		
Remove cure and waning assumption			1.841		
Cure starting at 3 finishing at 5 years			1.577		
Exclude pembro treatment waning			1.534		
Exclude utility adjustment based on age			1.863		
Cure starting at 7 finishing at 9 years			1.642		
35 year time horizon			1.659		
Utilities based on time until death			1.667		
Remove the background mortality SMR			1.762		
10% get no further treatment after progressing			1.727		
Utilities based on multivariate regression			1.680		
Exclude end of life cost			1.715		
6 monthly GP visit post 5 years PFS			1.715		
Replacing the cost of Avastin with biosimilars			1.715		
PD and PD2 utility are equal			1.711		
Exclude adverse event disutilities			1.719		
No treatment hazard ratio = 3			1.720		
Weighting PPS curve by the implied weighted average of pre and post 2.5 year progressors in the pembro arm			1.720		
No treatment hazard ratio = 1.5			1.717		
Both arm A18 PFS/TTP is generalised gamma			1.715		

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Subs pembro use set equal to trial (8.3% in pembro arm, 26.4% in CCRT arm). Calibration factors 0.47 and 0.35.			1.793		

2.5.4 Discussion and conclusions

The model's results have changed somewhat since the initial submission. The principal changes are the arrival of the final analysis, the suggestions by the EAG to include spline models, including only the prior-CRT patients from the KN-826 survival analysis and the model's underprediction of (particularly pembrolizumab) OS necessitating the introduction of a calibration factor. Several other changes were made based on suggestions by the EAG that improved the technical validity of the model but had a small cumulative effect on the ICER.

The ICERs for pembrolizumab are now higher than before. This is driven by a reduction in the absolute difference in the population the model predicts will be cured between the arms. There are some key scenario analyses that shift the ICER up or down. The most important is when PFS extrapolations are based on BICR rather than INV. The reason for this is that there is a much more consistent timing of events by BICR and so no significant plateau is visible or projected by the parametric models in the standard of care arm. Interestingly, while there are obvious morphological differences between the PFS-INV and PFS-BICR curves for the CCRT arm, no such differences exist for the pembrolizumab+CCRT arm. PFS-BICR KM estimates in the pembrolizumab+CCRT arm are similar morphologically and sit slightly above the estimates for PFS-INV. Other important drivers of the ICER include whether calibration is included and whether the population informing the KN-826 PFS and TTP curves is drawn from those who had prior chemo-radiotherapy or not.

Notable scenarios explored the impact of setting subsequent use of pembro equal to what was observed in the trial and calibrating OS to ensure that this matched the trial as well. These scenarios produced ICERs slightly higher than the base cases. Some differences were observed between the deterministic ICERs and the mean of the PSA iterations but we did not have sufficient time during this CQ response period to

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understand whether this was a real finding or due to some inappropriate parametrisation of the PSA.

The company considers that despite some scenarios producing ICERs higher than NICE's typical cost-effectiveness threshold, pembrolizumab can still be considered a cost-effective use of NHS resources in this setting when taking all the evidence together. It should be noted that advanced cervical cancer is a disease substantially associated with social deprivation and other socio-economic factors that correlate with lack of engagement with the NHS's highly successful screening programme. The company's DCEA (section 3.13 of the CS) highlighted the significant social gradient in cervical cancer. However, this gradient relates to all stages of cervical cancer and 74% of cases are diagnosed at stage 1 or 2, primarily through the screening programme. The company considers that the social gradient of stage III-IV disease would be substantially greater still and warrants NICE applying a higher decision threshold as has been the case in some other recent appraisals (e.g. TA1003,⁽⁴⁾ TA1044⁽⁵⁾) with profound health inequalities issues.

Repeating the DCEA⁽⁶⁾ with a population size of [REDACTED] yields a net health inequality benefit of 59 QALYs under primary base case assumptions and 84 QALYs under secondary base case assumptions.

3 Economic SLRs

3.1 Published cost-effectiveness studies

3.1.1 Summary

An SLR of published cost-effectiveness analyses in this indication was conducted with a search date of 20th Feb 2025. Full details are provided in section 3.1.4. No analyses were identified which focussed on any UK jurisdiction. Two recent cost-effectiveness analyses were identified which were based on the KEYNOTE-A18 trial. ^(7, 8) One of these ⁽⁷⁾ reports the results of a multi-national cost-effectiveness analysis but this is a conference abstract, and limited details are available of the methodology used. The other relevant publication ⁽⁸⁾ uses a four state Markov model with a 50-year time horizon to assess the cost-effectiveness of pembrolizumab + CCRT in the US. However, the analysis includes the ITT population of KEYNOTE-A18, including FIGO 2014 stage IB2 – IIB cervical cancer with node-positive

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disease, as well as stage III-IVA. It is therefore not directly relevant to the current decision problem, which only focusses on the FIGO 2014 stage III-IVA population, in line with the UK license. ⁽⁹⁾

The results of this update do not invalidate the original assertion for the need for a *de novo* economic analysis to estimate the incremental costs, life years (LY), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) for pembrolizumab + CCRT versus CCRT alone for first-line treatment of high-risk locally advanced CC in adults in England and Wales.

3.1.2 Search Strategy

The SLRs of published evidence used a reproducible and validated search strategy comprised disease terms, a study design filter, and outcome terms. The research-based adapted search strategies used for identifying studies are based on the filters developed by:

SIGN (Scottish Intercollegiate Guideline Network; <https://www.sign.ac.uk/what-we-do/methodology/search-filters/>) and CADTH (Canadian Agency for Drugs and Technologies in Health; <https://www.cadth.ca/resources/finding-evidence/strings-attached-cadth-database-search-filters#health>).

Comprehensive search strategies were designed to retrieve relevant data from published literature. A combination of Emtree subject headings (Embase®), MeSH (medical subject headings, PubMed®), and free-text terms was used to retrieve relevant publications. Searches were carried out on the following key biomedical databases: Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®) via embase.com, MEDLINE in-process (searched via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR) via the Cochrane Library. PubMed was searched to identify In-process citations, which provide records for articles before those records are indexed with MeSH or converted to out-of-scope status. "Ahead of Print" citations that precede the article's final publication in a MEDLINE indexed journal were also searched in PubMed.

In addition, the economic searches leveraged the National Health Service Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews (DARE), and the HTA database (HTAD) from the Centre for Reviews and Dissemination (CRD) York Database. It should be noted that these additional databases ceased to be updated after March 31, 2015, due to the discontinuation of NIHR (National Institute for Health Research) funding. However, the bibliographic records published until March 31, 2015, were archived until at least 2021 in

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the CRD York Database. The search was run on 23rd August 2023 and updated on 20th February 2025.

The search strategies used for retrieving information from the published economic literature are provided in Table 55, Table 56, and Table 57.

Table 55: Summary of search hits retrieved from Embase® and MEDLINE® searched via embase.com (From Database inception to 20th February 2025) – Economic review (Cost-effectiveness and cost and healthcare resource use)

No	Search strings	Hits
#1	'uterine cervix cancer'/syn	158,332
#2	'cervical tumor' OR 'cervical neoplasm'	1,977
#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)	207,763
#4	#1 OR #2 OR #3	208,026
#5	advanc* OR malignan* OR metastat* OR unopera* OR ('non' NEAR/5 resect*) OR nonresect* OR unresect* OR inopera* OR refractory OR relapsed OR ('late' NEAR/2 'stage') OR 'stage ib2' OR 'stage 1b2' OR 'stage iia' OR 'stage iia1' OR 'stage iia2' OR 'stage iib' OR 'stage iiaa' OR 'stage iiib' OR 'stage iva' OR 'stage ii*' OR (stage AND ii) OR 'stage 2*' OR 'stage-2*' OR 'stage iii*' OR (stage AND iii) OR 'stage 3*' OR 'stage-3*' OR 'stage iv*' OR (stage AND iv) OR 'stage 4*' OR 'stage-4*' OR 'stage b' OR 'stage c' OR 'stage d' OR 'stage-b' OR 'stage-c' OR 'stage-d' OR (stage NEAR/3 ('ib2' OR 'ii' OR 'iii' OR 'iv' OR '2' OR '3' OR '4' OR 'b' OR 'c' OR 'd' OR 't2' OR 't2a' OR 't2a1' OR 't2a2' OR 't2b' OR 't3' OR 't3a' OR 't3b' OR 't4' OR 'n1' OR 'n2' OR 'n3' OR 'm0' OR 'm1' OR 'high')) OR 'distant metastasis' OR 'non-metastatic' OR 'non metastatic' OR 'metastatic' OR 'locally advanced' OR ('local' NEAR/2 'advanced') OR 'stage two' OR 'stage three' OR 'stage four' OR (('high-risk' OR 'high risk') NEAR/2 ('locally advanced' OR 'advanced'))	4,723,458
#6	#4 AND #5	68,012
#7	'cost benefit analysis'/exp OR ('cost benefit' NEAR/3 method*) OR ('cost benefit' NEAR/3 analys*) OR ('cost benefit' NEAR/3 model*) OR ('cost benefit' NEAR/3 simulation*) OR ('cost benefit' NEAR/3 assessment*)	102,055
#8	'cost effectiveness analysis'/exp OR ('cost effectiveness' NEAR/3 analys*) OR ('cost effectiveness' NEAR/3 model*) OR ('cost effectiveness' NEAR/3 simulation*) OR ('cost effective' NEAR/3 analys*) OR ('cost effective' NEAR/3 model*) OR ('cost effective' NEAR/3 simulation*) OR ('cost effective' NEAR/3 assessment*)	208,008
#9	'cost efficiency analysis'/exp OR ('cost efficiency' NEAR/3 analys*) OR ('cost efficiency' NEAR/3 model*) OR ('cost efficiency' NEAR/3 simulation*) OR ('cost efficiency' NEAR/3 assessment*)	200,301
#10	'cost utility analysis'/exp OR ('cost utility' NEAR/3 method*) OR ('cost utility' NEAR/3 analys*) OR ('cost utility' NEAR/3 model*) OR ('cost utility' NEAR/3 simulation*) OR ('cost utilities' NEAR/3 analys*) OR ('cost utilities' NEAR/3 model*) OR ('cost utilities' NEAR/3 simulation*) OR ('cost utilities' NEAR/3 assessment*)	15,287
#11	('markov' NEAR/3 method*) OR ('markov' NEAR/3 analys*) OR ('markov' NEAR/3 model*) OR ('markov' NEAR/3 simulation*) OR ('markov' NEAR/3 assessment*) OR (markov NEAR/3 analys*) OR ('markov' NEAR/3 chain*)	45,107

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#12	'monte carlo method'/exp OR ('monte carlo' NEAR/3 method*) OR ('monte carlo' NEAR/3 analys*) OR ('monte carlo' NEAR/3 model*) OR ('monte carlo' NEAR/3 simulation*) OR ('monte carlo' NEAR/3 chain*)	73,307
#13	'economic evaluation'/exp	381,360
#14	(cost NEAR/3 analys*) OR (cost NEAR/3 model*) OR (cost NEAR/3 simulation*) OR (cost NEAR/3 assessment*) OR (economic NEAR/3 analys*) OR (economic NEAR/3 model*) OR (economic NEAR/3 simulation*) OR (economic NEAR/3 assessment*)	337,357
#15	'cost minimization analysis' OR ('cost minimization' NEAR/3 analys*) OR ('cost minimization' NEAR/3 model*) OR ('cost minimization' NEAR/3 simulation*) OR ('cost minimization' NEAR/3 assessment*) OR 'cost minimisation analysis' OR ('cost minimisation' NEAR/3 analys*) OR ('cost minimisation' NEAR/3 model*) OR ('cost minimisation' NEAR/3 simulation*) OR ('cost minimisation' NEAR/3 assessment*)	4,745
#16	'budget impact analysis' OR ('budget impact' NEAR/3 analys*) OR ('budget impact' NEAR/3 model*) OR ('budget impact' NEAR/3 simulation*) OR ('budget impact' NEAR/3 assessment*)	4,298
#17	'productivity' OR 'absenteeism' OR 'disability absence' OR 'sickness absence' OR 'sickness absenteeism' OR 'work absence' OR 'work absenteeism' OR 'work day loss' OR 'work time loss' OR 'presenteeism' OR 'presenteism' OR 'sickness presence' OR 'working while ill' OR 'working while sick' OR 'work productivity' OR 'work productivity loss'	154,269
#18	'economics'/exp OR 'economic aspect'/exp OR 'cost'/exp OR 'health care cost'/exp OR 'drug cost'/exp OR 'hospital cost'/exp OR 'socioeconomics'/exp OR 'health economics'/exp OR 'pharmacoeconomics'/exp OR 'fee'/exp OR 'budget'/exp OR 'hospital finance'/exp OR 'financial management'/exp OR 'health care financing'/exp OR 'low cost' OR 'high cost' OR (health*care NEXT/1 cost*) OR ('health care' NEXT/1 cost*) OR fiscal OR funding OR financial OR finance OR (cost NEXT/1 estimate*) OR 'cost variable' OR (unit NEXT/1 cost*) OR economic* OR pharmacoeconomic* OR price* OR 'pricing' OR (cost* NEAR/3 (treat* OR therap*)) OR (health*care NEXT/1 (utilisation OR utilization)) OR ('health care' NEXT/1 (utilisation OR utilization)) OR (resource NEXT/1 (utilisation OR utilization OR use))	3,726,433
#19	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	3,913,626
#20	'caregiver burden'/syn	15,702
#21	('caregiver' OR 'caregivers' OR 'family' OR 'adult children' OR 'spouses' OR 'family caregiver' OR 'carers' OR spous* OR senior* OR 'adult' OR 'adults' OR 'elderly' OR 'frail' OR pensioner* OR 'middle-aged' OR 'middle aged') NEAR/4 'burden'	26,765
#22	carer*:ab,ti OR caretaker*:ab,ti OR caregiver*:ab,ti OR 'care giver*':ab,ti OR 'caregiver time' OR 'family caregiver'	185,431
#23	'family caregiver'	3,894
#24	'family':ab,ti,kw OR 'families':ab,ti,kw OR 'kid':ab,ti,kw OR 'kids':ab,ti,kw OR child*:ab,ti,kw OR 'son':ab,ti,kw OR 'sons':ab,ti,kw OR daughter*:ab,ti,kw OR 'offspring':ab,ti,kw OR spouse*:ab,ti,kw OR 'partner':ab,ti,kw OR husband*:ab,ti,kw OR 'wife':ab,ti,kw OR 'wives':ab,ti,kw OR sibling*:ab,ti,kw OR grandchild*:ab,ti,kw OR parent*:ab,ti,kw OR sister*:ab,ti,kw OR brother*:ab,ti,kw OR uncle*:ab,ti,kw OR aunt*:ab,ti,kw OR niece*:ab,ti,kw OR nephew*:ab,ti,kw OR cousin*:ab,ti,kw	5,073,999
#25	'adult children' OR 'spouses' OR 'siblings' OR 'only child' OR 'nuclear family' OR 'parents' OR 'family'	2,086,332

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#26	#24 OR #25	5,468,481
#27	'care':ab,ti,kw OR 'caring':ab,ti,kw OR 'caregiving':ab,ti,kw OR carer*:ab,ti,kw OR caregiver*:ab,ti,kw OR 'cares':ab,ti,kw OR caretaker*:ab,ti,kw	2,969,582
#28	'caregivers'	119,693
#29	#27 OR #28	2,969,618
#30	#26 AND #29	731,967
#31	#20 OR #21 OR #22 OR #23 OR #30	813,375
#32	#19 OR #31	4,495,272
#33	#6 AND #32	6,289
#34	#33 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	21
#35	#33 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	264
#36	#34 OR #35	285
#37	#33 NOT #36 [Database inception to 23-08-2023]	4,662
#38	#33 NOT #36 [23-08-2023 to 20-02-2025]	1,342
#39	#37 OR #38	6,004

Table 56: Summary of search hits retrieved from MEDLINE® In-Process searched via PubMed® – Economic review (Cost-effectiveness and cost and healthcare resource use)

No	Search strings	Hits
1	"uterine cervix cancer"	503
2	"cervical tumor" OR "cervical neoplasm"	1,315
3	cervi* AND (cancer* OR oncolog* OR neoplas* OR carcinom* OR malignan* OR tumor* OR tumour* OR mass* OR growth* OR cyst* OR adenocarcinom* OR squamous)	201,013
4	#1 OR #2 OR #3	201,013
5	advanc* OR malignan* OR metastat* OR unopera* OR ("non" AND resect*) OR nonresect* OR unresect* OR inopera* OR refractory OR relapsed OR ("late" AND "stage") OR "stage ib2" OR "stage iia" OR "stage iia1" OR "stage iia2" OR "stage iib" OR "stage iia" OR "stage iib" OR "stage iva" OR "stage ii" OR (stage AND ii) OR "stage 2" OR "stage-2" OR "stage iii" OR (stage AND iii) OR "stage 3" OR "stage-3" OR "stage iv" OR (stage AND iv) OR "stage 4" OR "stage-4" OR "stage b" OR "stage c" OR "stage d" OR "stage-b" OR "stage-c" OR "stage-d" OR (stage AND ("ii" OR "iii" OR "iv" OR "2" OR "3" OR "4" OR "b" OR "c" OR "d" OR "t2" OR "t2a" OR "t2a1" OR "t2a2" OR "t2b" OR "t3" OR "t3a" OR "t3b" OR "t4" OR "n1" OR "n2" OR "n3" OR "m0" OR "m1" OR "high")) OR "distant metastasis" OR "non-metastatic" OR "non metastatic" OR "metastatic" OR "locally advanced" OR ("local" AND "advanced") OR "stage two" OR "stage three" OR "stage four" OR (("high-risk" OR "high risk") AND ("locally advanced" OR "advanced"))	4,482,945
6	#4 AND #5	69,393
7	"cost benefit analysis" OR ("cost benefit" AND method*) OR ("cost benefit" AND analys*) OR ("cost benefit" AND model*) OR ("cost benefit" AND simulation*) OR ("cost benefit" AND assessment*)	104,148
8	"cost effectiveness analysis" OR ("cost effectiveness" AND analys*) OR ("cost effectiveness" AND model*) OR ("cost effectiveness" AND simulation*) OR ("cost effective" AND analys*) OR ("cost effective" AND model*) OR ("cost effective" AND simulation*) OR ("cost effective" AND assessment*)	132,639

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9	"cost efficiency analysis" OR ("cost efficiency" AND analys*) OR ("cost efficiency" AND model*) OR ("cost efficiency" AND simulation*) OR ("cost efficiency" AND assessment*)	2,338
10	"cost utility analysis" OR ("cost utility" AND method*) OR ("cost utility" AND analys*) OR ("cost utility" AND model*) OR ("cost utility" AND simulation*) OR ("cost utilities" AND analys*) OR ("cost utilities" AND model*) OR ("cost utilities" AND simulation*) OR ("cost utilities" AND assessment*)	7,040
11	("markov" AND method*) OR ("markov" AND analys*) OR ("markov" AND model*) OR ("markov" AND simulation*) OR ("markov" AND assessment*) OR (markov AND analys*) OR ("markov" AND chain*)	37,286
12	"monte carlo method" OR ("monte carlo" AND method*) OR ("monte carlo" AND analys*) OR ("monte carlo" AND model*) OR ("monte carlo" AND simulation*) OR ("monte carlo" AND chain*)	72,885
13	"economic evaluation"	15,592
14	(cost AND analys*) OR (cost AND model*) OR (cost AND simulation*) OR (cost AND assessment*) OR (economic AND analys*) OR (economic AND model*) OR (economic AND simulation*) OR (economic AND assessment*)	850,107
15	"cost minimization analysis" OR ("cost minimization" AND analys*) OR ("cost minimization" AND model*) OR ("cost minimization" AND simulation*) OR ("cost minimization" AND assessment*) OR "cost minimisation analysis" OR ("cost minimisation" AND analys*) OR ("cost minimisation" AND model*) OR ("cost minimisation" AND simulation*) OR ("cost minimisation" AND assessment*)	1,612
16	"budget impact analysis" OR ("budget impact" AND analys*) OR ("budget impact" AND model*) OR ("budget impact" AND simulation*) OR ("budget impact" AND assessment*)	2,367
17	"productivity" OR "absenteeism" OR "disability absence" OR "sickness absence" OR "sickness absenteeism" OR "work absence" OR "work absenteeism" OR "work day loss" OR "work time loss" OR "presenteeism" OR "presenteism" OR "sickness presence" OR "working while ill" OR "working while sick"	111,086
18	"economics" OR "economic aspect" OR "cost" OR "health care cost" OR "drug cost" OR "hospital cost" OR "socioeconomics" OR "health economics" OR "pharmacoeconomics" OR "fee" OR "budget" OR "hospital finance" OR "financial management" OR "health care financing" OR "low cost" OR "high cost" OR (health*care AND cost*) OR ("health care" AND cost*) OR fiscal OR funding OR financial OR finance OR (cost AND estimate*) OR "cost variable" OR (unit AND cost*) OR economic* OR pharmacoeconomic* OR price* OR "pricing" OR (cost* AND (treat* OR therap*)) OR (health*care AND (utilisation OR utilization)) OR ("health care" AND (utilisation OR utilization)) OR (resource AND (utilisation OR utilization OR use))	4,013,522
19	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	4,159,485
20	"caregiver burden"	6,695
21	("caregiver" OR "caregivers" OR "family" OR "adult children" OR "spouses" OR "family caregiver" OR "carers" OR spous* OR senior* OR "adult" OR "adults" OR "elderly" OR "frail" OR pensioner* OR "middle-aged" OR "middle aged") AND "burden"	166,955
22	carer*[Title/Abstract] OR caretaker*[Title/Abstract] OR caregiver*[Title/Abstract] OR "care giver"*[Title/Abstract] OR "caregiver time" OR "family caregiver"	135,462
23	"family caregiver"	3,061

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24	"family"[Title/Abstract] OR "families"[Title/Abstract] OR "kid"[Title/Abstract] OR "kids"[Title/Abstract] OR child*[Title/Abstract] OR "son"[Title/Abstract] OR "sons"[Title/Abstract] OR daughter*[Title/Abstract] OR "offspring"[Title/Abstract] OR spouse*[Title/Abstract] OR "partner"[Title/Abstract] OR husband*[Title/Abstract] OR "wife"[Title/Abstract] OR "wives"[Title/Abstract] OR sibling*[Title/Abstract] OR grandchild*[Title/Abstract] OR parent*[Title/Abstract] OR sister*[Title/Abstract] OR brother*[Title/Abstract] OR uncle*[Title/Abstract] OR aunt*[Title/Abstract] OR niece*[Title/Abstract] OR nephew*[Title/Abstract] OR cousin*[Title/Abstract]	3,882,444
25	"adult children" OR "spouses" OR "siblings" OR "only child" OR "nuclear family" OR "parents" OR "family"	1,687,244
26	#24 OR #25	4,220,733
27	"care":ab,ti,kw OR "caring"[Title/Abstract] OR "caregiving"[Title/Abstract] OR carer*[Title/Abstract] OR caregiver*[Title/Abstract] OR "cares"[Title/Abstract] OR caretaker*[Title/Abstract]	191,893
28	"caregivers"	109,772
29	#27 OR #28	200,393
30	#26 AND #29	108,678
31	#20 OR #21 OR #22 OR #23 OR #30	309,410
32	#19 OR #31	4,357,299
33	#6 AND #32	7,652
34	#33 AND (in process[sb] OR pubstatusaheadofprint) [Date: 23rd August 2023]	56
35	#33 AND (in process[sb] OR pubstatusaheadofprint) [Date: 20th Feb 2025]	75
36	#34 OR #35	131

Table 57: Summary of search hits retrieved from CRD York/EconLit/Tufts CEA registry (From Database inception to 20th February 2025) – Economic review (Cost-effectiveness and cost and healthcare resource use)

No		Search strings	Hits
#1	CRD York	((cervical cancer)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA	447
#2	EconLit	Cervical/Cervix	103
#3	Tufts CEA registry	Cervical/Cervix	322

Supplementary searches of conference proceedings were undertaken for eight years (2018-25) as listed below:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Europe and International)

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- American Society of Clinical Oncology (ASCO)
- American Society of Clinical Oncology – Genitourinary (ASCO-GU)
- American Association for Cancer Research (AACR)
- European Society for Medical Oncology (ESMO)
- European Society of Gynaecological Oncology (ESGO)
- International Gynecologic Cancer Society (IGCS)

Since many conference proceedings are now included within Embase, one reviewer checked the coverage of specific conferences of interest by checking the Embase list of conferences (<https://www.elsevier.com/solutions/embase-biomedical-research/coverage-and-content>). As per the findings of Cochrane methodology reviews, studies with positive results tended to be published in approximately four years, and not all conference presentations were published ^(10, 11). Furthermore, over one-half of studies reported in conference abstracts never reach complete publication ^(12, 13). Thereby, we restricted the manual handsearching of conference proceedings to the last three years.

A summary of the search keywords and estimated search hits utilised to identify relevant conference publications are provided in Table 58.

Table 58: Summary of the conferences searched

Conference name	Year	Search keywords	Hits
ASCO, ASCO-GU, ASCO-Quality of life	2018	Indexed in biomedical database (Embase)	
	2019		
	2020		
	2021	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	685
	2022	Indexed in biomedical database (Embase)	
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2024	Indexed in biomedical database (Embase)	
ESMO	2018	Indexed in biomedical database (Embase)	
	2019		
	2020	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2021		
	2022	Indexed in biomedical database (Embase)	
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2024	Indexed in biomedical database (Embase)	
ISPOR Europe	2018	Indexed in biomedical database (Embase)	
	2019		
	2020	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	18
	2021		12
	2022	Indexed in biomedical database (Embase)	
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	28
	2024	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
ISPOR Asia Pacific	2018	Indexed in biomedical database (Embase)	
	2019	Conference conducted in one year gap	
	2020	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	16
	2021	Conference conducted in one year gap	
	2022	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	0
ISPOR US	2018	Indexed in biomedical database (Embase)	
	2019		
	2020	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	52
	2021		56
	2022	Indexed in biomedical database (Embase)	
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	11
	2024	Indexed in biomedical database (Embase)	
AACR	2018	Indexed in biomedical database (Embase)	

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	2019	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	160
	2020		124
	2021		46
	2022		(-)
	2023		(-)
	2024	Indexed in biomedical database (Embase)	
ESGO	2018	Indexed in biomedical database (Embase)	
	2019		
	2020		
	2021		
	2022		
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2024	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
IGCS	2025	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2018	Indexed in biomedical database (Embase)	
	2019		
	2020		
	2021		
	2022		
	2023	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)
	2024	Manually searched: Cervical cancer OR cervix cancer OR cervical OR cervix	(-)

(-): Search hits not countable; the conference was searched by screening through multiple research categories.

In addition, targeted keyword searches and bibliographic searching of included studies and relevant literature reviews were conducted to supplement the evidence retrieved from the biomedical databases. Lastly, NICE and SMC websites were searched to identify pertinent technology appraisals that matched our PICOTS criteria.

3.1.3 Study selection

Studies identified in the literature had to meet pre-defined eligibility criteria in the review (Table 59). This review was carried out in strict accordance with the NICE recommendations. First, two independent reviewers reviewed abstracts of citations identified through the searches for inclusion based on title and abstract alone; a third reviewer reconciled any discrepancies. Next, full-text copies of studies that met the screening criteria were obtained and screened by two independent reviewers; a third reviewer reconciled any discrepancies. Finally, two independent reviewers extracted data from the studies, and a third independent reviewer

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reconciled any discrepancies. The different phases of the literature review are outlined in Figure 82.

Figure 82: Project approach and methodology for the review

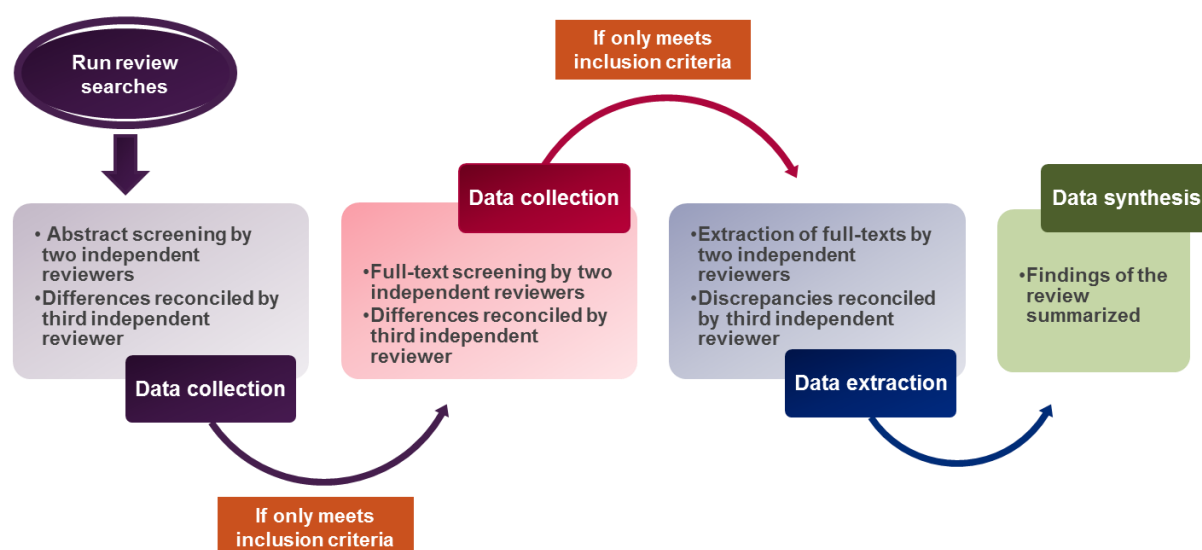


Table 59: Key inclusion and exclusion criteria (PICOTS) – Cost-effectiveness review

Criteria	Inclusion	Exclusion	Rationale
Population	Disease: Patients with high-risk (stage IB2-IIB with node-positive disease or stage III-IVA), locally advanced cervical cancer	Patients with other types of cancer, e.g., ovarian, uterine, vaginal, vulvar, OR overall cancer with no further segregation Patients with disease stage IA and/or IB1 only Patients with disease stage IVB only Patients with disease stage unclear. Patients with no subgroup data for cervical cancer (stage IB2-IVA)	Cancer category and disease staging included and excluded according to the KEYNOTE trial.
	Age: Adult (≥18 years) patients	Studies evaluating children	(-)
	Race: No restriction	Not applicable	(-)
	Gender: No restriction	Not applicable	(-)
Line of therapy	First-line only OR treatment naïve patients (that have not received prior systemic therapy)	Studies evaluating second-line or later line therapy only Studies with a mixed line of treatment but with no subgroup analysis reported for the first-line category Studies with the line of therapy unclear	Patient population aligned with the KEYNOTE trial.

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	Please refer to page 91 for additional details of the selection criteria		
Interventions and comparators	No restriction	(-)	(-)
Outcomes	Economic evaluations Intervention and comparator details (dosage, admin route, length of treatment, number of cycles, concomitant medication, stopping rule, etc.) Evaluation details (perspective, time horizon, source of clinical data, source of cost data, source of resource use data, source of utility data, discounting, cost year, cycle length, type of economic model used, model description and justification, model inputs such as survival extrapolations) Cost-analysis (any assumptions/hypothesis, discounting, year of cost, type of costs, budget impact details, results, total and disaggregated cost, and resource use) Cost-effectiveness and/or cost-utility analysis (total and disaggregated cost, total and disaggregated effectiveness, incremental costs, incremental cost/quality-adjusted life-years gained, incremental cost/life-years gained, cost/year of PFS gained, subgroup analysis, sensitivity analysis) Utility values for health states, e.g. pre-progression, post-progression, stable disease, responders, etc. Country-specific tariff used in the scoring of the utility values Details on different instruments measuring utility values, e.g., types and appropriateness of health states, mapping,	Studies not reporting relevant outcomes of interest were excluded	The standard set of outcomes extracted in these reviews

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	method of elicitation, uncertainty Disutility values associated with adverse events and duration of adverse events Details on patient population, any subgroups evaluated Details on any non-curative surgery- surgery type, number of patients receiving surgery, and cost.		
Study design	Cost-effectiveness analysis Cost minimization analysis Cost-utility analysis Cost-benefit analysis Literature reviews/systematic reviews/relevant general reviews for bibliographic searching	Case reports Case series	The standard set of study designs considered in these reviews
Timeframe	Original review: Database inception to 31 st October 2021 Update review: 1 st Nov 2021-23 rd Aug 2023 Second update: 24 th August 2023 – 20 th February 2025	Not applicable	To retrieve comprehensive and latest evidence to support the review objectives
Country	No restriction Global approach followed	Not applicable	
Language	Studies with full-texts published in the English language only	Studies with full-texts published in the non-English language	(-)
Publication type	Peer-reviewed journal articles and conference abstracts (searched for the previous eight years, 2018-2025)	Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews	(-)

ICER: Incremental cost-effectiveness ratio; LY: Life year; QALY: Quality-adjusted life year

For each economic evaluation, we conducted a quality assessment based on preapproved assessment criteria for the representativeness of the study population, strength of the study Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

design, validity of study measures, and presentation of outcomes and conclusions. The quality assessment was performed for each economic evaluation identified for inclusion in the review using the Drummond checklist ⁽¹⁴⁾ (Table 63).

For studies reporting cost and resource use data only, quality assessment based on preapproved assessment criteria for the representativeness of the study was not conducted as there are no recommended guidelines for its critical appraisal.

After applying the primary study selection criteria mentioned in Table 59, it was observed that some studies did not report relevant information on the line of therapy (LOT) but fulfilled the rest of the PICOTS criteria. This is primarily due to the nature of reviews conducted, and authors do not generally report adequate information on the prior treatment history. However, many of these LOT unclear studies evaluated chemoradiotherapy (CRT)/chemotherapy (CT) as the primary treatment(s) in high-risk locally advanced cervical cancer settings. Since CRT is commonly recommended as the standard first-line treatment across scientific guidance, we assumed the LOT unclear studies to fall under the same category.

Of all the LOT unclear studies, we prioritised including only those that evaluated CRT/CT in high-risk, locally advanced settings. The remaining LOT unclear studies evaluating surgery alone, radiotherapy alone, and surgery + radiotherapy remained under the exclusion category. Studies evaluating mixed treatments, i.e., surgery +/- radiotherapy + CRT/CT with no subgroup data for CRT/CT, also remain excluded.

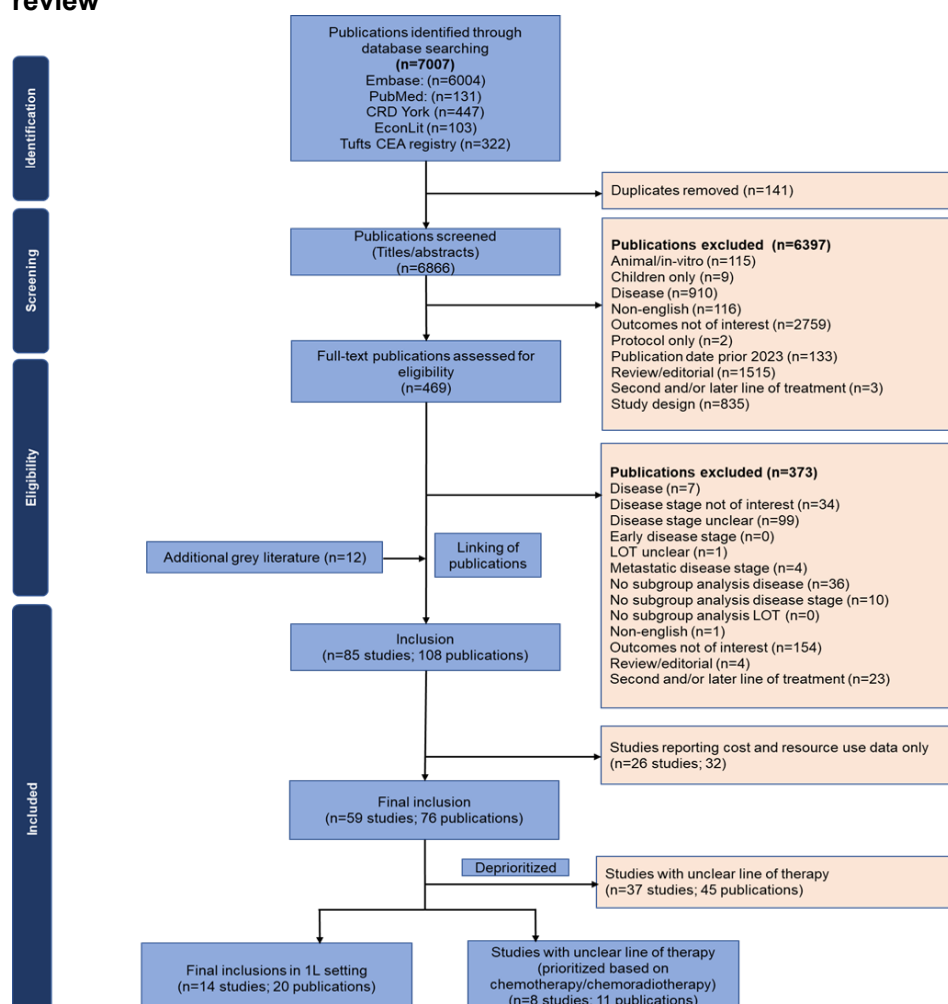
3.1.4 Search results

The PRISMA diagram detailing the number of publications identified, screened and included in the SLR can be found in Figure 83. The literature search yielded 6,866 separate publications, after removal of 141 duplicate abstracts due to the coverage overlap between the databases. Following the first pass of the publications, 469 potentially relevant references were identified. Full-text reports of these publications were retrieved for a more detailed evaluation. In total, 108 publications were identified, including 12 retrieved through the searching of conference proceedings and bibliographies of relevant articles. Multiple reports (journal articles, conference abstracts) of the same studies were linked together so that each study rather than each report is the unit of interest in the systematic review. This resulted in the inclusion of 31 publications, reporting on 22 studies, 14 of which specifically reported on first line therapies.

The economic review identified a limited number of cost-effectiveness/cost-utility analyses (n=22). The review identified evidence for 12 countries, with those carried out in the US (or including the US) the most common (10/22). Where the modelling approach employed was Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

reported (n=14/22), 5 studies used decision trees, 7 used Markov or modified Markov state-transition models and one used a hybrid decision tree/Markov model. One study used the WHO PRIME tool, a static non-communicable disease model. Most studies adopted a payer perspective. Overall, where reported, the time horizons adopted by the studies ranged from four weeks to lifetime. The applied discount rates for health and economic outcomes ranged from 1.5% to 5.0% annually. Chemoradiation with gemcitabine + cisplatin was the most explored systemic regimen and was also cost-effective in some scenarios. Other interventions included were cisplatin-based chemoradiation, chemoradiation alone, radiation alone (e.g., brachytherapy, radical therapy), modulated electro-hyperthermia, etc. Two recent studies investigated pembrolizumab in the current regime, using KEYNOTE-A18 for clinical input parameters. One was conducted from a US perspective and one was multinational (US, China and Italy). No studies identified were based in the UK or adopted a UK perspective.

Figure 83: Flow of studies through the systematic review process – cost-effectiveness review



LOT: Line of therapy

Note: Since a combined search strategy was developed for identifying economic evaluations and cost/resource use studies, the flow of citations is similar (except the concluding tabs)

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Table 60: Summary of the published economic evaluations; key study and patient characteristics (n=22 studies)

Study name, Country	Publication type	Treatments evaluated	Relevant disease stage	Description of key patient characteristics	Study design
Phippen 2012 ⁽¹⁵⁾ , United States	Peer-reviewed journal article	Gemcitabine + Cisplatin chemoradiation followed 2 cycles of gemcitabine and cisplatin Cisplatin chemoradiation	High-risk, locally advanced, and advanced	Median age: 45.5 years ECOG PS (0/1/2): NR Disease stage (IIB/IIIA/IIIB/IVA): 61.4%/0.4%/36.5%/1.8% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Rocconi 2005 ⁽¹⁶⁾ , United States	Peer-reviewed journal article	Radical hysterectomy with pelvic and para-aortic lymphadenectomy + tailored chemoradiation therapy (RHYST) Chemoradiotherapy (CTRT) Neoadjuvant chemotherapy followed by radical hysterectomy with pelvic and para-aortic lymphadenectomy + tailored chemoradiation therapy (NAC)	High-risk and locally advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (IB2): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Resnick 2010 ⁽¹⁷⁾ , United States	Conference abstract	Clinical staging followed by CTRT Radiologic staging with PET/CT followed by CTRT Radiologic staging with PET/CT + LND for PET-positive findings, followed by CTRT Surgical staging followed by CTRT	High-risk, locally advanced, and advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis

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Smith 2013 ⁽¹⁸⁾ , United States	Peer-reviewed journal article	RT/GC + GC: Radiation therapy with concurrent gemcitabine and cisplatin plus adjuvant gemcitabine and cisplatin RT/C: Radiation therapy with concurrent cisplatin	High-risk, locally advanced, and advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost- effectiveness analysis
Rose 2000 ⁽¹⁹⁾ , United States	Peer-reviewed journal article	Cisplatin chemoradiation Radiation alone or radiation plus hydroxyurea	Advanced	Median age: 46.6 ECOG PS (0/1/2): NR Disease stage (IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost- effectiveness analysis
Perdrizet 2020 ⁽²⁰⁾ , Canada	Peer-reviewed journal article	MRgBT (magnetic resonance- guided brachytherapy) CTgBT (computed tomography- guided brachytherapy) 2DBT (2-dimensional brachytherapy)	Stage IB2-IIIB (relevant stage; locally advanced) Stage IB1 also included (not of interest)	Median age: NR ECOG PS (0/1/2): NR Disease stage (IB-IIIB): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-utility analysis
Rongsriyam 2020 ⁽²¹⁾ , Thailand	Peer-reviewed journal article	Concurrent chemoradiation therapy (external pelvic radiation, brachytherapy, and weekly cisplatin) Adjuvant chemotherapy (paclitaxel and carboplatin) + concurrent chemoradiation therapy	Locally advanced or advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (II/III-IVA): 64%/36% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-utility analysis

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Manusirivithaya 2005 ⁽²²⁾ , Thailand	Peer-reviewed journal article	Concurrent chemotherapy (cisplatin; 5-fluorouracil) Radiation only	Stage IB2-IVA (relevant stage; locally advanced) Stage IB1 also included (not of interest)	Median age: NR ECOG PS (0/1/2): NR Disease stage (IB-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Sanif 2018 ⁽²³⁾ , Indonesia	Peer-reviewed journal article	Chemotherapy Chemoradiotherapy	Stage IIB-IVA (relevant stage; locally advanced or advanced; majority) Unknown stage (not of interest)	Median age: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVA): 91.49% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Chai 2016 ⁽²⁴⁾ , China	Peer-reviewed journal article	Radical hysterectomy combined with adjuvant external beam radiotherapy Radical radiotherapy	Locally advanced	Median age: 49.5 ECOG PS (0/1/2): NR Disease stage (IIB): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Phippen 2016 ⁽²⁵⁾ , US	Peer-reviewed journal article	Post chemoradiation Arm 1: Routine surveillance without positron emission tomography (PET)/computed tomography (CT) Arm 2: Routine surveillance with Positron emission tomography (PET)/computed tomography (CT)- Hysterectomy	Locally advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (LA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-Effectiveness

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Van Ballegooijen 1992 ⁽²⁶⁾ , Netherlands	Peer-reviewed journal article	Surgery Radiotherapy Chemotherapy	Advanced	Median age: NR ECOG PS (0/1/2): NR Disease stage (Advanced): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-Effectiveness
Nelson 2016 ⁽²⁷⁾ , Tanzania	Peer-reviewed journal article	Radiotherapy Chemotherapy	Stage I-IV (Stagewise data reported)	Median age: NR ECOG PS (0/1/2): NR Disease stage: Stage 1: 12% Stage 2: 49.2% Stage 3: 35.5% Stage 4: 3.1% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-Effectiveness
Jewell 2007 ⁽²⁸⁾ , US	Peer-reviewed journal article	Arm 1: Surgery + Adjuvant therapy Arm 2: Chemoradiation	Stage IB2	Median age: NR ECOG PS (0/1/2): NR Disease stage (IB2): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Lee 2015 ⁽²⁹⁾ , Korea	Peer-reviewed journal article	Pelvic CRT Nodal staging surgery followed by extended-field CRT	Locally advanced (Stage IIB or higher)	Median age: NR ECOG PS (0/1/2): NR Disease stage (locally advanced): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis

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Puspitasari 2021 ⁽³⁰⁾ , Indonesia	Peer-reviewed journal article	Chemoradiation Radiotherapy	Stage IIB-IIIB	Median age: NR ECOG PS (0/1/2): NR Disease stage: Stage IIB: 51.8% Stage IIIA: 1.3% Stage IIIB: 46.9% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Carmona 2015 ⁽³¹⁾ , US, Turkey	Conference abstract	Conventional RT + Concurrent/adjuvant G/C (Gemcitabine + Cisplatin) Conventional RT + concurrent cisplatin IMRT + concurrent and adjuvant G/C IMRT + concurrent cisplatin	Locally advanced (Stage IIB-IVA)	Median age: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Van Minh 2017 ⁽³²⁾ , Vietnam	Peer-reviewed journal article	Chemoradiation	Stage IIB-IVB	Median age: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVB): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis
Katanyoo 2021 ⁽³³⁾ , Thailand	Peer-reviewed journal article	Arms: CT without LL CT with LL MRI without LL MRI with LL PET/CT without LL	Stage IB3-IVA	Median age (SD): NR ECOG PS (0/1/2): NR Disease stage (IB3-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Cost-effectiveness analysis

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		PET/CT with LL No investigation Concurrent chemoradiation therapy			
Minnaar 2022 (34), South Africa	Peer- reviewed journal article	Chemoradiotherapy (CRT) alone CRT with Modulated electro- hyperthermia (mEHT)	Stage IIB-IIIB	Overall Median age (Min-Max): 49.2 (28.3-72.8) ECOG (0/1): 4.7%/95.2% Disease stage (IIB/IIIA/IIIB):36.1%/ 0.95%/62.8% Smoking status: NR HPV status: NR Race (African/Caucasian/Indian/Asian/Mixed): 92.8%/2.3%/0%/0%/4.7%	Cost- effectiveness analysis
Courtney 2025 (35), USA	Peer- reviewed journal article	Pembrolizumab Placebo	Locally advanced (stage IB2–IIB with node- positive disease or stage III–IVA)	Overall Median age: 50 years	Cost- effectiveness analysis
Liu 2024 (36), Multinational (USA, China, Italy)	Conference abstract	Pembrolizumab Placebo	Locally advanced (stage IB2–IIB with node- positive disease or stage III–IVA)	NR	Cost- effectiveness analysis

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Table 61: Details related to the model structures implemented in economic evaluations (n=22 studies)

Study name, Country	Model type	Health states	Cost year, ccy	Time horizon	Discount rate: for costs; for outcomes	Cycle length	Study perspective	Sensitivity and probabilistic sensitivity analyses
Resnick 2010 ⁽¹⁷⁾ , United States	NR	NR	NR, USD (\$)	NR	NR	NR	NR	NR
Rocconi 2005 ⁽¹⁶⁾ , United States	Decision analysis model	NR	2003, USD (\$)	NR	NR	NR	Third-party payer perspective	One way sensitivity analysis performed
Smith 2013 ⁽¹⁸⁾ , United States	NR	NR	2006, USD (\$)	3 years	NR	NR	NR	A series of one-way sensitivity analyses performed
Rose 2000 ⁽¹⁹⁾ , United States	NR	NR	NR, USD (\$)	NR	NR	NR	Healthcare payer perspective	NR
Perdrizet 2020 ⁽²⁰⁾ , Canada	Markov model	No disease Local or pelvic disease Paraaortic lymph node metastatic disease Death	2016, CAD	5 years	1.5% annually for outcome and cost beyond 1 year	6 months	Payer perspective	Deterministic sensitivity analyses and probabilistic sensitivity analyses performed

Rongsriyam 2020 ⁽²¹⁾ , Thailand	Decision tree model	Complete response A complete response to recurrence A complete response to the death Stable disease Stable disease to death Progressive disease to death Recurrence to death	2018, USD (\$)	3 years	3% for costs and outcomes annually	NR	Payer perspective	One-way sensitivity analyses and probabilistic sensitivity analyses performed
Manusirivithaya 2005 ⁽²²⁾ , Thailand	Decision tree analysis	Concurrent chemoradiation – Death; recurrence; No recurrence Radiation - Death; recurrence; No recurrence	NR, Thai Baht	5 years	5% annually for the cost incurred after 1 year	NR	Payer perspective	Sensitivity analyses performed
Sanif 2018 ⁽²³⁾ , Indonesia	NR	NR	2014, IDR	NR	NR	NR	NR	Sensitivity analysis performed
Chai 2016 ⁽²⁴⁾ , China	Decision tree model	NR	2012, USD (\$)	5 years	3% yearly	6 months	Payer perspective	Structural sensitivity analysis conducted

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Phippen 2012 ⁽¹⁵⁾ , United States	Modified Markov state transition model	Active treatment Completed primary treatment - (-) late bowel/(-) late bladder toxicity Completed primary treatment - (+) late bowel/(-) late bladder toxicity Completed primary treatment - (-) late bowel/(+) late bladder toxicity Completed primary treatment- (+) late bowel/(+) late bladder toxicity Dead	2011, USD (\$)	5 years	3% per year	6 months	Payer perspective	One-way sensitivity analyses assessed variations in the cost and adverse events
Phippen 2016 ⁽²⁵⁾ , US	Decision analysis model	NR	2015, USD (\$)	3 years	NR	NR	Single payer perspective	1-way sensitivity analyses performed

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Van Ballegooijen 1992 ⁽²⁶⁾ , Netherlands Linked to Koopmanschap 1992, Netherlands	NR	NR	1990, Dutch guilder (DFL)	NR	5%	Length of episode: 3 weeks	NR	Sensitivity analyses performed
Nelson 2016 ⁽²⁷⁾ , Tanzania	NR	NR	NR, USD (\$)	NR	3%	NR	Institutional perspective	NR
Jewell 2007 ⁽²⁸⁾ , US	Markov state transition model	NR	2007, USD (\$)	NR	Not performed	NR	A third party (payer) perspective	One-way sensitivity analyses performed
Lee 2015 ⁽²⁹⁾ , Korea	Modified Markov model	Active treatment Completed primary treatment without complications. Completed primary treatment with acute complications. Completed primary treatment with late complications. Death	2013, USD (\$)	5 years	5%	1 year	Payer perspective	One-way sensitivity and probabilistic sensitivity analyses

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Puspitasari 2021 ⁽³⁰⁾ , Indonesia	NR	NR	2019, USD (\$)	4 weeks	NR	NR	Healthcare perspective	Sensitivity analysis performed
Carmona 2015 ⁽³¹⁾ , US, Turkey	NR	NR	NR, USD (\$)	NR	NR	NR	NR	Sensitivity analysis performed
Van Minh 2017 ⁽³²⁾ , Vietnam	PRIME (Papillomavirus Rapid Interface for Modeling and Economics), a static model	NR	NR, USD (\$)	Lifetime	3%	5-10 years	Healthcare perspective	Sensitivity analysis performed
Katanyoo 2021 ⁽³³⁾ , Thailand	Hybrid decision tree and Markov models	Four health states No disease or disease free Disease progression Severe late side effects in terms of GI and GU systems Death	2019, USD \$	5 years	3%	6 months	Provider and societal Perspective	One-way sensitivity and probabilistic sensitivity analyses (PSA) state
Minnaar 2022 ⁽³⁴⁾ , South Africa	Markov model	NR	NR, ZAR	3 years	NR	6 months	Perspective of both public healthcare funders (the state) and private healthcare funders (medical aid scheme).	NR

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Courtney 2025 ⁽³⁵⁾ , USA	Markov model	Four health states Stable, partially responded, or completely responded disease on first-line treatment Stable, partially responded, or completely responded disease on second-line treatment Progressive disease Death	2024, USD\$	50-year	3%	1-month	US payer perspective Societal perspective	One- and three-way sensitivity analysis, and probabilistic sensitivity analysis were performed
Liu 2024 ⁽³⁶⁾ , Multinational (USA, China, Italy)	Markov model	NR	NR, USD\$	Lifetime	NR	NR	Payer perspective	Sensitivity analysis

NR: Not reported; GU: Genitourinary s; GI: Gastrointestinal

Table 62: Outcome results reported across the economic evaluations (n=22 studies)

Study name, Country	Cost year, ccy	Interventions and comparators	Total costs per patient	Total LYs per patient	Total QALYs per patient	Incremental (intervention minus comparator) – per patient			ICERs (intervention vs. comparator) – per patient		Sensitivity analysis
						Costs	LYs gained	QALYs gained	Cost per LY gained	Cost per QALY gained	
Phippen 2012 ⁽¹⁵⁾ , United States	2011, USD	Treatment arm (Gemcitabine + cisplatin - G)	\$60,974	NR	NR	NR	NR	NR	NR	\$33,080	The ICER increased to standard willingness-to-pay thresholds of 50K and 100K when QoL utility scores during G active treatment declined to 0.64 and 0.53 (baseline 0.76), respectively. The model was insensitive to changes in adverse event rates, costs of treatment, or adverse event hospitalization costs.
		Treatment arm (Cisplatin - C)	\$41,330	NR	NR						
Resnick 2010 ⁽¹⁷⁾ , United States	NR, USD	PET/CT	NR	NR	NR	NR	NR	NR	\$1,164	NR	Sensitivity analysis were performed on
		LND + PET/CT	NR	NR	NR	NR	NR	NR	\$15,186	NR	
		LND	NR	NR	NR	NR	NR	NR	\$44,040	NR	

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											pertinent uncertainties.
Rocconi, 2005 ⁽¹⁶⁾ , United States	2003, USD	RHYST	284 million/10,000 women	NR	NR	NR	NR	NR	\$41,212 (CE ratio)		A series of one-way sensitivity analyses were performed in which the value for a single estimate was varied across a reasonable range while all other estimates were maintained at their baselines.
		CTRT	508 million/10,000 women	NR	NR	NR	NR	NR	\$72,613 (CE ratio)		
		NAC	299 million/10,000 women	NR	NR	NR	NR	NR	\$43,197 (CE ratio)		
Smith 2013 ⁽¹⁸⁾ , United States	NR, USD	Concurrent and adjuvant chemoradiation with gemcitabine/ cisplatin (RT/GC + GC)	259.8 million	NR	NR	86.0 million	NR	NR	ICER per PF-LYS: 97,799 CER (comparing cost of therapy per patient with 3-year PFS): 35,335		A series of one-way sensitivity analyses were performed. First, variations of management of neutropenia and anemia with different providers may change the cost-effectiveness of treatment, so model numbers were adjusted using a
		Concurrent radiation with cisplatin (RT/C)	173.9 million						CER (comparing cost of therapy per patient with 3-year PFS): 26,853		

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											hospitalization rate of 4.3% for both arms.
Rose 2000 ⁽¹⁹⁾ , United States	NR, USD	GOG 85	689	NR	NR	9,620	NR	NR	Published: 14,576 Estimated: 2,821 Incremental cost/patient benefited: \$87,455	NR	NR
		GOG 120 (weekly Cisplatin)	1,769			2,575			Published: 2,384 Estimated: 308 Incremental cost/patient benefited: \$9,537		
		COG 120 (3-drug regimen)	1,142			9,929			Published: 9,929 Estimated: 1,281 Incremental cost/patient		

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									benefited : \$39,716		
		RTOG 9001	1,011			10676			Publishe d: 14,235 Estimate d: 2,224 Incremen tal cost/patie nt benefited : \$71,173		
		GOG 123	1,930			4,325			Publishe d: 6,758 Estimate d: 711 Incremen tal cost/patie nt benefited : \$27,031		
		SWOG 8797 (GOG109)	2,023			20,714			Publishe d: 28,770 Estimate d: 3,712 Incremen tal cost/patie		

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									nt benefited : \$115,078		
		Cisplatin + Fluorouraci I (Inpatient setting)	8,839			NR			NR		
		Cisplatin + Fluorouraci I (Outpatient setting)	3,590			NR			NR		
Perdrizet 2020 ⁽²⁰⁾ , Canada	2016, CAD	MRgBT (full population)	28,510 (95% CI: 26,290 - 30,720)	NR	Mean : 3.51 (95% CI 3.31- 3.70)	NR	NR	NR	NR	NR	Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were performed.
		MRgBT (High-risk subgroup IIB-IIIB)	31,210 (95% CI: 28,460 - 34,060)	NR	Mean : 3.42 (95% CI 3.22- 3.61)	NR	NR	NR	NR	NR	

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		CTgBT (full population)	29,910 (95% CI: 27,730 - 32,120)	NR	Mean : 3.51 (95% CI 2.97-3.33)	-1,400 (vs. MRgBT)	NR	0.36 (vs. MRgBT)	NR	MRgBT dominated	
		CTgBT (High-risk subgroup IIB-IIIB)	33,320 (95% CI 30,560 - 36,020)	NR	Mean : 2.98 (95% CI 2.79-3.18)	-2,110 (vs. MRgBT)	NR	0.44 (vs. MRgBT)	NR	MRgBT dominated	
		2DBT (full population)	30,550 (95% CI: 28,330 - 32,750)	NR	Mean : 3.13 (95% CI 2.96-3.32)	-2,040 (vs. MRgBT)	NR	0.38 (vs. MRgBT)	NR	MRgBT dominated (<\$10,000)	
		DBT (High-risk subgroup IIB-IIIB)	33,930 (95% CI: 31,140 - 36,620)	NR	Mean : 2.97 (95% CI 2.78-3.17)	-2,720 (vs. MRgBT)	NR	0.45 (vs. MRgBT)	NR	MRgBT dominated (<\$10,000)	
Rongsriyam	2018, USD	CCRT	Provider viewpoint	NR	Provider viewpoint	NR	NR	NR	NR	Ref	One-way sensitivity

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2020 ⁽²¹⁾ , Thailand			ints: 3,058		points : 2.314 80						analysis (PSA) was performed.
			Societ al viewpo ints: 4,309		Socie tal view- points : 2.314 80						
			All stage (PP): 4,336		All stage (PP): 2.120 24						
			Stage II (ITT): 4,255		Stage II (ITT): 2.406 35						
			Stage III-IVA (ITT): 4,288		Stage III- IVA (ITT): 2.226 38						

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		CCRT/ACT	Provider viewpoints: 6,896 Societal viewpoints: 7,480 All stage (PP): 7,485 Stage II (ITT): 7,401 Stage III-IVA (ITT): 7,665	NR	Provider viewpoints : 2.320 45 Societal viewpoints : 2.320 45 All stage (PP): 2.121 89 Stage II (ITT): 2.294 22 Stage III- IVA (ITT):	NR	NR	NR	NR	Provider viewpoints: 679,292 Societal viewpoints: 569,575 All stage (PP): 1,908,083 Stage II (ITT): - 28,050 Stage III-IVA (ITT): 66,820	

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					2.276 99						
Manusiri vithaya 2005 ⁽²²⁾ , Thailand	NR, Baht	Concurrent chemoradi ation branches FN-Death	140,28 8.83 Baht	In mont hs:0	In mont hs: 1.34	NR	NR	NR	US \$2,384 - US \$22,770	NR	Sensitivity analysis was performed.
		FN- recurrence	211,09 2.23 Baht	22	15.46						
		FN-No recurrence	157,55 8.44 Baht	62	61.34						
		NFN- Recurrence	175,41 8.63 Baht	22	15.62						
		NFN-not recurrence	121,88 4.84 Baht	62	61.50						
		No side effect- recurrence	173,36 2.43 Baht	22	15.78						
		No side effect not recurrence	119,82 8.64 Baht	62	61.66						
		Radiothera py No side effect- recurrence	99,475 .91 Baht	22	15.96	NR	NR	NR	NR	NR	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

		No side effect-not recurrence	45,942.12 Baht	62	61.84						
Sanif 2018 ⁽²³⁾ , Indonesia	2014, IDR	Chemother apy: complete response	1,647,140,590 IDR	NR	NR	NR	NR	NR	1.7 (CER)		Sensitivity analysis was performed. Through sensitivity analysis, chemotherapy, and chemoradiation toward salary, investment, operational, stationery, electricity, and any other budgets which are not medical budget. From the CER value, chemotherapy has a higher value in chemoradiation without salary, investment, and maintenance budget.
		Chemoradi otherapy: complete response	2,419,343,010 IDR	NR	NR				1.3 (CER)		
		Chemother apy: Partial response	780,224,490 IDR	NR	NR	NR	NR	NR	1.8 (CER)		
		Chemoradi otherapy: Partial response	483,868,602 IDR	NR	NR				6 (CER)		
		Chemother apy: No response	390,112,245 IDR	NR	NR	NR	NR	NR	7.3 (CER)		
		Chemoradi otherapy: No response	0 IDR	NR	NR				NR		
		Chemother apy: Progressive	43,345,805 IDR	NR	NR	NR	NR	NR	65 (CER)		
		Chemoradi otherapy: Progressive	241,934,301 IDR	NR	NR				13 (CER)		

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Chai 2016 ⁽²⁴⁾ , China	2012, USD	Radical hysterectomy combined with adjuvant EBRT	\$10,872	NR	4.37	\$5,173	NR	-0.07	NR	-\$76,453	A structural sensitivity analysis was conducted. The impact of the cost of surgery on the CE was evaluated by sensitivity analysis. In this analysis, the total cost was highly affected by the surgery cost.
		Radical radiotherapy	\$5,169	NR	4.44						
Phippen 2016 ⁽²⁵⁾ , US	2015, USD	Routine Surveillance	\$15,450	NR	Effectiveness: 0.68	\$1,129	NR	Incremental effectiveness: 0.06	ICER: \$20,761	NR	In sensitivity analysis, when the probability of recurrence following hysterectomy was assumed to be less than 37%, PET/CT was a dominant strategy (less expensive and more effective than standard surveillance).
		PET/CT at 3 months	\$16,579	NR	Effectiveness: 0.74						
		PET	NR	NR			NR		ICER: \$12,364	NR	
Van 1992 ⁽²⁶⁾ , Netherlands	1990, Dutch guild	Screening policy	682	NR	NR	289	13,321	NR	21,713 (Dfl)	NR	The main uncertainty in the analysis of national hospital data on the
		No early detection	393	NR	NR						

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

	er (Dfl)										number of hospital days is the number of admission days per brachytherapy session in primary therapy
Nelson 2016 ⁽²⁷⁾ , Tanzania	NR, USD	Discounted life-years: Intervention	\$185,9 80	NR	NR	\$6,107	Incremental effectiveness: 27.9	NR	ICER: \$219 Status quo: Dominant	NR	NR
		Discounted life-years: Status quo	\$179,8 73								
		Number of cancer- related deaths: Intervention	\$185,9 80			\$6,107	Incremental effectiveness: 1.3	NR	ICER: \$4597 Status quo: Dominant	NR	
		Number of cancer- related deaths: Status quo	\$179,8 73				NR			NR	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Jewell 2007 ⁽²⁸⁾ , US	2007, USD	Surgery + Adjuvant therapy (RH + TA)	Mean cost: \$27,840	NR	NR	NR	NR	NR	\$63,689 (ICER/LYS)	NR	Sensitivity analysis was performed around survival estimates for CR. When the OS of patients receiving CR with a true negative PET/CT was lowered from 79% to 70%, the ICER of RH + TA compared to CR dropped to \$17,242 per YLS. When the OS of this group was raised to 85%, CR was the dominant strategy. When the cost of adjuvant simple hysterectomy (\$15,276) was applied to all patients treated with CR, RH+TA became the dominant strategy (less expensive and
		Chemoradiation (CR)	Mean cost: \$21,403	NR	NR						

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											more effective than CR).
Lee 2015 ⁽²⁹⁾ , Korea	2013, USD (\$)	Pelvic CRT	\$12,960	NR	3.755	921	NR	0.048	NR	\$19,505/QALY	Under deterministic sensitivity analyses, the model was relatively sensitive to survival reduction in patients who undergo pelvic CRT alone despite having occult PALN metastasis. A probabilistic sensitivity analysis demonstrated the robustness of the case results, with a 91% probability of cost-effectiveness at the willingness-to-pay thresholds of \$60,000/QALY.
		Nodal staging surgery followed by extended-field CRT	\$13,881	NR	3.803						
Puspitar 2021 ⁽³⁰⁾ ,	2019, USD (\$)	Chemoradiation	\$3,231 (Average cost	NR	NR	NR	NR	\$48.6 cost saved for each percent	ICER per %CR (complete response): \$48.60		Sensitivity analysis was conducted to measure and

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Indonesia			per patient)					increase in CR (complete response).			evaluate uncertainty. There were four factors that had the greatest influence on the ICER: the cost of radiotherapy had the greatest influence, followed by inpatient services, laboratory examination, and chemotherapy drugs.
		Radiotherapy	\$2,944 (Average cost per patient)	NR	NR						
Carmona 2015 ⁽³¹⁾ , US, Turkey	NR, USD (\$)	Conventional RT + Gemcitabine/ Cisplatin	\$196.1 M (million)	NR	NR	NR	NR	NR	\$26,227	NR	Sensitivity analysis was performed.
		Conventional RT + Cisplatin	\$173.1 M	NR	NR						
		IMRT + Gemcitabine/ Cisplatin	\$257.9 M	NR	NR				NR		
		IMRT + Cisplatin	\$238.5 M	NR	NR						
Van Minh 2017 ⁽³²⁾ , Vietnam		HPV vaccine with negotiated price	NR	NR	NR	NR	NR	NR	Incremental cost per discounted life	NR	Model uncertainty was explored by varying parameters

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		from GAVI (13.65 US\$ for 3 doses)							saved: \$401		
	NR, USD (\$)	Cervarix vaccine with 106.8 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted life saved: \$97,619		
		Gardasil vaccine with 167.4 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted life saved: \$161,388		
		HPV vaccine with negotiated price from GAVI (13.65 US\$ for 3 doses)	NR	NR	NR				Incremental cost per discounted life year saved: \$20		
		Cervarix vaccine with 106.8 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted life year		
											governing vaccine delivery and treatment costs according to the scenarios above. Vaccine prices were also varied between the Gavi negotiated price of United States Dollar (USD) 4.55 per dose, the market price of Cervarix in Vietnam of USD 35.60 per dose and the market price of Gardasil in Vietnam of USD 55.80 per dose.

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									saved: \$4,768		
		Gardasil vaccine with 167.4 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted life year saved: \$7,882		
		HPV vaccine with negotiated price from GAVI (13.65 US\$ for 3 doses)	NR	NR	NR		NR	NR	Incremental cost per discounted DALY averted: \$18		
		Cervarix vaccine with 106.8 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted DALY averted: \$4,397		
		Gardasil vaccine with 167.4 US\$ for 3 doses	NR	NR	NR				Incremental cost per discounted DALY averted: \$7,269		

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Katanyo o 2021 (33), Thailand	2019, USD \$/THB	No Investigation	NR	NR	QALY : 3.70	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): NR Dominated	The most meaningful parameter which influenced the ICER values to be positive value for using diagnostic tests were DFS for patients who had positive finding at PALN by CT regardless of TP or FP result. When this value was at the lower bar of 95% CI, the ICER values were increased to about 700% by decreasing the cost and gaining QALYs for CT with no LL.
		Provider	US\$/T HB: 8,026/ 256,829	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB: 11,444 /366,202	NR	NR	NR	NR	NR	NR	NR	
		CT without LL	NR	NR	QALY : 3.63	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -29,679/ -949,740 Dominated	
		Provider	US\$/T HB: 9,643/ 308,569	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB:13, 279/424,927	NR	NR	NR	NR	NR	NR	NR	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

		CT with LL	NR	NR	QALY : 3.62	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -23,505/ -752,152 Dominated	
		Provider	US\$/T HB: 9,619// 307,81 4	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB:13, 179/42 1,724	NR	NR	NR	NR	NR	NR	NR	
		MRI without LL	NR	NR	QALY : 3.63	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -32,536/ -1,041,160 Dominated	
		Provider	US\$/T HB: 9,852/ 315,27 2	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB: 13,466 /430,9 18	NR	NR	NR	NR	NR	NR	NR	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

		MRI with LL	NR	NR	QALY : 3.62	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -26,340/ -842,864 Dominated	
		Provider	US\$/T HB: 9,874/ 315,983	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB: 13,431/ 429,796	NR	NR	NR	NR	NR	NR	NR	
		PET/CT without LL	NR	NR	QALY : 3.65	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -87,656/-2, 804,992 Dominated	
		Provider	US\$/T HB: 11,862/ 379,588	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB: 15,446/ 494,270	NR	NR	NR	NR	NR	NR	NR	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

		PET/CT with LL	NR	NR	QALY : 3.63	NR	NR	NR	NR	ICER (US\$ per QALY/THB per QALY): -60,586/ -1,938,750 Dominated	
		Provider	US\$/T HB: 12,051 /385,6 24	NR	NR	NR	NR	NR	NR	NR	
		Society	US\$/T HB: 15,620 /499,8 24	NR	NR	NR	NR	NR	NR	NR	
		CT									
		Incidence of PALN metastasis of 16%	Cost per case detect ed US\$/T HB: 154,85 8/4,95 5,443	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 146,832/4,6 98,614	
		Incidence of PALN metastasis of 30%	Cost per case detect ed US\$/T	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 74,565/2,38 6,074	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

			HB: 82,591 /2,642, 903								
		MRI									
		Incidence of PALN metastasis of 16%	Cost per case detect ed US\$/T HB: 167,14 4/5,34 8,619	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 159,118/5,0 91,789	
		Incidence of PALN metastasis of 30%	Cost per case detect ed US\$/T HB: 89,114 /2,852, 597	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 81,118/2,59 5,767	
		PET/CT									
		Incidence of PALN metastasis of 16%	Cost per case detect ed US\$/T HB:	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 148,988/4,7 67,609	

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

			157,014/5,024,438								
		Incidence of PALN metastasis of 30%	Cost per case detected US\$/THB: 83,741/2,679,700	NR	NR	NR	NR	NR	NR	ICER US\$/THB: 75,715/2,422,871	
Minnaar 2022 ⁽³⁴⁾ , South Africa	NR, ZAR	Government									NR
		mEHT	412,433.37 ZAR	NR	4.84	36,836.65 ZAR	NR	-0.24	NR	ICER: Dominated (CRT)	
		CRT	449,290.02 ZAR	NR	4.60						
		Private Payer									
		mEHT	579,998.97 ZAR	NR	4.84	37,422.82 ZAR	NR	-0.24	NR	ICER: Dominated (CRT)	
		CRT	617,421.79 ZAR	NR	4.60						
Courtney 2025 ⁽³⁵⁾ , USA	2024, USD \$	Payer perspective									One- and three-way sensitivity analysis:

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

		Pembrolizu mab + CCRT	\$363,2 00	NR	11.90	\$257,0 00	NR	1.40	NR	\$183,400	The monthly cost of pembrolizumab or maximum allowable duration would have to decrease from \$16 990 to \$9190 (45.6% reduction) or from 24 months to 10 months, respectively, to become cost- effective at a WTP threshold of \$100 000 per QALY. Probabilistic sensitivity analysis: at a WTP threshold of \$100 000 per QALY, the probability that concurrent and adjuvant pembrolizumab would be the cost-effective option was 37.3%
		Placebo + CCRT	\$106,2 00	NR	10.50	NR	NR	NR	NR	NR	
		Societal perspective									
		Pembrolizu mab + CCRT	NR	NR	NR	NR	NR	NR	NR	\$199,100	

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Liu 2024 ⁽³⁶⁾ , Multinational (USA, China, Italy)	NR, USD \$	Payer perspective in USA									
		Pembrolizu mab + CCRT	\$346,479	3.11	2.52	NR	NR	NR	\$111,499	\$137,500	Pembrolizumab- CCRT was exhibited cost- effectiveness opportunities of 62.68% at the selected WTP threshold of \$150,000
		Payer perspective in Europe (Italy)									
		Pembrolizu mab + CCRT	\$236,776	2.81	2.30	NR	NR	NR	\$84,192	\$102,758	Pembrolizumab- CCRT was exhibited cost- effectiveness opportunities of 12.53% at the selected WTP threshold of \$43,749
		Payer perspective in Asia (China)									
		Pembrolizu mab + CCRT	\$29,027	2.12	1.79	NR	NR	NR	13,726	\$16,217	Pembrolizumab- CCRT was exhibited cost- effectiveness opportunities of 75.23% at the selected WTP threshold of \$37,766

2DBT: 2-Dimensional brachytherapy; ACT: Adjuvant chemotherapy; CCRT: Concurrent chemoradiation; CE: Cost-effectiveness; CER: Cost-effectiveness ratio; CI: Confidence interval; CT: Computed tomography; CTgBT: Computed tomography-guided brachytherapy; CTRT: Chemoradiation therapy; Dfl: Dutch Guilder (currency); EBRT: External beam

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radiation therapy; FN: Febrile neutropenia; ICER: Incremental cost-effectiveness ratio; ITT: Intent to treat; LL: laparoscopic lymphadenectomy; LND: Lymph node dissection; LY: Life year; LYS: Life-year saved; MRgBT: Magnetic resonance-guided brachytherapy; MS: Mean survival; NAC: Neoadjuvant chemotherapy; NFN: Non-febrile neutropenia; NR: Not reported; PET: Positron emission tomography; PF: Progression-free; PFS: Progression-free survival; PP: Per-protocol; QALY: Quality-adjusted life year; QoL: Quality of life; RHYST: Radical hysterectomy with pelvic and para-aortic lymphadenectomy followed by tailored chemoradiation therapy; WTP: willingness to pay. *Median overall survival reported

Table 63: Critical appraisal of the included economic evaluations (n=22 studies)

Questions	Phippen 2012	Resnick 2010	Rocconi 2005	Smith 2013	Rose 2000	Perdrizet 2020	Rongsriyam 2020	Manusirivithaya 2005	Sanif 2018	Chai 2016	Phippen 2016	Jewell 2007	Van 1992,	Nelson 2016	Katanyoo 2021	Minnaar 2022	Lee 2015	Puspitasari 2021	Carmona 2015	Van Minh 2017	Courtney 2025	Liu 2024
Was a well-defined question posed in answerable form?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was a comprehensive description of the competing alternatives given?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓/X
Was the effectiveness of the programme or services established?	✓	X	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓/X	✓	✓

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Were all the important and relevant costs and consequences for each alternative identified?	✓	X	✓	✓/X	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓/X	✓	✓	✓/X
Were costs and consequences measured accurately in appropriate physical units?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓/X
Were the cost and consequences valued credibly?	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were costs and consequences adjusted for differential timing?	✓	X	X	X	✓	✓	✓	✓	✓	X	✓	X	X	✓	✓	✓	X	X	X	X	✓	X	✓/X
Was an incremental analysis of costs and consequences of	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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alternatives performed?																						
Was allowance made for uncertainty in the estimates of costs and consequences?	✓	X	✓	✓	X	✓	✓	✓	✓/X	✓	✓	✓	✓	X	✓	X	✓	✓	✓	✓	✓	✓
Did the presentation and discussion of study results include all issues of concern to users?	✓	✓	✓	✓	✓	✓	✓	✓	✓/X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓/X	✓	✓	✓/X

X, no (item not properly addressed); ✓, yes (item properly addressed); ✓/X, partially (item partially addressed)

3.1.5 Technology appraisal reviews

NICE

The systematic search of relevant technology appraisals (TA) initially resulted in the retrieval of 34 guidance documents. However, after a detailed evaluation of the patient population, the review did not identify any comparator TA that strictly matched our PICOTS. While one TA matched the PICOTS criteria, it is currently in progress and expected to be published on 15th October 2025.

SMC

The systematic search of relevant TAs did not identify any submission that strictly matched our PICOTS.

3.2 Health-related quality-of-life studies

3.2.1 Summary

An SLR was conducted to identify evidence for utility and HRQoL in LACC. Searches were run in October 2021, updated in August 2023, and again in February 2025. In total, 71 unique studies were identified as appropriate to provide evidence for utility and HRQoL in LACC. Almost all (n=68) only reported HRQoL measures. Only three studies identified directly reported health state utility values based on EQ-5D, based in Thailand, Indonesia and Canada.^(33, 37, 38) Only the Indonesian study focussed on later-stage LACC patients comparable with the population of interest in the present analysis. No studies identified were UK based.

Katanyoo (2022)⁽³⁹⁾ explored multiple different EQ-5D models in LACC using a Thai value set. All the approaches were significantly differentiated for disease status (i.e., treatment, disease-free, and progression) and presence of symptoms (i.e., no symptoms, one symptom, and >1 symptoms).

None of the literature identified in the SLR was deemed suitable for use in the evaluation of pembrolizumab with CCRT in stage III-IVA LACC in England and Wales.

3.2.2 Search Strategy

An SLR was performed to identify published studies on health-related quality of life (HRQoL) / utility in adult patients with LACC. The same data sources were searched as for the SLR of published cost-effectiveness studies in section 3.1.2.

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The search strategies used for retrieving information from the published economic literature are provided in .

Table 64: Summary of search hits retrieved from Embase® and MEDLINE® searched via embase.com (Database inception to 20th February 2025) – Humanistic review

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

#12	#10 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	111
#13	#11 OR #12	124
#14	#10 NOT #13 – Database inception to 23-08-2023	3,705
#15	#10 NOT #13 – 23-08-2023 to 20-02-2025	604
#16	#14 OR #15	4,309

Table 65: Summary of search hits retrieved from MEDLINE® In-Process searched via PubMed® – Humanistic review

No	Search terms	Hits
#1	"uterine cervix cancer"	503
#2	"cervical tumor" OR "cervical neoplasm"	1,315
#3	(cervi* AND (cancer* OR oncolog* OR neoplas* OR carcinom* OR malignan* OR tumor* OR tumour* OR mass* OR growth* OR cyst* OR adenocarcinom* OR squamous))	200,991
#4	#1 OR #2 OR #3	200,991
#5	advanc* OR malignan* OR metastat* OR unopera* OR ("non" resect*) OR nonresect* OR unresect* OR inopera* OR refractory OR relapsed OR ("late" stage) OR "stage ib2" OR "stage iia" OR "stage iia1" OR "stage iia2" OR "stage iib" OR "stage iiaa" OR "stage iibb" OR "stage iva" OR "stage ii" OR (stage AND ii) OR "stage 2" OR "stage-2" OR "stage iii" OR (stage AND iii) OR "stage 3" OR "stage-3" OR "stage iv" OR (stage AND iv) OR "stage 4" OR "stage-4" OR "stage b" OR "stage c" OR "stage d" OR "stage-b" OR "stage-c" OR "stage-d" OR (stage AND ("ii" OR "iii" OR "iv" OR "2" OR "3" OR "4" OR "b" OR "c" OR "d" OR "t2" OR "t2a" OR "t2a1" OR "t2a2" OR "t2b" OR "t3" OR "t3a" OR "t3b" OR "t4" OR "n1" OR "n2" OR "n3" OR "m0" OR "m1" OR "high")) OR "distant metastasis" OR "non-metastatic" OR "non metastatic" OR "metastatic" OR "locally advanced" OR ("local" "advanced") OR "stage two" OR "stage three" OR "stage four" OR (("high-risk" OR "high risk") ("locally advanced" OR "advanced"))	4,482,192
#6	#4 AND #5	69,382
#7	"quality of life" OR "quality-of-life" OR "qol" OR "hrqol" OR "hqol" OR "short form 36" OR "short form 36" OR "sf36" OR "sf-36" OR "sf 36" OR "short form 12" OR "short form 12" OR "sf12" OR "sf-12" OR "sf 12" OR "short form 6" OR "sf6" OR "sf-6" OR "sf 6" OR "euroqol" OR euro*qol OR "eq5d" OR "eq-5d" OR "eq 5d" OR "fact-g" OR "functional assessment of cancer therapy" OR "whoqol-bref" OR "fact-cx" OR rosser OR ((visual NEXT/1 analog*) AND (analog* NEXT/1 scale*))	522,784
#8	(utilit* (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)) OR "health utility index" OR "hui" OR (utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*) OR (("health" OR "health") AND (state NEXT/1 utilit*)) OR ((health NEXT/1 state*) AND (state* NEXT/1 preference*)) OR "quality adjusted life year" OR "quality adjusted life" OR ("quality adjusted" NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly* OR "health survey" OR (health utility*) OR "wellbeing" OR (quality well*being) OR (willingness pay) OR (standard gamble) OR disutili* OR (time trade*off) OR ("discrete choice" NEXT/1 experiment*)	552,825
#9	#7 OR #8	1,007,071
#10	#6 AND #9	2,603
#11	#10 AND (inprocess[sb] OR pubstatusaheadofprint) [Date: 23 rd August 2023]	95

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

#12	#10 AND (inprocess[sb] OR pubstatusaheadofprint) [Date: 20 th February 2025]	18
#13	#11 OR #12	113

Table 66: Summary of search hits retrieved from CENTRAL and CDSR searched via Cochrane Library (Database inception to 20th February 2025) – Humanistic review

No	Search terms	Hits
#1	MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees	3,457
#2	"cervical tumor" or "cervical neoplasm"	44
#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)	8,994
#4	#1 or #2 or #3	8,994
#5	advanc* or malignan* or metastat* or unopera* or ("non" near/5 resect*) or nonresect* or unresect* or inopera* or refractory or relapsed or ("late" near/2 "stage") or "stage ib2" or "stage iia" OR "stage iia1" OR "stage iia2" OR "stage iib" OR "stage iia" OR "stage iib" OR "stage iva" OR (stage AND ii) OR "stage 2" OR "stage-2" OR "stage iii" OR (stage AND iii) OR "stage 3" OR "stage-3" OR "stage iv" OR (stage AND iv) OR "stage 4" OR "stage-4" OR "stage b" OR "stage c" OR "stage d" OR "stage-b" OR "stage-c" OR "stage-d" OR (stage NEAR/3 ("ii" OR "iii" OR "iv" OR "2" OR "3" OR "4" OR "b" OR "c" OR "d" OR "t2" OR "t2a" OR "t2a1" OR "t2a2" OR "t2b" OR "t3" OR "t3a" OR "t3b" OR "t4" OR "n1" OR "n2" OR "n3" OR "m0" OR "m1" OR "high")) OR "distant metastasis" OR "non-metastatic" OR "non metastatic" OR "metastatic" OR "locally advanced" OR ("local" NEAR/2 "advanced") OR "stage two" OR "stage three" OR "stage four" OR (("high-risk" OR "high risk") NEAR/2 ("locally advanced" OR "advanced"))	269,907
#6	#4 AND #5	3,909
#7	"quality of life" OR "quality-of-life" OR "qol" OR "hrqol" OR "hqol" OR "short form 36" OR "short form 36" OR "sf36" OR "sf-36" OR "sf 36" OR "short form 12" OR "short form 12" OR "sf12" OR "sf-12" OR "sf 12" OR "short form 6" OR "sf6" OR "sf-6" OR "sf 6" OR "euroqol" OR euro*qol OR "eq5d" OR "eq-5d" OR "eq 5d" OR "Functional Assessment of Cancer Therapy" OR "WHOQOL-BREF" OR "Cervical Cancer Concerns Questionnaires" OR "Functional Assessment of Cancer Therapy-Cervix Cancer" OR "FACT-Cx" OR "rosset" OR (visual NEXT/1 analog* AND analog* NEXT/1 scale*)	275,431
#8	(utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)) OR "health utility index" OR "hui" OR utilit* NEXT/1 (score* OR value* OR evaluation*) OR health NEXT/2 utilit* OR ("health" OR "health" AND state NEXT/1 utilit*) OR (health NEXT/1 state* AND state* NEXT/1 preference*) OR "quality adjusted life year" OR "quality adjusted life" OR "quality adjusted" NEXT/1 survival* OR qaly* OR qald* OR qale* OR qtime* OR "disability adjusted life" OR daly* OR "health survey" OR health*year*equivalent OR health NEAR/2 utility* OR "wellbeing" OR quality NEAR/2 well*being OR willingness NEAR/2 pay OR standard NEAR/2 gamble OR disutili* OR time NEAR/2 trade*off OR 'discrete choice' NEXT/1 experiment*	464,974
#9	#7 or #8	618,830
#10	#6 AND #9 in Trials and Reviews [Database inception to August 2023]	759
#11	#6 AND #9 in Trials and Reviews [August 2023 to Feb 2025]	186
#12	#10 OR #11	945

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3.2.3 Study selection

Studies identified in the literature had to meet pre-defined eligibility criteria in the review (Table 67). This review was carried out in strict accordance with the NICE recommendations. First, two independent reviewers reviewed abstracts of citations identified through the searches for inclusion based on title and abstract alone; a third reviewer reconciled any discrepancies. Next, full-text copies of studies that met the screening criteria were obtained and screened by two independent reviewers; a third reviewer reconciled any discrepancies. Finally, two independent reviewers extracted data from the studies, and a third independent reviewer reconciled any discrepancies. The different phases of the literature review are outlined in Figure 82 in section 3.1.3.

Table 67: Key inclusion and exclusion criteria (PICOTS) – HRQoL review

Criteria	Inclusion	Exclusion	Rationale
Population	Disease: Patients with high-risk (stage IB2-IIB with node-positive disease or stage III-IVA), locally advanced cervical cancer	Patients with other types of cancer, e.g., ovarian, uterine, vaginal, vulvar, OR overall cancer with no further segregation Patients with disease stage IA and/or IB1 only Patients with disease stage IVB only Patients with disease stage unclear. Patients with no subgroup data for cervical cancer (stage IB2-IVA)	Cancer category and disease staging included and excluded according to the KEYNOTE trial.
	Age: Adult (≥ 18 years) patients	Studies evaluating children	(-)
	Race: No restriction	Not applicable	(-)
	Gender: No restriction	Not applicable	(-)
Line of therapy	First-line only OR treatment naïve patients (that have not received prior systemic therapy)	Studies evaluating second-line or later line therapy only Studies with a mixed line of treatment but with no subgroup analysis reported for the first-line category Studies with the line of therapy unclear	Patient population aligned with the KEYNOTE trial.
	Please refer to section 3.1.3, for additional details of the selection criteria		
Interventions and comparators	No restriction	(-)	(-)

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Outcomes	Type of treatments administered Type of QoL scales, e.g., European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EORTC QLQ-Cervical Cancer Module (EORTC QLQ-CX24), Functional Assessment of Cancer Therapy (FACT) Additional quality of life measurement scales Pre-treatment/baseline scores Post-treatment scores at different time points Change from baseline (absolute differences) at different time points Percentage change from baseline (fraction differences) at different time points, p-value, 95% CI The proportion of patients reporting an improvement or deterioration in the quality of life at different time points	Studies not reporting relevant outcomes of interest were excluded	The standard set of outcomes extracted in these reviews
Study design	Randomized controlled trials Non-randomized controlled trials Cohort studies (retrospective observational) Cohort studies (prospective observational) Single-arm studies Database/registry-based studies Questionnaires/surveys Case-control and cross-sectional studies Literature reviews/systematic reviews/relevant general reviews for bibliographic searching	Case reports Case series	The standard set of study designs considered in these reviews

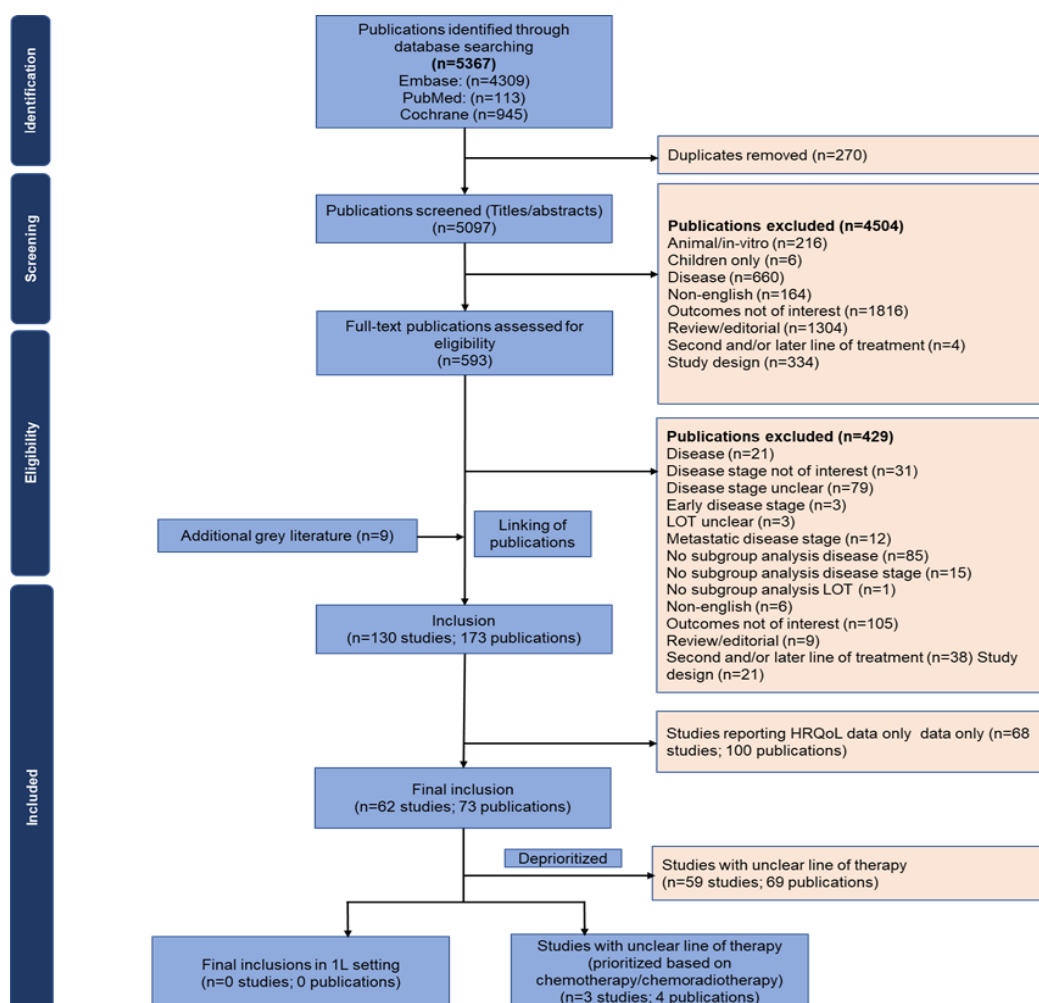
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Timeframe	Original review: Database inception to October 31 st , 2021 Update review: 1 st Nov 2021-23 rd Aug 2023 2 nd update: 24 th August 2023 – 20 th February 2025	Not applicable	To retrieve comprehensive and latest evidence to support the review objectives
Country	No restriction Global approach followed	Not applicable	
Language	Studies with full-texts published in the English language only	Studies with full-texts published in the non-English language	(-)
Publication type	Peer-reviewed journal articles and conference abstracts (searched for the previous eight years, 2018-2025)	Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews	(-)

3.2.4 Search results

Figure 84 shows the flow of studies through the literature review process. The literature search yielded 5,367 separate publications. Due to the coverage overlap between the databases, 270 abstracts were duplicates. Following the first pass of the publications, 593 potentially relevant references were identified. Full-text reports of these publications were retrieved for a more detailed evaluation. In total, 173 relevant publications were identified, including 9 retrieved through the searching of conference proceedings and bibliographies of relevant articles. Multiple reports (journal articles, conference abstracts) of the same studies were linked together so that each study rather than each report is the unit of interest in the systematic review. This resulted in the inclusion of 130 unique studies (173 publications).

Figure 84: Flow of studies through the systematic review process



Sixty-eight studies reported on health-related quality of life data only (as presented in the pale orange box) and were subsequently excluded from the SLR. Of these, 55 were identified in the original SLR conducted in August 2023 and are summarised in Table 68. None of the additional 13 studies identified in the updated SLR in February 2025 reported UK data and they were therefore considered to be highly unlikely to contain any information of direct relevance to the present decision problem.

62 studies (73 publications) reported utility values and therefore met the final inclusion criteria. However it was not clear in any of these studies whether they referred to the first-line treatment setting in LACC. Three of these studies (4 publications) were prioritised as they reported utility values relating to chemotherapy/chemoradiotherapy, which are commonly used as first-line treatments in high-risk LACC (in line with the prioritisation criteria explained in section 3.1.3). These 3 studies are summarised in Table 69 and detailed study outcomes are listed in Table 70.

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Table 68: Summary of the published studies identified in August 2023 reporting health-related quality of life data only; key study and patient characteristics (n=55 studies)

Study name, Country	Publication type	Treatments evaluated	Relevant disease stage	Description of key patient characteristics	Study design
Dahiya 2016 ⁽⁴⁰⁾ , India	Peer-reviewed journal article	Radiotherapy + Chemotherapy Radiotherapy Radiotherapy after surgery Palliative treatment	High-risk, locally advanced, and advanced	Mean age (SD): 52.28 (11.29) years ECOG PS (0/1/2): NR Disease stage: (IIB/IIIB/IIIA+IVA): 40%/53.73%/6.27% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational
Gupta 2009 ⁽⁴¹⁾ , India	Peer-reviewed journal article	Epoetin Beta + Pelvic irradiation + Cisplatin (Treatment arm) Standard supportive care (control arm)	High-risk, locally advanced, and advanced	Mean age (SD): 48.21 (NR) years ECOG PS (0/1/2): NR Disease stage (IIB/IIIB): 41.7%/58.2% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Randomized controlled
Shanmugam 2019 ⁽⁴²⁾ , India	Peer-reviewed journal article	Concurrent chemoradiation therapy (CCRT) – Cisplatin and Paclitaxel Preoperative chemoradiation (PCRT) followed by a radical hysterectomy Preoperative chemotherapy (PCHEMO) followed by radical hysterectomy	High-risk and locally advanced	Mean age (SD): 47.67 (5.7) years ECOG PS (1/2): 85%/15% Disease stage (IB2/IIA2/IIIB): 12%/15%/73% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Randomized controlled

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Subramaniyan 2019 ⁽⁴³⁾ , India	Peer-reviewed journal article	Chemoradiotherapy	High-risk, locally advanced, and advanced	Mean age (range): 51.2 (25-65) years ECOG (0/1/2): NR Disease stage (IB2-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational
Kumar 2021 ⁽⁴⁴⁾ , India	Peer-reviewed journal article	Chemoradiation	Stage IB2-IVB: High-risk, locally advanced, advanced, and metastatic Stage IB1 also included (not of interest)	Median (range) age: 49.5 (36-63) years ECOG PS (0/1/2/3): NR Disease stage (I/II/III/IV): 13.2%/49%/35%/2.8% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational
Noviyani 2017 ⁽⁴⁵⁾ , Indonesia	Peer-reviewed journal article	Paclitaxel cisplatin Chemotherapy regimen	Advanced	Mean age (SD): NR ECOG PS (0/1/2): NR Disease stage (IIIB): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational
Saraswati 2021 ⁽⁴⁶⁾ , Indonesia	Peer-reviewed journal article	Medical therapy (paracetamol and codeine) + electroacupuncture Medical therapy (paracetamol and codeine)	Locally advanced	Mean age (SD): 48.9 (9.2) years ECOG PS (0/1/2): NR Disease stage (III): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Randomized controlled

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Wang 2020 ⁽⁴⁷⁾ , China	Peer-reviewed journal article	Neoadjuvant chemotherapy with surgery TP regimen: Cisplatin + Paclitaxel TC regimen: Carboplatin + Paclitaxel TN regimen: Nedaplatin + Paclitaxel Surgery alone (Control)	High-risk/early stage	Mean age (SD): 48 (5) years ECOG PS (0/1/2): NR Disease stage (IB2/IIA/IIB): 39.1%/35.8%/15% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Retrospective observational
Wu 2021 ⁽⁴⁸⁾ , China	Peer-reviewed journal article	CCRT group (concurrent chemoradiotherapy alone) – platinum-based chemotherapy CCRT-ACT group (adjuvant chemotherapy after CCRT) – platinum-based chemotherapy	High-risk, locally advanced, and advanced	Median age (range): 52 (26-73) years ECOG PS (0/1/2): NR Disease stage (IB2/IIA2/IIB/IIIA/IIIB/ IVA): 6.8%/12.3%/60.4%/4.06%/14.7%/1.75% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Retrospective observational
Aishanjiang 2021 ⁽⁴⁹⁾ , China	Peer-reviewed journal article	UAIC group: Docetaxel + nedaplatin UAIC combined with intensity-modulated radiotherapy Control group: Docetaxel + nedaplatin intravenous chemotherapy combined with intensity-modulated radiotherapy UAIC: Uterine arterial interventional chemoembolization	High-risk and locally advanced	Mean age (SD): 50.4 (10) years ECOG PS (0/1/2): NR FIGO stage (IIB/IIIA/IIIB): 9.55%/62.5%/23.5% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Retrospective observational

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Vistad 2011 ⁽⁵⁰⁾ , Norway	Peer-reviewed journal article	External beam radiotherapy (EBRT) and intra-cavitary radiotherapy (ICRT)	High-risk, locally advanced, and advanced	Median age (range): 62 (37-92) years ECOG PS (1/2): NR Disease stage (IB2/IIB/IIIA-IIIB/IVA): 14%/72%/13%/1% Smoking status (daily smokers): 48% HPV status: NR Race (White/Caucasian): NR	Cross-sectional questionnaire-based
Nunes 2020 ⁽⁵¹⁾ , Brazil	Peer-reviewed journal article	(NACT) Neoadjuvant chemotherapy arm – Cisplatin/Gemcitabine followed by Cisplatin/Pelvic radiotherapy/Brachytherapy (CRT) Chemoradiation arm – Cisplatin/Pelvic radiotherapy/Brachytherapy	Locally advanced and advanced	Median age (SD): 53.5 (12.45) years ECOG PS (1/2): NR Disease stage (IIB/IIIA/IIIB/IVA): 42.95%/0.95%/44.75%/11.2% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Randomized controlled
Du Toit 2015 ⁽⁵²⁾ , South Africa	Peer-reviewed journal article	Radiation therapy Chemoradiation therapy Cisplatin and carboplatin chemotherapy External beam radiation therapy and brachytherapy	Stage IB2-IVB: High-risk, locally advanced, advanced, and metastatic Stage IB1 also included (not of interest)	Mean age (SD): 50.71 years ECOG PS (0/1/2/3): NR Disease stage (IB1-IVB): 100% Smoking status: NR HPV status: NR Race (White/Mixed/Black): 50%/50%/50%	Prospective observational
Akbarov 2017 ⁽⁵³⁾ , Azerbaijan	Conference abstract	Chemoradiotherapy	Locally advanced and advanced	Mean age (SD): 48 (9.8) years ECOG (0/1/2): NR Disease stage (IIB-IVA): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational

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Seppenwoolde 2021 ⁽⁵⁴⁾ , United States	Peer-reviewed journal article	EBRT techniques, including volumetric modulated arc therapy (VMAT) and adaptive radiotherapy (ART)	Stage IB2-IVB: High-risk, locally advanced, advanced, and metastatic (relevant cohort) Stage IB1 also included (not of interest)	Mean age (range): 54 (NR) years ECOG PS (0/1/2): NR Disease stage (IB-IVB): 100% Smoking status (Yes/No/Quit): 46%/35%/15% HPV status: NR Race (White/Caucasian): NR	Prospective observational
Ramondetta 2011 ⁽⁵⁵⁾ , United States	Conference abstract	NR	Stage IB2-IVB: High-risk, locally advanced, advanced, and metastatic (relevant cohort) Stage IA1-IB1 also included (not of interest)	Median age: 45 years ECOG PS (0/1/2): NR Disease stage (IA1-IB1/IB2-IIB/IIIA-IV): 18.5%/62%/30.4% Smoking status: NR HPV status: NR Race (White/African American/Hispanic): 16%/27%/56%	Survey-based
Salih 2009 ⁽⁵⁶⁾ , United States	Conference abstract	Laparoscopic ovarian transposition (LOT) prior to radiotherapy	Stage IB2-IIB: High-risk, early-stage, and locally advanced (relevant cohort) Stage IB1 also included (not of interest)	Mean age: 31.5 years ECOG PS (1/2): NR Disease stage (IB-IIB): 100% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational
Al-Saleh 1997 ⁽⁵⁷⁾ , Canada	Peer-reviewed journal article	Cisplatin + Etoposide	Stage IB2-IVB: High-risk, locally advanced, advanced, and metastatic (relevant cohort)	Median age: 48 (27-71) years ECOG PS (0/1/2/3): 2/20/12/4 Disease stage (I/II/III/IV): 45%/13%/26%/16% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Prospective observational

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			Stage IA1-IB1 also included (not of interest)		
Nagy 2007 ⁽⁵⁸⁾ , Romania	Peer- reviewed journal article	Chemoradiotherapy (chemotherapy with cisplatin-based regimens)	High-risk and locally advanced (complete cohort relevant)	Mean age (range): 47.2 (24-70) years ECOG (0/1/2): NR Disease stage (IIB/IIIA/IIIB): 48.5%/31.5%/20% Smoking status: NR HPV status: NR Race (White/Caucasian): NR	Randomized controlled
Mell 2017 ⁽⁵⁹⁾ , Multicenter International	Peer- reviewed journal article	Cisplatin + Intensity-modulated radiation therapy + Intracavitary Brachytherapy	Stage IB2-IVA: High-risk, locally advanced, and advanced (relevant cohort) Stage IB1 also included (not of interest)	Mean age (SD): 53.5 (12.45) years ECOG PS (1/2): NR Disease stage (IB1/IB2/IIA1/IIIB/IIIB/ IVA): 2.5%/10.2%/2.5%/64.6%/ 19.1%/2.1% Smoking status: NR HPV status: NR Race (Black/Asian/Latina- Hispanic/White/Other-Unknown): 2.1%/24.3%/9.25%/63.95%/2.9%	Single-arm (Prospective controlled)
Mileshkin 2019 ⁽⁶⁰⁾ , Multicenter International	Conference abstract	Adjuvant carboplatin/paclitaxel chemotherapy after definitive chemoradiation (one group received and other did not)	Locally advanced (complete cohort relevant)	Mean age (range): NR ECOG PS (1/2): NR Disease stage (III/IV): NR Smoking status: NR	Randomized controlled

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				HPV status: NR Race (White/Caucasian): NR	
Fokdal 2018 ⁽⁶¹⁾ , Multicenter International	Peer- reviewed journal article	External beam radiotherapy (EBRT) and concomitant chemotherapy followed by brachytherapy	Stage IB2-IVB: High-risk, locally advanced, and metastatic (relevant cohort) Stage IB1 also included (not of interest)	Median age (range): 49 (22-91) years ECOG PS (0-1/2-3): 98%/2% Disease stage (IB/IIA/IIB/IIIA/IIIB/IVA/ IVB): 19%/5%/52%/<1%/15%/3%/5% Smoking status (Smoked/quit/non-smoker): 45.8%/14.6%/35.4% HPV status: NR Race (White/Caucasian): NR	Prospective observational
Zhang 2021 ⁽⁶²⁾ , China	Peer- reviewed journal article	Vincristine + Cisplatin + IMRT IMRT	Advanced (IIIB- IV)	Mean age (SD): 66.29 (3.3) years ECOG PS (0-1/2-3): NR Disease stage (IIIB/IV): 42.2%/57.78% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective clinical trial
Ljuca 2011 ⁽⁶³⁾ , Bosnia and Herzegovina	Peer- reviewed journal article	Chemoradiotherapy	Stage IIB	Median age (range): NR ECOG PS (0-1/2-3): NR Disease stage (IIB): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective prospective study

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Zhuang 2018 ⁽⁶⁴⁾ , China	Peer-reviewed journal article	Observational group: Chemotherapy (Docetaxel + cisplatin) + Concurrent radiotherapy Control group: Chemotherapy (Cisplatin) + Concurrent radiotherapy	Advanced (II-IV)	Mean age (SD): 55.9 (7.5) ECOG PS (0-1/2-3): NR Disease stage (II/III/IV): 60.85%/22.95%/16.2% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective study
Li 2019 ⁽⁶⁵⁾ , China	Peer-reviewed journal article	Treatment group: Radiochemotherapy + autologous cytokine induced killer (CIK) cells. Control group: Radiochemotherapy	Advanced (II-IV)	Median age years: 54 ECOG PS (0-1/2-3): NR KPS score: >70 Disease stage (IIA-IIB/IIIA-IIIB/IV): 38.2%/51.7%/10.1% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Randomized non-blind study
Akbaba 2018 ⁽⁶⁶⁾ , Germany, Switzerland	Peer-reviewed journal article	Radio chemotherapy	Stage I-IV	Median age years (range): 57 (32-90) ECOG PS (0-1/2-3): NR Disease stage (I/II/IIIV): 2.4%/48.2%/18.1%/31.3% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study
Kirchheiner 2015 ⁽⁶⁷⁾ , Austria	Peer-reviewed journal article	External-beam radiotherapy (EBRT), chemotherapy and image-guided adaptive brachytherapy (IGABT)	Locally advanced (Stage IB-IVA)	Median age years (range): 54, (35-78) ECOG PS (0-1/2-3): NR Disease stage (IB/IIA/IIB/IIIA/IIIB/IVA): 8%/14%/52%/8%/16%/2% Smoking status (Smoker): NR	Prospective study

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				HPV status: NR Race (White/Caucasian): NR	
Gargiulo 2016 ⁽⁶⁸⁾ , Italy	Peer-reviewed journal article	Arm 1: Chemoradiotherapy Arm 2: Neoadjuvant chemotherapy + Radical surgery	Locally advanced (Stage IB2-IVA)	Overall: Mean age years (SD): 55 (11.0) ECOG PS (0/1/2): 93.2%/3.4%/3.4% Disease stage (IB2/IIA+IIB/IIIA+IIIB/IVA): 18.2%/65.5%/14.5%/1.8% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Observational study
Likhacheva 2013 ⁽⁶⁹⁾ , US	Peer-reviewed journal article	Chemoradiotherapy	Locally advanced (Stage IB1-IIIB)	Mean age years (range): 45 (24-75) ECOG PS (0/1/2): NR Disease stage (IB1/IB2/IIA/IIB/IIIB): 8%/33%/10%/35%/15% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective study

Xie 2020 ⁽⁷⁰⁾ , China	Peer-reviewed journal article	Arm 1: IMRT + Chemotherapy Arm 2: VMAT + Chemotherapy	Stage IIB-IIIB	Mean age years (SD): 53.63 (9.85) ECOG PS (0/1/2): NR KPS score (80-90/70-80): 48.95%/21.85% Disease stage (IIA/IIIA/IIIB): 20.85%/26.05% 52.1% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study
Locsei 2021 ⁽⁷¹⁾ , Hungary	Peer-reviewed journal article	Radio-chemotherapy (RCT)	Stage IIB-IVA	Mean age years (range): NR ECOG PS (0/1/2): NR Disease stage (IIB/IIIB/IVA): 14%/7%/78% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective Pilot Study
Sawant 2021 ⁽⁷²⁾ , India	Peer-reviewed journal article	CTRT NACT-surgery NACT-Surgery-adj RT NACT-CTRT	Stage IB2, IIA, IIB	Median age years (range): 54 (37–70) ECOG PS (0/1/2): NR Disease stage (IB2/IIA/IIB): 13%/21%/66% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective cross- sectional study

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Andring 2023 ⁽⁷³⁾ , US	Peer-reviewed journal article	Definitive chemoradiation + Brachytherapy	Stage IB3-IVA	Median age years (range): 48 (25–85) ECOG PS (0/1/2): NR Disease stage (IB3/IIB//IIIB/IIIC1/IIIC2/IVA): 6%/6%/3%/49%/21%/15% Smoking status (Smoker): NR HPV status: NR Race (White/Hispanic/African American/Asian/Pacific islander): 49%/30%/15%/3%/3%	Prospective clinical trial
Zhao 2021 ⁽⁷⁴⁾ , China	Peer-reviewed journal article	Arm 1: Endo + Radiotherapy + chemotherapy Arm 2: Radiotherapy + chemotherapy	Stage IIB-IVA	Mean age years (SD): 56.75 (6.4) ECOG PS (0/1/2): NR KPS scores mean SD: 78.1 (2.9) Disease stage (IIB/III/IVA): 25 %/9.16%/35.83% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study
Ma 2015 ⁽⁷⁵⁾ , China	Conference abstract	Arm 1: Brachytherapy and chemotherapy + Chemoradiation (Chemo RT group) Arm 2: Brachytherapy and chemotherapy + Surgery (OT group)	Stage IB2-IIA	Mean age years (range): NR ECOG PS (0/1/2): NR Disease stage (IIB/IIIB/IVA): Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study

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Benhami 2018 ⁽⁷⁶⁾ , Morocco	Conference abstract	Chemoradiotherapy	Locally advanced and metastatic	Mean age years (SD): 50 (11) ECOG PS (0/1/2): NR Disease stage (Locally advanced): 70% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective study
Case 2020 ⁽⁷⁷⁾ , US	Conference abstract	Chemoradiation	Advanced	Mean age years (range): NR ECOG PS (0/1/2): NR Disease stage (IIB/IIIB/IVA): NR Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Survey
Conway 2018 ⁽⁷⁸⁾ , Canada	Conference abstract	Chemoradiation	Locally advanced	Median age years (range): 46 (30-77) ECOG PS (0/1/2): NR Disease stage (IB/IIA-B/IIIA-B): 31%/52%/17% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study
Lachi 2013 ⁽⁷⁹⁾ , India	Conference abstract	Chemoradiotherapy	Locally advanced	Mean age years (range): 52 (34-69) ECOG PS (0/1/2): NR Disease stage (II/III): 65%/35% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective study

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Vaz 2010 ⁽⁸⁰⁾ , Portugal	Conference abstract	Chemoradiation	Locally advanced	Overall Mean age years (range): 54 (35.5-77.5) ECOG PS (0/1/2): NR Disease stage (IIB/IIIB/IVA): NR Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Case-control study
Singh 2019 ⁽⁸¹⁾ , India	Conference abstract	Neoadjuvant chemotherapy followed by chemoradiation	Locally advanced (IB2-IVA)	Median age years: 53 ECOG PS (0/1/2): NR Disease stage (II/III): 40%/53% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective study
Flores- Cisneros 2019 ⁽⁸²⁾ , Mexico	Conference abstract	Chemoradiotherapy	Locally advanced (IB2-IVA)	Mean age years (SD): 48.7 (14.4) ECOG PS (0/1/2): NR Disease stage (IB2-IVA): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Longitudinal study
Feroli 2021 ⁽⁸³⁾ , Italy	Conference abstract	Arm 1: Chemoradiation followed by brachytherapy Arm 2: Chemoradiation followed by surgery	Locally advanced	Median age years: CRT/BT:55 CRT/RS: 47 ECOG PS (0/1/2): NR Disease stage (IIB): CRT/BT:76% CRT/RS: 72% Smoking status (Smoker): NR	Questionnaire- based study

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				HPV status: NR Race (White/Caucasian): NR	
Gudipudi 2014 ⁽⁸⁴⁾ , India	Conference abstract	Intensity-modulated radiation therapy (IMRT) Conventional external beam radiation therapy (CXRT)	Stage IIA-IIIB	Age range years: 20-85 ECOG PS (0/1/2): NR Disease stage (IIA-IIIB): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospectively randomized trial
Pushpalatha 2013 ⁽⁸⁵⁾ , India	Conference abstract	Pelvic radiation + concurrent cisplatin + intracavitary boost of 15 Grays	Advanced stage	Mean age years: 38.8 year ECOG PS (0/1/2): NR Disease stage (Advanced): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Cross-sectional study
Tahapary 2021 ⁽⁸⁶⁾ , Belgium	Conference abstract	Concomitant chemoradiation therapy (CCRT) followed by brachytherapy. Neoadjuvant chemotherapy followed by surgery (NACT-S)	Locally advanced stage	Median age years: NR ECOG PS (0/1/2): NR Disease stage (LA): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Cross-sectional study
Kirchheiner 2016 ⁽⁸⁷⁾ , Austria	Conference abstract	Pelvic EBRT + Chemotherapy + Adaptive brachytherapy	Locally advanced stage	Median age years: NR ECOG PS (0/1/2): NR Disease stage (LA): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Observational study

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Peerawong 2020 ⁽⁸⁸⁾ , Thailand	Peer-reviewed journal article	Chemoradiotherapy	Stage IB2-III	Mean age years (SD): 50.34 (12) ECOG PS (0-1/2-3): 95.5%/4.5% Disease stage (IB2/II/III): 2%/64.9%/ 33.1% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Cross-sectional study
Minnaar 2022 ⁽³⁴⁾ , South Africa	Peer-reviewed journal article	Modulated electro-hyperthermia (mEHT) arm: Chemotherapy: Cisplatin + Radiotherapy (external beam radiation; high dose rate brachytherapy) + modulated electro-hyperthermia Control arm: Chemotherapy: Cisplatin + Radiotherapy (external beam radiation; high dose rate brachytherapy)	Locally Advanced Stage IIB-IIIB	Overall: Median age (Min-Max): 50.1 (27.3-74.8) years ECOG PS (0/1): 4.7%/95.2% Disease stage (IIB/IIIA/IIIB): 36.2%/ 0.9%/ 62.8% Smoking status (Smoker): NR HPV status: NR Race (African/Caucasian/Indian/Asian/ Mixed race): 92.8%/2.3%0%/0%/4.7%	Randomized controlled trial
Singh 2023 ⁽⁸⁹⁾ , India	Conference abstract	Brachytherapy, Intracavitary (ICRT) or Interstitial brachytherapy (ISBT)	Locally advanced (IIB-IVA)	Median age years: NR ECOG PS (0/1/2): NR Disease stage (IIB-IVA): 100% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Prospective randomized study
El Naby El-Tawab 2023 ⁽⁹⁰⁾ , Egypt	Peer-reviewed journal article	Arm 1: Standard IMRT (group A) Arm 2: Bone marrow sparing IMRT (Group B)	Locally advanced (IB2 to IVA)	Overall Mean age years (SD): 51.8 (6.3) ECOG PS (0-1/2): 55%/45% Disease stage (II/III/IV): 70%/13.3%/3.3% Smoking status (Smoker): NR	Prospective randomized study

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				HPV status: NR Race (White/Caucasian): NR	
Kaneyasu 2021 ⁽⁹¹⁾ , Japan	Peer-reviewed journal article	Radical radiotherapy Surgery	Stages IB1–IIB	Overall: Mean age years (SD) range: 48.5± 11 (26-68.5) ECOG PS (0/1): 86%/14% Disease stage (IB1/IIB): 50%/50% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	A multi-institutional survey
Wei 2022 ⁽⁹²⁾ , China	Peer-reviewed journal article	Concurrent platinum-based chemoradiation therapy (CCRT) Open radical hysterectomy (ORH) Laparoscopic nerve-sparing ultra-radical hysterectomy (LNSURH)	Locally advanced (Stage IB3 or IIA2)	Mean age years (SD): 51.3 (10.13) ECOG PS (0/1): NR Disease stage (IB3/IIA2): 59.4%/40.5% Smoking status (Smoker): NR HPV status: NR Race (White/Caucasian): NR	Retrospective study
Rodrigues 2022 ⁽⁹³⁾ , Brazil	Peer-reviewed journal article	NR	Stages I–IVB (Stagewise data reported)	Mean age years (SD): 49.3 (13.9) ECOG PS (0/1): NR Disease stage (I/II/III/IV): 11.9%/35.2%/36.1%/10.5%/6.3%	Prospective cohort (EVITA)

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				Smoking status (Never/former/current/missing): 51.7%/36.3%/10.6%/1.4% HPV status: NR Skin color (White/Non-white/missing): 32.9%/65.3%/1.8%/6.3%	

ECOG: Eastern Cooperative Oncology Group; HPV: Human papillomavirus; NR: Not reported; PS: Performance status; SD: Standard deviation

Table 69. Summary of the studies reporting utility estimates for LACC (n=3)

Study name, country	Study design	Patient population	Disease stage	Intervention and comparator(s)	Sample size	Response rates	Instrument
Katanyoo 2024 ⁽³⁹⁾ , Thailand	Cross-sectional study	Age, mean (SD) [range]: 53.4 years (11.4) [29-80]	LACC (i.e., stages IB3 to IVA)	Concurrent chemoradiation therapy	194	NR	EQ-5D-3L VAS TTO EQ-5D-5L
Sari 2024 ⁽⁹⁴⁾ , Indonesia	Retrospective observational	Age group, n (%) Early Adult (18-40 years): 15 (11.1%) Middle Adult (41-60 years): 99 (73.3%) Advanced Adult (>60 years): 21 (15.6%)	Advanced cervical cancer (IIIB-IVA)	Chemotherapy	200	135/200 (67.5%)	EQ-5D-5L EQ-VAS

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Conway 2023 ⁽⁹⁵⁾ , Canada	Prospecti ve cross- sectional study	Age, median (range): 49.5 years (25-81) FIGO cT2b: 51%	Stage IB-IVA	Chemo- radiation and brachytherapy	74	NR	EQ-5D

Table 70: Study outcomes for studies reporting utility estimates for LACC (n=3)

Study name, country	Study design	Description of health states	Adverse reaction	Method of elicitation/valuation	Mapping
Katanyoo 2024 ⁽³⁹⁾ , Thailand	Cross- sectional study	Utility, mean (SD)/median (range) EQ-5D-3L: 0.755 (0.248)/0.726 (–0.085–1) VAS: 0.806 (0.156)/0.8 (0.300–1) TTO: 0.801 (0.280)/0.95 (0.100–0.950) EQ-5D-5L (cTTO model): 0.871 (0.184)/0.938 (0.031–0.959) EQ-5D-5L (DCE model): 0.900 (0.142)/0.952 (0.256–0.965) EQ-5D-5L (Hybrid model): 0.875 (0.168)/0.934 (0.140–0.944) Utility-treatment, mean (SD)/median (range) EQ-5D-3L: 0.750 (0.219)/ 0.726 (0.178–1) VAS: 0.800 (0.150)/ 0.800 (0.500–1) TTO: 0.637 (0.350)/ 0.800 (0.100–0.950) EQ-5D-5L (cTTO model): 0.889 (0.135)/ 0.927 (0.518–1) EQ-5D-5L (DCE model): 0.914 (0.098)/ 0.952 (0.665–1)	NR	EQ-5D/VAS & TTO	No

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		EQ-5D-5L (Hybrid model): 0.889 (0.123)/ 0.934 (0.577–1) Utility-disease free, mean (SD)/median (range) EQ-5D-3L: 0.829 (0.190)/ 1.000 (0.116–1) VAS: 0.851 (0.128)/ 0.850 (0.500–1) TTO: 0.943 (0.066)/ 0.950 (0.300–0.950) EQ-5D-5L (cTTO model): 0.924 (0.121)/ 0.959 (0.149–1) EQ-5D-5L (DCE model): 0.943 (0.088)/ 0.965 (0.385–1) EQ-5D-5L (Hybrid model): 0.927 (0.107)/ 0.944 (0.262–1) Utility progression, mean (SD)/median (range) EQ-5D-3L: 0.572 (0.314)/ 0.677 (–0.085–1) VAS: 0.701 (0.173)/ 0.725 (0.300–1) TTO: 0.691 (0.304)/ 0.925 (0.100–0.950) EQ-5D-5L (cTTO model): 0.709 (0.268)/ 0.793 (0.031–0.959) EQ-5D-5L (DCE model): 0.772 (0.214)/ 0.851 (0.256–0.965) EQ-5D-5L (Hybrid model): 0.718 (0.245)/ 0.808 (0.140–0.944)			
Sari 2024 ⁽⁹⁴⁾ , Indonesia	Retrospective observational	Utility EQ-5D-5L Mean (SD): 0.4653 (0.3322)	NR	EQ-5D-5L/NR	NR

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		Median (min-max): 0.577 (-0.739-1) EQ-VAS Mean (SD): 0.6850 (0.1429) Median (min-max): 0.70 (0.30-0.99)			
Conway 2023 (95), Canada	Prospective cross-sectional study	EQ-5D index value, median (range): 0.8 (0.4-1)	NR	EQ-5D/NR	NR

3.2.4.1 Utility Estimates reported in Cost-Utility Analyses

Six of the 20 economic evaluations identified in the SLR detailed in section 3.1 reported utility values. Two were based in the US, one in Canada, one in Korea, and two in Thailand. None used the UK value set.

Study name, Country	Reported health states	Utility values	Source
Phippen 2012, United States ⁽¹⁵⁾	Treatment arm (Gemcitabine + cisplatin)	Values in fraction (range)	(96, 97)
	QoL utility score during active treatment	0.76 (0.4-1)	
	QoL utility score for bowel late toxicity	0.86 (NR)	
	QoL utility score for bladder late toxicity	0.79 (NR)	
	Treatment arm (Cisplatin)	Values in fraction (range)	
	QoL utility score during active treatment	0.76 (NR)	
	QoL utility score for bowel late toxicity	0.86 (NR)	
	QoL utility score for bladder late toxicity	0.79 (NR)	
Perdrizet 2020, Canada ⁽²⁰⁾	No disease	Mean: 0.85 DSA: Min 0.80; Max: 0.90 PSA: SD 0.03	Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index 2020 Cancer Care Ontario. Cervical cancer treatment pathway map. 2020 (98)
	Disease and/or toxicity	Mean: 0.55 DSA: Min 0.50; Max: 0.60 PSA: SD 0.03	
Rongsriyam 2020, Thailand ⁽²¹⁾	CCRT group Utility of complete response and no recurrence	All patients: 0.94 (0.01) Stage II: 0.93 (0.02) Stages III-IVA: 0.97 (0.03)	Thai Clinical Trials Registry, (TCTR 20140106001) (99-101)
	Utility of recurrence	All patients: 0.84 (0.04) Stage II: 0.85 (0.06) Stages III-IVA: 0.81 (0.05)	
	Utility of stable disease	All patients: 0.86 (0.07) Stage II: 0.86 (0.07)	

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		Stages III-IVA: 0.86 (0.07)	
	Utility of progressive disease	All patients: 0.85 (0.01) Stage II: 0.81 (0.13) Stages III-IVA: 0.92 (0.03)	
	CCRT/ACT group Utility of complete response and no recurrence	All patients: 0.95 (0.01) Stage II: 0.92 (0.02) Stages III-IVA: 0.96 (0.02)	
	Utility of recurrence	All patients: 0.91 (0.03) Stage II: 0.99 (0.02) Stages III-IVA: 0.84 (0.08)	
	Utility of stable disease	All patients: 0.91 (0.02) Stage II: 0.85 (0.02) Stages III-IVA: 0.99 (0.02)	
	Utility of progressive disease	All patients: 0.85 (0.01) Stage II: 0.81 (0.13) Stages III-IVA: 0.92 (0.03)	
Lee 2015, Korea ⁽²⁹⁾	Radiation	0.76	(102)
	Recovery	0.86	
	Acute GU	0.68	
	Chronic GU	0.55	
	Acute GI	0.62	
	Chronic GI	0.63	
	Survivor (after 1 year)	0.90	
Katanyoo 2021, Thailand ⁽³³⁾	Four health states No disease or disease free Disease progression Severe late side effects in terms of GI and GU systems Death	Utility, 95% CI: Treatment period to first six months: 0.89 (0.86–0.92) Follow-up period No disease and no severe side effects: 0.93 (0.91–0.95) No disease with grades 3–4 GI side effects: 0.86 (0.81–0.89)	Utility data were collected from interviewing LACC patients during the entire study period using the EQ-5D-5L (Thai version) questionnaire ⁽¹⁰³⁾

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		No disease with grades 3–4 GU side effects: 0.89 (0.84–0.94) Disease progression: 0.72 (0.64–0.80)	
Courtney 2025, USA (35)	Stable disease	0.736	(104)
	Partially responded disease	0.880	(105)
	Completely responded disease	0.909	(105)
	Disutility of being on active treatment	0.008	(104)
	Disutility of disease progression	0.038	(106)
	Pembrolizumab toxic effects disutility	0.229	(107–110)
	Placebo toxic effects disutility	0.221	(107, 109, 110)
	Death	0	

3.3 Cost and healthcare resource use studies

3.3.1 Summary

An SLR was conducted to investigate costs and resource use in LACC. Twenty six publications were retrieved, half of which reported on costs in the US. Only one publication was identified which discussed costs associated with LACC in Europe (Italy), and no publications reporting on costs and resource use in any UK jurisdictions were identified. Therefore UK clinicians and clinical guidelines were consulted, with costs sourced from national databases.

3.3.2 Search Strategy

An SLR was performed to identify published studies on cost and healthcare resources use in adult patients with advanced/ recurrent EC. The same data sources were searched as for the SLR of published cost-effectiveness studies in section 3.1.2. The same search terms were used as in Table 55, Table 56, and Table 57

3.3.3 Study selection

Studies identified in the literature had to meet pre-defined eligibility criteria in the review (Table 71). This review was carried out in strict accordance with the NICE recommendations. First, two independent reviewers reviewed abstracts of citations identified through the searches for

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inclusion based on title and abstract alone; a third reviewer reconciled any discrepancies. Next, full-text copies of studies that met the screening criteria were obtained and screened by two independent reviewers; a third reviewer reconciled any discrepancies. Finally, two independent reviewers extracted data from the studies, and a third independent reviewer reconciled any discrepancies. The different phases of the literature review are outlined in Figure 82 in section 3.1.3.

Table 71: Key inclusion and exclusion criteria (PICOTS) – Cost and resource use review

Criteria	Inclusion	Exclusion	Rationale
Population	Disease: Patients with high-risk (stage IB2-IIIB with node-positive disease or stage III-IVA), locally advanced cervical cancer	Patients with other types of cancer, e.g., ovarian, uterine, vaginal, vulvar, OR overall cancer with no further segregation Patients with disease stage IA and/or IB1 only Patients with disease stage IVB only Patients with disease stage unclear. Patients with no subgroup data for cervical cancer (stage IB2-IVA)	Cancer category and disease staging included and excluded according to the KEYNOTE-A18 trial.
	Age: Adult (≥ 18 years) patients	Studies evaluating children	(-)
	Race: No restriction	Not applicable	(-)
	Gender: No restriction	Not applicable	(-)
Line of therapy	First-line only OR treatment naïve patients (that have not received prior systemic therapy)	Studies evaluating second-line or later line therapy only Studies with a mixed line of treatment but with no subgroup analysis reported for the first-line category Studies with the line of therapy unclear	Patient population aligned with the KEYNOTE trial.
	Please refer to section 3.1.3, for additional details of the selection criteria		
Interventions and comparators	No restriction	(-)	(-)
Outcomes	Direct cost (medical/non-medical), indirect cost (e.g., productivity loss, costs related to caregiver support/burden, transportation costs) Drug acquisition cost, administration cost, drug and non-drug treatment cost, adverse event cost,	Studies not reporting relevant outcomes of interest were excluded	The standard set of outcomes extracted in these reviews

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	health state-related costs, terminal care costs, etc. including their sources Resource use data (e.g., outpatient/inpatient visits, emergency care, hospitalizations, length of stay) including their sources.		
Study design	Cost studies/surveys/analyses Cost/economic burden of illness Database studies collecting cost data (e.g., claims databases and hospital records) Studies providing resource use data Registry-based studies Literature reviews/systematic reviews/relevant general reviews for bibliographic searching	Case reports Case series	The standard set of study designs considered in these reviews
Timeframe	Original review: Database inception to October 31 st , 2021 Update review: 1 st Nov 2021-23 rd Aug 2023	Not applicable	To retrieve comprehensive and latest evidence to support the review objectives
Country	No restriction Global approach followed	Not applicable	
Language	Studies with full-texts published in the English language only	Studies with full-texts published in the non-English language	(-)
Publication type	Peer-reviewed journal articles and conference abstracts (searched for the previous six years, 2018-2023)	Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews	(-)

3.3.4 Search results

The PRISMA diagram detailing the number of publications identified, screened and included in the SLR can be found in Figure 85. Of the 108 relevant publications (including 85 unique studies) identified in the SLR of economic evaluations and cost and resource use, 26 studies focussed on costs and/or healthcare resource utilisation only. Additionally, 22 economic evaluations (already summarised in section 3.1) provided costs and/or resource use data as input parameters for economic model development. This section discusses the 26 studies that

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focus on estimating healthcare resource use and associated costs in cervical cancer. Seventeen of the 26 studies were reported as referring to the 1L setting, while 9 had been prioritised for inclusion based on the use of chemotherapy or chemoradiotherapy, despite the line of therapy being unclear.

Of the 26 studies, 17 were retrospective, using data that had already been collected, either within regional or national commercial or public health insurance databases or within health institutions, such as hospitals. Two studies were cost of illness studies while two were cost analyses. One study was a prospective health belief survey that included questions about barriers to care and knowledge of cervical cancer while in one study the cohort data was prospectively collected from database. One study was a single arm exploratory non-inferiority study.

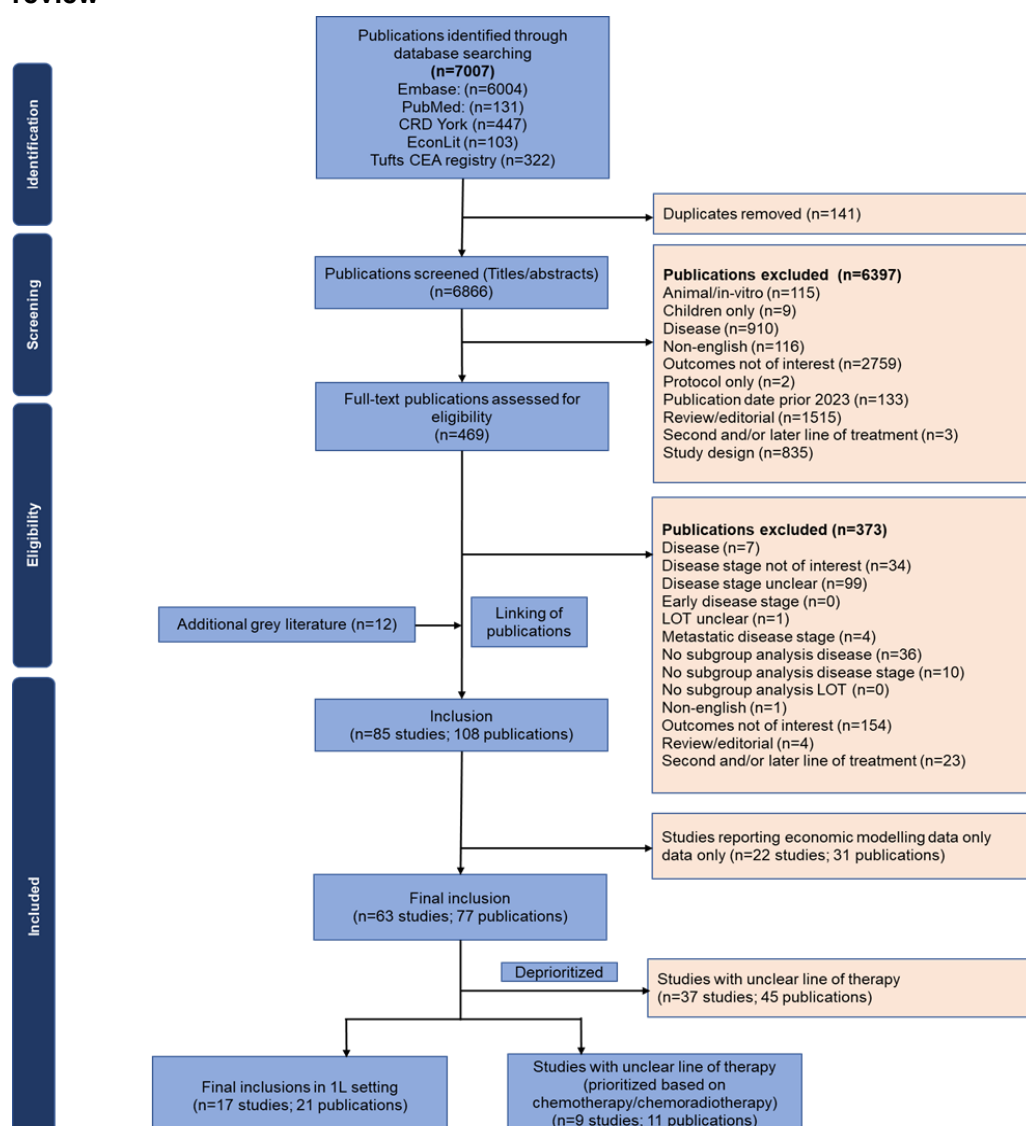
Twenty-two studies were published as peer-reviewed journal articles (11 from the United States, 2 from China and one each from Italy, Morocco, Malaysia, Thailand, Australia, Eswatini, Peru, Brazil and Uganda). The remaining four studies were published as conference abstracts with limited information on results and methodology (2 from the United States and one each from Guyana and Tanzania).

The treatments included surgery (simple and radical hysterectomy), radiotherapy (brachytherapy and conventional form of radiotherapy) administered alone or in combination with chemotherapy (chemoradiotherapy), biological therapy, systemic chemotherapy, and systemic therapies. Five studies did not report the type of treatments administered.

Among the studies identified, it was observed that cervical cancer patients had significantly high total all-cause health care costs, outpatient, inpatient, and emergency department visit costs.

No studies reported cost or resource use in the UK and given the majority of studies related to the health care systems in North and South America and Asia, the generalisability of these data to the current decision problem is poor.

Figure 85: Flow of studies through the systematic review process – cost and resource use review



LOT: Line of therapy

Note: Since a combined search strategy was developed for identifying economic evaluations and cost/resource use studies, the flow of citations is similar (except the concluding tabs)

Table 72: Summary of the published studies reporting cost and/or resource use data; outcome results (n=26 studies)

Study name, Pub type, Country	Sample size	Data collection period, source	Treatments	Cost year, ccy	Resource use data reported in the study	Cost data reported in the study
						Cost valuation details
Ramondetta 2015 ⁽¹¹¹⁾ , Journal article, United States	108	2006-2013, NR	NR	NR, NR	Stage IB2 and above: ER visits for symptoms before diagnosis 0 visits: 26 (24.1%) 1 visit: 51 (47.2%) 2 or more visits: 31 (28.7%) Emergency care: 95% Transfusion prior to first visit: 30.6%	NR
Desai 2016 ⁽¹¹²⁾ , Conference abstract, United States	54	2012-2014, NR	Chemotherapy including brachytherapy	NR, US Dollars (\$)	NR	Reimbursement for outpatient method: Average, \$21,150 per patient (min \$18,582; max \$31,492) Average cost savings using the outpatient method: \$10,315 per patient Reimbursement for the traditional method: Average, \$31,465 per patient (min \$18,620; max \$83,171) Overall actuarial savings during 2 years of analysis from the outpatient method: \$495,106
Ricciardi 2009 ⁽¹¹³⁾ , Journal article, Italy	2927	1998-2002, Italian Network of cancer registerie (AIRTum)	Radical hysterectomy Radio-chemotherapy Palliative chemotherapy	2005, Euro €	NR	Unit cost Laboratory analyses (IB to II): 383.54

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		2002-2004, Modena cancer registries 2005, Italian National Institute of Statistics (ISTAT)	Brachytherapy Palliative surgery			Laboratory analyses (III and IVA): 552.42 Laboratory analyses (IVB): 417.85 Total costs of newly diagnosed cervical cancer during the first year of treatment FIGO IB2: Excluding follow-up & terminal phase: 1,984,470 Including follow-up & terminal phase: 2,453,412 FIGO II: Excluding follow-up & terminal phase: 4,956,213 Including follow-up & terminal phase: 5,877,527 FIGO III: Excluding follow-up & terminal phase: 2,514,878 Including follow-up & terminal phase: 2,514,878 FIGO IV: Excluding follow-up & terminal phase: 1,610,764 Including follow-up & terminal phase: 1,610,764 Terminal phase: Including follow-up & terminal phase: 6,258,461 Unit costs of newly diagnosed cervical cancer during the first year of treatment FIGO I B2: Excluding follow-up & terminal phase: 5,225.95

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						Including follow-up & terminal phase: 6,024.93 FIGO II: Excluding follow-up & terminal phase: 8,914.05 Including follow-up & terminal phase: 10,571.09 FIGO III: Excluding follow-up & terminal phase: 9,709.96 Including follow-up & terminal phase: 11,367.00 FIGO IV: Excluding follow-up & terminal phase: 8,706.83 Including follow-up & terminal phase: 8,706.83 Terminal phase: Including follow-up & terminal phase: 5,854.50
Berraho 2012 ⁽¹¹⁴⁾ , Journal article, Morocco	1978	2008, GLOBOCAN 2009, Cancer Plan in Morocco (Lalla Salma Association against Cancer, National Cancer Plan) 2011, AROME NR, University Hospital of Fez	Surgery Chemotherapy Radiotherapy Brachytherapy	NR, US Dollars (\$)	NR	Cost of 1 cancer case by stage and types of treatment (USD\$) Stage IB2, IIA, and IIB, respectively Brachytherapy: 2,813 Radiotherapy: 2,570 Chemotherapy: 242 Surgery: 975 Total: 6,600 Stage IIIA and IIIB, respectively Brachytherapy: 3,750 Radiotherapy: 2,570 Chemotherapy: 242 Total: 6,562

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						Stage IVA Brachytherapy: 3,750 Radiotherapy: 2,083 Chemotherapy: 1,710 Total: 7,543 The annual management cost of cervical cancer by stage of diagnosis Stage IB2 One patient: 6,883 All patients: 626,353 Stage IIA One patient: 6,883 All patients: 1,335,302 Stage IIB One patient: 6,883 All patients: 4,618,493 Stage IIIA One patient: 6,846 All patients: 622,986 Stage IIIB One patient: 6,846 All patients: 3,703,686 Stage IV One patient: 7,827 All patients: 1,127,088
Puteh 2008 ⁽¹¹⁵⁾ , Journal article, Malaysia	NR	July 2006-December 2006, Malaysia	Hysterectomy Radiotherapy Chemotherapy Brachytherapy	NR, US Dollars (\$)	Stage IB (1 and 2) and IIA Radical surgical procedure: 70% Radiotherapy and chemotherapy (usually with cisplatin and antiemetics) post-operation: 33% Radiotherapy (with or without brachytherapy) and	The annual cost of managing abnormal smears, pre-invasive and invasive cervical cancer Stage IB (I and II)-IIA Base (Min – Max): 3,622,186.20 (2,392,914.72- 2,392,914.72)

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					chemotherapy not fit for operating 30% Stage IIB till IVA All patients: radiotherapy with concurrent chemotherapy and intra cavity radiation Urethral stenting with J-stents and blood transfusion: 10% Post-treatment, vault smear twice per year, yearly blood tests, and CT scans Stage IVB Visceral metastasis (50%): Palliative chemotherapy with palliative radiotherapy Non-visceral metastasis (50%): radiotherapy and chemotherapy and extra psychosocial support	Stage IIB-IVA Base (Min – Max): 21,012,237.42 (14,586,321.47 - 40,443,627.30) Stage IVB Base (Min – Max): 24,472,522.09 (13,981,546.93 - 36,353,918.10)
Tatkan 2020 ⁽¹¹⁶⁾ , Conference abstract, Guyana	NR	NR, Oncology Department, and from the Obstetrics and Gynecology Department of the Georgetown Public Hospital Corporation NR, Cancer institute of Guyana 2003 2013; 2014-2016, Guyana cancer registry	Radical hysterectomy	NR, US Dollars (\$)	NR	Cost to treat Stage IIB/IIA: 12,038 Stage IIB/III/IVA: 8,846 Stage IVB: 4,211
Maguire 2021 ⁽¹¹⁷⁾ , Journal	16363	The California Cancer Registry (2006-2017)	NR	NR	Symptomatic ED visits, n (%): Stage II: 581 (3.55)	NR

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article, United States					Stage III: 1,312 (8.02) Stage IV: 1,199 (7.33)	
Mariotto 2020 ⁽¹¹⁸⁾ , Journal article, United States	NR	SEER Medicare Dataset (2000-2012)	NR	2019, US Dollars (\$)	NR	Medical services costs Initial phase Local: \$41.1 Regional: \$66.3 Distant: \$78.2 Continuation phase Local: \$2.7 Regional: \$4.4 Distant: \$15.4 End of life phase Local: \$77.9 Regional: \$92.2 Distant: \$111.0 Oral prescription drug costs Initial phase Local: -\$0.2 Regional: - \$0.5 Distant: - \$0.7 Continuation phase Local: - \$0.4 Regional: - \$1.0 Distant: \$0.8 End of life phase Local: \$2.9 Regional: \$0.3 Distant: -\$0.4
Bauer-Nilsen 2018 ⁽¹¹⁹⁾ , Journal article, US	NR	NR, Department of Radiation Oncology, University of	Radiation therapy (EBRT/BT)	2016, USD \$	Relative value unit (RVUs) per course: HDR brachytherapy: 77.08 IMRT: 59.03	Component of treatment course Consultation Total personnel costs (\$):195.77 Space and equipment costs (\$): 0

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		Virginia School of Medicine			3D-CRT: 45.82 Attending time (h): HDR brachytherapy: 7.3 IMRT: 1.4 3D-CRT: 1.4 A full course of definitive therapy provides radiation oncology attending physicians IMRT: 149.77 RVUs 3D-CRT: 135.90 RVUs Attending radiation Oncologist time (min): Consultation: 26 Initial simulation and Planning: 13 EBRT delivery (3D-CRT or IMRT): 60 HDR brachytherapy: 423 Cumulative total: 522 Radiation Oncology resident time (min): Consultation: 68 Initial simulation and Planning: 38 EBRT delivery (3D-CRT or IMRT): 25	Consumable supplies costs (\$): 0 Total cost (\$):195.77 Initial simulation and planning Total personnel costs (\$): 290.83 Space and equipment costs (\$): 29.89 Consumable supplies costs (\$):0 Total cost (\$): 320.72 EBRT delivery (3D-CRT or IMRT) Total personnel costs (\$): 1,517.80 Space and equipment costs (\$): 2,572.46 Consumable supplies costs (\$): 0 Total cost (\$): 4,090.26 HDR brachytherapy Total personnel costs (\$): 4,797.35 Space and equipment costs (\$): 1,592.39 Consumable supplies costs (\$): 2,219.50 Total cost (\$): 8,609.24 Cumulative total Total personnel costs (\$): 6,801.75 Space and equipment costs (\$): 4,194.74 Consumable supplies costs (\$): 2,219.50 Total cost (\$): 13,215.99 Radiation treatment modality HDR brachytherapy

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					HDR brachytherapy: 371 Cumulative total: 502 Physicist time (min): Consultation: 0 Initial simulation and Planning: 30 EBRT delivery (3D-CRT or IMRT): 10 HDR brachytherapy: 415 Cumulative total: 455 Total staff time (min): Consultation: 136 Initial simulation and Planning: 246 EBRT delivery (3D-CRT or IMRT): 1,645 HDR brachytherapy: 2,349 Cumulative total: 4,376 Days off per year: RO (Radiation oncology) attending: 43 RO Resident: 20 Physicist: 43 Reception staff: 30 Registered nurse: 30 Dosimetrist: 43 Radiation therapist: 30 Anaesthesia attending: 43 Anaesthesia certified. registered nurse:	Global reimbursement (\$): 4,593.66 Technical only reimbursement (\$):1,994.17 Physician only reimbursement (\$):165.32 Total reimbursement (\$): 6,753.15 IMRT Global reimbursement (\$): 2,019.48 Technical only reimbursement (\$):10,926.00 Physician only reimbursement (\$):1,091.87 Total reimbursement (\$):14,037.35 3D-CRT Global reimbursement (\$): 1,337.67 Technical only reimbursement (\$): 5,331.00 Physician only reimbursement (\$):1,091.87 Total reimbursement (\$):7,760.54 Total reimbursement for a full course of definitive therapy IMRT: \$23,321.71 3D-CRT: \$16,071.90 Total costs Definitive radiation therapy: \$12,861.68 Personnel costs: \$6,399.44 Space and equipment costs: \$4,242.74 Salary:

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					43 Anaesthesia resident: 20 Total Number work days per year: RO (Radiation oncology) attending: 217 RO Resident: 240 Physicist: 217 Reception staff: 230 Registered nurse: 230 Dosimetrist: 217 Radiation therapist: 230 Anaesthesia attending: 217 Anaesthesia certified. registered nurse: 217 Anaesthesia resident: 240 Total hours per year: RO (Radiation oncology) attending: 1,736 RO Resident: 1,920 Physicist: 1,736 Reception staff: 1,840 Registered nurse: 1,840 Dosimetrist: 1,736 Radiation therapist: 1,840 Anaesthesia attending: 1,736 Anaesthesia certified. registered nurse: 1,736 Anaesthesia resident: 1,920	RO (Radiation oncology) attending: 556,400 RO Resident: 58,255 Physicist: 192,000 Reception staff: 33,280 Registered nurse: 85,000 Dosimetrist: 110,000 Radiation therapist: 83,000 Anaesthesia attending: 496,600 Anaesthesia certified. registered nurse: 208,000 Anaesthesia resident: 58,255 CCR [Capacity cost rate]: Cost in US dollars per minute: RO (Radiation oncology) attending: 5.34 RO Resident: 0.51 Physicist: 1.84 Reception staff: 0.30 Registered nurse: 0.77 Dosimetrist: 1.06 Radiation therapist: 0.75 Anaesthesia attending: 4.77 Anaesthesia certified registered nurse: 2.00 Anaesthesia resident: 0.51 Equipment Classification: Cost/year (\$) EBRT: CT simulator: 55,000 Linear Accelerator: 608,000 EBRT TPS: 102,000 HDR Brachytherapy:

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						Brachytherapy CT scanner: 100,000 HDR Afterloader: 80,000 Brachytherapy TPS: 113,000 Cost per treatment (\$) EBRT: CT simulator: 29.89 Linear Accelerator: 88.12 EBRT TPS: 29.57 HDR Brachytherapy: Brachytherapy CT scanner: 108.70 HDR Afterloader: 86.96 Brachytherapy TPS: 122.83 Total Cost for Treatment Course (\$) CT simulator: 29.89 Linear Accelerator: 2,573.10 EBRT TPS: 47.30 HDR Brachytherapy: Brachytherapy CT scanner: 543.50 HDR Afterloader: 434.80 Brachytherapy TPS: 614.15
Lachance 2008 ⁽¹²⁰⁾ , Journal article, US	46	1994-2004, tumor registry data reviewed at the University of Virginia Health System	Arm 1: Chemoradiation + one brachytherapy followed by second brachytherapy. Arm 2: Chemoradiation + one brachytherapy followed by simple hysterectomy.	NR, USD \$	Median hospital stay: Second brachytherapy: 4 days Hysterectomy: 2 days	Costs by services used Mean USD ± SD Room and board Second brachytherapy: 1,264 ± 1,127 Hysterectomy: 3,134 ± 714 OR costs (time) Second brachytherapy: 415 ± 113 Hysterectomy: 1,520 ± 651 Total OR costs

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						Second brachytherapy: 741 ±209 Hysterectomy: 2,247±731 Supplies Second brachytherapy: 445±202 Hysterectomy: 1,532±536 Pharmacy Second brachytherapy: 343 ±313 Hysterectomy: 675 ±318 Laboratory Second brachytherapy: 86 ±86 Hysterectomy: 149 ±141 Pathology Second brachytherapy: 4 ±17 Hysterectomy: 448 ±202 Radiation Second brachytherapy: 2,495 ±2,339 Hysterectomy: 0 Costs by type Total hospital cost Second brachytherapy: 5,508±2,664 Hysterectomy: 8,316 ±1,390 Direct costs Second brachytherapy: 2,930±1,506 Hysterectomy: 4,234 ±701 Indirect costs Second brachytherapy: 2,577±1,193 Hysterectomy: 4,068 ±795 Physician charges

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						Second brachytherapy: 6,222 ±6,649 Hysterectomy: 7,638 ±5,125
Ramondetta 2006 ⁽¹²¹⁾ , Journal article, US	36	2001-2004, indigent Harris County residents with cervical cancer from LBJ hospital to M. D. Anderson Cancer Center	Chemoradiation + Brachytherapy	NR, USD \$	Median number of external beam radiation treatments given on outpatient basis: Study: 19 Control: 25 Median number of external beam radiation treatments given on inpatient basis: Study: 7 Control: 0 Median number of chemotherapy cycles given on outpatient basis: Study: 2 Control: 3.5 Median number of chemotherapy cycles given on inpatient basis: Study: 1 (0-7) Control: 1 (0-2) Median number of days admitted: Study: 13 Control: 0	Median cost per patient (USD \$) Antiemetic Control (9): 296.18 Study (23): 1,251.70 IV fluid cost Control (9): 1,175.08 Study (23): 4,690.18 Inpatient bed cost Control (9): 2,760.64 Study (23): 6,211.44 Blood total Control (9): 383.55 Study (23): 977.29 Pain Control (9): 7.98 Study (23): 20.16 Facility (total) Control (9): 27,758.20 Study (23): 50,778.54 Physician (total) Control (9): 7,718.76 Study (23): 9,062.30 Total cost Control (9): 33,047.64 Study (23): 61,940.06 Median difference: \$28,892 Estimated household income: Adjusted gross income (AGI), per patient:

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						Control: \$33,911 Study: \$33,169 Combined mean AGI per patient: \$33,354 Combined mean AGI per patient (divided by the number of family members): Control: \$11,381 ± 7,467 Study: \$8,077 ± 4,270
Dessources 2019 ⁽¹²²⁾ , Conference abstract, US	50	CCCNP database at a tertiary care, public, safety net hospital.	Chemoradiation	NR, USD (\$)	Overbooked clinic visits: 16% Infusion center visits: 10% UC visits: 2% Direct hospital admissions: 8% ED visits: 10% Non face to face encounters: 36%	Navigated cohort: Total cost of acute episodic care needs of the: \$352,839 Cost of navigation being \$709 per patient Cost savings for navigation is \$140,424 Non-navigated cohort: The emergency department or an urgent care setting increasing the cost to \$493,264.
Ngcamphala 2021 ⁽¹²³⁾ , Journal article, Eswatini	268	Ministry of Health, Report on Cases of Cancers in Swaziland (2018) Swaziland National Cancer registry (SNCR)	Radiotherapy Chemotherapy	2018, USD (\$)	Patient time for staging, cancer treatment and follow-up by FIGO stage. Treatment time including staging (weeks): Ib2-II: 17 III: 17 IV: 42 Follow-up (hours): Ib2-II: 15	Costs for staging, management, and treatment of cervical cancer per FIGO stage, (\$) Stage IB2-II: Transport including from Eswatini and between treatment sites: 1,771 Lodging including meals: 2,310 Hospital admission for early stage treatment: 0 Hospital admission in step down facility: 105 Radical hysterectomy with anesthesia: 0

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				III: 15 IV: 15 Valuing treatment time (weekly income \$56) Ib2-II: 952 III: 952 IV: 2,408 Valuing follow-up time (\$) Ib2-II: 22 III: 22 IV: 22 Productivity loss (sum of the value for treatment time and follow-up time) (\$) Ib2-II: 973 III: 973 IV: 2,429 Productivity loss by number of women corresponding per FIGO stage in 2018 (\$) Ib2-II: 38,938 III: 52,567 IV: 391,144	Clinical examination with colposcopy under anesthesia: 362 CT planning scan: 235 Brachytherapy treatment: 4,969 Radiotherapy treatment: 14,070 Follow-up during brachytherapy & radiotherapy: 408 Chemotherapy: 3,689 Follow-up during chemotherapy: 612 Follow-up after treatment: 2,448 MRI: 965 Nurses' and drivers' allowance: 926 Total cost: 32,870 Stage III: Transport including from Eswatini and between treatment sites: 1,771 Lodging including meals: 2,310 Hospital admission for early stage treatment: 0 Hospital admission in step down facility: 105 Radical hysterectomy with anesthesia: 0 Clinical examination with colposcopy under anesthesia: 362 CT planning scan: 235 Brachytherapy treatment: 4,969 Radiotherapy treatment: 14,070 Follow-up during brachytherapy & radiotherapy: 408

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						Chemotherapy: 3,689 Follow-up during chemotherapy: 408 Follow-up after treatment: 2,448 MRI: 965 Nurses' and drivers' allowance: 926 Total cost: 32,666 Stage IV: Transport including from Eswatini and between treatment sites: 1,771 Lodging including meals: 2,310 Hospital admission for early stage treatment: 0 Hospital admission in step down facility: 105 Radical hysterectomy with anesthesia: 0 Clinical examination with colposcopy under anesthesia: 362 CT planning scan: 235 Brachytherapy treatment: 0 Radiotherapy treatment: 14,070 Follow-up during brachytherapy & radiotherapy: 408 Chemotherapy: 3,689 Follow-up during chemotherapy: 204 Follow-up after treatment: 29,376 MRI: 965 Nurses' and drivers' allowance: 926 Total cost: 54,421

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						Annual direct (health care) costs: (Direct & Indirect) Cost per item Average cost (2018) FIGO IB2-II: 32,870 FIGO III: 32,666 FIGO IV: 54,421 Base case cost (2018) FIGO IB2-II: 1,314,800 (range: 986,100 - 1,643,500) FIGO III: 1,763,964 (range: 1,322,973 - 2,204,955) FIGO IV: 8,761,781 (range: 6,571,336 - 10,952,226)
Díaz 2023 ⁽¹²⁴⁾ , Journal article, Peru	44	From 02/01/2022 to 05/01/2023 Medical records and pharmacy archives	Chemoradiotherapy (CTRT) + High-dose-rate brachytherapy (HDRBT) Radiation therapy: Three-dimensional (3D) radiation therapy Intensity-modulated radiation therapy (IMRT) Volumetric-modulated arc therapy (VMAT)	NR, USD (\$)	Hospital stays: 3D CTCT28 + HDRBT + VMAT RT25 (IIIC2): 131 hours IMRT CTCT28 + HDRBT (IIIC2): 97 hours Procedure delivery: Special techniques planning: Stage IIB/IIIA/IIIB: 6.3 to 5.4 hours Stage IIIC1: 7.0 to 6.1 hours Stage IIIC2: 12.4 to 7 hours	RT and CT-related unit costs: in Dollars (\$) RT Costs: Radiation oncologist per minute: 0.23 Medical technician per minute: 0.14 Nurse per minute: 0.15 Nursing technician per minute: 0.08 Medical physicist per minute: 0.15 MSCT simulator: 0.08 Laser alignment system: 0.02 Simulation infrastructure: 0.01 Simulation equipment: 0.01 Immobilisation device: 0.01 Software: 0.06 3D planning infrastructure and equipment: 0.01

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						IMRT/VMAT planning infrastructure and equipment: 0.01 Synergy platform linear accelerator: 1.39 Synergy full linear accelerator: 2.16 3D teletherapy infrastructure: 0.01 IMRT/VMAT teletherapy equipment: 0.61 IMRT/VMAT teletherapy infrastructure: 0.01 BT infrastructure: 0.05 BT equipment: 0.39 Iridium source: 2.85 Sodium diclofenac 75 mg Inj. per unit: 0.04 Capecitabine 0.5 mg tablet per unit: 0.01 Misoprostol 200 ucg per unit: 0.58 Foley catheter N° 14 French per unit: 0.39 Sterile glove per pair: 0.58 5 mL syringe per unit: 0.04 10 mL syringe per unit: 0.04 60 mL syringe per unit: 5 Sodium chloride 9% 1,000 mL per unit: 0.65 Iodovopidone 8.5% 1,000 mL per unit: 3.95 Iodopovidone 10% 1,000 mL per unit: 3.95 Lidocaine hydrochloride 2% gel per unit: 0.59

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						Sterile Gauze 10 × 10 cm per package: 0.47 Disposable speculum per unit: 1.32 Protective suit for 6 hours: 1.81 CT Costs: Medical oncologist per minute: 0.23 Pharmaceutical chemist per minute: 0.16 Nurse per minute: 0.15 Nursing technician per minute: 0.08 Cisplatin 50 mg Inj. per unit: 4.66 Ranitidine 50 mg Inj. per unit: 0.09 Dexamethasone 20 mg Inj. per unit: 2.49 Ondansetron 8 mg Inj. per unit: 0.15 Chlorphenamine 10 mg Inj. per unit: 0.04 Sodium chloride 9% 1,000 mL per unit: 0.65 Manitol 20% Inj. per unit: 1.85 Magnesium sulphate 200 mg Inj. per unit: 0.17 Omeprazole 20 mg cap per unit: 0.02 Metoclopramide 10 mg tab per unit: 0.02 Ondansetron 8 mg tab per unit: 0.29 Infusion set: 1.8 Heparin syringe: 0.66

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						20 mL syringe: 0.1 Sterile gloves: 0.58 Protective suit for 6 hours: 1.81 Saline solution 250 mL: 0.89 Sterile Gauze 10 × 10 cm per package: 0.47 Cotton swabs: 0.08 Surgical tape: 0.06 Alcohol: 0.01 RT costs Direct Cost: Tridimensional Stage: IB/IIIA/IIIB- 3D QTRT25 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 34.05 Planning: 36.26 Teletherapy: 1,127.91 BT: 978.42 Subtotal: 2,277.48 Stage: IIIC1- 3D QTRT28 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 39.72 Planning: 42.3 Teletherapy: 1,263.26 BT: 978.42 Subtotal: 2,424.55 Stage: IIIC2- 3D QTRT28 + BATD + VMAT RT25 Consultation: 44.54 Simulation: 144.08 Delimitation: 79.45

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						Planning: 107.97 Teletherapy: 2,527.23 BT: 978.42 Subtotal: 3,881.69 Stage: IVA- 3D QTRT28 + 3D RT5 Consultation: 27.83 Simulation: 157.14 Delimitation: 73.77 Planning: 68.49 Teletherapy: 1,488.84 BT: 0 Subtotal: 1,816.08 Direct Cost: Special technique Stage: IB/IIIA/IIIB- IMRT QTRT25 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 39.72 Planning: 76.96 Teletherapy: 1,606.81 BT: 978.42 Subtotal: 2,802.76 Stage: IB/IIIA/IIIB- VMAT QTRT25 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 39.72 Planning: 76.96 Teletherapy: 1,241.12 BT: 978.42 Subtotal: 2,437.07

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						Stage: IIIC1- IMRT QTRT28 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 46.82 Planning: 101.14 Teletherapy: 1,799.62 BT: 978.42 Subtotal: 3,026.84 Stage: IIIC1- VMAT QTRT28 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 46.82 Planning: 101.14 Teletherapy: 1,390.05 BT: 978.42 Subtotal: 2,617.27 Stage: IIIC2- IMRT QTRT28 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 55.33 Planning: 133.37 Teletherapy: 2,106.80 BT: 978.42 Subtotal: 3,374.76 Stage: IIIC2- VMATC2 QTRT28 + BATD Consultation: 22.27 Simulation: 78.57 Delimitation: 55.33 Planning: 133.37

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						Teletherapy: 1,594.84 BT: 978.42 Subtotal: 2,862.80 CT Costs: Direct Cost: Tridimensional Stage: IB/IIIA/IIIB- 3D QTRT25 + BATD Consultation :34.95 CT preparation :283.89 CT administration :452.53 Subtotal :771.37 Stage: IIIC1- 3D QTRT28 + BATD Consultation: 34.95 CT preparation: 396.8 CT administration: 543.04 Subtotal: 974.78 Stage: IIIC2- 3D QTRT28 + BATD + VMAT RT25 Consultation: 34.95 CT preparation: 396.8 CT administration: 543.04 Subtotal: 974.78 Stage: IVA- 3D QTRT28 + 3D RT5 Consultation: 34.95 CT preparation: 396.8 CT administration: 543.04 Subtotal: 974.78 Direct Cost: Special technique Stage: IB/IIIA/IIIB- IMRT QTRT25 + BATD/VMAT QTRT25 + BATD

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						Consultation: 34.95 CT preparation: 283.89 CT administration: 452.53 Subtotal: 771.37 Stage: IIIC1, C2- IMRT QTRT28 + BATD/VMAT QTRT28 + BATD Consultation: 34.95 CT preparation: 396.8 CT administration: 543.04 Subtotal: 974.78 Tridimensional: Stage: IB/IIIA/IIIB- 3D QTRT25 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 11,585.62 Total per patient (Dollars): 3,048.85 Stage: IIIC1- 3D QTRT28 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 12,917.47 Total per patient (Dollars): 3,399.33 Stage: IIIC2- 3D QTRT28 + BATD + VMAT RT25 Total per patient (Peruvian Nuevo Sol (S/.): 18,454.6 Total per patient (Dollars): 4,856.47 Stage: IVA- 3D QTRT28 + 3D RT5

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						Total per patient (Peruvian Nuevo Sol (S/.): 10,605.29 Total per patient (Dollars): 2,790.87 Special technique IB/IIIA/IIIB- IMRT QTRT25 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 13,581.67 Total per patient (Dollars): 3,574.12 IB/IIIA/IIIB- VMAT QTRT25 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 12,192.05 Total per patient (Dollars): 3,208.43 IIIC1 - IMRT QTRT28 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 15,206.17 Total per patient (Dollars): 4,001.62 IIIC1 - VMAT QTRT28 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 13,649.80 Total per patient (Dollars): 3,592.05 IIIC2- IMRT QTRT28 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 16,528.27

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						Total per patient (Dollars): 4,349.55 IIIC2- VMAT QTRT28 + BATD Total per patient (Peruvian Nuevo Sol (S/.): 14,582.81 Total per patient (Dollars): 3,837.58 Indirect Costs: Tridimensional Stage: IB/IIIA/IIIB- 3D QTRT25 + BATD Loss of productivity due consultation and treatment: 134.62 Transportation: 213.16 loss of household productivity: 218.47 Total per patient (Peruvian Nuevo Sol (S/.): 2,151.74 Total per patient (Dollars): 566.25 Stage: IIIC1- 3D QTRT28 + BATD Loss of productivity due consultation and treatment: 147.2 Transportation: 230.92 loss of household productivity: 241.43 Total per patient (Peruvian Nuevo Sol (S/.): 2,354.30 Total per patient (Dollars): 619.55 Stage: IIIC2- 3D QTRT28 + BATD + VMAT RT25 Loss of productivity due consultation and treatment: 203.53

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						Transportation: 388.42 loss of household productivity: 346.63 Total per patient (Peruvian Nuevo Sol (S/.): 3,566.60 Total per patient (Dollars): 938.58 Stage: IVA- 3D QTRT28 + 3D RT5 Loss of productivity due consultation and treatment: 140.59 Transportation: 242.76 loss of household productivity: 252.46 Total per patient (Peruvian Nuevo Sol (S/.): 2,416.06 Total per patient (Dollars): 635.81 Special technique Stage: IIB/IIIA/IIIB- IMRT QTRT25 + BATD Loss of productivity due consultation and treatment: 135.92 Transportation: 213.16 loss of household productivity: 219.77 Total per patient (Peruvian Nuevo Sol (S/.): 2,161.60 Total per patient (Dollars): 568.84 Stage: IIB/IIIA/IIIB- VMAT QTRT25 + BATD Loss of productivity due consultation and treatment: 133.32 Transportation: 213.16

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						loss of household productivity: 217.17 Total per patient (Peruvian Nuevo Sol (S/.): 2,141.88 Total per patient (Dollars): 563.65 Stage: IIIC1- IMRT QTRT28 + BATD Loss of productivity due consultation and treatment: 148.66 Transportation: 230.92 loss of household productivity: 242.88 Total per patient (Peruvian Nuevo Sol (S/.): 2,365.35 Total per patient (Dollars): 622.46 Stage: IIIC1- VMAT QTRT28 + BATD Loss of productivity due consultation and treatment:145.75 Transportation:230.92 loss of household productivity:239.98 Total per patient (Peruvian Nuevo Sol (S/.):2,343.26 Total per patient (Dollars):616.65 Stage: IIIC2- IMRT QTRT28 + BATD Loss of productivity due consultation and treatment: 150.84 Transportation: 230.92 loss of household productivity: 245.06 Total per patient (Peruvian Nuevo Sol (S/.): 2,381.91

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						Total per patient (Dollars): 626.82 Stage: IIC2- VMATC2 QTRT28 + BATD Loss of productivity due consultation and treatment: 147.2 Transportation: 230.92 loss of household productivity: 241.43 Total per patient (Peruvian Nuevo Sol (S/.): 2,354.30 Total per patient (Dollars): 619.55
Ko 2022 ⁽¹²⁵⁾ , Journal article, US	663	2000-2015, SEER	Chemotherapy	NR, \$	Inpatient admissions Mean (SD): GYO: 0.39 (0.48) MEDONC: 0.36 (0.47) ED visits Mean (SD): GYO: 0.13 (0.28) MEDONC: 0.15 (0.37) ED (Rate, 95%CI) GYO (gynaecologic oncologist): 0.114 (0.093–0.140) MEDONC (medical oncologist): 0.122 (0.104–0.142) Admission (Rate, 95%CI) GYO: 0.298 (0.263–0.339) MEDONC: 0.278 (0.252–0.308) Unadjusted outcomes: GYO vs. MEDONC as ref, Mean Ratio, 95%CI GYO: Spending: 1.07 (0.91, 1.25) ED: 0.94 (0.73, 1.21) Admission: 1.07 (0.91, 1.26)	Spending (geometric mean, 95%CI) GYO: \$6,135 (5,389, 6,984) MEDONC: \$5,758 (5,230, 6,339)

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					IPTW outcomes models adjusted for residual confounding: GYO vs. MEDONC, Mean Ratio, 95%CI GYO: Spending: 1.14 (0.97, 1.34) ED: 1.05 (0.92, 1.20) Admission: 1.26 (1.05, 1.51) IPTW adjusted outcomes GynOnc: Spending: 1.10 (.93, 1.30) ED: 1.05 (0.81, 1.36) Admission: 1.18 (1.01, 1.39)	
Hari 2022⁽¹²⁶⁾, Conference abstract, Tanzania	71	January 2020-December 2020, Bugando Medical Center (BMC)	Chemoradiation	NR	Author reported that most of the funding went towards investigative studies, chemotherapy, and radiation treatment costs, as well as hostel funding. Renting the 16-bed-hostel for the year: 30% of the funding Labs and imaging: 12% of the funding Chemotherapy: 13% of the funding Radiation: 21% of the funding	NR
Zhang 2022⁽¹²⁷⁾, Journal article, China	206	2010-2015, Hospital of Guangxi Medical University	Primary surgical treatment (PST) Neoadjuvant chemotherapy followed by radical surgery (NAC + RS), Concurrent chemoradiotherapy (CCRT)	NR, \$	LOS (days), Mean ± SD: PST: 49.72 ± 19.40 NAC + RS: 63.08 ± 15.26 CCRT: 54.22 ± 8.50	Hospitalization costs \$, Mean ± SD: PST: 7,969.77 ± 3,115.07 NAC + RS: 9,915.97 ± 2,553.34 CCRT: 7,646.62 ± 2,872.94

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McGarvey 2022 ⁽¹²⁸⁾ , Journal article, US	1866 Stage II: 198 Stage III: 215 Stage IV: 153	2016-2020, Optum's de- identified Integrated Claims-Clinical data set	NR	2020, USD	NR	Mean cost by cancer and stage, year 1 post diagnosis: 1-6 months Stage II: \$104,560 Stage III: \$113,088 Stage IV: \$129,338 7-12 months Stage II: \$37,591 Stage III: \$56,642 Stage IV: \$86,533 Cervical cancer mean cost by stage at diagnosis, year 1–4 post diagnosis: Year 1 Stage II: \$142,151 Stage III: \$169,730 Stage IV: \$215,871 Year 2 Stage II: \$48,094 Stage III: \$57,990 Stage IV: \$135,078 Year 3 Stage II: \$23,214 Stage III: \$39,105 Stage IV: \$60,096

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Year 4 Stage II: \$11,606 Stage III: \$58,219 Stage IV: \$28,457 Total cost, year 1 Post Diagnosis (diagnosed 2016-2020), Mean (SD), Median (range) Stage II Mean (SD): \$142,151 (\$96,193) Median (range): \$22,974 (\$126 - \$2,377,589) Stage III Mean (SD): \$169,730 (\$105,101) Median (range): \$37,828 (\$84 - \$2,638,260) Stage IV Mean (SD): \$215,871 (\$134,889) Median (range): \$61,262 (\$121 - \$2,718,433) Mean Monthly Cost in Year 1 Per Patient, Coefficient, Std. Error Stage II Diagnosis: 7,210 (575) Stage III Diagnosis: 7,503 (607) Stage IV Diagnosis: 8,229 (705) Cervical Cancer Mean Cost by Stage at Diagnosis, Cumulative Through Year 4 Post Diagnosis Month 6

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Stage II: \$104,560 Stage III: \$113,088 Stage IV: \$129,338 Year 1 Stage II: \$142,151 Stage III: \$169,730 Stage IV: \$215,871 Year 2 Stage II: \$190,245 Stage III: \$227,720 Stage IV: \$350,949 Year 3 Stage II: \$213,459 Stage III: \$266,825 Stage IV: \$411,045 Year 4 Stage II: \$225,065 Stage III: \$325,044 Stage IV: \$439,502 Mean Cancer-specific Cost by Cancer and Stage, Year 1 Post Diagnosis: 1-6 months and 7-12 months: 1-6 months Stage II: \$80,626 Stage III: \$92,694 Stage IV: \$98,397

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						7-12 months Stage II: \$27,117 Stage III: \$40,268 Stage IV: \$64,056 Cervical Cancer Mean Cancer-specific Cost by Stage at Diagnosis, Year 1-4 Post Diagnosis Year 1 Stage II: \$107,743 Stage III: \$132,962 Stage IV: \$162,453 Year 2 Stage II: \$26,525 Stage III: \$26,001 Stage IV: \$84,815 Year 3 Stage II: \$10,283 Stage III: \$16,505 Stage IV: \$32,642 Year 4 Stage II: \$3,100 Stage III: \$33,382 Stage IV: \$19,555 Cervical Cancer Mean Cancer-Specific Cost by Stage at Diagnosis, Cumulative Through Year 4 Post Diagnosis

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Month 6 Stage II: \$80,626 Stage III: \$92,694 Stage IV: \$98,397 Year 1 Stage II: \$107,743 Stage III: \$132,962 Stage IV: \$162,453 Year 2 Stage II: \$134,268 Stage III: \$158,963 Stage IV: \$247,268 Year 3 Stage II: \$144,551 Stage III: \$175,468 Stage IV: \$279,910 Year 4 Stage II: \$147,651 Stage III: \$208,850 Stage IV: \$299,465
Stevens 2023 ⁽¹²⁹⁾ , Journal article, Australia	14	2020-2022	Magnetic Resonance Imaging (MRI)-image guided adaptive Brachytherapy (IGABT) following CRT	2021, Australian dollars (AUD)	NR	Procedure cost for 3 fractions versus 4 fractions Cost (AUD): 3 fractions: Theatre: 496.40 Recover 40.49

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						RadOncologist: 1,459.11 Diagnostic (US+MRI): 130.22 Pain CNC: 65.00 Ward 8F (2 nights): 1,488.00 Equipment sterilisation: 77.27 Total cost: 3,756.49 4 fractions: Theatre: 992.80 Recover 80.98 RadOncologist: 2,918.22 Diagnostic (US+MRI): 260.44 Pain CNC: 130.00 Ward 8F (2 nights): 1,488.00 Equipment sterilisation: 154.54 Total cost: 6,024.98
Reddy 2022 ⁽¹³⁰⁾ , Journal article, US	3389	2012-2016, SEER registry-Medicare claims database	Chemotherapy Biological therapy	NR, USD \$	NR	Total cancer-related healthcare costs, Mean SD: Year 1 Stage II: \$52,969 (56,235) Stage III: \$76,750 (87,691) Stage IV: \$116,473 (137,059) Year 2 Stage II: \$17,315 (49,038) Stage III: \$31,550 (76,987) Stage IV: \$55,740 (79,922) Year 3 Stage II: \$9,332 (35,329) Stage III: \$28,006 (76,686)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Stage IV: \$34,074 (62,126) Year 4 Stage II: \$7,263 (28,567) Stage III: \$16,203 (41,606) Stage IV: \$33,824 (77,918) Year 5 Stage II: \$8,534 (31,174) Stage III: \$10,230 (30,335) Stage IV: \$21,568 (50,677) Differential total cancer-related healthcare costs, stage IV vs other stages, Difference (95% CI): Months 1–6 Stage IV – Stage II: \$23,420 (15,020–31,820) Stage IV – Stage III: \$14,178 (6574–21,781) Months 7-12 Stage IV – Stage II: \$17,734 (11,840–23,628) Stage IV – Stage III: \$10,738 (5200–16,277) Year 1 Stage IV – Stage II: \$63,504 (49,465–77,542) Stage IV – Stage III: \$39,723 (26,878–52,569)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Year 5 Stage IV – Stage II: \$13,034 (6354–19,713) Stage IV – Stage III: \$11,338 (4663–18,012) Semi-annual costs Month 1-6 Total cancer-related healthcare costs Stage II: \$44,906 (34,709) Stage III: \$54,147 (47,406) Stage IV: \$68,325 (73,413) Cancer-related inpatient services costs Stage II: \$15,482 (33,812) Stage III: \$27,023 (44,668) Stage IV: \$43,883 (70,353) Cancer-related outpatient services costs Stage II: \$29,303 (16,766) Stage III: \$26,876 (18,652) Stage IV: \$24,288 (18,950) Cancer-related pharmacy costs Stage II: \$120 (437) Stage III: \$248 (2920) Stage IV: \$154 (916) Month 7-12 Total cancer-related healthcare costs

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Stage II: \$10,251 (25,285) Stage III: \$17,247 (31,630) Stage IV: \$27,985 (34,890) Cancer-related inpatient services costs Stage II: \$5,963 (230,065) Stage III: \$9,147 (27,887) Stage IV: \$13,950 (29,610) Cancer-related outpatient services costs Stage II: \$4,227 (6,672) Stage III: \$8,074 (17,992) Stage IV: \$13,607 (14,836) Cancer-related pharmacy costs Stage II: \$61 (415) Stage III: \$26 (95) Stage IV: \$428 (4,693) Annual costs Year 1 Total cancer-related healthcare costs Stage II: \$52,969 (56,235) Stage III: \$76,750 (87,691) Stage IV: \$116,473 (137,059) Cancer-related inpatient services costs Stage II: \$21,734 (50,196)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Stage III: \$41,277 (75,992) Stage IV: \$76,884 (128,831) Cancer-related outpatient services costs Stage II: \$31,063 (23,061) Stage III: \$35,090 (37,853) Stage IV: \$39,138 (30,994) Cancer-related pharmacy costs Stage II: \$172 (667) Stage III: \$383 (5,380) Stage IV: \$451 (3,986) Year 2 Total cancer-related healthcare costs Stage II: \$17,315 (49,038) Stage III: \$31,550 (76,987) Stage IV: \$55,740 (79,922) Cancer-related inpatient services costs Stage II: \$10,675 (41,220) Stage III: \$19,803 (67,299) Stage IV: \$32,107 (68,872) Cancer-related outpatient services costs Stage II: \$6,323 (16,590) Stage III: \$11,613 (23,030) Stage IV: \$22,657 (30,432)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Cancer-related pharmacy costs Stage II: \$316 (2,788) Stage III: \$134 (1,516) Stage IV: \$975 (4,928) Year 3 Total cancer-related healthcare costs Stage II: \$9,332 (35,329) Stage III: \$28,006 (7,6686) Stage IV: \$34,074 (62,126) Cancer-related inpatient services costs Stage II: \$4,487 (23,335) Stage III: \$17,879 (63,268) Stage IV: \$18,205 (48,254) Cancer-related outpatient services costs Stage II: \$4,435 (16,343) Stage III: \$9,402 (21,562) Stage IV: \$15,134 (28,369) Cancer-related pharmacy costs Stage II: \$410 (4,064) Stage III: \$725 (10,646) Stage IV: \$734 (6,066) Year 4 Total cancer-related healthcare costs Stage II: \$7,263 (28,567) Stage III: \$16,203 (41,606) Stage IV: \$33,824 (77,918) Cancer-related inpatient services costs

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						Stage II: \$3,261 (22,427) Stage III: \$9,159 (31,316) Stage IV: \$18,800 (63,547) Cancer-related outpatient services costs Stage II: \$3,526 (13,072) Stage III: \$6,927 (17,723) Stage IV: \$14,315 (26,893) Cancer-related pharmacy costs Stage II: \$476 (5,144) Stage III: \$118 (1,344) Stage IV: \$710 (7,476) Year 5 Total cancer-related healthcare costs Stage II: \$8,534 (31,174) Stage III: \$10,230 (30,335) Stage IV: \$21,568 (50,677) Cancer-related inpatient services costs Stage II: \$3,270 (18,436) Stage III: \$5,720 (22,810) Stage IV: \$12,194 (41,486) Cancer-related outpatient services costs Stage II: \$4,846 (19,401) Stage III: \$4,466 (14,443) Stage IV: \$8,958 (22,189) Cancer-related pharmacy costs Stage II: \$418 (4,634) Stage III: \$44 (209) Stage IV: \$416 (2,140)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Kebede 2022 ⁽¹³¹⁾ , Journal article, US	1229	2014-2019, 2015-2018 Optum Clininformatics DataMart 2014-2019: 1229 2015-2018: 1004	Systemic therapy (Carboplatin, paclitaxel, bevacizumab, cisplatin, other chemotherapy)	2018, USD \$	Healthcare resource use, Mean (SD): LOT1 Number of inpatient visits PPPM: 0.14 (0.25) Number of ED visits, PPPM: 0.09 (0.18) Number of outpatient visits, PPPM: 5.38 (3.46) Inpatient length of stay (days): 2.21 (3.86) Proportion of patients with cervical with an instance of healthcare resource use LOT1 Inpatients visits: 50% ED visits: 42.9% Outpatient visits: 99.9% Proportion of newly diagnosed patients with cervical with healthcare resource use Pre-treatment Inpatients visits: 13.7% ED visits: 8.4% Outpatient visits: 86.9% LOT1 Inpatients visits: 48.2% ED visits: 35.6% Outpatient visits: 99.7% PPPM HCRU, Mean (SD) Pre-treatment	Healthcare costs per patient per month, Mean (SD) LOT1 (n=1,229) Total costs: \$15,892 (\$16,544) Inpatient costs: \$2,776 (\$8,086) ED Costs: \$262 (\$779) Outpatient costs: \$12,431 (\$14,170) Pharmacy costs: \$423 (\$1,297) PPPM healthcare costs, Mean (SD) Pre-treatment (n=655) Total costs: \$17,210 (\$38,250) Inpatient costs: \$4,518 (\$28,384) ED Costs: \$135 (\$743) Outpatient costs: \$12,301 (\$26,119) Pharmacy costs: \$256 (\$1,827) LOT1 (n=655) Total costs: \$10,929 (\$13,693) Inpatient costs: \$1,732 (\$3,956) ED Costs: \$162 (\$515) Outpatient costs: \$8,762 (\$12,765) Pharmacy costs: \$273 (\$703) Mean PPPM healthcare cost from diagnosis to end of follow-up (\$): 10,121 Mean PPPM healthcare costs of 1L (\$): 10,929 Mean PPPM inpatient cost of 1L (\$): 1,732 Mean PPPM ER cost 1L (\$): 162

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

					Inpatient visits: 0.25 (1.16) ED visits: 0.08 (0.43) Outpatient visits: 5.21 (3.79) Inpatient length of stay (days): 9.34 (15.63) LOT1 Inpatient visits: 0.10 (0.17) ED visits: 0.06 (0.12) Outpatient visits: 3.65 (2.72) Inpatient length of stay (days): 1.39 (2.34)	Mean PPPM outpatient cost 1L (\$): 8,762 Mean PPPM pharmacy cost 1L (\$): 273 Mean PPPM inpatient cost 1L without prior cancers (\$): Mean PPPM inpatient cost of 1L (\$): 1,523 Mean PPPM ER cost 1L (\$): 324 Mean PPPM outpatient cost 1L (\$): 10,931 Mean PPPM pharmacy cost 1L (\$): 265 Mean PPPM inpatient cost 1L prior cancers (\$): Mean PPPM inpatient cost of 1L (\$): 2,993 Mean PPPM ER cost 1L (\$): 251 Mean PPPM outpatient cost 1L (\$): 12,692 Mean PPPM pharmacy cost 1L (\$): 450
Katanyoo 2021 ⁽¹³²⁾ , Journal article, Thailand	194	June to December 2019, Two tertiary hospitals i.e., Faculty of Medicine Vajira Hospital (teaching hospital) and the National Cancer Institute of Thailand (tertiary hospital)	Groups: Group 1: Receiving treatment: CCRT (2D or 3D CRT) Group 2: Follow up time with no disease. Group 3: Follow up time with disease recurrence.			Cost of Illness for Scenario 1: No Disease at 5 Years without Severe Late Side Effects (US dollar in 2019), Mean SD: Direct medical cost 2D: 5,985 (120) 3D-CRT: 8,013 (112) Direct non-medical cost: 1,677 (194) Travel: 347 (18) Food: 221 (24) Informal care: 941 (163) Indirect cost 729 (28)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						COI using 2D: 8,391 (216) COI using 3D-CRT: 10,418 (214) Cost of Illness for Scenario 2.1: No Disease at 5 Years with Severe Late Gastrointestinal Side Effects (US dollar in 2019), Mean SD: Direct medical cost 2D: 12,735 (488) 3D-CRT: 14,763 (488) Direct non-medical cost: 3,763 (188) Travel: 766 (28) Food: 368 (26) Informal care: 2,466 (164) Indirect cost: 1,519 (38) COI using 2D: 18,018 (541) COI using 3D-CRT: 20,045 (540) Cost of Illness for Scenario 2.2: No Disease at 5 Years with Severe Late Genitourinary Side Effects (US dollar in 2019), Mean SD Direct medical cost 2D: 14,544 (515) 3D-CRT: 16,571 (514) Direct non-medical cost: 2,372 (197) Travel: 400 (19) Food: 238 (24) Informal care: 1,467 (510) Indirect cost: 992 (29) COI using 2D: 17,908 (515) COI using 3D-CRT: 19,936 (514)

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						Cost of Illness for Scenario 3: Recurrence of Disease and Death (US dollar in 2019), Mean SD Direct medical cost 2D: 16,546 (514) 3D-CRT: 18,574 (512) Direct non-medical cost: 2,788 (599) Travel: 563 (28) Food: 351 (27) Informal care: 1,708 (553) Indirect cost: 41,742 (323) Productivity loss: 1,763 (321) Mortality cost at 5 years: 39,979 COI using 2D: 61,076 (861) COI using 3D-CRT: 63,103 (858) Estimated of 5-Year Economic Burden from Newly Diagnosed Locally Advanced Cervical Cancer Patients in Thailand in 2018 (US dollar in 2019), Cost No disease with no severe late side effects 2D: 24,644,803 3D-CRT: 30,599,020 No disease with severe late GI side effects 2D: 3,175,132 3D-CRT: 1,177,462 No disease with severe late GU side effects 2D: 8,941,410 3D-CRT: 4,098,552 Recurrence of disease and death

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

						2D: 92,408,033 3D-CRT: 95,475,356 Total cost 2D: 129,169,379 3D-CRT: 131,350,391
McGarvey 2023 ⁽¹³³⁾ , journal article, USA	Stage II: 78	June 1, 2015–July 31, 2020	NR	2020, USD	NR	Out of pocket cost Stage II Year 1 post diagnosis Mean (SD): 8,495 (9,938) Median (range): 1,849 (0-96,753) Year 2 post diagnosis Mean (SD): 6,329 (5,876) Median (range): 1,483 (19-66,168) Year 3 post diagnosis Mean (SD): 3,185 (1,485) Median (range): 1,790 (101-12,018)
	Stage III: 82					Out of pocket cost Stage III Year 1 post diagnosis Mean (SD): 12,344 (11,552) Median (range): 1,617 (0-173,255) Year 2 post diagnosis Mean (SD): 7,659 (8,405) Median (range): 861 (0,-88,806) Year 3 post diagnosis Mean (SD): 4,469 (6,132) Median (range): 923 (20-33,810)
	Stage IV: 68					Out of pocket cost Stage IV Year 1 post diagnosis

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						Mean (SD): 10,001 (10,534) Median (range): 1,406 (0-135,444) Year 2 post diagnosis Mean (SD): 5,532 (6,512) Median (range): 595 (14-46,651) Year 3 post diagnosis Mean (SD): 6,823 (8,237) Median (range): 1,057 (78-21,611)
Campuzano 2024 ⁽¹³⁴⁾ , journal article Brazil	Stage II: 24,737	January 2014 to December 2020	NR	NR	Stage II Hospitalization Mean (SD) per patient: 2.19 (2.33) Median (IQR) per patient: 1.0 (1.0–3.0) Median PPPM [CI]: 0.07 [0.07–0.07] LOS per hospitalization (days) Mean (SD): 6.07 (7.4) Median (IQR): 4.0 (2.0–7.0) Outpatient visit N (%): 23,414 (94.7) Mean (SD) per patient: 23.85 (31.34) Median (IQR) per patient: 14.0 (7.0–28.0) Median PPPM [CI]: 0.63 [0.62–0.64] Visits for Chemotherapy N (%): 19,038 (77) Mean (SD) per patient: 5.6 (8.76) Median (IQR) per patient: 3.0 (3.0–5.0)	NR

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					Median PPPM [CI]: 1.50 [1.50–1.50] Visits for Radiotherapy N (%): 22,078 (89.3) Mean (SD) per patient: 3.35 (1.87) Median (IQR) per patient: 3.0 (2.0–4.0) Median PPPM [CI]: 1.50 [1.50–1.50]	
	Stage III: 35,587				Stage III Hospitalization Mean (SD) per patient: 2.34 (2.26) Median (IQR) per patient: 2.0 (1.0–3.0) Median PPPM [CI]: 0.09 [0.09–0.10] LOS per hospitalization (days) Mean (SD): 6.46 (7.82) Median (IQR): 4.0 (2.0–8.0) Outpatient visit N (%): 33,816 (95) Mean (SD) per patient: 23.9 (30.66) Median (IQR) per patient: 15.0 (7.0–28.0) Median PPPM [CI]: 0.75 [0.75–0.76] Visits for Chemotherapy N (%): 29,365 (82.5) Mean (SD) per patient: 5.82 (7.9) Median (IQR) per patient: 3.0 (3.0–6.0) Median PPPM [CI]: 1.48 [1.48–1.48]	

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					Visits for Radiotherapy N (%): 30,717 (86.3) Mean (SD) per patient: 3.23 (1.75) Median (IQR) per patient: 3.0 (2.0–4.0) Median PPPM [CI]: 1.50 [1.50–1.50]	
	Stage IV: 19,132				Stage IV Hospitalization Mean (SD) per patient: 2.37 (2.03) Median (IQR) per patient: 2.0 (1.0–3.0) Median PPPM [CI]: 0.11 [0.11–0.11] LOS per hospitalization (days) Mean (SD): 6.56 (7.71) Median (IQR): 4.0 (2.0–8.0) Outpatient visit N (%): 18,220 (95.2) Mean (SD) per patient: 27.41 (36.41) Median (IQR) per patient: 16.0 (7.0–33.0) Median PPPM [CI]: 0.96 [0.93–0.98] Visits for Chemotherapy N (%): 16,271 (85) Mean (SD) per patient: 6.8 (7.38) Median (IQR) per patient: 5.0 (3.0–8.0) Median PPPM [CI]: 1.20 [1.20–1.20]	

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					Visits for Radiotherapy N (%): 12,743 (66.6) Mean (SD) per patient: 2.78 (1.66) Median (IQR) per patient: 2.0 (2.0–4.0) Median PPPM [CI]: 1.50 [1.49–1.50]	
Chen 2023 (135), journal article, China	Stage IB: 610	August 2020 – June 2021	Radical hysterectomy/extensive trachelectomy/ultra-extensive hysterectomy/chemoradiotherapy	NR, USD	NR	Stage IB Total cost: 19,438.6 Direct medical cost: 18,290.9 (0.94) Diagnosis: 301.4 (0.02) Initial treatment: 6,292.8 (0.34) Chemoradiotherapy: 7,943.8 (0.43) Follow up: 2,600.1 (0.14) Recurrence/progression/metastasis: 1,152.8 (0.06) Direct non-medical cost: 419.8 (0.02) Indirect cost: 727.8 (0.04)
	Stage IIA: 487		Radical hysterectomy/ /ultra-extensive hysterectomy/ preoperative neoadjuvant chemotherapy /chemoradiotherapy			Stage IIA Total cost: 22,968.8 Direct medical cost: 21,691 (0.94) Diagnosis: 279.6 (0.01) Initial treatment: 6,039.6 (0.28) Chemoradiotherapy: 11,314.6 (0.52) Follow up: 2,277.5 (0.1) Recurrence/progression/metastasis: 1,779.7 (0.08) Direct non-medical cost: 443.6 (0.02) Indirect cost: 834.2 (0.04)
	Stage IIB: 282		Radical hysterectomy/ /ultra-extensive hysterectomy/ concurrent			Stage IIB Total cost: 26,936 Direct medical cost: 25,067.3 (0.93)

Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

			chemoradiotherapy /chemoradiotherapy			Diagnosis: 421 (0.02) Initial treatment: 7,104.7 (0.28) Chemoradiotherapy: 10,555.4 (0.42) Follow up: 3,613.3 (0.14) Recurrence/progression/metastasis: 3,373 (0.13) Direct non-medical cost: 601.7 (0.02) Indirect cost: 1,267 (0.05)
	Stage III-IV: 514 (stage III: 452, stage IV: 62)		Concurrent chemoradiotherapy/radical hysterectomy//simple chemotherapy/ultra-extensive hysterectomy/palliative chemotherapy			Stage III-IV Total cost: 27,332.6 Direct medical cost: 25,304 (0.93) Diagnosis: 431.2 (0.02) Initial treatment: 13,605.9 (0.54) Chemoradiotherapy: 5,249 (0.21) Follow up: 6,017.9 (0.24) Recurrence/progression/metastasis: 1,040.9 (0.04) Direct non-medical cost: 987.7 (0.04) Indirect cost: 1,267 (0.05)
Dau 2024 ⁽¹³⁶⁾ , journal article, Uganda	338	19 th September 2022 – 17 th January 2023	Chemotherapy/radiation/surgery/palliative care	NR, UGX and CAD	NR	The out-of-pocket expenses ranged between 500,001 to 2,000,000 UGX (between CAD\$ 130-530)

1L: First-line; CT: Computed tomography; ED: Emergency department; ER: Emergency room; NR: Not reported; PPM: Per-patient-per-month

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Company response to clarification questions for pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

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Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Patient Organisation Submission

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

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

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

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

Information on completing this submission

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

About you

1. Your name	[REDACTED]
2. Name of organisation	UK Cervical cancer
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation was set up to work towards the elimination of HPV and prevent cervical cancer. The organisation releases upon the goodwill of donations- we are a non profit organisation and totally run by volunteers. There are at present 6 of us including 3 people who work in Australia with our sister charity Australian Cervical cancer
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No

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?	By people contacting UK cervical cancer with their stories, requesting funding or support

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?	N/A

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People feel that they wish more help and support was available
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	I cannot answer

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	I cannot answer

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.	N/A

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	BME people always feel marginalised

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

In up to 5 bullet points, please summarise the key messages of your submission.	• My main reason for this submission is to be able to support NICE in making changes in helping people gain access to treatment and ongoing support for their condition

Thank you for your time.

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

Your privacy

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

Please select YES if you would like to receive information about other NICE topics - YES

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Single Technology Appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

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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 as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

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send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 1 December 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating untreated high-risk locally advanced 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	Dr Asma Sarwar
2. Name of organisation	University College London Hospitals
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 untreated high-risk locally advanced cervical cancer ? ☐ A specialist in the clinical evidence base for untreated high-risk locally advanced 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.	Nil

Clinical expert statement

8. What is the main aim of treatment for untreated high-risk locally advanced cervical cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim is to cure the cancer primarily, in the process any symptoms the cancer is causing are also treated
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)	For this patient cohort, I would define a complete metabolic response as a PET-CT demonstrating SUV values reduced to background levels 12 weeks after chemoradiation, accompanied by resolution of previously noted restricted diffusion on MRI of the cervix at the same time point.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated high-risk locally advanced cervical cancer ?	Yes. Although standard chemoradiation achieves good cure rates in this cohort, approximately 20–25% of patients relapse or are not fully cured following primary treatment. There remains clear scope for improving outcomes..
11. How is untreated high-risk locally advanced 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?	- BGCS cervical cancer guidelines, https://www.bgcs.org.uk/wp-content/uploads/2020/05/FINAL-Cx-Ca-Version-for-submission.pdf - ESTRO guidelines Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, Fischerová D, Jahn-Kuch D, Joly F, Kohler C, Lax S, Lorusso D, Mahantshetty U, Mathevet P, Naik R, Nout RA, Oaknin A, Peccatori F, Persson J, Querleu D, Bernabé SR, Schmid MP, Stepanyan A, Svintsitskyi V, Tamussino K, Zapardiel I, Lindegaard J. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. Int J Gynecol Cancer. 2023 May 1;33(5):649-666. doi: 10.1136/ijgc-2023-004429. PMID: 37127326; PMCID: PMC10176411. - The treatment pathway is well defined. Concurrent weekly cisplatin-based chemotherapy combined with daily pelvic radiotherapy for five weeks, followed by brachytherapy (internal radiotherapy), remains the standard of care approach. - In light of the INTERLACE trial (McCormack et al.) findings, some UK clinicians have adopted induction chemotherapy—six weekly cycles of carboplatin and paclitaxel—administered immediately before standard

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	treatment. However, its use remains controversial and is not currently considered standard of care. - The additional pembrolizumab, if given as per the A18 trial, would elongate the current standard pathway. - The prolonged use of pembrolizumab for up to 2 years in total would entail additional visits at either end of the standard treatment. This would be 3weekly for the first 5 cycles pre chemoradiation, which will then reduce to 6weekly for 15 cycles post chemoradiation. This would involve additional 3-6weekly clinical appointments, blood tests and scans. - Of note the CALLA trial (Monk et al), which looked at PDL1 inhibition with durvalumab (pembrolizumab- PD1 inhibitor) alongside chemoradiation and for 24cycles (each cycle 4 weeks long) was a negative trial so the results of the A18 trial need to be taken in the context of this.
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)	- Yes healthcare resource does differ. The new technology would involve the addition of pembrolizumab infusions every 3weeks for 5 cycles followed by standard chemo radiotherapy and brachytherapy, followed by 15cycles of 6weekly pembrolizumab infusions. Whereas standard treatment is 5 weeks of chemoradiotherapy with weekly cisplatin chemotherapy and brachytherapy. This commits the patient to additional follow up appointments, infusional treatment, blood tests and side effects long after their 5weeks of chemo radiation. - Secondary care in a specialist oncology clinic - Additional chemotherapy daycare slots, blood testing slots consultant clinic appointments, scan slots every 12weeks.
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?	- The results of the A18 study (Lorusso et al) suggest an improvement in progression free and overall survival at 3years. However this was not universal for all subgroups in the trial, more benefit (more significant hazard ratios) were seen in the FIGO stage III/IV group. - Some questions remain unanswered over its use.

Clinical expert statement

	- No, it will worsen QOL due to the higher rates of toxicity, also the prolonged nature of the treatment (pembrolizumab- 15cycles every 6weeks) will result in side effects of treatment to continue or develop at later stages.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	- Hazard ratios were more favourable in patients with FIGO stage III/IV disease compared with those with earlier stage I/II disease, suggesting a greater treatment response in the later-stage group. However, these findings should be interpreted cautiously, as patients with advanced disease are more likely to have micrometastatic disease—an entity known to benefit from pembrolizumab in the first-line palliative setting. - There are no available data stratifying results by PD-L1 status.
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)	- Implementation will be more challenging, as it requires additional treatment both before and after standard chemoradiation. This includes extra chemotherapy infusion slots, additional blood tests for the patient, and further clinic review appointments—which will need to be face-to-face, given the close monitoring required during pembrolizumab therapy. - The prolonged nature of the ‘maintenance’ pembrolizumab for 15 cycles after chemoradiation will reduce patient acceptability
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	- As this is an immunotherapy treatment, management will follow ESMO guidelines or local trust protocols for immunotherapy-related toxicity. These outline the recommended approach for recognising, treating, and, where appropriate, rechallenging with immunotherapy. - Additional investigations will be required if a patient develops immunotherapy-related toxicity, as these tests help guide management. For example, patients who experience diarrhoea while receiving pembrolizumab will require stool testing—including viral PCR, C. difficile, and ova/cyst screening, in some cases a flexible sigmoidoscopy—to aid assessment and management decision-making.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	No

Clinical expert statement

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	
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 is a step change in the management of cervical cancer - Yes there is an unmet need for these women with advanced cancers - Yes is innovative but more clarity needed on whether so many cycles of pembrolizumab before and after chemoradiotherapy are necessary. This is quite a commitment for patients. Biomarkers for treatment response are needed to aid more personalised care for patients
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?	- Immunotherapy has a completely different side-effect profile compared with chemotherapy. - The current standard of care for these patients involves chemotherapy—weekly cisplatin at 50 mg/m² administered alongside daily radiotherapy. - Adding pembrolizumab would require clinical review every three weeks for five cycles, followed by ongoing reviews for up to 24 cycles after radiotherapy, to ensure close monitoring for treatment-related toxicity. - In the A18 study, 32% of patients receiving immunotherapy experienced immune-related adverse events, including 4% with grade ≥3 events requiring medical intervention. In comparison, the standard treatment arm reported 10% immune-mediated adverse events, with fewer than 1% reaching grade 3 severity. - The side-effect profile of immunotherapy varies, but commonly includes permanent hypothyroidism, colitis, skin rashes, and immune suppression.

Clinical expert statement

	-The core component of curative treatment remains chemoradiation. There is a potential risk that pembrolizumab-related toxicity could delay this, although the A18 study did not show significant delays. -Quality of life may be affected by immunotherapy toxicity, depending on its severity and the organ system involvement. Grade ≥ 3 toxicity was more frequent in patients treated with pembrolizumab.
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?	- The standard arm of the keynote A18 and CALLA trials reflect UK practice - The most important outcomes—toxicity and overall survival—were assessed. However, it would be valuable to know what treatments were offered to patients who relapsed after receiving this and what their subsequent outcomes were. As patients who have already received pembrolizumab in the first-line setting, would not be able to access it at relapse. - No surrogates used - Pembrolizumab is a widely used drug in other cancer types, side effect profile is predictable and well known
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	I'm not aware of any published real world evidence data of its use in this way.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	- This disease often affects younger patients, and in London the majority of cases occur in individuals born outside the UK, where HPV vaccination and cervical screening may not be routine. These patients can be challenging to engage due to language barriers. All patients have other barriers to treatment such as caring responsibilities and work commitments. Many may struggle to commit to nearly two years of therapy compared with the current six-week standard.

Clinical expert statement

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • 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.	- Because pembrolizumab is an infusional immunotherapy, it requires face-to-face medical review before each cycle, adding further appointments. For patients from lower socioeconomic backgrounds—which is common in this group—the cost and time associated with frequent hospital visits may be prohibitive. Their younger age and competing responsibilities may further limit their ability to adhere to such an extended treatment schedule.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is an unmet need in this group of patients with advanced cervical cancer

Pembrolizumab appears to offer a overall survival and progression free survival advantage

Clarity is needed to understand which patients would benefit most from this treatment

Pembrolizumab use at this stage of a patients journey reduces their options if they relapse at a later stage

Pembrolizumab use is associated with higher rates of toxicity

Thank you for your time.

Your privacy

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Single Technology Appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Clinical expert statement

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Clinical expert statement

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

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Part 1: Treating untreated high-risk locally advanced 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 Foundation Trust
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 untreated high-risk locally advanced cervical cancer ? ☒ A specialist in the clinical evidence base for untreated high-risk locally advanced 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.	None

Clinical expert statement

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

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8. What is the main aim of treatment for untreated high-risk locally advanced cervical cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To cure disease
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)	Complete response
10. In your view, is there an unmet need for patients and healthcare professionals in untreated high-risk locally advanced cervical cancer ?	Yes, the treatment outcomes for persistent and recurrent/metastatic cervical cancer are poor. In cervical cancer, achieving local control translates into survival benefits. For stage III/IVA cervical cancer, the chance of achieving cure is <50%, and having a treatment that increases cure rates is very important.
11. How is untreated high-risk locally advanced 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?	Locally advanced cervical cancer is treated with definitive chemo-radiation with EBRT, weekly cisplatin chemotherapy and followed by intrauterine brachytherapy. This is the international standard of care and there is no alternative for locally advanced disease. The BGCS and ESGO-ESTRO guidelines underline this approach. In terms of the radiotherapy technical details, the EMBRACE II study protocol is followed. The INTERLACE trial assessed induction chemotherapy prior to chemoradiation and there are some centres in the UK that have adopted this. However, the patient cohort for INTERLACE was very different to A18, with patients with more advanced disease in the A18 study.
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?	The radiotherapy and concurrent chemotherapy will remain the same as current care in the NHS, while the addition of concurrent and adjuvant pembrolizumab would be additional. It will be delivered in specialist cancer centres. No additional investment would be needed as centres will already be using pembrolizumab in the first line recurrent setting, so will have the experience and pathways for delivery and management of any toxicities.

Clinical expert statement

• 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?	This would increase the number of patients with cervical cancer that are completely cured from cancer.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The indication is for Stage III/IVA (FIGO 2014) cervical cancer
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)	There will be additional treatment of immunotherapy which means additional visits, blood tests and possible toxicities.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional 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	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	The addition of immunotherapy to radiotherapy is a step-change for this disease – to date no other adjuvant therapies have been shown to improve cure.
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 chemo-radiotherapy is very unlikely to be impacted by the addition of immunotherapy – in the KEYNOTE A18 trial there was not an increase in patients not completing radiotherapy/brachytherapy compared to the control arm.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, the radiotherapy, chemotherapy and brachytherapy in A18 is consistent with UK practice. Most important outcome would be complete response, overall survival and PFS.

Clinical expert statement

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	These results seem consistent with real world data
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could - exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation - 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.	

Clinical expert statement

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here](#).

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The addition of immunotherapy to chemoradiation significantly improves complete response rates which translates into long term cure for locally advanced cervical cancer.

This is achieved with acceptable toxicity

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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**Pembrolizumab with chemoradiation for untreated high-risk locally
advanced cervical cancer [ID6138]**

External Assessment Group Report

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
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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.

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Paul Tappenden led the assessment. Mark Clowes critiqued the company's search strategy. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Jen-Yu Amy Chang and Kate Ren critiqued the statistical aspects of the submission. Mon Yee, Paul Tappenden and Esther Chanakira critiqued the health economic analysis submitted by the company and conducted additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

2D	Two-dimensional
AE	Adverse event
AIC	Akaike Information Criterion
APaT	All Participants as Treated
ASA	Additional sensitivity analysis
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BSA	Body surface area
CCRT	Concurrent chemoradiotherapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Controlled Register of Trials
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRT	Chemoradiotherapy
CS	Company's submission
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
DCEA	Distributional cost-effectiveness analysis
DCO	Data cut-off
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
eMIT	electronic Market Information Tool
EOL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-CX24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module
EQ-5D	Euroqol 5-Dimensions
EQ-5D-3L	Euroqol 5-Dimensions 3-Level
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
FA	Final Analysis
FAS	Full Analysis Set
FIGO	International Federation of Gynecology and Obstetrics
GP	General Practitioner
Gy	Gray
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment

IA2	Interim Analysis 2
ICD 10	International Classification of Diseases Version 10
ICER	Incremental cost-effectiveness ratio
IGABT	Image-guided adaptive brachytherapy
IMD	Index of Multiple Deprivation
IMRT	Intensity modulated radiation therapy
INAHTA	International Network of Agencies for Health Technology
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LACC	Locally advanced cervical cancer
LS	Least squares
LYG	Life year gained
MCM	Mixture-cure models
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
MPSC	Medicines Procurement and Supply Chain
MRI	Magnetic resonance imaging
MSD	Merck Sharp and Dohme
N	Number
N/a	Not applicable
NCI	National Cancer Institute
NHB	Net health benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed/progressive disease
PD1	First disease progression
PD-1	Programmed cell death 1
PD2	Second disease progression
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors

RoB 2	Risk of Bias Version 2.0
SAE	Serious adverse event
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
TA	Technology Appraisal
TNM	Tumour, Node, Metastasis
TP	Transition probability
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
VMAT	Volumetric modulated arc therapy
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses pembrolizumab plus concurrent chemoradiotherapy (CCRT) for the treatment of adults with International Federation of Gynecology and Obstetrics (FIGO) 2014 Stage III-IVA locally advanced cervical cancer (LACC) who have not received prior definitive therapy. This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the EAG's preferred analysis are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are detailed in the [main EAG report](#).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6138	Summary of issue	Report sections
Issue 1	Uncertainty surrounding the magnitude of long-term benefit of pembrolizumab plus CCRT, including its curative potential	4.3.5 (critical appraisal points 2, 3, 4, and 6)
Issue 2	Poor OS model fit based on the Final Analysis data-cut of KEYNOTE-A18	5.1.3

EAG - External Assessment Group; CCRT - concurrent chemoradiotherapy; OS - overall survival

Within the company's original economic model, as described in the company's submission (CS), transition probabilities out of the progression-free (PF) health state are informed by standard parametric survival models fitted to data on progression-free survival (PFS) and time to progression (TTP) from Interim Analysis 2 (IA2) of KEYNOTE-A18. Following the clarification round, the company provided an updated economic model which included the use of flexible parametric models fitted to updated data from the Final Analysis data-cut of this trial. The company's updated economic model addresses the key concerns raised by the EAG at the clarification stage. The company's updated primary base case model (informed by investigator-assessed PFS) and the EAG's preferred model are very similar; the latter includes the correction of some minor errors which leads to a slightly lower ICER for pembrolizumab plus concurrent chemoradiotherapy (CCRT) versus CCRT alone.

1.2 Overview of the key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with CCRT alone, pembrolizumab plus CCRT is assumed to impact on QALYs by:

- Extending PFS, including a higher proportion of patients achieving cure
- Extending overall survival (OS), including a higher proportion of patients achieving cure
- Slightly reducing HRQoL due to a higher burden of adverse events (AEs).

Compared with CCRT alone, pembrolizumab plus CCRT is assumed to affect costs by:

- Increasing overall costs due to the acquisition cost of pembrolizumab
- Reducing the downstream costs of treatments for progressed disease
- Slightly increasing disease management costs
- Slightly increasing the costs associated with managing AEs.

The modelling assumptions that have the greatest effect on the ICER for pembrolizumab plus CCRT versus CCRT alone are:

- The choice of parametric survival model for PFS and TTP data from the Final Analysis data-cut of KEYNOTE-A18 (informing transition probabilities out of the PF health state)
- Whether transition probabilities out of the first progression state (PD1) state are adjusted using calibration factors
- The structural assumptions applied to model cure and treatment effect waning for pembrolizumab (at first- and second-line) in both treatment groups.
- The use of Blinded Independent Central Review (BICR) assessed PFS and TTP data from the Final Analysis data-cut of KEYNOTE-A18 (used in the company's updated secondary base case analysis).

1.3 The decision problem: Summary of the EAG's key issues

The decision problem addressed in the CS is in line with the final NICE scope. The company's proposed positioning of pembrolizumab is alongside CCRT as first-line treatment for adult patients with untreated FIGO 2014 Stage III-IVA LACC. The proposed use of pembrolizumab includes a stopping rule at 2 years. The proposed positioning of pembrolizumab and the stopping rule are consistent with the European Medicines Agency (EMA) marketing authorisation for pembrolizumab in the LACC indication. The CS includes a single comparator - CCRT alone. The EAG's clinical advisors confirmed that CCRT using cisplatin-based chemotherapy, external beam radiotherapy (EBRT) and brachytherapy represents the current standard of care for patients with untreated Stage III-IVA LACC.

The final NICE scope lists three subgroups of interest relating to histology, combined positive score (CPS) of programmed death-ligand 1 (PD-L1) expression and tumour mutational burden. However, the CS does not present any clinical or economic subgroup analyses relating to these factors. The absence of subgroup analyses based on these factors is not discussed in the CS. It is unclear whether the clinical effectiveness and cost-effectiveness of pembrolizumab plus CCRT would differ across these subgroups.

The CS states that inequalities exist across the pathway for cervical cancer and that deprivation is a key factor affecting the diagnosis and prognosis of people with cervical cancer. The CS provides details of the results of a distributional cost-effectiveness analysis (DCEA) of pembrolizumab plus CCRT. This type of analysis does not form part of NICE's Reference Case.

1.4 The clinical effectiveness evidence: Summary of the EAG's key issues

The key clinical effectiveness evidence reported in the CS comes from KEYNOTE-A18: this is an ongoing, Phase III, multi-centre, double-blind randomised controlled trial (RCT). The trial compared pembrolizumab plus CCRT versus placebo plus CCRT. The trial included adult patients with FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stage III-IVA (with node-positive or -negative disease) who had not received prior definitive therapy (surgical, radiation, systemic therapy for cervical cancer, or immunotherapy) and who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. In line with the marketing authorisation for pembrolizumab for LACC, only data relating to the FIGO 2014 Stage III-IVA subgroup of KEYNOTE-A18 are of relevance to this appraisal. Within the trial, the intervention group received pembrolizumab 200mg every 3 weeks (Q3W) for 5 infusions, plus cisplatin 40mg/m² weekly for 5 infusions plus EBRT followed by brachytherapy, followed by pembrolizumab 400mg every 6 weeks (Q6W) for 15 infusions. The control group received the same regimen but received placebo instead of pembrolizumab. The primary outcomes were OS and PFS.

The clinical results from KEYNOTE-A18 presented in the CS relate to IA2 (data-cut-off [DCO] 8th January 2024). The results of the Final Analysis (DCO 7th January 2025) were provided in an addendum to the CS following the clarification round.

At IA2, for Stage III-IVA participants, the hazard ratio (HR) for OS favoured pembrolizumab plus CCRT (HR 0.57; 95% confidence interval [CI] 0.39 to 0.83; $p=$ [REDACTED]). The HRs for PFS also favoured pembrolizumab plus CCRT when assessed by investigators (HR [REDACTED]) and by BICR (HR [REDACTED]). At the Final Analysis DCO, the HRs for OS and PFS continued to favour the pembrolizumab group: OS (HR 0.64 (95% CI 0.46 to 0.88; $p=0.0031$); investigator-assessed PFS (HR 0.63; 95% CI 0.48 to 0.82; $p=0.0002$ [REDACTED])

[REDACTED]

[REDACTED]

The EAG considers the results for the FIGO 2014 Stage III-IVA subgroup of the KEYNOTE-A18 trial to be of direct relevance to the decision problem. The EAG notes the following issues:

- The EAG's clinical advisors commented that the Stage III-IVA subgroup in KEYNOTE-A18 is similar to the expected eligible UK population in terms of age and disease type. The trial population differs from the expected eligible UK population in terms of ethnicity; however, ethnicity is unlikely to be a treatment effect modifier.
- The CCRT regimen used in KEYNOTE-A18 (including cisplatin, EBRT and brachytherapy) is representative of current UK practice; however, the total radiation dose used in the trial is lower than that used in NHS practice. It is uncertain whether the relative treatment effects of pembrolizumab plus CCRT on PFS and OS would be different had a higher total radiation dose been used in the trial.
- Despite the availability of additional data from the Final Analysis data-cut of the trial, there remains uncertainty around long-term outcomes after completion of pembrolizumab treatment.

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company's economic model assesses the cost-effectiveness of pembrolizumab plus CCRT versus CCRT alone for the treatment of adult patients with untreated high-risk FIGO 2014 Stage III-IVA LACC over a lifetime horizon from the perspective of the NHS and Personal Social Services (PSS). The company's original model uses a state-transition (semi-Markov) approach, informed by time-to-event data from IA2 of the KEYNOTE-A18 RCT (DCO 8th January 2024), as well as external data on post-progression outcomes from the Final Analysis of the KEYNOTE-826 RCT (pembrolizumab plus chemotherapy [with or without bevacizumab] versus placebo plus chemotherapy [with or without bevacizumab] as first-line treatment for patients with recurrent, persistent or metastatic cervical cancer; CPS ≥ 1 subgroup). The model includes four health states: (i) Progression-free; (ii) Progressed Disease 1; (iii) Progressed Disease 2 and (iv) Dead. The model includes an assumption that pembrolizumab re-challenge is permitted for patients who experience a first progression event at least 2.5 years after initiating first-line pembrolizumab treatment (i.e., at least 6 months after completing first-line pembrolizumab). A structural assumption of cure is applied in both treatment groups, whereby the predicted probabilities of progression are reduced by 0% at the end of Year 5, increasing approximately linearly to 95% by the end of Year 7. The model includes a Patient Access Scheme (PAS) discount for pembrolizumab in both the first- and second-line settings. The company's original model suggests that the probabilistic ICER for pembrolizumab plus CCRT versus CCRT alone is [REDACTED] per QALY gained. The deterministic ICER is slightly lower at [REDACTED] per QALY gained.

The probabilities of transitioning out of the progression-free state in the company's original model were obtained from standard parametric survival models fitted to PFS and TTP data from IA2 of KEYNOTE-A18. These survival models did not provide a good representation of the observed time-to-event data for these end points. Following the clarification round, the company provided an updated economic model which included substantial amendments. The most notable changes in the company's updated primary base case model are: (i) the use of 1-knot odds restricted cubic spline (RCS) models fitted to data on PFS and TTP from the Final Analysis data-cut of KEYNOTE-A18; (ii) the use of 2-knot odds RCS models fitted to data on PFS and TTP for the CPS ≥ 1 with prior chemoradiotherapy (CRT) subgroup of KEYNOTE-826; and (iii) the inclusion of calibration factors applied to all post-progression transition probabilities out of the PD1 health state which force model-predicted OS to better fit the observed OS data from the Final Analysis data-cut of KEYNOTE-A18. The updated model also includes updated utility values, updated unit costs and the correction of several errors identified by the EAG at the clarification stage of the appraisal. The probabilistic version of the company's updated primary base case model suggests that the ICER for pembrolizumab plus CCRT versus CCRT alone is [REDACTED] per QALY gained. The deterministic version of the updated model suggests a slightly higher ICER of [REDACTED] per QALY gained. The company's addendum also describes a secondary base case analysis based on BICR-assessed PFS and TTP which suggests a lower deterministic ICER of [REDACTED] per QALY gained. The company's additional scenario analyses suggest that the updated model is particularly sensitive to: (i) the cure and treatment effect waning assumptions; (ii) the selection of alternative parametric survival models fitted to PFS and TTP from KEYNOTE-A18 and (iii) the use of BICR vs. investigator-assessed PFS/TTP.

The EAG is generally satisfied that the company's updated model addresses many of the limitations which were evident in the original economic model. As such, the EAG's preferred model is very similar to the company's updated primary base case model (based on investigator-assessed PFS and TTP from KEYNOTE-A18), but includes some minor error corrections. The EAG notes that despite the availability of longer-term data on PFS and OS from the Final Analysis of KEYNOTE-A18, there remains uncertainty around the long-term benefits of pembrolizumab plus CCRT, including the extent of its curative potential (see [Issue 1](#)). The EAG also notes that the need to calibrate the transition probabilities in the updated model to force modelled OS to fit the observed OS data from KEYNOTE-A18 is problematic and the exact cause of this discrepancy cannot be easily determined (see [Issue 2](#)).

Issue 1: Uncertainty surrounding the magnitude of long-term benefit of pembrolizumab plus CCRT, including its curative potential

Report section	4.3.5 (critical appraisal points 2, 3, 4 and 6)
Description of issue and why the EAG has identified it as important	The company's updated model uses longer-term data of PFS and TTP from the Final Analysis data-cut of KEYNOTE-A18 ([REDACTED]). This updated data-cut provides around one year of additional follow-up compared to IA2. However, the EAG considers the magnitude of the long-term benefit for pembrolizumab plus CCRT to remain uncertain for the following reasons: (i) Relative to the standard parametric survival models, the selected 1-knot odds RCS models provide an improved fit to the PFS and TTP data from the Final Analysis data-cut of KEYNOTE-A18. However, the company has not obtained any clinical input regarding the plausibility of the models fitted to the PFS and TTP data from the updated data-cut. (ii) Whilst cure is expected for a proportion of patients receiving pembrolizumab plus CCRT or CCRT alone, the extent of this is uncertain. The CS states that no epidemiological evidence is available to inform long-term cure rates. In addition, the company has not attempted to estimate cure fractions by fitting mixture-cure models (MCMs) to the PFS and OS data from KEYNOTE-A18. Instead, the economic model applies a structural assumption of cure which relies on arbitrary assumptions (i.e., the approximately linear increase in the cure proportion which is applied as a reduction in the predicted probabilities of progression obtained from the parametric survival models) between Years 5 and 7. (iii) The model includes an assumption of treatment effect waning for pembrolizumab. Longer follow-up of KEYNOTE-A18 would be required to support or refute this assumption. (iv) Model-predicted OS does not reflect the observed OS from the Final Analysis data-cut of KEYNOTE-A18 (further details are provided in Issue 2).
What alternative approach has the EAG suggested?	The EAG sought input from its clinical advisors regarding the plausibility of the RCS models fitted to the PFS and TTP data from Final Analysis of KEYNOTE-A18. The advisors considered the selected 1-knot odds RCS models to be reasonable, but noted that further follow-up would be required to have confidence that the predicted PFS benefit would be maintained in the longer-term. The EAG has undertaken additional sensitivity analyses to explore the use of alternative 1- and 2-knot RCS models and to assess the impact of removing the cure "warm-up" period between Year 5 and Year 7. The company's scenario analyses using the updated model explore the impact of removing both the cure and treatment waning assumptions in the updated model; because the EAG's preferred model is very similar to the company's primary base case model, the EAG has not repeated this analysis.
What is the expected effect on the cost-effectiveness estimates?	The deterministic version of the EAG's preferred model (EA1a) suggests that the ICER for pembrolizumab plus CCRT versus CCRT alone is [REDACTED] per QALY gained. The ICER is sensitive to the choice of RCS models for both PFS and TTP from KEYNOTE-A18, ranging from [REDACTED] per QALY gained to [REDACTED] per QALY gained (ASA1a-d). Removing the cure warm-up period has a minimal impact on the ICER (ASA8). The company's scenario analysis which removes the cure and treatment waning assumption has a significant impact on the model results, increasing the company's updated primary base case ICER from [REDACTED] to [REDACTED] per QALY gained.

What additional evidence or analyses might help to resolve this key issue?	Further input from clinical experts regarding the plausibility of the company's updated modelled PFS and OS estimates would be valuable. The company could attempt to estimate cure fractions by fitting MCMs to the PFS and OS data from the Final Analysis data-cut of KEYNOTE-A18. Longer-term follow-up of PFS and OS data from KEYNOTE-A18 may provide greater confidence in the company's model predictions. However, the EAG is unsure whether any additional data-cuts of this trial are anticipated.

Issue 2: Poor OS model fit based on the Final Analysis data-cut of KEYNOTE-A18

Report section	5.1.2
Description of issue and why the EAG has identified it as important	Within the company's economic model, OS is modelled as a function of the parametric survival models fitted to data on PFS and TTP from KEYNOTE-A18, the parametric survival models fitted to data on PFS, TTP and post-progression survival (PPS) from KEYNOTE-826, as well as structural assumptions regarding cure, treatment effect waning and subsequent treatment pathways. The company's updated economic model does not provide a good representation of the observed OS from the Final Analysis data-cut of KEYNOTE-A18. The company's updated model applies calibration factors to the transition probabilities out of the PD1 state (derived from KEYNOTE-826) which force model-predicted OS to better fit the observed OS from KEYNOTE-A18. The EAG considers the company's calibration approach to be pragmatic, but far from ideal. The EAG is unable to determine the precise cause of the discrepancy between model-predicted OS and observed OS, but considers that it is likely to be a consequence of one or more of the following factors: (i) the company's decision not to properly account for competing risks in the derivation of progression and death risks (ii) the misspecification of one or more parametric survival models used to inform any of the transition probabilities which inform OS (iii) the use of data from the KEYNOTE-826 CPS ≥ 1 with prior CRT subgroup which may not be fully representative of the progressed population in KEYNOTE-A18.
What alternative approach has the EAG suggested?	The EAG has explored the impact of removing the calibration factors from the model. However, this results in an underestimation of modelled OS, particularly for the pembrolizumab plus CCRT group.
What is the expected effect on the cost-effectiveness estimates?	The deterministic version of the EAG's preferred model (including calibration factors) results in an ICER of ██████ per QALY gained (EA1a). Removing the calibration factors results in a higher ICER of ██████ per QALY gained (ASA3).
What additional evidence or analyses might help to resolve this key issue?	The company could revise its survival analysis to adjust for competing risks. However, this may not be the sole cause of the discrepancy. Should longer-term OS data become available from KEYNOTE-A18, the use of a partitioned survival approach (including the use of cure models or assumptions) would likely result in an improved fit to the observed OS data.

1.6 Summary of the EAG's preferred model results

The EAG's preferred analysis is based on the company's updated primary base case analysis (informed by investigator-assessed PFS). The results of the EAG's preferred analysis are summarised in Table 2. Results are presented separately using the probabilistic and deterministic versions of the company's updated model. The results of the EAG's additional sensitivity analyses are presented in Table 3. These

ICERs includes the PAS discount for pembrolizumab but exclude price discounts for bevacizumab biosimilars.

Modelling errors identified by the EAG are described in Section 4.3.5 (company's original model) and Section 5.1.1 (company's updated model). For further details of the exploratory analyses undertaken by the EAG, see Section 5.2.

Table 2: EAG's preferred model results, pembrolizumab plus CCRT versus CCRT alone, including pembrolizumab PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's original base case, deterministic	*****	2.05	*****	*****
Company's original base case, probabilistic	*****	1.99	*****	*****
Company's updated primary base case, deterministic	*****	1.21	*****	*****
Company's updated primary base case, probabilistic	*****	1.24	*****	*****
Company's updated secondary base case, deterministic	*****	1.72	*****	*****
EA1a: EAG-preferred analysis, deterministic	*****	1.24	*****	*****
EA1b: EAG-preferred analysis, probabilistic	*****	1.24	*****	*****

* Undiscounted

EAG - External Assessment Group; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PAS - Patient Access Scheme

Table 3: EAG's additional sensitivity analysis results, including pembrolizumab PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA1a: EAG-preferred analysis, deterministic	*****	1.24	*****	*****
ASA1a: PFS, TTP = 1-knot normal RCS model	*****	1.41	*****	*****
ASA1b: PFS, TTP = 2-knot hazard RCS model	*****	0.92	*****	*****
ASA1c: PFS, TTP = 2-knot odds	*****	1.03	*****	*****
ASA1d: PFS, TTP = 2-knot normal	*****	1.12	*****	*****
ASA2: KEYNOTE-826 CPS $\geq$ 1 subgroup, PFS, TTP = 3-knot hazard RCS model, PPS = generalised gamma model, calibration factors 0.49 and 0.73	*****	1.23	*****	*****
ASA3: Exclusion of calibration factors for OS	*****	0.93	*****	*****
ASA4: Application of calibration factors for four years	*****	1.35	*****	*****
ASA5: Pembrolizumab-treated proportion following disease progression = 80%	*****	1.12	*****	*****
ASA6: Exclusion of pembrolizumab re-challenge	*****	1.07	*****	*****
ASA7: Exclusion of PD-L1 testing costs	*****	1.24	*****	*****
ASA8: Removal of the cure warm-up period	*****	1.22	*****	*****
ASA9: No additional treatment effect for pembrolizumab vs. chemotherapy in late progressors	*****	1.07	*****	*****
ASA10: 50% reduction in utility value for PD2 state (utility value = 0.75)	*****	1.27	*****	*****

ASA - additional sensitivity analysis; EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PFS - progression-free survival; TTP - time to progression; RCS - restricted cubic spline; CPS - combined positive score; PD-L1 - programmed death-ligand 1; CCRT - concurrent chemoradiotherapy; PD2 - second disease progression

* Undiscounted

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease, the company's overview of the current treatment pathway and its intended positioning of pembrolizumab, and a summary and critique of the decision problem addressed in the CS.¹

2.1 Critique of the company's description of the underlying health problem

2.1.1 Cervical cancer

Cervical cancer is cancer which starts in the cervix, the lower part of the uterus (womb). The majority (80-90%) of cervical cancers have squamous histology and around 20% are adenocarcinomas; less common histological subtypes include adenosquamous cancers (3-10%) and small cell cancers (<5%).² The main risk factor for cervical cancer is human papillomavirus (HPV). More than 90% of cases of cervical cancer are caused by HPV, with the most common types being HPV 16 and HPV 18.¹ A national HPV immunisation programme was introduced in England in 2008; under this programme, girls who are aged 12 to 13 years are invited to receive routine HPV vaccine.

2.1.2 Incidence

According to Cancer Research UK, there were an average of 2,688 cases of cervical cancer per year in England during the period 2017-2019.³ The age-standardised incidence rate for cervical cancer in England is 4.9 cases per 100,000 female population. Incidence rates rise sharply for females aged 15-19 years and peak in the 30-34 years age group; incidence rates decrease in older age groups. The incidence rate for cervical cancer in the UK decreased by approximately 24% between 1993-1995 and 2017-2019 but has remained stable between 2007-2009 and 2017-2019.³

2.1.3 Staging

Cervical cancer is staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system. FIGO stage is determined by physical examination and diagnostic tests including palpation, inspection, colposcopy and endocervical curettage.¹ The most recent version of the FIGO staging system was published in 2019.⁴ The marketing authorisation for pembrolizumab in the LACC indication relates to women with Stage III-IVA cervical cancer based on the previous FIGO 2014 staging system. Under the 2014 staging system, Stage III refers to when the cancer has extended onto the pelvic sidewall or when there is involvement of the lower vagina (including all cases of hydronephrosis or non-functioning kidney); Stage IVA refers to when the cancer has spread beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum and has spread to adjacent pelvic organs. Under the 2018 FIGO staging system, imaging evaluation may be used in addition to clinical examination (using ultrasound, computed tomography [CT], magnetic resonance imaging [MRI] and/or positron emission tomography [PET]).

2.1.4 Mortality

According to Cancer Research UK, there were an average of 685 deaths due to cervical cancer per year in England during the period 2017-2019. The age-standardised mortality rate is estimated to be 1.3 deaths per 100,000 female population.⁵ Survival is strongly related to stage at diagnosis; data from NHS Digital indicate a substantially lower 5-year net survival rate for women with advanced disease stage compared to those with earlier stage (Stage 1 - 95%; Stage 2 - 72%; Stage 3 - 44%; Stage 4 - 18%).⁶

2.1.5 Burden of disease

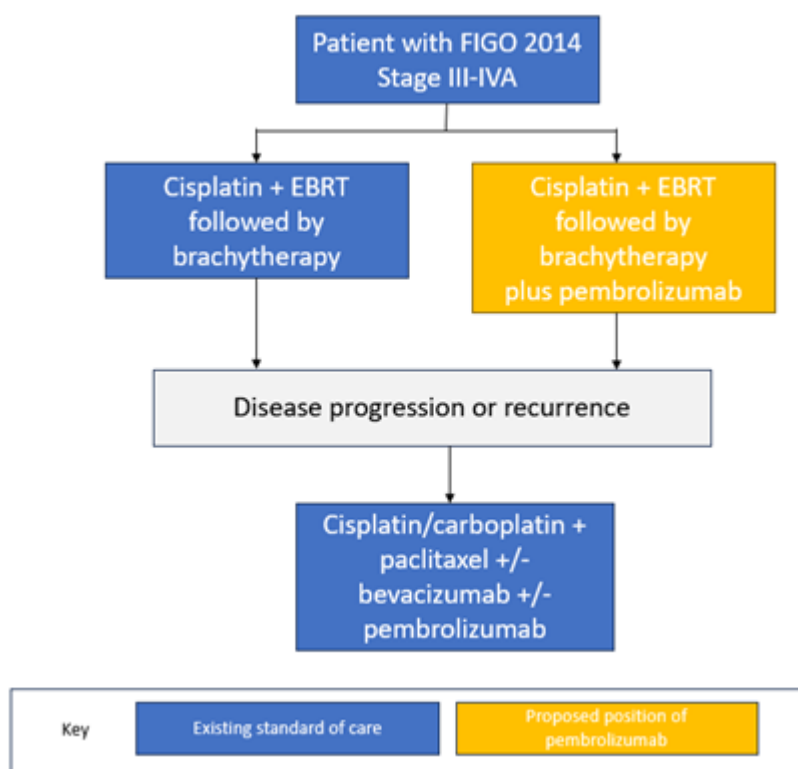
The CS¹ refers to a survey conducted by Jo's Cervical Trust in 2016 which included 35 women who were diagnosed with cervical cancer in the previous two years. The survey was conducted to understand what women valued and found difficult, their experiences of cervical cancer treatment and provision of care, whether the care received met their expectations and potential support, information and policy-related solutions.⁷ The survey found that following diagnosis, women experienced a range of emotions including feeling isolated in decision-making, and being concerned about future fertility, trust in clinicians and being comfortable with their proposed treatment plan. Many respondents who received chemotherapy experienced physical and psychological side effects including nausea, anxiety and feeling lonely. Radiotherapy, particularly brachytherapy, was reported as being a very difficult process to go through. Women who were diagnosed with later or advanced cervical cancer required more radical treatment options, which resulted in much longer recovery periods compared with those who had been diagnosed with earlier stage disease. The survey also reported impacts on the women's wider family unit, including disruption to their children's routine, a lack of energy to play, and negative effects on intimate relationships. The background chapter of the CS does not report any information related to HRQoL for women with FIGO Stage III-IVA LACC using a quantitative instrument.

2.2 Company's overview of current service provision

2.2.1 EAG's critique of the company's treatment pathway

The company's view of the current treatment pathway for patients with untreated high-risk LACC (FIGO 2014 Stage III-IVA), together with the company's proposed positioning of pembrolizumab, is reproduced in Figure 1. Current recommendations on the use of specific technologies for treating advanced cervical cancer from the National Institute for Health and Care Excellence (NICE) are summarised in Table 4.

Figure 1: Clinical pathway of care for patients with FIGO Stage III-IVA cervical cancer and the proposed placement of pembrolizumab* (reproduced from CS, Figure 3)



FIGO - International Federation of Gynecology and Obstetrics; EBRT - external beam radiotherapy

* Some patients may receive no further active therapy after first or second progression. Patients who experience a second disease progression may receive further treatment using chemotherapy. These situations are not shown in the company's treatment pathway diagram.

Table 4: Current NICE recommendations for treatments for locally advanced or metastatic cervical cancer

NICE TA	NICE recommendation
TA183: Topotecan (2009) ⁸	Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin.
TA885: Pembrolizumab plus chemotherapy with or without bevacizumab (2023) ⁹	This guidance was updated and replaced by TA939.
TA939: Pembrolizumab plus chemotherapy with or without bevacizumab (2023) ¹⁰	Pembrolizumab plus chemotherapy with or without bevacizumab is recommended as an option for treating persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS of at least 1. It is recommended only if: - Pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if the cancer progresses, and - The company provides it according to the commercial arrangements.

TA - Technology Appraisal; NICE - National Institute for Health and Care Excellence; PD-L1 - programmed death-ligand 1; CPS - combined positive score

The company's view of the overall treatment pathway for high-risk LACC is briefly summarised below (further details are provided in CS,¹ Section 1.3.5). The EAG's critique has been integrated into this summary.

Treatment of newly diagnosed high-risk locally advanced cervical cancer

Based on the 2020 British Gynaecological Cancer Society (BGCS) clinical practice guidelines for cervical cancer,¹¹ the recommended treatment for patients with LACC (FIGO 2018 Stage IIIA/IIIB and IVA) is definitive chemoradiotherapy with an additional radiation boost to the involved lymph nodes in patients with unequivocally involved pelvic lymph nodes on imaging. Chemoradiotherapy is comprised of external beam radiation (EBRT) followed by intracavity brachytherapy with concomitant cisplatin treatment. This has been the standard of care for LACC for almost two decades in England. The most commonly used dose of cisplatin is 40mg/m² weekly. The BGCS guidelines state that EBRT should be delivered at a dose of 45-50.4 Gy in 1.8 Gy per fraction. The guidelines also state that image-guided adaptive brachytherapy (IGABT) is recommended. In IGABT, the aim should be to deliver a total radiation dose (EBRT plus brachytherapy) of 85-90 Gy EQD2 (equivalent dose in 2 Gy per fraction) to the high-risk volume and 60 Gy to the intermediate risk volume.

Treatment of recurrent, persistent or metastatic cervical cancer

In patients with recurrent, persistent or metastatic disease following first-line chemoradiotherapy, whose tumours continue to express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) of at least 1, subsequent treatment options in the second-line setting include: (i) pembrolizumab with chemotherapy (cisplatin or carboplatin and paclitaxel) with or without bevacizumab, which is also in line with the marketing authorisation for pembrolizumab in the metastatic setting,¹² (ii) chemotherapy (cisplatin or carboplatin and paclitaxel) with or without bevacizumab, and (iii) no active treatment. Further chemotherapy (e.g., paclitaxel) is the only treatment option in the third-line setting. Clinical trials may be an option for some patients.

The company's economic model assumes that re-challenging with pembrolizumab is permitted for patients who experience disease progression at least six months after completing first-line treatment with pembrolizumab. The company's assumptions regarding treatment pathways and pembrolizumab re-challenge in the company's economic model are detailed in Section 4.2.

2.2.2 EAG's critique of the company's positioning of pembrolizumab

The company's proposed positioning of pembrolizumab in England is in line with the full marketing authorisation for pembrolizumab, that is, pembrolizumab given with concurrent chemoradiotherapy (CCRT), followed by pembrolizumab monotherapy, in adults with FIGO 2014 Stage III-IVA LACC who have not received prior definitive therapy. The EAG's clinical advisors considered the company's proposed positioning of first-line pembrolizumab plus CCRT for LACC to be appropriate. With respect

to pembrolizumab re-challenge, one of the EAG's clinical advisors stated that they are unlikely to use this treatment approach because there is no evidence available to support its efficacy and safety. The EAG's other clinical advisor stated that, despite uncertainty around its effectiveness, they might consider re-challenge with pembrolizumab, given the limited treatment options available in the second-line setting.

2.3 Critique of the company's definition of the decision problem

A summary of the decision problem as outlined in the final NICE scope¹³ and addressed in the CS¹ is presented in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: The decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	Adults with high-risk LACC	Adults with FIGO 2014 Stage III-IVA LACC who have not received prior definitive therapy	To align with licensed population
Subgroups*	If the evidence allows, the following subgroups will be considered: • Histology (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and poorly differentiated carcinoma) • Combined positive score (CPS) of PD-L1 expression (less than 10, greater than or equal to 10 and all-comers) • Tumour mutational burden.	No economic subgroup analyses are presented.	None presented
Intervention	Pembrolizumab with chemoradiation	As per NICE scope	N/a
Comparator(s)	Chemoradiotherapy (cisplatin-based, unless contraindicated)	As per NICE scope	N/a
Outcomes	• Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life.	As per NICE scope	N/a
Special considerations including issues related to equity or equality		Deprivation	MSD considered deprivation to be an important characteristic to explore due to the inequalities experienced by those from the most deprived quintile.

CS - company's submission; LACC - locally advanced cervical cancer; NICE - National Institute for Health and Care Excellence; FIGO - International Federation of Gynecology and Obstetrics; MSD - Merck Sharp and Dohme

* Details relating to subgroups listed in the NICE scope are not included in the decision problem table presented in the CS.

2.3.1 Population

The final NICE scope¹³ specifies the relevant population as adults with high-risk LACC. The clinical evidence for pembrolizumab plus CCRT included in the CS¹ comes from the FIGO 2014 Stage III - IVA subgroup of the KEYNOTE-A18 trial.¹⁴ Patients enrolled in KEYNOTE-A18 were female adults who had not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer. The Summary of Product Characteristics (SmPC) for pembrolizumab¹² states that pembrolizumab in combination with chemoradiotherapy (EBRT followed by brachytherapy) is indicated for the treatment of FIGO 2014 Stage III - IVA LACC in adults who have not received prior definitive therapy. The population considered in the CS is narrower than that defined in the final NICE scope, but is consistent with the wording of the marketing authorisation for pembrolizumab.

The final NICE scope¹³ lists three potential subgroups relating to histology, CPS of PD-L1 expression and tumour mutational burden. The CS¹ does not present any economic analyses relating to these subgroup factors. The absence of subgroup analyses based on these factors is not discussed in the CS.

2.3.2 Intervention

The intervention included in the CS¹ is pembrolizumab (Keytruda®) given in combination with CCRT. This is consistent with the final NICE scope.¹³ Pembrolizumab is administered by intravenous (IV) infusion over 30 minutes. Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2.¹² Pembrolizumab has a current marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) / European Medicines Agency (EMA) for two cervical cancer indications: (i) in combination with chemoradiotherapy (EBRT followed by brachytherapy) for the treatment of FIGO 2014 Stage III-IVA LACC in adults who have not received prior definitive therapy (the indication relevant to the current appraisal) and (ii) in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS of ≥ 1 .

The recommended dose of pembrolizumab in adults is 200mg every 3 weeks or 400mg every 6 weeks. The list price per vial is £2,630.00. A Patient Access Scheme (PAS) discount is available for pembrolizumab. Details of the PAS price can be found in CS Appendix J.¹⁵

The definition of the intervention detailed in the NICE scope¹³ does not specify a maximum treatment duration for pembrolizumab. The SmPC for pembrolizumab¹² (page 6) states that within its LACC indication, pembrolizumab should be continued until disease progression, unacceptable toxicity or up to a maximum treatment duration of 24 months. The company's health economic model includes a stopping rule whereby the maximum treatment duration for pembrolizumab is assumed to be 2 years

(see Section 4.2.2). The chemoradiotherapy (CRT) regimen used in the KEYNOTE-A18¹⁴ included five cycles of 40mg/m² cisplatin once weekly plus EBRT followed by brachytherapy. The company's economic model also includes an assumption that patients with disease progression may be re-challenged with pembrolizumab (in combination with chemotherapy) after 2.5 years (at least 6 months after completing first-line treatment with pembrolizumab); re-challenge with pembrolizumab in the LACC indication is not mentioned in the SmPC.

The SmPC¹² lists several special warnings and precautions relating to the use of pembrolizumab, including: immune-related pneumonia; immune-related colitis; immune-mediated hepatitis; immune-nephritis; immune-mediated endocrinopathies; immune-mediated skin adverse reactions and other immune-mediated adverse reactions (including uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective, hypoparathyroidism and pericarditis). The SmPC states that depending on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids should be administered. Pembrolizumab should be permanently discontinued for recurrent Grade 3 or 4 immune-mediated adverse reactions and for Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome.

2.3.3 Comparators

The CS¹ includes a single comparator - CCRT. This is broadly consistent with the final NICE scope¹³ which defines the comparator as chemoradiotherapy (cisplatin-based, unless contraindicated). KEYNOTE-A18¹⁴ excluded patients who had a contraindication to the use of cisplatin.¹ The CCRT regimen applied in the comparator arm of the trial is the same as that described in Section 2.3.2 (i.e., five cycles of 40mg/m² cisplatin once weekly plus EBRT followed by brachytherapy).

2.3.4 Outcomes

The following outcomes are listed in the final NICE scope:¹³

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS¹ reports on all of these outcomes for the FIGO 2014 Stage III-IVA subgroup of the KEYNOTE-A18 trial.¹⁴ The company's economic model is informed by data on PFS, time to progression (TTP), time to treatment discontinuation (TTD), OS, adverse events (AEs) and HRQoL from KEYNOTE-A18 (see Section 4.2).

2.3.5 *Other relevant factors*

The CS¹ states that inequalities exist across the pathway for cervical cancer and that deprivation is a key factor affecting the diagnosis and prognosis of people with cervical cancer. The CS reports the results of a distributional cost-effectiveness analysis (DCEA); this is discussed in Section 5.3.

3. CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical effectiveness evidence included in the CS.¹ Section 3.1 provides a summary and critique of the methods of the company's systematic literature review (SLR) of clinical and safety evidence. Sections 3.2 to 3.4 focus on the one included study of pembrolizumab from the SLR - KEYNOTE-A18.¹⁴ This study compared pembrolizumab plus CCRT versus placebo plus CCRT. Section 3.4 briefly discusses the company's exploration of the feasibility of conducting an indirect treatment comparison (ITC) using other studies included in the company's SLR. Section 3.5 describes additional work conducted by the EAG. Section 3.6 presents the EAG's conclusions on the clinical effectiveness of pembrolizumab plus CCRT for the treatment of LACC.

The data from KEYNOTE-A18 presented in the CS¹ relate to Interim Analysis 2 (IA2) (data cut-off [DCO] 8th January 2024).¹⁴ Following the clarification round, the company provided an additional addendum to the CS¹⁶ which includes longer-term data from the Final Analysis data-cut of the trial (DCO 7th January 2025). Selected tables and figures based on this updated data-cut are presented in Appendix 1.

3.1 Critique of the methods of review

The systematic review methods for the clinical evidence are detailed in Section 2.1 of the CS¹ and CS Appendix B.¹⁵ The company undertook an SLR to identify randomised controlled trials (RCTs) relating to the efficacy and safety of pembrolizumab and comparator treatments for adults with FIGO 2014 Stage III-IVA LACC who have not received prior definitive therapy.

3.1.1 Searches

CS Appendix B¹⁵ reports the methods for identifying and selecting clinical evidence. The company searched for RCTs and observational studies on the clinical efficacy and safety of chemotherapy, immunotherapy or chemoimmunotherapy agents for the management of LACC.

Literature searches covering the core databases required by NICE (MEDLINE; EMBASE and the Cochrane Controlled Register of Clinical Trials [CENTRAL]) are reported in Section B1.1 of the CS appendices.¹⁵ The EAG considers that the searches have been competently designed and executed, using appropriate Emtree and MeSH subject headings as well as free text terms. The EAG notes that these terms only include pembrolizumab and its comparators – not the accompanying treatment (chemoradiation) – but concludes that since this would only affect the retrieval of studies of chemoradiation with other drugs, it is unlikely to result in the omission of any evidence relevant to the decision problem for the current appraisal.

The company's searches applied an English language limit and study type filters including unvalidated (but widely adopted) Scottish Intercollegiate Guidelines Network (SIGN) strings to identify clinical trials. It is unclear why the company deemed it necessary to apply these in the CENTRAL database (which only contains trials), but doing so is unlikely to have been detrimental to study retrieval. The company also used terms to identify observational studies, but did not report where these had been sourced from. At the clarification stage, the EAG asked the company to clarify the source; however, the company's response does not provide this information (see clarification response,¹⁷ question A2). While it is understandable that trial evidence of efficacy is preferred, the company also expressed an interest in safety data, and the EAG believes that the company's search approach would have benefited from following guidance from Golder *et al.*¹⁸ with respect to this evidence type.

Section B1.1 of the CS appendices¹⁵ states that the reference lists of previously published SLRs and meta-analyses were hand-searched for relevant papers. The company's response to clarification question A2¹⁷ provides a list of those studies identified, although the company acknowledges that these had not been retrieved through dedicated searches.

The company conducted supplementary searches of relevant conference proceedings from the last two years, plus the clinicaltrials.gov register. The EAG was initially confused by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart (CS Appendix B,¹⁵ Figure 1, page 23) which reports that 143 records were excluded prior to screening "marked as trial registry"; the company clarified that these were in fact duplicate records of which the CENTRAL versions were excluded because those listed in clinicaltrials.gov were more up-to-date. Overall, the EAG is broadly satisfied with the approach taken and concludes that it is unlikely that the company has overlooked evidence that is relevant to the decision problem for the current appraisal.

3.1.2 Inclusion criteria and study selection

The inclusion criteria for the company's SLR are described in Table 4 of CS Appendix B.1.2.¹⁵ The inclusion criteria relating to the population in the company's SLR were more specific than the population defined in the final NICE scope¹³ (defined as high-risk LACC, without specifying the staging classification system or relevant disease stages), and were designed to cover the population of KEYNOTE-A18.¹⁴ The population of the SLR included FIGO 2009 or 2014 Stage IB2-IVA, or FIGO 2018 Stage IB3-IVA. The company defined the sub-population with high-risk LACC as patients with FIGO 2014 Stage IB2-IIB (with node-positive disease) or FIGO 2014 Stage III-IVA (with node-positive or -negative disease). Hence, the EAG considers that the population of the SLR reflected in the final NICE scope, that is, adults with high-risk LACC, would be included with these selection criteria.

The inclusion criteria relating to intervention and outcomes in the company's SLR were broader than those listed in the final NICE scope,¹³ and were designed to cover induction or consolidation chemotherapy, or both, with chemoradiation. The EAG considers that any RCTs which included the intervention and comparators listed in the final NICE scope, that is pembrolizumab with CCRT versus CCRT (cisplatin-based, unless contraindicated), would be included with these selection criteria.

The inclusion criteria relating to outcomes in the company's SLR were in line with the final NICE scope.¹³ These included: PFS; OS; objective response rate (ORR); duration of response (DoR), AEs of treatment, discontinuation and death due to AEs, and HRQoL.

3.1.3 Results of the company's SLR

One study of pembrolizumab was included in the company's SLR: KEYNOTE-A18¹⁴ (see Table 6). Five other studies were identified but were deemed to be unsuitable for evidence synthesis (see CS,¹ Section 2.9). The included study compared pembrolizumab plus CCRT versus placebo plus CCRT. The CS argues that the CCRT regimen used in KEYNOTE-A18 reflects CCRT used in current UK clinical practice. The EAG's clinical advisors agreed with this view, but noted that the total radiation dose received in KEYNOTE-A18 was lower than the usual target total radiation dose in current NHS practice.

Table 6: KEYNOTE-A18 study characteristics

Population	Intervention	Comparator	Co-primary outcomes
Adults with previously untreated high-risk LACC: FIGO 2014 Stages III-IVA (the subgroup of relevance to the current appraisal); or FIGO 2014 Stage IB2-IIB with node-positive disease (not considered further in this assessment)	Pembrolizumab with CCRT CCRT= cisplatin plus EBRT followed by brachytherapy	Placebo with CCRT CCRT= cisplatin plus EBRT followed by brachytherapy	- Investigator-assessed PFS - OS

LACC - locally advanced cervical cancer; FIGO - International Federation of Gynecology and Obstetrics; CCRT - concurrent chemoradiotherapy; EBRT - external beam radiation therapy; PFS - progression-free survival; OS - overall survival

Further details regarding the design of KEYNOTE-A18¹⁴ are provided in Section 3.2. Neither the EAG nor its clinical advisors are aware of any additional RCTs of pembrolizumab plus CCRT within the scope of this appraisal.

3.1.4 Data extraction

According to CS Appendix B.1.2.2,¹⁵ two reviewers extracted data with involvement of a third reviewer to resolve disagreements. This reflects good practice for systematic reviews.

As noted above, the data from KEYNOTE-A18 contained in the CS¹ relate to IA2 (DCO 8th January 2024). The EAG cross-checked the data relating to IA2 in the CS against the statistical analysis report for the FIGO 2014 Stage III-IV subgroup of KEYNOTE-A18,¹⁴ including results and patient numbers for key end points. At the time of writing, trial results had not been posted on clinicaltrials.gov (NCT04221945).¹⁹ The publication for IA2 of KEYNOTE-A18 (Lorusso *et al.*, 2024)²⁰ relates to the whole study population (including patients with FIGO 2014 Stage IB2-IIB with node-positive disease). However, the Lorusso *et al.* publication includes forest plots of subgroup analyses reporting hazard ratios (HRs) for investigator-assessed PFS and OS for the FIGO 2014 Stage III-IVA subgroup. Therefore, data in addition to OS/PFS HRs were checked only against the KEYNOTE-A18 statistical report for the FIGO 2014 Stage III-IVA subgroup.¹⁴

As part of its clarification response,¹⁷ the company provided an additional addendum to the CS which contains updated results from the Final Analysis data-cut of KEYNOTE-A18¹⁶ (DCO 7th January 2025) and an updated version of the statistical analysis report relating to this DCO.²¹ The EAG checked the data contained in the company's addendum against those reported in the updated statistical analysis report.

3.1.5 Risk of bias assessment

The company assessed the risk of bias in KEYNOTE-A18¹⁴ using the Cochrane Risk of Bias tool Version 2.0 (RoB 2).²² This is widely regarded as a robust tool for the assessment of bias in RCTs. According to CS Appendix B.1.2.3,¹⁵ two reviewers assessed study quality, with involvement of a third reviewer to resolve disagreements. This reflects good practice for systematic reviews.

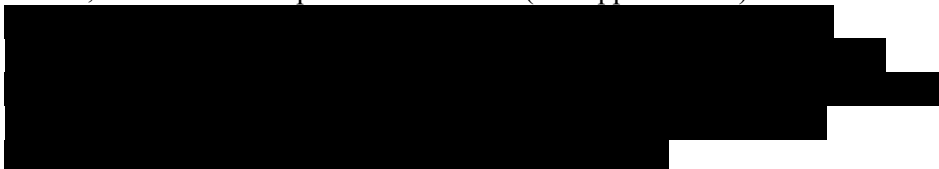
The company's quality assessment of KEYNOTE-A18¹⁴ is presented in CS Appendix B1.3.¹⁵ The results of the quality assessment undertaken by the company and the EAG are presented in Section 3.2.2.

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Included pembrolizumab trial - KEYNOTE-A18

The CS¹ (Section B.2) included one study: KEYNOTE-A18.¹⁴ KEYNOTE-A18 assessed the effectiveness of pembrolizumab in combination with CCRT in patients with FIGO 2014 Stage IB2 to IIB node-positive, or Stage III-IVA (regardless of nodal status) LACC. This trial (specifically data for the Stage III-IVA subgroup) formed the basis of the marketing authorisation for the LACC indication for pembrolizumab.¹² The key features of the trial are summarised in Table 7.

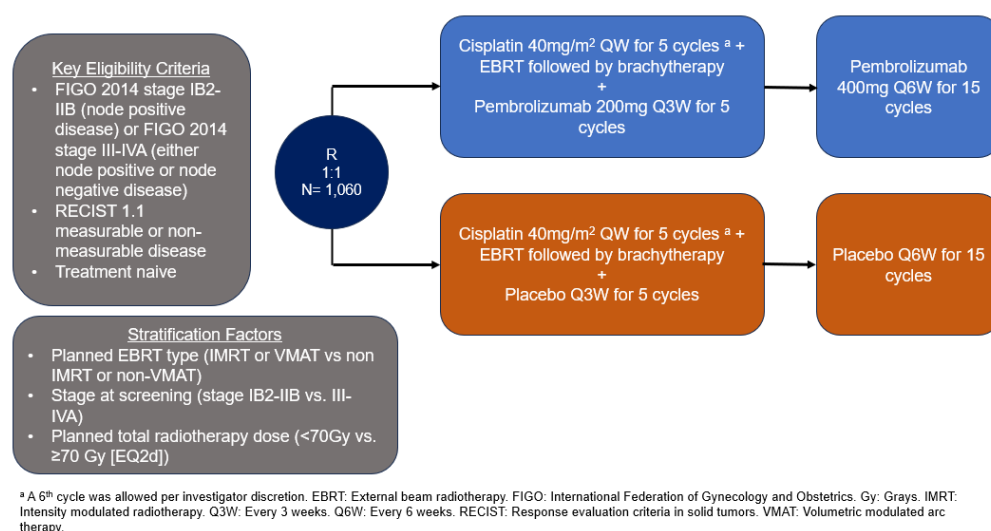
Table 7: Summary of KEYNOTE-A18 study design

Study name	KEYNOTE-A18
Study design	Phase III, multi-centre, blinded, placebo-controlled RCT
Patient group	Trial subgroup of relevance to this appraisal: Adults with FIGO 2014 Stage III-IVA (node-negative or node-positive disease) LACC who have not received prior definitive therapy (surgical, radiation, systemic therapy for cervical cancer, or immunotherapy), ECOG PS 0 or 1. Participants with Stage IB2-IIB (node-positive disease) are not relevant to this appraisal as they are not covered by the marketing authorisation.
Randomisation stratification factors	- Planned type of EBRT: IMRT/VMAT vs. non-IMRT and non-VMAT. - FIGO 2014 Stage: IB2 to IIB node-positive disease vs. III-IVA regardless of nodal status - Planned total radiotherapy dose: <70Gy vs. 70 and over Gy
Planned subgroup analysis	- Planned type of EBRT: IMRT/VMAT vs. non-IMRT and non-VMAT. - FIGO 2014 Stage: IB2 to IIB with node-positive disease vs. III-IVA regardless of nodal status. - Planned total radiotherapy dose: <70Gy vs. 70 and over Gy. - Age: <65 vs. 65 and over. - Race: White vs. Other. - Baseline ECOG PS: 0 vs. 1.
Key exclusion criteria	- Histological subtypes other than SCC, adenocarcinoma, or adenosquamous carcinoma of the cervix. - Hysterectomy. - Contraindication to cisplatin.
Intervention	Pembrolizumab 200mg Q3W for 5 infusions, plus cisplatin 40mg/m ² weekly for 5 infusions plus EBRT followed by brachytherapy. Followed by pembrolizumab 400mg Q6W for 15 infusions.
Comparator	Placebo Q3W for 5 infusions, plus cisplatin 40mg/m ² weekly for 5 infusions plus EBRT followed by brachytherapy. Followed by placebo Q6W for 15 infusions.
Primary endpoints	- OS - PFS assessed by investigators
Key secondary endpoints	- PFS assessed by BICR - CR rate at 12 weeks after completion of CCRT - ORR as assessed by investigators - ORR as assessed by BICR - HRQoL assessed by EORTC QLQ-C30 and EORTC QLQ-CX24 - AEs
Duration	At IA2, median follow-up was 27.5 months (CS Appendix B ¹⁵) 
Location	Latin America (36.6%); Asia Pacific (33.6%); Europe, the Middle East and Africa (24.6%); North America (5.2%). ¹⁴ 3 patients were from the UK.

RCT - randomised controlled trial; FIGO - International Federation of Gynecology and Obstetrics; LACC - locally advanced cervical cancer; PFS - progression-free survival; OS - overall survival; ECOG - Eastern Cooperative Oncology Group; PS - performance status; Gy - Gray; EBRT - external beam radiation therapy; Q3W - every 3 weeks; Q6W - every 6 weeks; CCRT - concurrent chemoradiotherapy; CR - complete response; ORR - objective response rate; HRQoL - health-related quality of life; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CX24 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; SCC - squamous cell carcinoma; IA2 - Interim Analysis 2; BICR - Blinded Independent Central Review; AE - adverse event; N - number

All participants in KEYNOTE-A18¹⁴ were adults who had not received prior definitive therapy (surgical, radiation, systemic therapy for cervical cancer, or immunotherapy) and who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The population eligible for enrolment into the trial was broader than the population defined by the marketing authorisation for pembrolizumab in the LACC indication,¹² as it also recruited patients with FIGO 2014 Stage IB2-IIB (with node-positive disease). For the purposes of this EAG report, only data relating to the subgroup of patients with FIGO 2014 Stage III-IVA (regardless of nodal status) LACC are considered. Figure 2 summarises the design of KEYNOTE-A18.

Figure 2: KEYNOTE-A18 trial design (reproduced from CS, Figure 4)



KEYNOTE-A18¹⁴ was ongoing at the time of writing. All data reported in the CS¹ were from IA2 (DCO 8th January 2024). According to Table 10 of the CS, IA2 was scheduled to be conducted “around 34 months after the first participant is randomized, when approximately 304 PFS events are observed” in the whole trial population (including patients with FIGO 2014 Stage IB2-IIB LACC). The power calculation reported in CS Table 10 is for the whole study population rather than the subgroup of Stage III-IVA patients. However, the EAG considers that the limitations of the power calculation are unlikely to substantially influence the interpretation of the direction of the treatment effect for the primary end points at IA2, given the magnitude of the observed treatment effects observed (OS: HR [REDACTED]; PFS: [REDACTED]; see Section 3.3), the inclusion of FIGO 2014 stage category as a stratification factor, and the large sample size for the Stage III-IVA subgroup (which represents more than half of the intention-to-treat [ITT] population). In the FIGO 2014 Stage III-IVA patients, IA2 occurred after 204 PFS events (and 116 OS events).¹⁴ Median follow-up was reported to be 27.5 months in both trial arms [REDACTED].

¹⁴

Following the clarification round, the company provided an addendum to the CS which contained the results of the Final Analysis of trial (DCO 7th January 2025).¹⁶ Selected key results from this updated data-cut are contained in Appendix 1. [REDACTED]

KEYNOTE-A18¹⁴ is an international multi-centre RCT. Randomisation was stratified by:

- Planned EBRT: Intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) versus non-IMRT and non-VMAT
- Stage of cervical cancer FIGO 2014: Stage IB2-IIB versus Stage III-IVA
- Planned total radiotherapy dose (EBRT + brachytherapy dose): <70 Gy versus ≥70 Gy (equivalent dose).

The KEYNOTE-A18 Stage III-IVA subgroup, and thus the population eligible for pembrolizumab plus CCRT according to the marketing authorisation,¹² was based on the FIGO 2014 staging classification. The version of the FIGO staging classification currently used in the UK is FIGO 2018 (see Table 8). FIGO 2018 has been revised so that the presence of nodal involvement is upstaged to the new category of Stage IIIC.^{23 4 24 25} A major difference between the FIGO 2014 and 2018 classifications is that patients classified as earlier than Stage IIIA in FIGO 2014 may be reclassified as Stage IIIC1 or IIIC2 in FIGO 2018 due to nodal involvement. Hence, Stage III-IVA would involve overlapping patients for FIGO 2014 and 2018, with FIGO 2018 involving a different mix of patients for Stage III (i.e., with smaller tumours but having nodal involvement). The EAG's clinical advisors commented that although the marketing authorisation for pembrolizumab for LACC is based on FIGO 2014, it is possible to map these criteria onto newer versions of the criteria.

Table 8: FIGO 2014, FIGO 2018 and TNM staging classifications

Stage	FIGO 2014	FIGO 2018	TNM
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall	Carcinoma involves the lower third of the vagina with no extension to the pelvic wall	T3a Carcinoma involves the lower one-third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney	Extension to the pelvic wall and and/or causes hydronephrosis or non-functioning kidney (unless known to be due to another cause)	T3b Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Not applicable (new stage category introduced 2018)	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumour size and extent (Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC)	
IIIC1	Not applicable (new stage category introduced 2018)	Pelvic lymph node metastasis only	N1 Regional lymph node metastasis to pelvic lymph nodes only
IIIC2	Not applicable (new stage category introduced 2018)	Para-aortic lymph node metastasis	N2 Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
IVA	Spread of the growth to adjacent organs	Spread to adjacent pelvic organs (beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum)	T4 Carcinoma has involved (biopsy-proven) the mucosa of the bladder or rectum or has spread to adjacent organs (bullous edema, as such, does not permit a case to be assigned to stage IVA)

FIGO - International Federation of Gynecology and Obstetrics; TNM - Tumour, Node, Metastasis
Adapted from Singh et al.,²³ Bhatla et al.,⁴ Pecorelli et al.,²⁵ and Olawaiye et al.²⁶

The intervention in KEYNOTE-A18¹⁴ was as follows: Pembrolizumab 200mg every 3 weeks (Q3W) for 5 IV infusions, plus cisplatin 40mg/m² weekly for 5 infusions plus EBRT followed by brachytherapy, followed by pembrolizumab 400mg every 6 weeks (Q6W) for 15 infusions (CS,¹ Section 2.3). EBRT was given across 23-28 fractions (1.8 Gy to 2 Gy per fraction); 45 Gy to 50 Gy ± boost doses; for 40 days. Brachytherapy was given across 4-6 fractions (5 Gy to 7 Gy per fraction); 25 Gy to 30 Gy. The total radiation treatment duration (EBRT plus brachytherapy) was not to exceed 50 days, although an extension to a maximum of 56 days for unforeseen delays was permitted (CS, Section 2.3).²⁷ The same CCRT regimen was used in the control arm, with placebo used instead of

pembrolizumab. Treatment was stopped after completion of planned treatment (i.e., after 2 years), progression, recurrence, unacceptable toxicity, pregnancy, or investigator or patient decision.²⁷

The EAG's clinical advisors commented that the average total radiotherapy dose (EBRT plus brachytherapy) in KEYNOTE-A18¹⁴ was lower than what would be used in UK clinical practice and lower than the total dose recommended in the BGCS guidelines¹¹ (see Section 2.2.1).

The primary outcomes in KEYNOTE-A18¹⁴ were PFS and OS (CS,¹ Table 9). OS was defined as the time from randomisation to death due to any cause. PFS was defined as the time from randomisation to the first documented progressive disease (PD) or death due to any cause (whichever occurs first). As per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or by histopathologic confirmation of suspected disease progression, PD was defined as a $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. The appearance of one or more new lesions was also considered as PD. Unequivocal progression of non-target lesions was also considered as PD.¹⁹

Secondary outcomes included ORR, HRQoL and AEs.

ORR was defined as the percentage of participants who have a complete response (CR) (defined as the disappearance of all target and non-target lesions and also includes reduction of all nodal lesions to < 10 mm) or a partial response (PR) (defined as at least a 30% decrease in the sum of diameters of target lesions and includes no unequivocal progression in non-target lesions) per RECIST 1.1.¹⁹

HRQoL was measured using the Euroqol 5-Dimensions 5-Level (EQ-5D-5L) and two European Organisation for Research and Treatment of Cancer (EORTC) questionnaires: (i) the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) which includes five questions about physical functioning and twenty-eight questions on global health status, scored on a 4-point scale, with total scores ranging from 0 to 100, whereby higher scores indicates better quality of life; (ii) the EORTC Quality of Life Questionnaire Symptom Specific Scale for Cervical Cancer (EORTC QLQ-CX24) which evaluates the impact of disease and/or treatments and includes 24 items using a 4-point scale, with 3 multi-question scales and 6 single items, scored from 0 to 100. A high score for the symptom scales/single-items indicates worse symptomatology or problems, whereas a high score for the functional single-items indicates a high level of functioning.^{19, 28} Outcomes were assessed based on the change from baseline.

KEYNOTE-A18¹⁴ also measured AEs and discontinuations due to AEs. Serious adverse events (SAEs) were defined as events resulting in death, being life-threatening, requiring hospitalisation, resulting in persistent/significant disability, or congenital anomaly/birth defect.²⁷ The severity of AEs was graded

according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, which ranges from Grade 1 (mild) to Grade 5 (death).²⁹

OS and PFS outcomes were based on the ITT population (of the planned FIGO 2014 III-IVA subgroup analysis). ORR was assessed in patients with measurable disease at baseline; however, an ITT analysis was also provided in the statistical report.¹⁴ AE data were analysed for patients who received at least one dose of allocated treatment (the ‘All Participants as Treated’ [APaT] population). HRQoL data were based on the patient-reported outcome (PRO) Full Analysis Set (FAS), which comprised participants with at least one PRO assessment who received at least one dose of treatment (CS,¹ Section 2.4.2). In response to clarification question B21,¹⁷ the company stated that of the 601 patients with FIGO 2014 Stage III–IVA disease enrolled in KEYNOTE-A18, two did not receive treatment (N = 599 APaT). Of these, 46 had no completed EQ-5D questionnaires, leaving 553 patients in the PRO FAS.

3.2.2 *Risk of bias assessment KEYNOTE-A18*

The company assessed the quality of KEYNOTE-A18¹⁴ using the RoB 2 tool. A summary of the risk of bias assessment undertaken by the company and the EAG is presented in Table 9. The EAG’s quality assessment is similar to that reported by the company.

Given that the randomisation of KEYNOTE-A18¹⁴ was stratified by FIGO 2014 Stage IB2-IIB [node-positive disease] versus Stage III-IVA [regardless of nodal status]), the EAG concurs with the company (CS,¹ Section B.2.2) that the FIGO 2014 Stage III-IVA subgroup was adequately randomised. Hence, it should be expected that participants are balanced between treatment groups.

Patients and investigators were unblinded. Unblinding occurred if AEs dictated, or on progression/recurrence with discontinuation of the study intervention when the participant was being considered for alternative treatment necessitating knowledge of prior treatment on the study.²⁷ The outcomes of PFS and ORR included assessment by Blinded Independent Central Review (BICR) as secondary outcomes.

Table 9: Risk of bias assessment - KEYNOTE-A18

Type of bias	Review authors' judgement (CS Appendix B1.3)	EAG's judgement ^{20, 27}	Support for EAG's judgement ^{20, 27}
Bias arising from the randomisation process	Low risk	Low risk	Allocation sequence - stratified randomisation via interactive voice/web response system implies computer-generated random numbers Allocation concealment - randomisation performed centrally using an interactive voice/web response system Baseline characteristics - balanced across treatment groups for the FIGO 2014 Stage III-IVA subgroup, and for whole study population
Bias due to deviations from intended interventions	Low risk	Low risk	Participant awareness of assigned intervention - blinded, placebo-controlled Clinician/carer awareness of assigned intervention - blinded, placebo-controlled (drug provided by unmasked pharmacist) Outcomes assessed by investigators or patients (HRQoL). PFS and ORR were additionally assessed by BICR. Trial context - no strong reason to believe that the trial context led to failure to implement the protocol interventions Appropriate analyses - ITT analyses planned for effectiveness measures.
Bias due to missing outcome data	Low risk	Low risk	Available outcome data - OS and PFS ITT analyses However, data at IA2 were immature (i.e., median OS and PFS by investigator assessment was not reached in either treatment group)
Bias in measurement of the outcome	Low risk	Low risk	Method of measuring outcomes - appropriate Outcome measurement for treatment groups - same measurements and same time points
Bias in selection of the reported result	Low risk	Low risk	Analyses pre-specified - subgroup analyses pre-specified for stratification factors

EAG - External Assessment Group; FIGO - International Federation of Gynecology and Obstetrics; HRQoL - health-related quality of life; PFS - progression-free survival; ORR - objective response rate; BICR - Blinded Independent Central Review; ITT - intention-to-treat; OS - overall survival; IA2 - Interim Analysis 2

3.2.3 Baseline characteristics in KEYNOTE-A18

Baseline characteristics for the subgroup of patients with Stage III-IVA LACC in KEYNOTE-A18 are presented in Table 10. Section 2.12.3 of the CS¹ states that 3 patients with Stage III-IVA LACC were from the UK (N=6 in the overall ITT population). At the Final Analysis, there was a minor change in geographic region for one patient who was re-allocated from Peru to Italy (see Appendix 1, Table 45).

The EAG's clinical advisors stated that the Stage III-IVA subgroup in KEYNOTE-A18¹⁴ was similar to the LACC population who would be offered pembrolizumab plus CCRT in NHS practice with respect to age and disease type. However, the trial population differs from the UK target population in terms of ethnicity. The trial had a higher proportion of Hispanic/Latino (38.3%) and Asian patients (33.8%), and a lower proportion of White (36.1%) and Black (1.5%) patients (CS,¹ Table 8), than would be expected in the target population in the UK. Nevertheless, the EAG's clinical advisors considered it unlikely that ethnicity would be a treatment effect modifier.

Table 10: Baseline patient characteristics - KEYNOTE-A18, Stage III-IVA subgroup, IA2 (reproduced with minor amendments from CS, Table 8)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	N	(%)	N	(%)	N	(%)
Participants in population	296		305		601	
Sex						
Female	296	100	305	100	601	100
Age (Years)						
< 65					502	83.5
>= 65					99	16.5
Mean					51.5	
SD					12.3	
Median					51	
Range					22 to 87	
Race						
American Indian or Alaska Native					41	6.8
Asian					203	33.8
Black or African American					9	1.5
Multiple					129	21.5
Native Hawaiian or Other Pacific Islander					2	0.3
White					217	36.1
Ethnicity						
Hispanic or Latino					230	38.3
Not Hispanic or Latino					369	61.4
Not Reported					2	0.3
Geographic Region						
Asia Pacific					202	33.6
EMEA					148	24.6
North America					31	5.2
Latin America					220	36.6

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	N	(%)	N	(%)	N	(%)
Geographic Region 2						
North America	■	■	■	■	31	5.2
Western Europe	■	■	■	■	107	17.8
Rest of the World	■	■	■	■	463	77
Age Group (Years)						
< 65	■	■	■	■	502	83.5
65 - 74	■	■	■	■	91	15.1
75 - 84	■	■	■	■	7	1.2
85+	■	■	■	■	1	0.2
Baseline ECOG						
0	■	■	■	■	406	67.6
1	■	■	■	■	195	32.4
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic	■	■	■	■	425	70.7
No Positive Pelvic nor Para-Aortic	■	■	■	■	176	29.3
Histology Subtype						
Non-squamous	■	■	■	■	99	16.5
Squamous	■	■	■	■	502	83.5
Planned Type of EBRT						
IMRT or VMAT	■	■	■	■	519	86.4
non-IMRT and non-VMAT	■	■	■	■	82	13.6
Planned Total Radiation Therapy Dose per (EQD2)						
< 70 Gy	■	■	■	■	61	10.1
>= 70 Gy	■	■	■	■	540	89.9
PD-L1 Status						
CPS <1	■	■	■	■	34	5.7
CPS >=1	■	■	■	■	559	93
Missing	■	■	■	■	8	1.3

CCRT - concurrent chemoradiotherapy; EMEA - Europe, the Middle East and Africa; ECOG - Eastern Cooperative Oncology Group; EBRT - external beam radiation therapy; IMRT - intensity modulated radiotherapy; VMAT - volumetric modulated arc therapy; PD-L1 - programmed death-ligand 1; CPS - combined positive score N - number
Source: KEYNOTE-A18 IA2 TLF (DCO 8th January 2024)

3.3 Summary of the results from KEYNOTE-A18

This section reports results from KEYNOTE-A18 based on IA2,¹⁴ as per the trial results reported in the CS.¹ As noted in Section 3.2, following the clarification round, the company provided an additional addendum to the CS¹⁶ which provides the results of the Final Analysis (DCO 7th January 2025). Selected key tables and figures relating to this updated data-cut can be found in Appendix 1. Updated data from the Final Analysis are also discussed briefly throughout this section.

KEYNOTE-A18¹⁴ randomised 601 patients (FIGO 2014 Stage III-IVA): 296 to pembrolizumab plus CCRT; 305 to the control arm placebo plus CCRT. ■

■; ■ patients were still on treatment, of whom ■ were in the pembrolizumab plus CCRT arm and ■ were in the control arm

(CS,¹ Table 11); █ patients in the pembrolizumab plus CCRT arm and █ patients in the control arm had discontinued treatment (CS, Table 11 and CS Appendix, Table 15). At the Final Analysis, █ patients in the pembrolizumab plus CCRT arm and █ patients in the placebo plus CCRT arm had either completed study medication or discontinued.²¹

Drug exposure data are presented in Section 2.10.1 of the CS.¹ The median duration of therapy at IA2 was █ months in the pembrolizumab plus CCRT arm and █ months in the placebo arm.¹⁴ At the Final Analysis DCO, median duration on therapy was █ months in the pembrolizumab plus CCRT arm and █ months in the placebo arm.²¹

Key results for the primary end points (OS and investigator-assessed PFS) and secondary end points (PFS by BICR and ORR) are summarised in Table 11.

Table 11: Summary of results of KEYNOTE-A18, FIGO 2014 Stage III-IVA subgroup, IA2

End point		Pembrolizumab + CCRT	Placebo + CCRT	Effect estimate (95% CI, <i>p</i> -value)
Based on mITT population				
		(N=296)	(N=305)	
OS	OS events at IA2 N (%)	43 (14.5)	73 (23.9)	HR: 0.57 (0.39, 0.83), █
	Median OS, Months (95% CI)	NR (NR, NR)	NR (NR, NR)	
	OS rate at Month 24 (%) (95% CI)	█	█	NR (NR, NR)
PFS	PFS events at IA2, investigator-assessed N (%)	79 (26.7)	125 (41.0)	HR: 0.57 (0.43, 0.76), █
	Median PFS, investigator-assessed, Months (95% CI)	NR (NR, NR)	NR (26.3, NR)	
	PFS rate at Month 24, investigator-assessed (%) (95% CI)	█	█	█ ¹⁴
	PFS events at IA2, BICR N (%)	█	█	HR: █
	PFS rate at Month 24, BICR (%) (95% CI)	█	█	Difference %: █ ¹⁴
ORR	N objective responses, BICR, ITT population	█	█	
	ORR, % (95% CI), BICR, ITT	█	█	Difference Estimate: █

End point		Pembrolizumab + CCRT	Placebo + CCRT	Effect estimate (95% CI, <i>p</i> -value)
Based on participants with measurable disease at baseline				
		N=292	N=300	
ORR	Number of objective responses, investigator-assessed			
	ORR, % (95% CI), investigator-assessed			Difference Estimate:

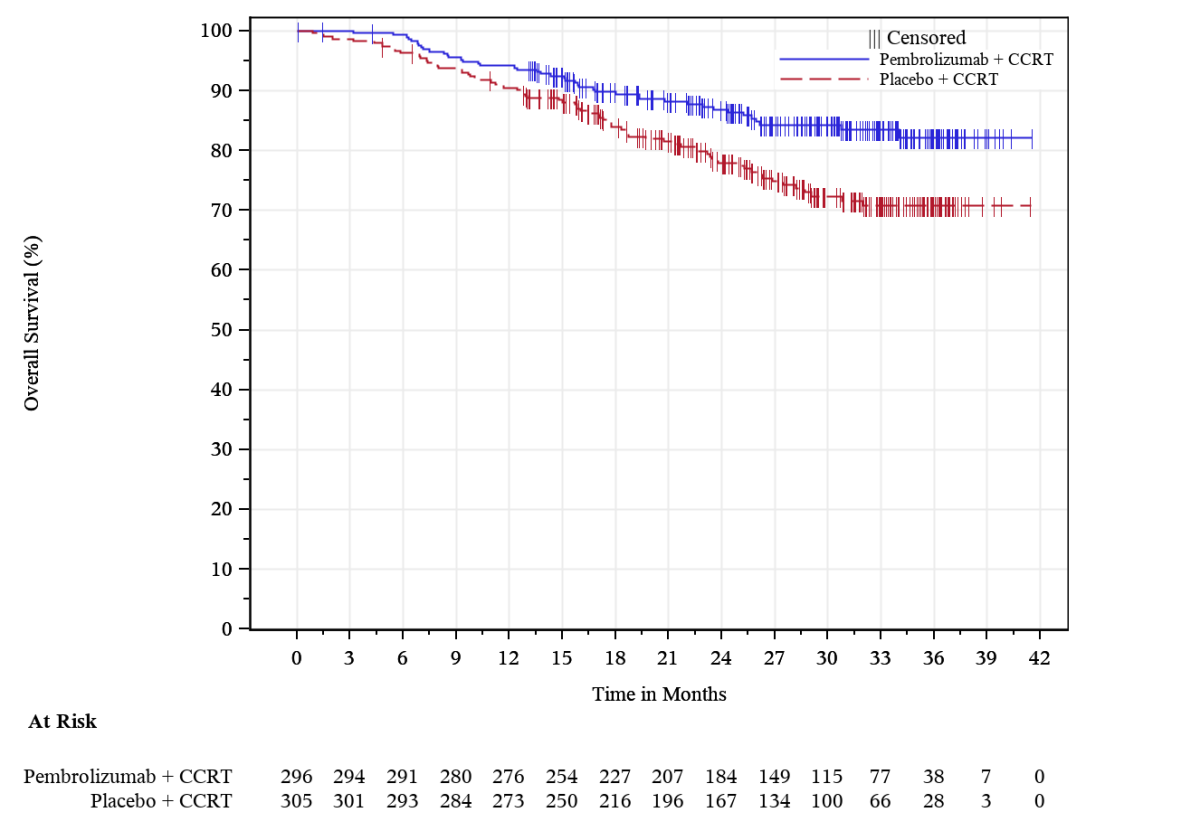
FIGO - International Federation of Gynecology and Obstetrics; IA2 - Interim Analysis 2; mITT - modified intention-to-treat; CI - confidence interval; OS - overall survival; PFS - progression-free survival; ORR - objective response rate; BICR - Blinded Independent Central Review; NR - not reported; N - number

OS and investigator-assessed PFS in the Stage III–IVA subgroup were immature at IA2 (median PFS and OS were not reached in either treatment arm). The HR for OS was reported to be 0.57 (95% CI 0.39 to 0.83) and the HR for PFS was reported to be 0.57 (95% CI 0.43 to 0.76). Trial randomisation was stratified by FIGO Stage (IB2–IIB vs III–IVA), and this subgroup analysis was pre-specified. The EAG considers that limitations in the power calculation at IA2 would not materially affect the interpretation of the clinical results (i.e., relative treatment effect direction and statistical significance).

3.3.1 Overall survival (OS)

At IA2, median OS had not been reached in either trial arm (see Table 11). Figure 3 presents the Kaplan-Meier plot for OS. A breakdown of OS results at 6-month landmark time points is presented in CS,¹ Table 12; for brevity, these data have not been reproduced here. At IA2, there were 43 (14.5%) events in the pembrolizumab plus CCRT arm, and 73 (23.9%) events in the placebo arm. The HR for OS significantly favoured the pembrolizumab plus CCRT group (HR 0.57; 95% CI 0.39 to 0.83;) (CS, Section 2.6.1.1).¹⁴

Figure 3: Kaplan-Meier plot for overall survival, mITT population, IA2 (reproduced from CS, Figure 5)



CCRT - concurrent chemoradiotherapy; mITT - modified intention-to-treat; IA2 - Interim Analysis 2

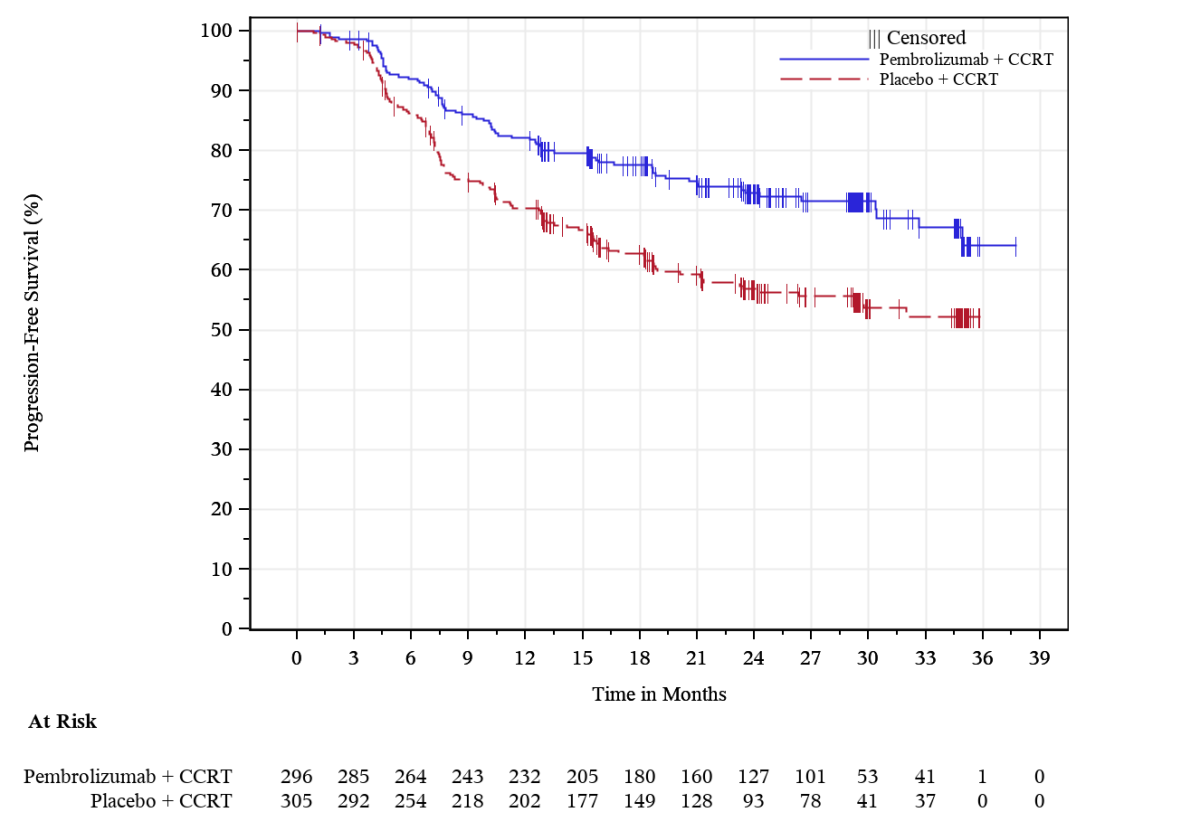
At the Final Analysis (DCO 7th January 2025), the HR for OS statistically significantly favoured the pembrolizumab plus CCRT group over the placebo plus CCR group (HR 0.64; 95% CI 0.46 to 0.88; *p*=0.0031) (see Appendix 1, Table 46 and Figure 34).

3.3.2 Progression-free survival (PFS)

PFS was measured in KEYNOTE-A18¹⁴ by investigators and by BICR. At IA2, median investigator-assessed PFS had not been reached in either trial arm (see Table 11). Figure 4 presents the Kaplan-Meier plot for investigator-assessed PFS. A breakdown of PFS results at 6-month landmark time points is presented in CS,¹ Table 13 and CS Appendix Table 20; for brevity, these data have not been reproduced here.

The HR for investigator-assessed PFS was reported to be 0.57 (95% CI 0.43 to 0.76; *p*<0.0001)

Figure 4: Kaplan-Meier plot of progression-free survival (primary censoring rule) based on investigator assessment, mITT population, IA2 (reproduced from CS, Figure 6)



CCRT - concurrent chemoradiotherapy; mITT - modified intention-to-treat; IA2 - Interim Analysis 2

At the Final Analysis (DCO 7th January 2025), the HR for investigator-assessed PFS was reported to be 0.63 (0.48, 0.82, $p=0.0002$). (see Appendix 1, Table 46, and Figure 35).

3.3.3 Subgroup analysis of PFS and OS

Forest plots for pre-planned subgroup analyses of OS and PFS at IA2 are presented in Figure 5 and Figure 6, respectively.



Figure 5: Forest plot of OS HR by subgroup factors, ITT population (reproduced from CS, Figure 9)

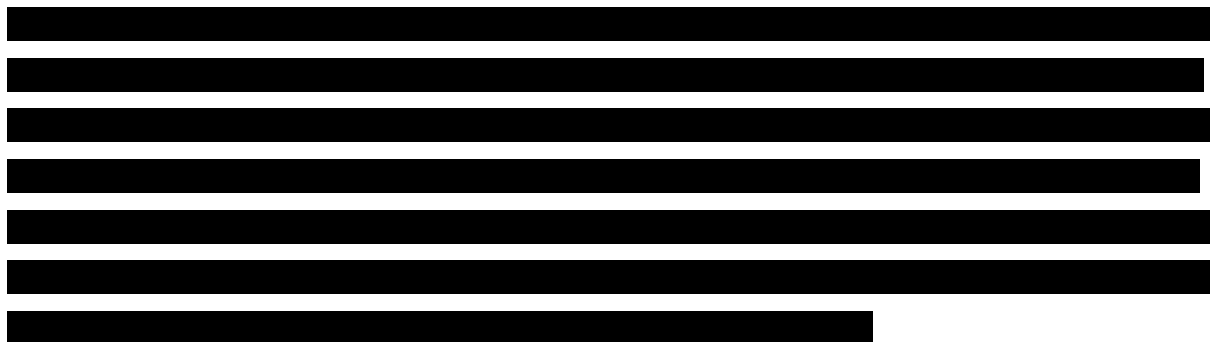


OS - overall survival; ITT - intention-to-treat; CS - company's submission; HR - hazard ratio; N - number; CI - confidence interval; EBRT - external beam radiation therapy; FIGO - International Federation of Gynecology and Obstetrics; ECOG - Eastern Cooperative Oncology Group

Figure 6: Forest plot of PFS HR by subgroup factors based on investigator assessment (primary censoring rule, ITT population (reproduced from CS, Figure 10))



PFS - progression-free survival; ITT - intention-to-treat; CS - company's submission; HR - hazard ratio; N - number; CI - confidence interval; EBRT - external beam radiation therapy; FIGO - International Federation of Gynecology and Obstetrics; ECOG - Eastern Cooperative Oncology Group



3.3.4 PFS after next-line treatment (PFS2)

Figure 36 presents the Kaplan-Meier plot for PFS2 assessed by study investigators at IA2. 



Figure 7: Kaplan-Meier plot of PFS after next-line treatment (PFS2), based on investigator assessment, ITT population, IA2 (reproduced from CS, Appendix E3, Figure 5)



PFS - progression-free survival; BICR - Blinded Independent Central Review; RECIST - Response Evaluation Criteria in Solid Tumors; ITT - intention-to-treat; CS - company's submission; CCRT - concurrent chemoradiotherapy

[Redacted text block]

3.3.5 Objective response rate (ORR)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

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3.3.6 Health-related quality of life (HRQoL)

HRQoL measured by EQ-5D-5L at IA2 is presented in Section 2.6.2.3 of the CS,¹ and EORTC results are contained in CS Appendix E.4.¹⁵ [REDACTED]

[REDACTED]

[REDACTED]

3.3.7 Subsequent oncologic treatments

The CS¹ reports both the number of patients receiving subsequent treatment and the treatment mix amongst those who reached PFS endpoint in the APaT population at IA2 ([REDACTED] vs. [REDACTED] patients, respectively; see Table 12). Among these patients: [REDACTED] in the pembrolizumab plus CCRT arm vs [REDACTED] in the placebo arm received subsequent treatment; [REDACTED] and [REDACTED] remained alive without receiving subsequent treatment, respectively; and [REDACTED] in both groups ([REDACTED], respectively) died without receiving subsequent treatment (i.e., these deaths likely occurred whilst reaching the PFS endpoint or shortly thereafter).

Accordingly, among patients who had reached the PFS endpoint and had not died without receiving subsequent treatment at IA2, [REDACTED] in the pembrolizumab plus CCRT arm and [REDACTED] in the placebo arm received subsequent therapy. The most frequent first subsequent treatment regimens were: [REDACTED]

[REDACTED]

Table 12: Subsequent oncologic therapies, APaT, KEYNOTE-A18, IA2 (reproduced from CS, Table 18)

	Pembrolizumab + CCRT (N=70) N (%)	Placebo + CCRT (N=111) N (%)
Participants who did not receive subsequent oncologic therapies		
Participants who died		
Participants who are alive		
Participants who received subsequent oncologic therapies		
1st subsequent line		
carboplatin + paclitaxel		
bevacizumab + carboplatin + paclitaxel		
cisplatin + paclitaxel		
bevacizumab + carboplatin + paclitaxel + pembrolizumab		
bevacizumab + cisplatin + paclitaxel		
carboplatin + paclitaxel + pembrolizumab		
cisplatin		
paclitaxel		
paclitaxel nanoparticle albumin-bound		
bevacizumab + carboplatin + cisplatin + paclitaxel		
bevacizumab + carboplatin + paclitaxel nanoparticle albumin-bound		
pembrolizumab		
bevacizumab + cadonilimab + capecitabine + catequentinib + cisplatin + paclitaxel		
bevacizumab + cisplatin + paclitaxel + paclitaxel nanoparticle albumin-bound		
bevacizumab + cisplatin + paclitaxel + pembrolizumab		
bevacizumab + denosumab + paclitaxel + topotecan		
bevacizumab + paclitaxel + pembrolizumab + topotecan		
bevacizumab + paclitaxel nanoparticle albumin-bound		
bevacizumab + zimberelimab		
cadonilimab		
carboplatin		
carboplatin + catequentinib + docetaxel		
carboplatin + gemcitabine + paclitaxel + pembrolizumab		
carboplatin + paclitaxel + paclitaxel nanoparticle albumin-bound		
carboplatin + paclitaxel nanoparticle albumin-bound		
cisplatin + gemcitabine + paclitaxel		
cisplatin + paclitaxel + zoledronic acid		
cisplatin + paclitaxel nanoparticle albumin-bound		
cyclophosphamide + doxorubicin + vincristine		
paclitaxel + topotecan		
2nd subsequent line		
bevacizumab + carboplatin + paclitaxel		
bevacizumab		
bevacizumab + cisplatin + paclitaxel		
bevacizumab + paclitaxel		
bevacizumab + pembrolizumab		

	Pembrolizumab + CCRT (N=70)	Placebo + CCRT (N=111)
gemcitabine		
topotecan		
carboplatin + paclitaxel + pembrolizumab		
cadonilimab		
carboplatin + paclitaxel		
cemiplimab		
cisplatin + gemcitabine		
cisplatin + paclitaxel		
doxorubicin		
gemcitabine + pemetrexed		
marsdenia tenacissima stem		
paclitaxel nanoparticle albumin-bound + zimberelimab		
pembrolizumab		
tisotumab vedotin		
vinorelbine		
3rd subsequent line		
angelica sinensis + paeonia lactiflora + poria cocos + rehmannia glutinosa + reynoutria multiflora		
bevacizumab + carboplatin + paclitaxel		
bevacizumab + cisplatin + paclitaxel + pembrolizumab		
cisplatin + gemcitabine		
irinotecan		
pembrolizumab		
cemiplimab		
4th subsequent line		
bevacizumab + carboplatin		
5th subsequent line		
doxorubicin		

Notes: Number of participants: all-participants-as-treated population; Every participant is counted once for each applicable row and column; Percentages are based on the number of participants who progressed based on Investigator Review; If a treatment reflects a combination of regimens, the duration is derived using the first initiation date of any treatment within the regimen and the last date at which any treatment within the regimen is observed; To be included in this summary, start date of individual component must be on or after date of progression based on Investigator Review.

DCO 8th January 2024

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.3.8 Adverse events (AEs)

AEs in KEYNOTE-A18 (IA2)¹⁴ are reported in Section 2.10 of the CS¹ and CS, Appendix D.¹⁵ At IA2, the safety population comprised 295 patients in the pembrolizumab arm, and 304 patient in the placebo arm, with a median duration on therapy of [REDACTED]

A summary of the safety data from the Final Analysis of KEYNOTE-A18²¹ is presented in Table 13.

██████████, AEs of special interest occurred in ██████████ of pembrolizumab-treated patients, and ██████████ of placebo-treated patients (CS,¹ Table 26). The most common AEs of special interest in the pembrolizumab arm were hypothyroidism ██████████ and hyperthyroidism ██████████.

Table 13: AEs at the Final Analysis of KEYNOTE-A18 (DCO 7th January 2025) (adapted from Tables 4.5-1 and 4.5-2 from the company's Final Analysis statistical report)

Outcome	Pembrolizumab plus CCRT		Placebo plus CCRT	
	n	%	n	%
One or more AEs	100	100	100	100
Grade 3-5 AEs	10	10	10	10
SAEs	10	10	10	10
Death	1	1	1	1
Death due to a drug-related AE	1	1	1	1
Discontinued any drug due to an AE	10	10	10	10
Discontinued any drug due to an SAE	1	1	1	1
AEOSI	1	1	1	1

DCO - data cut-off; CCRT - concurrent chemoradiotherapy AE - adverse event; SAE - serious adverse event; AEOSI - adverse event of special interest

3.4 Critique of the indirect comparison or multiple treatment comparison

The CS¹ argues that the CCRT regimen used in the trial reflects that used in current UK clinical practice. Despite this, Section 2.9 of the CS states that the company assessed the generalisability of studies evaluating other combinations of chemotherapy and radiotherapy, with a focus on those involving CCRT in combination with either induction and/or consolidation chemotherapy and explored whether an ITC was feasible. The company concluded that an ITC was not feasible, and that any analysis conducted would be subject to severe limitations, in particular, due to differences in study populations and types of EBRT used across the studies. As such, the CS does not present an ITC. The EAG considers the company's decision not to conduct an ITC to be reasonable.

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG did not conduct any additional work on the clinical effectiveness of pembrolizumab plus CCRT.

3.6 Conclusions of the clinical effectiveness section

The EAG believes that no RCTs of pembrolizumab plus CCRT which are relevant to this appraisal have been missed or excluded from the CS.¹

The key clinical effectiveness evidence for the appraisal comes from one RCT – KEYNOTE-A18^{14, 21} – which compared pembrolizumab plus CCRT against placebo plus CCRT. KEYNOTE-A18 is a Phase III, multi-centre, double-blind, placebo-controlled RCT. This trial is of direct relevance to the decision problem defined in the final NICE scope.¹³

A quality assessment of KEYNOTE-A18¹⁴ conducted by the company and the EAG suggests that this trial is at low risk of bias. However, KEYNOTE-A18 enrolled a broader population than that defined in the marketing authorisation, and so the reported results were limited to the subgroup of FIGO 2014 Stage III-IVA LACC patients (N=601). As FIGO disease stage was one of the stratification factors, this is unlikely to introduce bias as the patient baseline characteristics were balanced between trial arms. The power calculation reported was for the whole study, rather than the subgroup of Stage III-IVA patients; however, the EAG believes that this is unlikely to represent a major issue.

The CCRT regimen used in KEYNOTE-A18¹⁴ reflects that used in current UK clinical practice. However, brachytherapy in the trial was given at lower dose than that recommended by the BGCS.¹¹ Radiation doses were the same in both treatment arms (pembrolizumab and placebo), and so the trial results reflect the relative treatment effect for pembrolizumab and placebo. It is however uncertain whether the treatment difference would be greater or smaller if both arms had received a total radiation dose in line with current BGCS guidelines.

The EAG's clinical advisors considered that the Stage III-IVA subgroup in KEYNOTE-A18¹⁴ is similar to the expected eligible UK population in terms of age and disease type. The trial population differed from the expected eligible UK population in terms of ethnicity. [REDACTED]

[REDACTED] The EAG's clinical advisors did not expect ethnicity to be a treatment effect modifier.

The primary outcomes in KEYNOTE-A18¹⁴ were OS and PFS. At IA2, for Stage III-IVA participants, the HR for OS favoured the pembrolizumab group (HR 0.57; 95% CI 0.39 to 0.83; $p=$ [REDACTED]). The HR for PFS also favoured the pembrolizumab group when assessed by investigators (HR 0.57; 95% CI 0.43 to 0.76) and by BICR (HR [REDACTED]). At the Final Analysis, the HRs for OS and PFS continued to favour the pembrolizumab group: OS (HR 0.64 (95% CI 0.46 to 0.88; $p=0.0031$); investigator-assessed PFS (HR 0.63; 95% CI 0.48 to 0.82; $p=0.0002$; [REDACTED])

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

4. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analysis of pembrolizumab plus CCRT for the treatment of patients with high-risk LACC. Section 4.1 describes and critiques the company's review of existing economic evaluations. Section 4.2 describes the original version of the company's economic model presented in the CS¹ (informed by IA2 of KEYNOTE-A18¹⁴) and summarises its results. Section 4.3 presents the EAG's critical appraisal of the company's original economic model. Following the clarification round, the company submitted an updated version of the economic model which includes substantial amendments, including updated analyses of data from the Final Analysis data-cut of KEYNOTE-A18.²¹ The results of the company's updated (post-clarification) model and the EAG's exploratory analyses based on this model are presented separately in Chapter 5.

4.1 Summary and critique of the company's review of cost-effectiveness evidence

4.1.1 *Summary and critique of company's searches*

CS Appendices F, G and H¹⁵ report SLRs of economic evaluations, utility studies and cost and health care resource use studies, respectively. The searches for these reviews were conducted in August 2023 (approximately two years before the date of the CS). During the clarification process, the EAG queried whether any attempt had been made to update them in the interim (see clarification response,¹⁷ question B2). The company subsequently provided an addendum to the CS¹⁶ which contains updated searches for the SLRs conducted in February 2025.

The EAG considers that the searches themselves appear to have been competently executed (including the original and the update searches), covering databases including EMBASE and MEDLINE – with the caveat that they were conducted together in a multi-file search, making it impossible for the EAG to reproduce them. Multi-file searching is generally not advisable for systematic searches as it loses some of the precision that can be achieved by searching databases one at a time; however, the EAG recognises its advantages in terms of time saved. At the clarification stage, the EAG also noted some minor anomalies in the numbering of tables in the original submission, which the company corrected in its response to clarification question B1.¹⁷

The company also searched the Cochrane Library and the now defunct NHS Economic Evaluation Database (NHS EED). The archives of the Health Technology Assessment (HTA) database (up to 2015) were searched on the Centre for Reviews and Dissemination (CRD) website but not, apparently, the current version of the database (which has been hosted by The International Network of Agencies for Health Technology [INAHTA] since 2020); however, the company did also search the NICE and Scottish Medicines Consortium (SMC) websites, as well as a selection of related conference proceedings.

Following the receipt of the company's updated searches provided as part of the company's clarification response,¹⁷ the EAG is broadly satisfied with the company's approach.

4.1.2 Summary and critique of company's review of existing economic evaluations

The inclusion criteria for the company's SLR of published economic evaluations are detailed in Table 37 of CS Appendix F.¹⁵ Studies were eligible for inclusion in the review if the population included in the analysis related to adult patients (aged ≥ 18 years) with high-risk LACC (Stage IB2–IVA), in alignment with the full KEYNOTE-A18 trial population.³⁰ Studies of patients with Stage IA/IB1, Stage IVB LACC or unclear staging were excluded. Only studies assessing first-line treatments in patients who have not received prior systemic therapy were included; analyses of later-line therapies were excluded unless subgroup analyses relating to previously untreated patients were reported separately. With the exception of the criterion relating to line of therapy, no further restrictions were applied either to interventions or comparators. Publication types were restricted to peer-reviewed full-text articles published in English and conference abstracts from the previous six years (2018-2023). No geographical restrictions were applied.

Based on the SLR reported in CS Appendix F,¹⁵ a total of 20 cost-effectiveness (CEA) or cost-utility (CUA) studies met the inclusion criteria. The majority of identified studies were model-based evaluations, with seven studies employing state transition models and two using decision trees. Several studies did not report model type. The included studies demonstrated considerable variation in the time horizon adopted, ranging from 4 weeks to the patient's remaining lifetime. Analyses were primarily conducted from a payer perspective, although several studies adopted a societal perspective.

A range of treatment strategies were evaluated across the included studies, with gemcitabine plus cisplatin CRT being the most commonly assessed regimen. Other CRT approaches included cisplatin monotherapy or paclitaxel-carboplatin combinations. Evaluations also encompassed diverse radiotherapy modalities, including conventional radiotherapy, IMRT, and brachytherapy guided by MRI, CT or two-dimensional (2D) planning. In addition, several included studies assessed surgical strategies, such as radical hysterectomy with or without lymphadenectomy, nodal staging surgery, and surgery combined with adjuvant therapy. Some of the included analyses evaluated diagnostic or surveillance strategies, including the use of PET/CT, MRI, or surgical staging prior to initiating therapy. None of the included studies evaluated pembrolizumab plus CCRT for the treatment of high-risk LACC. The majority (approximately 64%) of the included studies reflected a US setting. None of the identified studies reflect a UK setting.

The EAG considers that given the absence of previous UK economic analyses of pembrolizumab (or any other therapy) for the first-line treatment of high-risk Stage III-IVA LACC, the findings of the

review are of limited relevance to the decision problem for the current appraisal. However, as noted in the CS,¹ the company's economic model draws on the previous economic model used to inform NICE TA939¹⁰ to inform downstream outcomes for patients with progressed disease.¹⁰

As noted in Section 4.1.1, the searches for the SLR of published economic analyses presented in CS Appendix F¹⁵ was the 23rd August 2023 which was nearly two years prior to the date on which the CS was shared with NICE. The company's additional addendum¹⁶ provided alongside its clarification response includes an updated SLR of economic analyses with a search cut-off date of 20th February 2025. As this cut-off date precedes the date on which the EAG's clarification letter response was submitted, the EAG is unsure why this SLR update was not included in the original CS.¹ The company's addendum states that two studies of pembrolizumab plus CCRT for LACC were identified from the February 2025 update search: Lui *et al.*³¹ and Courtney *et al.*³² The study reported by Lui *et al.* used a 3-state Markov model to compare pembrolizumab plus CCRT versus CCRT alone based on the overall population of KEYNOTE-A18²⁰ (FIGO 2014 Stages IB2-IIB and III-IVA) from a payer perspective in China, the US and Italy. The analysis was published in abstract form only and very limited details are provided regarding the methods adopted. Courtney *et al.* presents an economic analysis of pembrolizumab plus CCRT versus CCRT alone based on the same overall population of KEYNOTE-A18 from the perspective of the US health care payer. Neither of these analyses reflect the target population for the current appraisal due to the inclusion of patients with FIGO 2024 Stages IB2-IIB. The company's addendum argues that a *de novo* model was still required for the current appraisal as no previous study reflected a UK setting. The EAG acknowledges the company's position, but notes that it would have been prudent to consider the analysis reported by Courtney *et al.* as the basis for justification or comparison of the assumptions used in the model submitted for the current appraisal.

4.2 Summary of the company's original submitted economic evaluation

This section details the methods and results of the company's original submitted model, as described in the CS.¹ The original model is informed by data from IA2 of KEYNOTE-A18 (DCO 8th January 2024).¹⁴ Following the clarification round, the company submitted an updated model which includes the correction of several model errors identified by the EAG at the clarification stage¹⁷ as well as updated survival models and data relating to the Final Analysis of the trial (DCO 7th January 2025). The company's updated (post-clarification) model and its results are summarised separately in Section 5.1.

4.2.1 Scope of the company's economic analysis

As part of its submission to NICE,¹ the company submitted a fully executable model programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in Table 14. The model compares pembrolizumab plus CCRT versus CCRT alone for the treatment of adult patients with untreated high-risk FIGO 2014 Stage III-IVA LACC. The model uses a state transition (semi-Markov)

approach, informed by time-to-event data from KEYNOTE-A18,¹⁴ as well as external data for post-progression outcomes from KEYNOTE-826.³³ The economic analysis includes health outcomes and costs from the perspective of the NHS and Personal Social Services (PSS). Cost-effectiveness is assessed in terms of the incremental cost quality-adjusted life year (QALY) gained evaluated over a 50-year (lifetime) horizon. Unit costs are valued at 2023/24 prices, with the exception of drugs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Table 14: Scope of the company's economic analysis

Population	Adults with untreated high-risk FIGO 2014 Stage III-IVA LACC
Time horizon	50 years (lifetime)
Intervention	Pembrolizumab plus CCRT
Comparator	CCRT alone
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2023/24 (except for drugs which are valued at current prices)

FIGO - International Federation of Gynecology and Obstetrics; CCRT - concurrent chemoradiotherapy; LACC - locally advanced cervical cancer; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

Population

The population included in the company's economic model reflects the FIGO 2014 Stage III to IVA subgroup of KEYNOTE-A18.¹⁴ At model entry, patients are assumed to have a mean age of 51.5 years and 100% are female. These characteristics are used to estimate general population mortality risks and to adjust utility values for increasing age. Patients are assumed to have a mean body weight of 63.10 kg and body surface area (BSA) of 1.7m² based on KEYNOTE-A18.

Intervention

The intervention evaluated within the economic analysis is pembrolizumab in combination with CCRT. The recommended dose of pembrolizumab in adults is either 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W) administered as an IV infusion over 30 minutes. Section 4.2 of the SmPC¹² states that pembrolizumab can be administered until disease progression, unacceptable toxicity or for up to 24 months in the treatment of LACC.

During the combination therapy phase, pembrolizumab is assumed to be administered at a dose of 200mg Q3W via IV infusion for a maximum of 5 cycles concurrently with CCRT. During the maintenance therapy phase, pembrolizumab is assumed to be administered at a dose of 400mg Q6W via IV infusion until disease progression or for up to 15 cycles (corresponding to two years from the start of initial treatment, assuming no treatment delay). The CCRT regimen used in both the intervention and comparator groups of the model is described below.

Comparator

The CCRT regimen is assumed to include 5 cycles of 40mg/m² cisplatin administered weekly via IV infusion, in combination with EBRT, followed by brachytherapy. The dosing schedule for radiotherapy was based on the KEYNOTE-A18 protocol:³⁰ EBRT is assumed to be delivered at 45 Gy over 25 fractions, and brachytherapy is assumed to be delivered at 40-45 Gy over 4 fractions.

Downstream treatments following first-and second- disease progression

Table 15 summarises the treatment pathways following first and second progression assumed in the company's model. These pathways are described briefly below.

Table 15: Downstream treatment pathway assumed following disease progression

Model treatment group	Eligible for pembrolizumab re-challenge	Treatment after first disease progression (PD1)	Treatment after second disease progression (PD2)
Pembrolizumab plus CCRT	No*	80% receive chemotherapy with or without bevacizumab [‡] 20% receive no treatment	100% receive paclitaxel
	Yes [†]	51.20% receive pembrolizumab plus chemotherapy with or without bevacizumab [‡] 28.80% receive chemotherapy with or without bevacizumab [‡] 20% receive no treatment	
CCRT alone	N/a	51.20% receive pembrolizumab plus chemotherapy with or without bevacizumab [§] 28.80% receive chemotherapy with or without bevacizumab [§] 20% receive no treatment	

CCRT - concurrent chemoradiotherapy; PD1 - post-first-progression, PD2 - post-second-progression, N/a - not applicable

* Patients progressing within 2.5 years since starting treatment with pembrolizumab

† Patients progressing after 2.5 years since starting treatment with pembrolizumab

‡ Assumes paclitaxel (■■■■), carboplatin (■■■■), bevacizumab (■■■■) and cisplatin (■■■■).

§ Assumes paclitaxel (■■■■), carboplatin (■■■■), bevacizumab (■■■■) and cisplatin (■■■■).

Treatments following first disease progression (PD1)

Following first disease progression, 80% of patients are assumed to receive further active therapy, while the remaining 20% receive no treatment. Amongst those patients who progress within 2.5 years of initial pembrolizumab treatment ("early progressors"), all patients who receive treatment are assumed to receive chemotherapy using a combination of paclitaxel and carboplatin or cisplatin with or without bevacizumab. For patients who experience progression after 2.5 years of initial pembrolizumab treatment ("late progressors"), as well as all patients who progress in the CCRT alone group, 64% of treated patients are assumed to receive pembrolizumab plus chemotherapy with or without bevacizumab and 36% receive chemotherapy with or without bevacizumab. The dosing schedules for these regimens were based on the KEYNOTE-826 study protocol,³⁴ further details are provided in Section 4.2.3.

Treatments following second disease progression (PD2)

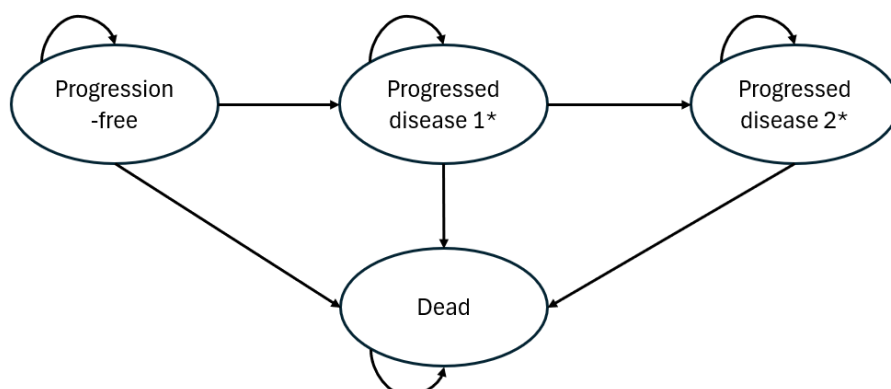
Following second disease progression, 100% of patients are assumed to be treated with paclitaxel at a dose of 80mg/m², administered weekly via IV infusion, for the mean treatment duration observed in KEYNOTE-826.³³

4.2.2 Company's model structure and assumptions

Model structure and logic

The company's economic model adopts a cohort-level semi-Markov approach, consisting of four health states: (i) Progression-free (PF), (ii) Progressed Disease 1 (PD1), (iii) Progressed Disease 2 (PD2) and (iv) Dead (see Figure 8). The model includes separate PD1 and PD2 states for early and late progressors in the pembrolizumab plus CCRT group and for progressors in the CCRT alone group to reflect the alternative distributions of subsequent treatments described in Table 15.

Figure 8: Model structure



**Separate sub-models for PD1 and PD2 are used to implement tunnel states to allow event risks to be conditional on time since state entry. In the pembrolizumab plus CCRT group, separate PD1 and PD2 sub-models are applied for early and late progressors.*

The model logic operates as follows. Patients enter the model in the PF state and receive treatment with either pembrolizumab plus CCRT or CCRT alone. Patients receive pembrolizumab for up to two years, cisplatin for up to 7 weeks and radiotherapy for up to 7 weeks, conditional on the observed time to treatment discontinuation (TTD) data from KEYNOTE-A18.¹⁴ The following health state transitions are permitted during each weekly model cycle:

- Patients in the PF state can either remain progression-free, transition to PD1 or die.
- Patients in the PD1 state can either remain in PD1, progress to PD2 or die.
- For patients in the PD2 state, the only remaining event is death.

PD1 and PD2 are intermediate health states represented by sub-models which use tunnel states to allow event risks to be dependent on the time since state entry.

Transitions out of the PF state to the PD1 and Dead states were modelled using standard parametric survival models fitted to PFS and TTP data from KEYNOTE-A18.¹⁴ The transitions from PD1 to PD2 and Dead were modelled using restricted cubic spline (RCS) models fitted to data on PFS and TTP from KEYNOTE-826.³³ The transition from PD2 to Dead was modelled using standard parametric survival models fitted to post-progression survival (PPS) data from KEYNOTE-826. The transition probabilities applied in each health state are not adjusted to account for competing risks. The transitions from all alive states to the Dead state include a constraint which ensures that the risk of death for people with LACC is at least as high as that for the standardised mortality ratio (SMR)-uplifted age-matched general population³⁵ (SMR=1.19).

The model includes structural assumptions of: (i) cure in both treatment groups and (ii) treatment effect waning for pembrolizumab in both the first-and second-line treatment settings.

With respect to the cure assumptions, the model assumes that the predicted probability of leaving the PF state due to disease progression is reduced by 0% at the end of Year 5, increasing approximately linearly to 95% by the end of Year 7. Beyond Year 7, the risk of leaving the PF state remains at 5% of the predicted probabilities obtained from the parametric survival models fitted to the PFS and TTP data from KEYNOTE-A18.¹⁴ For patients who are cured, the transition probability from PF to PD1 is zero, while the transition probability from PF to Dead follows the SMR-uplifted age-matched general population mortality risks. These cure assumptions are applied only to first-line treatments (pembrolizumab plus CCRT and CCRT alone) and do not apply to patients who have already experienced disease progression (i.e., those who have already reached the PD1 state).

With respect to treatment effect waning for pembrolizumab, the model assumes that 100% of the treatment effect is maintained up to Year 5 after starting treatment (in the PF or PD1 states). Between Years 5 and 7, the proportion of patients benefiting from the full treatment effect is assumed to decrease approximately linearly from 100% to 0%. Beyond Year 7, the treatment effect for pembrolizumab is assumed to be lost. From this time point onwards, the transition probabilities between health states are informed only by the CCRT arm of KEYNOTE-A18¹⁴ in the first-line setting, and from the chemotherapy (with or without bevacizumab) arm of KEYNOTE-826³³ in the second-line setting.

HRQoL is assumed to be dependent on the model health state, with a higher utility value applied in the PF state compared to the PD1 and PD2 states. The same utility values are applied in both treatment groups (treatment-dependent utility values are not applied). The model also includes short-term QALY losses resulting from treatment-related AEs in each model cycle for the first two years. The model does not include further QALY losses related to AEs arising as a consequence of second- and third-line treatments in the PD1 and PD2 states. Health state utility values are adjusted for increasing age.

The model includes costs associated with: (i) drug acquisition and administration (first-, second- and third-line treatments); (ii) monitoring; (iii) health state resource use; (iv) the management of AEs (applied as a per-cycle cost in the first two years); (v) PD-L1 testing; and (vi) end-of-life care (applied as a once-only cost).

Key assumptions employed in the company's original model

The company's model employs the following key assumptions:

- The modelled patient population is 51.50 years of age at model entry, and 100% are female. Mean body weight is 63.1 kg and BSA is 1.7m².
- Cisplatin-based CCRT alone is the only comparator for pembrolizumab plus CCRT.
- Outcomes for patients receiving first-line treatment are informed by KEYNOTE-A18 (IA2).¹⁴
- Outcomes for patients receiving second-line treatment are informed by KEYNOTE-826 (Final Analysis, CPS ≥ 1 subgroup).³³
- Standard parametric survival distributions and RCS models are used to estimate transition probabilities between the model health states over time. The specific models used to estimate each set of weighted transition probabilities are described in Section 4.2.3 (Table 17).
- The model includes the following structural constraints: (i) the per-cycle risk of death in patients with high-risk LACC cannot be lower than that of the SMR-uplifted age-matched general population, (ii) the cumulative probability of TTP cannot be lower than PFS at any time point.
- Cure is assumed for a proportion of patients in both treatment groups. The predicted probability of leaving the PF state due to disease progression is reduced by 0% at the end of Year 5, increasing approximately linearly to 95% by the end of Year 7. For cured patients, the transition probability from PF to PD1 is assumed to be zero, while the transition probability from PF to Dead follows the SMR-uplifted age-matched general population mortality risk.
- Treatment effect waning is assumed for pembrolizumab in both the first-and second-line treatment settings. The treatment effect is maintained at 100% up to Year 5 of initial treatment, and the proportion of patients benefiting from the full treatment effect is assumed to decrease approximately linearly from 100% to 0% between Years 5 and 7. When the treatment effect is lost (after Year 7), the transition probabilities between health states are informed by the per-cycle transition probabilities from the comparator groups of KEYNOTE-A18¹⁴ (first-line) and KEYNOTE-826³³ (second-line).
- HRQoL is assumed to be determined by the presence or absence of disease progression. The same utility values are applied in both treatment groups. The utility value for PF is higher than that for PD1 and PD2, and the values are adjusted for increasing age. QALY losses related to

Grade ≥ 3 AEs resulting from first-line treatments are applied to patients who remain alive and progression-free in each model cycle for up to two years.

- AEs related to second- and subsequent-line active treatments are not included in the model.
- Amongst patients who progress within 2.5 years of starting treatment with pembrolizumab plus CCRT (early progressors), 80% receive chemotherapy with or without bevacizumab and 20% receive no subsequent treatment. For patients who progress after 2.5 years of starting treatment with pembrolizumab plus CCRT (late progressors) and those who progress in the CCRT alone group, 51.20% receive pembrolizumab plus chemotherapy with or without bevacizumab, 28.80% receive chemotherapy with or without bevacizumab and 20% receive no subsequent treatment.
- Outcomes for patients receiving pembrolizumab in the PD1 state (late progressors) are assumed to be independent of prior treatment with pembrolizumab in the first-line setting (i.e., re-challenging with pembrolizumab is not associated with any reduction in effectiveness).
- Following second progression, 100% of patients are assumed to receive paclitaxel.
- All patients receiving first-line pembrolizumab treatment are assumed to require additional monitoring via blood tests and a CT scan in each treatment cycle. In addition, patients are assumed to require an MRI scan 3 months after the last dose of radiotherapy.
- Drug wastage is included for pembrolizumab and cisplatin in both the first-and second-line settings. Vial sharing is not assumed for other drugs used as subsequent-line therapy.
- Relative dose intensity (RDI) for all treatments is assumed to be 100%.

4.2.3 *Evidence used to inform the model parameters*

Table 16 summarises the evidence sources used to inform the parameters of the company's original base case model; these are discussed in detail in the subsequent sections. The original model is informed by data from IA2 of KEYNOTE-A18 (DCO 8th January 2024), with external data based on the CPS ≥ 1 subgroup of KEYNOTE-826³³ (Final Analysis DCO).

Following the clarification round, the company submitted an updated model which includes the use of alternative parametric survival models fitted to time-to-event data from the Final Analysis data-cut of KEYNOTE-A18 (DCO 7th January 2025) and external data from the CPS ≥ 1 with prior CRT subgroup of KEYNOTE-826³³ (Final Analysis DCO). The company's updated (post-clarification) model is described separately in Section 5.1. The updated data and analyses used in the company's updated model are summarised in Appendix 2.

Table 16: Evidence used to inform the company's original base case model

Parameter group	Source
Patient characteristics	Mean age, body weight and BSA taken from KEYNOTE-A18 ¹⁴
Transitions from PF to PF, PF to PD1 and PF to Dead	Informed by TTP and PFS data from KEYNOTE-A18 (IA2). ¹⁴ PF to Dead for cured patients based on SMR-uplifted age-matched general population mortality risks from ONS life tables. ³⁵
Transitions from PD1 to PD1, PD1 to PD2 and PD2 to Dead	Informed by TTP and PFS data from KEYNOTE-826 (CPS $\geq$ 1 subgroup). ³³
Transitions from PD2 to PD2 and PD2 to Dead	Informed by PPS data from KEYNOTE-826 (CPS $\geq$ 1 subgroup). ³³
Re-treatment probability and timepoint	Company's assumption based on clinical opinion.
Subsequent treatment distribution	Second-line treatments: Pembrolizumab based on clinical opinion, cisplatin and carboplatin use based on KEYNOTE-A18, ¹⁴ bevacizumab use based on Colombo <i>et al.</i> ³⁶ (KEYNOTE-826). Third-line treatments: Use of paclitaxel based on clinical opinion
Health state utility values	PF and PD1: Raw mean values from KEYNOTE-A18 (IA2). ¹⁴ PD2: Utility decrement between PF and PD from KEYNOTE-826 ³³ applied to the PD1 utility value from KEYNOTE-A18 (IA2). ¹⁴ AE disutility values: Regression coefficient from linear mixed-effects model fitted to data from KEYNOTE-A18 (IA2). ¹⁴
Pembrolizumab acquisition costs	PAS discount for pembrolizumab provided by the company (see CS Appendix J ¹⁵).
Acquisition costs of cisplatin and other subsequent treatments	BNF ³⁷ and eMIT ³⁸
Acquisition costs of radiotherapy	NHS Cost Collection 2023/24 ³⁹
Drug administration and monitoring costs	PSSRU, ⁴⁰ eMIT, ³⁸ NHS Cost Collection 2023/24. ³⁹ Monitoring requirements based on clinical opinion.
Health state management costs	Resource use data based on clinical opinion. Unit costs taken from NHS Cost Collection 2023/24. ³⁹
Costs of managing AEs	Frequency of AEs taken from Study KEYNOTE-A18 (IA2). ¹⁴ Unit costs taken from NHS Cost Collection 2023/24. ³⁹
End-of-life care costs	Georghiou and Bardsley 2014, ⁴¹ uplifted to 2023/24 prices

BSA - body surface area; PF - progression-free; PD - progressed disease; PD1 - first post-progression; PD2 - second post-progression; TTP - time to progression; PFS - progression-free survival; PPS - post-progression survival; AE - adverse events; PAS - Patient Access Scheme; BNF - British National Formulary; eMIT - electronic Market Information Tool; PSSRU - Personal Social Services Research Unit; ONS - Office for National Statistics; SMR - standardised mortality ratio

4.2.3.1 Transition probabilities

Summary of transition probabilities and data sources

The company's economic model includes 19 sets of transition probabilities, including 2 sets of transition probabilities out of the PF state for each treatment group (PF to PF, PF to PD1 and PF to Dead), 3 additional sets of transition probabilities for early progressors and late progressors in the pembrolizumab plus CCRT group and all progressors in the CCRT alone group (PD1 to PD1, PD1 to PD2 and PD1 to Dead), and a further 2 sets of transition probabilities following second progression in each treatment group (PD2 to PD2 and PD2 to Dead).

The transition probabilities from PF to PD1 and from PF to Dead were estimated using standard parametric survival models fitted to time-to-event data on PFS and TTP for each treatment group in the KEYNOTE-A18 trial¹⁴ (IA2, DCO 8th January 2024). Owing to the immaturity of the OS data in KEYNOTE-A18, the company used external data from the KEYNOTE-826 trial (CPS $\geq$ 1 subgroup)³³ to inform the transition probabilities relating to subsequent risks of progression and death. KEYNOTE-826 is a Phase 3, double-blind placebo-controlled RCT comparing pembrolizumab plus chemotherapy with or without bevacizumab against placebo plus chemotherapy with or without bevacizumab as first-line treatment for patients with recurrent, persistent or metastatic cervical cancer. This study formed the basis of TA885⁹ and TA939.¹⁰ The data from KEYNOTE-826 used in the economic model for the current appraisal reflect the Final Analysis (DCO October 2022); these data have not been updated since TA939 and no further data follow-up is available (see clarification response,¹⁷ question B15). A range of standard parametric survival models and RCS models were fitted to the time-to-event data on PFS and TTP in KEYNOTE-826; only standard parametric survival models were fitted to the PPS data from this study.

The fitted parametric survival distributions applied in the company's base case model are summarised in Table 17. The fitted distributions were also adjusted in the economic model to account for assumptions relating to cure and treatment effect waning and different distributions of subsequent treatments. For patients who do not receive active subsequent treatment following the first progression event, the transition probability from PD1 to PD2 was assumed to be zero, while the transition probability from PD1 to Dead was estimated by applying a multiplier of 2.0 to the per-cycle transition probability derived from data for the chemotherapy (with or without bevacizumab) arm of KEYNOTE-826.³³ This approach was necessary due to a lack of data on outcomes for patients who do not receive active treatment.

Cure assumptions applied in the company's model

The company's economic model includes a cure assumption whereby the predicted probabilities of leaving the PF state are reduced by 95% after Year 7 in both groups, with a preceding warm-up period starting after Year 5. During this warm-up period (between Years 5 and 7), the cured proportion was implemented as a proportionate reduction in the predicted probability of progression from the fitted parametric survival models, increasing approximately linearly during each weekly model cycle. Patients remaining in the PF health state who are cured are assigned SMR-uplifted age-matched general population mortality risks (SMR=1.19) and cannot transition to the PD1 state after the cure time point.

The cure assumptions were informed by clinical advice obtained by the company during an advisory board meeting held in 2024.⁴² The clinicians who attended the meeting supported the following assertions:

- A substantial proportion of patients with LACC are cured by chemoradiotherapy.
- All patients with LACC are treated with curative intent and it is reasonable to assume that there will be very few recurrences or disease-related deaths after 5 years.
- Patients are typically discharged at 5 years if no recurrence has occurred and these patients can be considered functionally cured.¹

Treatment effect waning assumptions applied in the company's model

The company's model includes assumptions of treatment effect waning for pembrolizumab when used as either first- or second-line therapy. The model assumes that 100% of the treatment effect for pembrolizumab is maintained up to Year 5, and the proportion of patients benefiting from the full treatment effect decreases approximately linearly from 100% to 0% between Year 5 and 7. After Year 7, the transition probabilities between health states are informed by the per-cycle transition probabilities from the comparator group only.

It should be noted that the plots of the model-predicted probabilities of TTP and PFS shown in Figure 9, Figure 10, Figure 11, and Figure 12 reflect the fitted parametric survival models and do not incorporate the impact of additional structural assumptions of cure and treatment effect waning for pembrolizumab. These assumptions are incorporated into the final model predictions shown in Figure 21 and Figure 22.

Table 17: Summary of parametric survival models used to inform transition probabilities in the company's economic model

Dataset	Trial arm	End point/event	Survival model selected	Transition probabilities used in model treatment group*
KEYNOTE-A18 (IA2) ¹⁴	Pembrolizumab + CCRT	TTP	Generalised gamma	TP from PF to PD1 (<i>pembro + CCRT</i>)
	CCRT alone	TTP	Generalised gamma	TP from PF to PD1 (<i>CCRT</i>)
	Pembrolizumab + CCRT	TTP, PFS	Generalised gamma	TP from PF to Dead (<i>pembro + CCRT</i>)
	CCRT alone	TTP, PFS	Generalised gamma	TP from PF to Dead (<i>CCRT</i>)
KEYNOTE-826 (CPS ≥ 1) ³³	Pembrolizumab + chemotherapy +/- bevacizumab	TTP	3-knot hazard RCS	TP from PD1 to PD2 (<i>pembro + CCRT</i> : 51.20% of late progressors) TP from PD1 to PD2 (<i>CCRT</i> : 51.20% of all progressors)
	Chemotherapy +/- bevacizumab	TTP	3-knot hazard RCS	TP from PD1 to PD2 (<i>pembro + CCRT</i> : 28.80% of late progressors) TP from PD1 to PD2 (<i>pembro + CCRT</i> : 80% of early progressors) TP from PD1 to PD2 (<i>CCRT</i> : 28.80% of all progressors)
	Pembrolizumab + chemotherapy +/- bevacizumab	TTP, PFS	3-knot hazard RCS	TP from PD1 to Dead (<i>pembro + CCRT</i> : 51.20% of late progressors) TP from PD1 to Dead (<i>CCRT</i> : 51.20% of all progressors)
	Chemotherapy +/- bevacizumab	TTP, PFS	3-knot hazard RCS	TP from PD1 to Dead (<i>pembro + CCRT</i> : 28.80% of late progressors) TP from PD1 to Dead (<i>pembro + CCRT</i> : 80% of early progressors) TP from PD1 to Dead (<i>CCRT</i> : 28.80% of all progressors)
	Pembrolizumab + chemotherapy +/- bevacizumab	PPS	Generalised gamma	TP from PD1 to Dead (<i>Both groups</i> : 20% of all progressors) [‡] TP from PD2 to Dead (<i>pembro + CCRT</i> : 0% of all patients experiencing second progression) TP from PD2 to Dead (<i>CCRT</i> : 64% of all patients experiencing second progression)
	Chemotherapy +/- bevacizumab	PPS	Generalised gamma	TP from PD2 to Dead (<i>pembro + CCRT</i> : 100% of all second-time progressors) TP from PD2 to Dead (<i>CCRT</i> : 36% of all patients experiencing second progression)
	General population life tables	Death	N/a	TP from PF to Dead (<i>Both groups</i> : cured patients). Includes SMR of 1.19

TP - transition probability; TTP - time to progression; PFS - progression-free survival; PPS - post-progression survival; TP - transition probability; PF - progression-free; PD1 - first post-progression; PD2 - second post-progression; RCS - restricted cubic spline; CCRT - concurrent chemoradiotherapy; pembro - pembrolizumab; IA2 - Interim Analysis 2; CPS - combined positive score; N/a - not applicable; SMR - standardised mortality ratio

* The TP from PD1 to PD2 for progressors who did not receive treatment was assumed to be zero.

‡ A multiplier of 2.0 was applied to the transition probability for PD1 to Dead to estimate survival outcomes for untreated patients in both treatment groups.

Modelling transitions out of the progression-free state (PF to PF, PF to PD1 and PF to Dead)

The probability of transitioning to the PD1 state (PF to PD1) was informed by data on TTP, the probability of transitioning to the Dead state (PF to Dead) was informed by the difference between TTP and PFS, and the probability of remaining in the PF state (PF to PF) was estimated as one minus the sum of the other transition probabilities out of the PF state.

The company fitted seven standard parametric survival models to the individual patient data (IPD) on investigator-assessed TTP and PFS from KEYNOTE-A18.¹⁴ The survival distributions were fitted separately to the TTP and PFS data for each treatment group. These included the exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma distributions. More flexible survival models such as mixture-cure models (MCMs) and RCS models were not considered. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for the fitted parametric survival models for PFS and TTP are presented in Table 18 and Table 19, respectively. The Kaplan-Meier survival functions and the parametric survival model predictions for PFS for the pembrolizumab plus CCRT and CCRT alone groups are shown in Figure 9 and Figure 10, respectively. The corresponding Kaplan-Meier survival functions and model predictions for TTP are presented in Figure 11 and Figure 12, respectively. Empirical and modelled hazard plots for PFS or TTP at IA2 of KEYNOTE-A18 are not presented in the CS.¹

The CS¹ states that the company's model selection process for survival distributions informing transitions out of the PF state included consideration of: (i) visual fit to the observed Kaplan-Meier estimates within the observed period of KEYNOTE-A18;¹⁴ (ii) plausibility of the model extrapolations, including input from clinical experts and comparison against relevant external data, where possible; (iii) assessment of the underlying hazard functions and (iv) relative goodness-of-fit statistics based on the AIC and BIC. The CS also refers to NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14⁴³ which recommends using the same parametric model type in both treatment groups unless there a strong rationale to do otherwise.

The CS¹ states that the company selected the generalised gamma model for PFS in the pembrolizumab plus CCRT group on the basis that: (a) all models except for the generalised gamma and Gompertz distributions had a poor visual fit against the KEYNOTE-A18 data;¹⁴ (b) the generalised gamma distribution had the lowest AIC and BIC values in the pembrolizumab plus CCRT group, with no other distribution being within 5 points, and (c) clinical experts who attended the 2024 advisory board meeting confirmed that the generalised gamma model including a 5-7 year cure point provided the most plausible long-term PFS estimates.⁴² The CS also states that the generalised gamma distribution was selected for PFS in the CCRT group because: (a) this distribution also provided a good visual fit to the KEYNOTE-A18 data and (b) it had the lowest AIC and BIC values in the CCRT group and (c) clinical

experts who attended the 2024 advisory board meeting confirmed that the generalised gamma model including a 5-7 year cure point provided the most plausible estimates for CCRT alone. The EAG notes that the CS does not present empirical or modelled hazard plots and it is unclear whether these plots were used to inform model selection in either treatment group.

The CS¹ highlights that the number of pre-progression death events in KEYNOTE-A18¹⁴ was low in both treatment groups (pembrolizumab plus CCRT N=■; CCRT N=■). The CS states that the same distributional form (i.e., the generalised gamma distribution) was applied to PFS/TTP pairs for each treatment group in order to avoid illogical extrapolations.

The use of the Gompertz distribution for PFS/TTP in both treatment groups was explored in the company's scenario analyses (see Section 4.2.6). Other parametric survival distributions were not considered.

Table 18: AIC and BIC statistics, PFS, KEYNOTE-A18, both groups

Distribution	Pembrolizumab + CCRT		CCRT alone	
	AIC	BIC	AIC	BIC
Exponential	1080	1083	1564	1568
Weibull	1082	1089	1566	1573
Gompertz	1078	1086	1557	1565
Log-normal	1071	1078	1544	1551
Log-logistic	1078	1086	1555	1562
Generalised gamma (base case)	1064	1075	1530	1541
Gamma	1081	1089	1566	1573

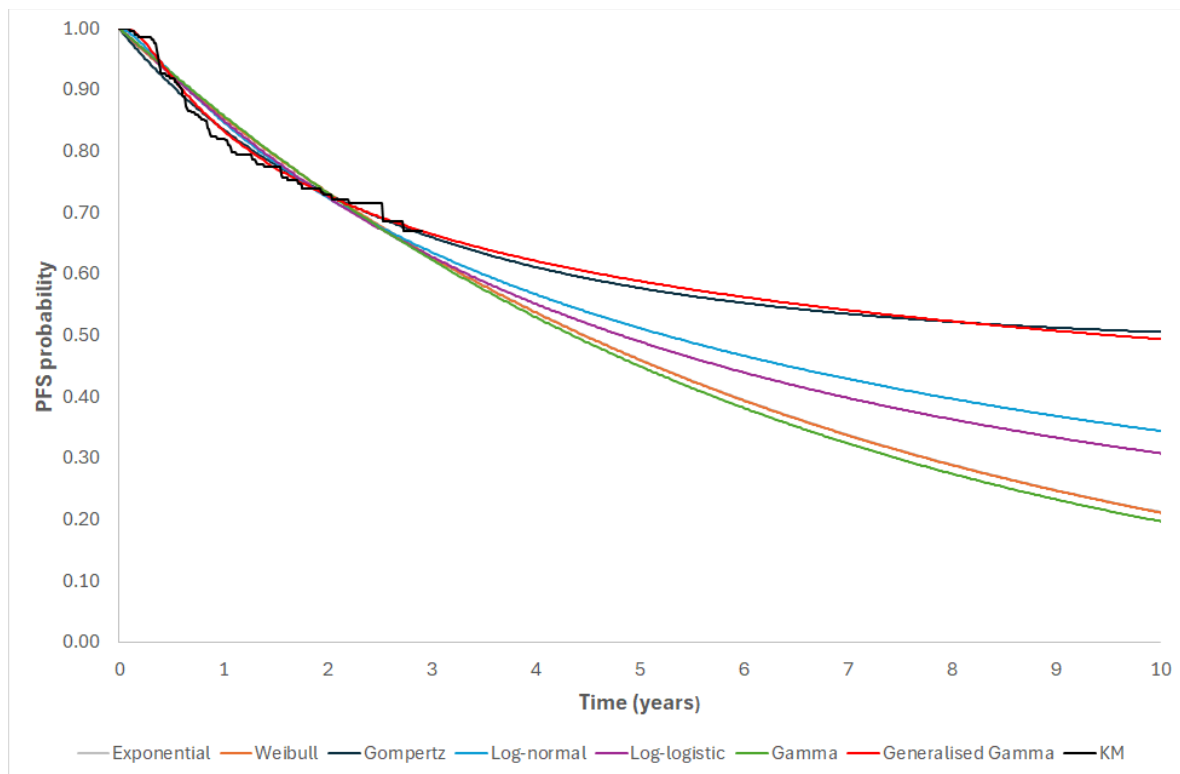
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CCRT - concurrent chemoradiotherapy
AIC/BIC for best-fitting model highlighted in bold.

Table 19: AIC and BIC statistics, TTP, KEYNOTE-A18, both groups

Distribution	Pembrolizumab + CCRT		CCRT alone	
	AIC	BIC	AIC	BIC
Exponential	974	977	1415	1419
Weibull	976	983	1417	1425
Gompertz	973	981	1409	1417
Log-normal	967	975	1394	1401
Log-logistic	973	981	1407	1414
Generalised gamma (base case)	963	974	1360	1372
Gamma	976	983	1417	1424

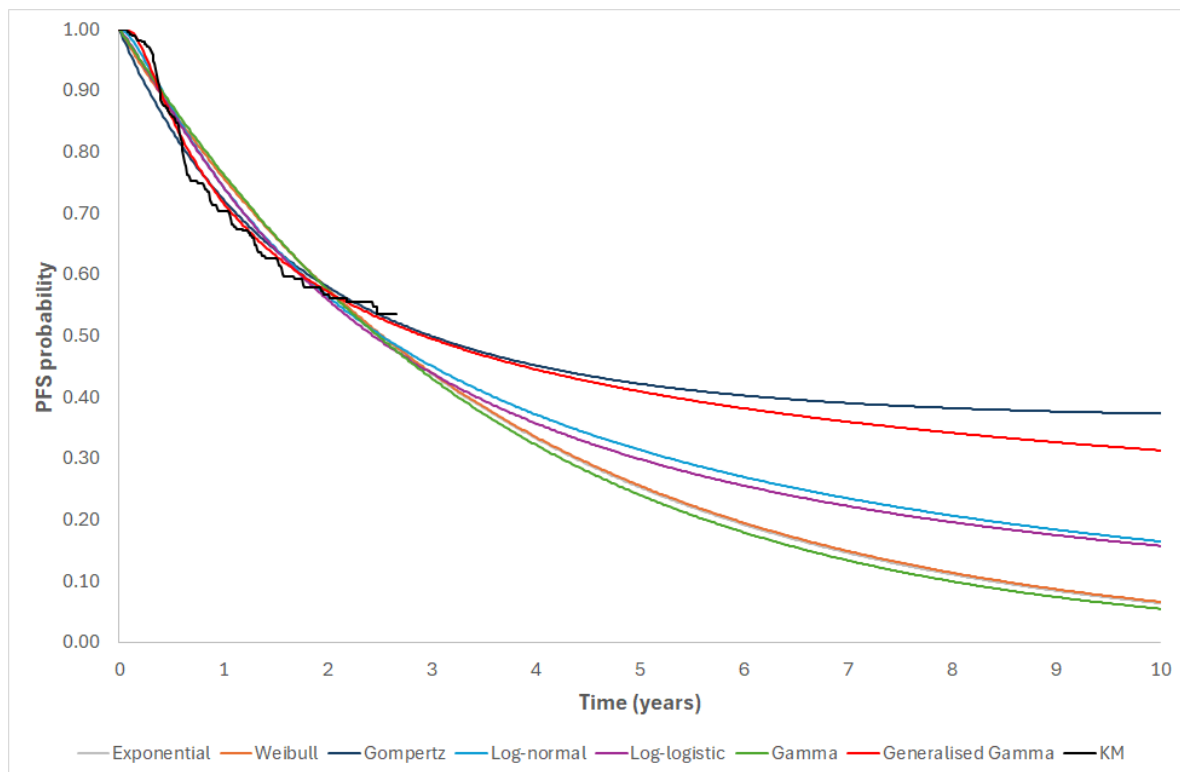
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CCRT - concurrent chemoradiotherapy
AIC/BIC for best-fitting model highlighted in bold.

Figure 9: Observed Kaplan-Meier plot and modelled survival distributions, PFS, KEYNOTE-A18, pembrolizumab plus CCRT group (generated by the EAG using the company's original model)



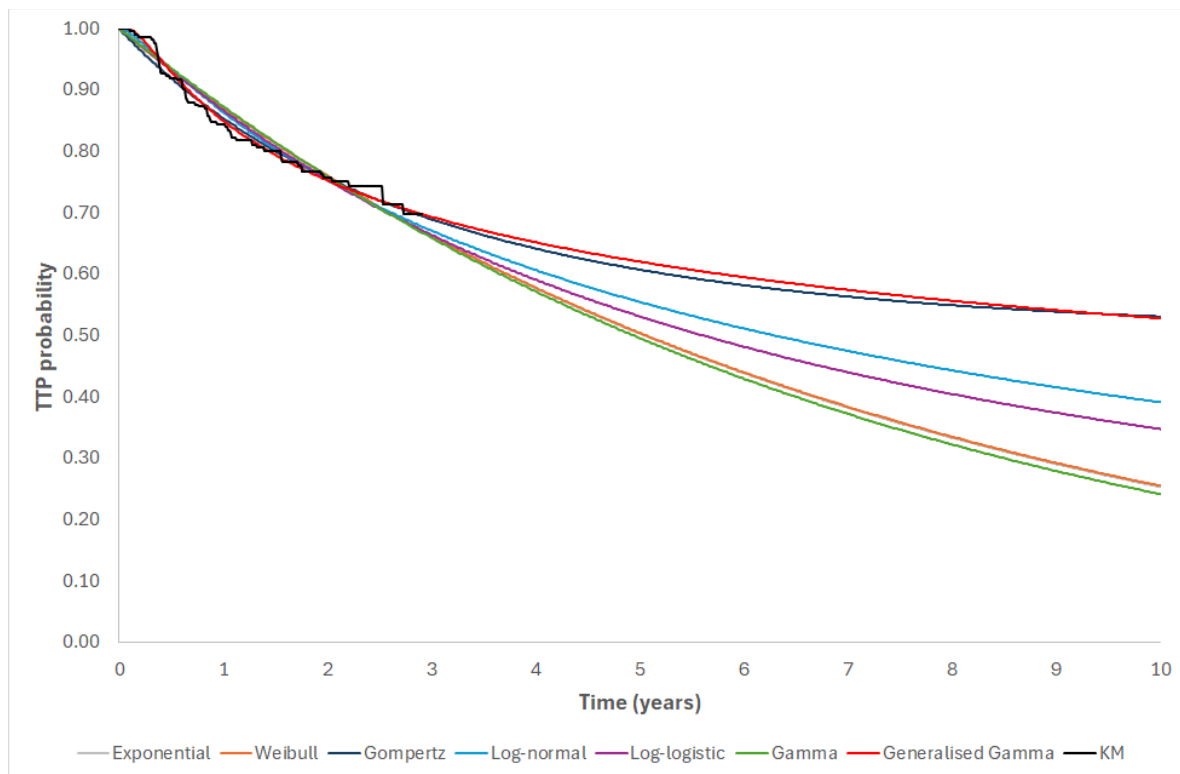
KM - Kaplan-Meier; PFS - progression-free survival

Figure 10: Observed Kaplan-Meier plot and modelled survival distributions, PFS, KEYNOTE-A18, CCRT group (generated by the EAG using the company's original model)



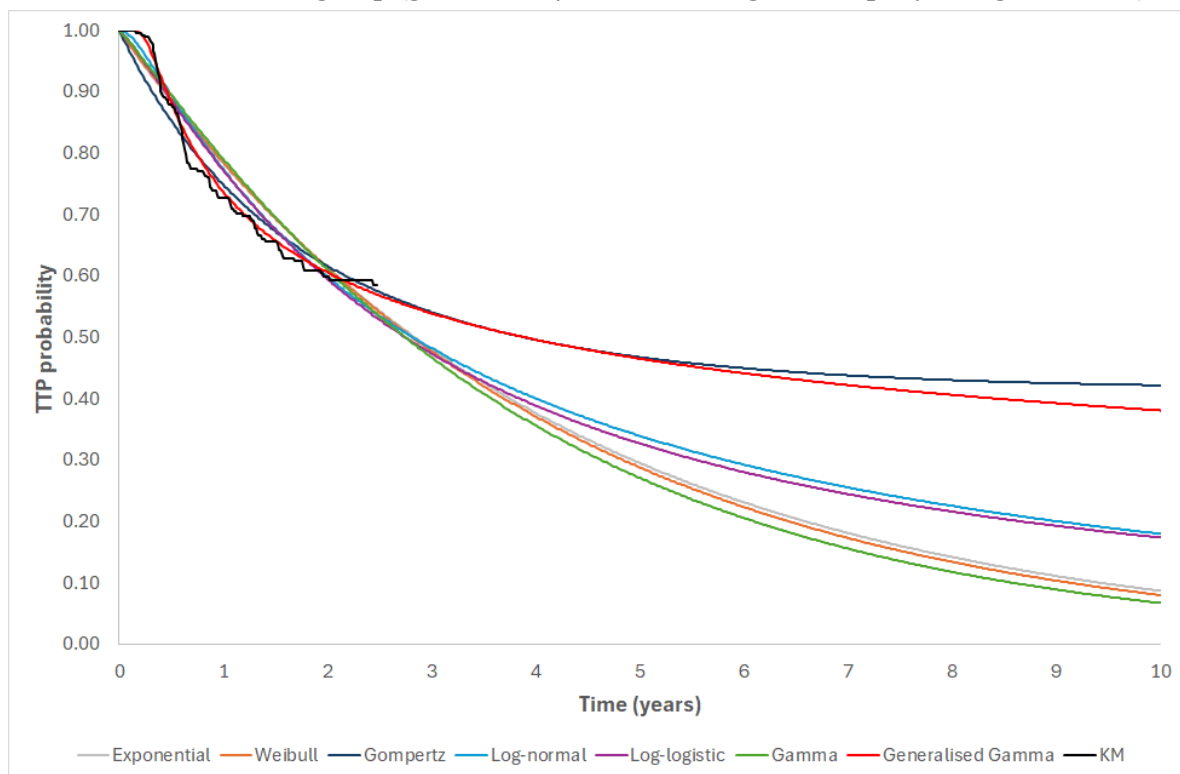
KM - Kaplan-Meier, PFS - progression-free survival

Figure 11: Observed Kaplan-Meier plot and modelled survival distributions, TTP, KEYNOTE-A18, pembrolizumab plus CCRT group (generated by the EAG using the company's original model)



KM - Kaplan-Meier; TTP - time to progression

Figure 12: Observed Kaplan-Meier plot and modelled survival distributions, TTP, KEYNOTE-A18, CCRT group (generated by the EAG using the company's original model)



KM - Kaplan-Meier; TTP - time to progression

Modelling transitions out of the first post-progression state (PD1 to PD1, PD1 to PD2 and PD1 to Dead)

The probability of transitioning to the PD2 state (PD1 to PD2) was informed by TTP2, the probability of remaining in the PD1 state (PD1 to PD1) was informed by PPS, and the probability of transitioning to dead (PD1 to Dead) was calculated as one minus TTP2 minus PPS.

The company's economic model applies three different sets of transition probabilities for patients leaving the PD1 state – one set for early progressors in the pembrolizumab plus CCRT group, one set for late progressors in the pembrolizumab plus CCRT group and one set for all progressors in the CCRT alone group. Each set of transition probabilities was estimated using both RCS models and standard parametric survival models fitted to the data on TTP (labelled as TTP2 in the model) and PFS (labelled as PPS in the model, excluding the mortality risk after second progression) from KEYNOTE-826 (CPS ≥ 1 subgroup).³³ The detailed calculations of weighted transition probabilities are as follows:

- *Pembrolizumab plus CCRT group, early progressors*: Transition probabilities were estimated using a weighted survival model comprising 80% of the PFS/TTP risks from a survival model fitted to data from the chemotherapy (with or without bevacizumab) arm of KEYNOTE-826³³ and 20% of the risks from a survival model fitted to the same data, with PFS adjusted using a multiplier of 2.0 for no treatment versus chemotherapy (with or without bevacizumab).
- *Pembrolizumab plus CCRT group, late progressors*: Transition probabilities were estimated using a weighted survival model comprising 51.20% of the PFS/TTP risks from a survival model fitted to the data from the pembrolizumab plus chemotherapy (with or without bevacizumab) arm of KEYNOTE-826,³³ 28.80% of the risks from a survival model fitted to the data from the chemotherapy (with or without bevacizumab) arm in KEYNOTE-826, and 20% of the risks from a survival model fitted to the data from the chemotherapy (with or without bevacizumab) arm in KEYNOTE-826, with PFS adjusted using a multiplier of 2.0 for no treatment versus chemotherapy (with or without bevacizumab).
- *CCRT alone group, all progressors*: The same calculations were applied as for late progressors in the pembrolizumab plus CCRT group, as described in the previous bullet point.

For brevity, only the company's fitted RCS models for TTP and PFS are discussed here, as both the EAG and the Appraisal Committee in TA939¹⁰ considered flexible spline models to be appropriate for reflecting the more complex pattern of hazards seen in the KEYNOTE-826 data,³³ particularly in the pembrolizumab arm. One-, two- and three-knot RCS models were fitted on the normal, hazard and odds scales. AIC statistics for the RCS models for PFS and TTP are presented in Table 20 and Table 21, respectively. The empirical (smoothed) and modelled hazard plots for both treatment groups are presented in Figure 13 (PFS) and Figure 14 (TTP). The Kaplan-Meier survival functions and the survival model predictions for the RCS models for PFS in the pembrolizumab plus chemotherapy (with

or without bevacizumab) and the chemotherapy (with or without bevacizumab) groups are shown in Figure 15 and Figure 16, respectively. The corresponding Kaplan-Meier survival functions and model predictions for TTP are presented in Figure 17 and Figure 18, respectively.

The company's model selection process for transitions out of the PD1 state were similar to those applied to the KEYNOTE-A18 data,¹⁴ and included consideration of: (i) goodness-of-fit (AIC and BIC statistics), (ii) visual fit; (iii) empirical and modelled hazard plots and (iv) clinical plausibility based on discussions during UK advisory board and NICE Appraisal Committee meetings in TA885.⁹

The CS¹ states that the company selected the 3-knot hazard RCS model including an assumption of treatment effect waning from 3-5 years post-treatment for both treatment groups, as applying this distribution within the economic state transition model provided estimates of OS which were close to estimates of 20-year OS provided by clinical experts at the advisory board meeting and the NICE Appraisal Committee meetings (original estimates: pembrolizumab plus SoC – 7%, SoC – 1.3%; 3-knot hazard RCS model estimates: pembrolizumab plus SoC – █████, SoC – █████).

As with the models selected to inform the transitions out of the PF health state, the same model form used for PFS (a 3-knot hazard RCS) was also applied to TTP. The use of 1- and 2-knot hazard RCS models for PFS/TTP pairs was explored in sensitivity analyses (see Section 4.2.6).

Table 20: AIC statistics for RCS models, PFS, KEYNOTE-826, both groups (adapted from CS, Table 32)

	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/- bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard	█████	█████	█████	█████	█████	█████
Odds	█████	█████	█████	█████	█████	█████
Normal	█████	█████	█████	█████	█████	█████

PFS - progression-free survival; RCS - restricted cubic spline

Table 21: AIC statistics for RCS models, TTP, KEYNOTE -826, both groups (adapted from CS, Table 33)

	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/- bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard	█████	█████	█████	█████	█████	█████
Odds	█████	█████	█████	█████	█████	█████
Normal	█████	█████	█████	█████	█████	█████

TTP - time to progression; RCS - restricted cubic spline

Figure 13: Smoothed empirical and modelled hazard functions, PFS, KEYNOTE-826, both treatment groups (reproduced from clarification response, Figure 3)



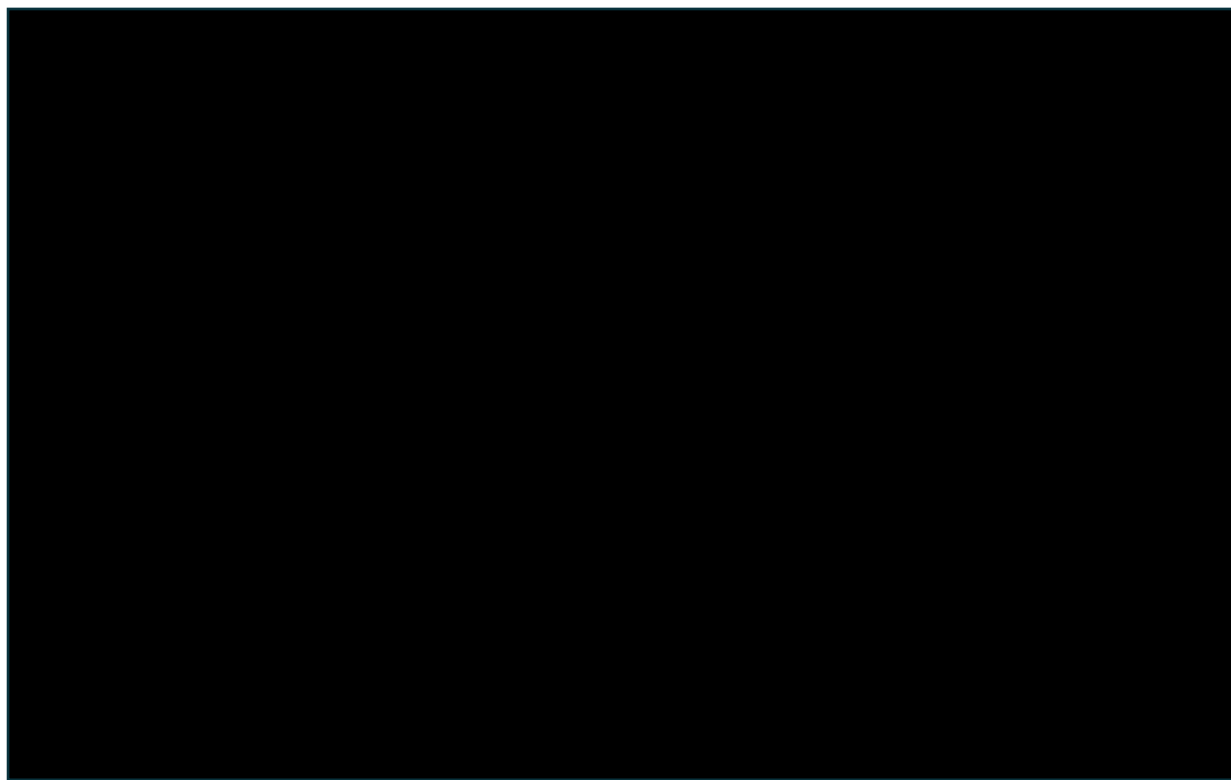
k - knot; PFS - progression free survival

Figure 14: Smoothed empirical and modelled hazard functions, TTP, KEYNOTE-826, both treatment groups (reproduced from clarification response, Figure 4)



k - knot; TTP - time to progression

Figure 15: Observed Kaplan-Meier plot and RCS model predictions, PFS, KEYNOTE-826, pembrolizumab plus chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)



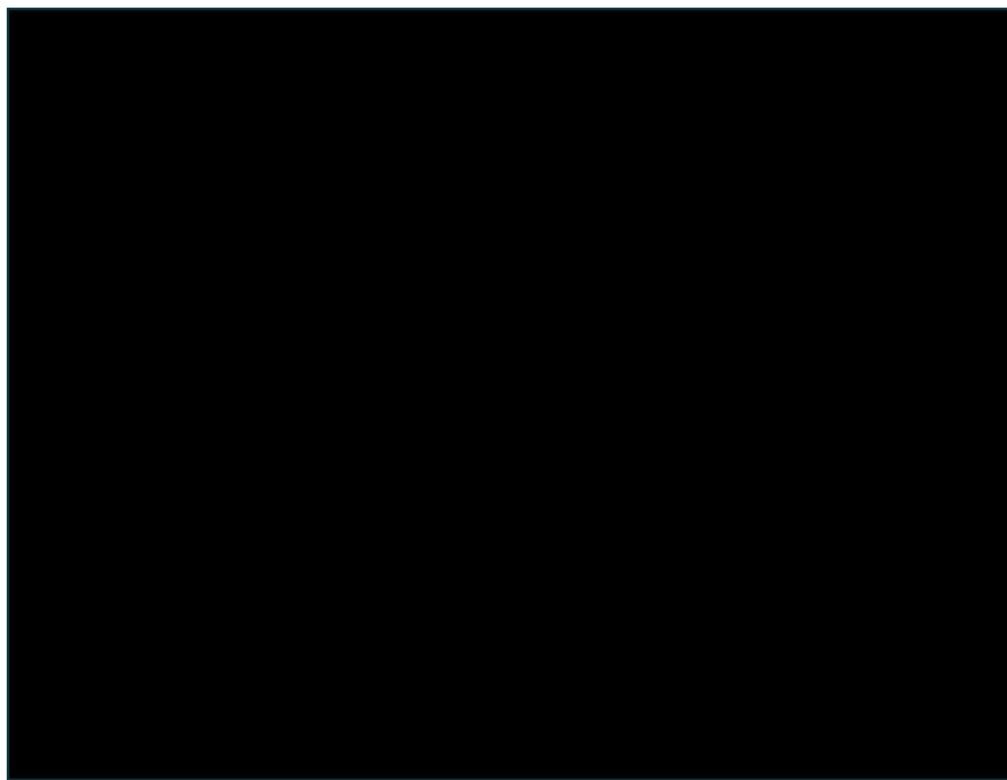
K - knot; KM - Kaplan-Meier, PFS - progression-free survival; RCS - restricted cubic spline

Figure 16: Observed Kaplan-Meier plot and RCS model predictions, PFS, KEYNOTE-826, chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)



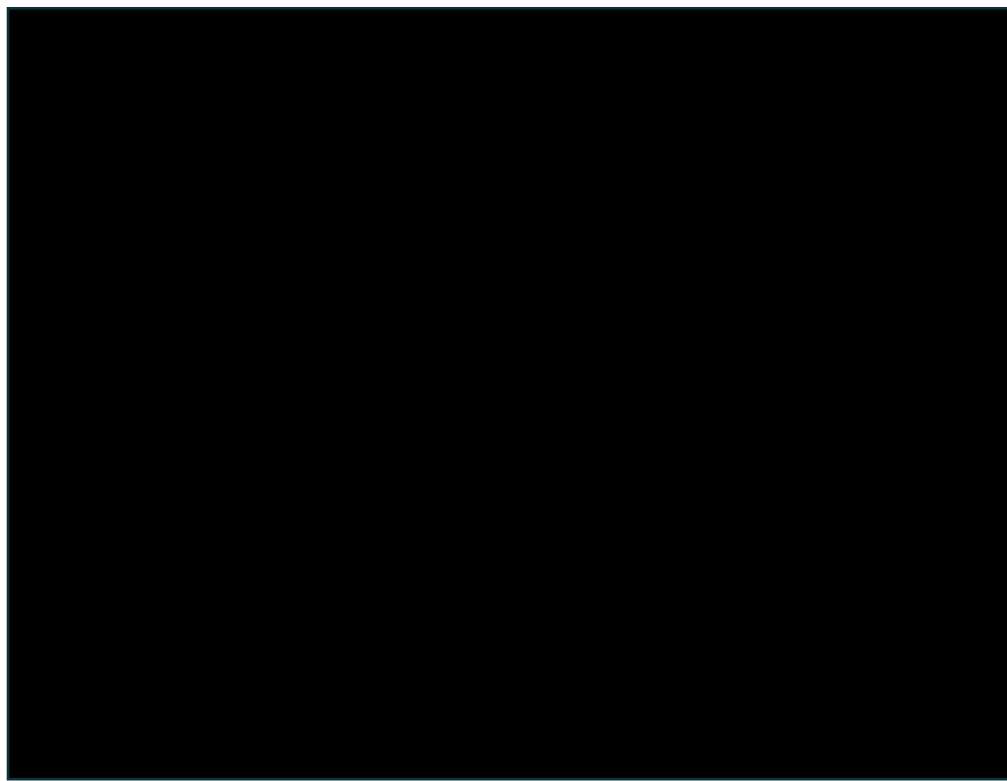
K - knot; KM - Kaplan -Meier; PFS - progression-free survival; RCS - restricted cubic spline

Figure 17: Observed Kaplan-Meier plot and RCS model predictions, TTP, KEYNOTE-826, pembrolizumab plus chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)



K - knot; KM - Kaplan-Meier; TTP - time to progression; RCS - restricted cubic spline

Figure 18: Observed Kaplan-Meier plot and RCS model predictions, TTP, KEYNOTE-826, chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)



K - knot; KM - Kaplan-Meier, TTP - time to progression; RCS - restricted cubic spline

Modelling transitions out of the second post-progression state (PD2 to PD2 and PD2 to Dead)

The probability of transitioning to the Dead state (PD2 to Dead) was informed by PPS2, and the probability of remaining in the PD2 state (PD2 to PD2) was estimated as one minus PPS2. The transition probabilities were adjusted in each treatment group to account for different survival probabilities for the subsequent treatments received in PD1. The detailed calculations of weighted transition probabilities are as follows:

- *Pembrolizumab plus CCRT group*: Transition probabilities were estimated from a standard parametric survival model fitted to PPS data from the chemotherapy (with or without bevacizumab) arm of KEYNOTE-826.³³
- *CCRT alone group*: Transition probabilities were estimated using a weighted survival model comprising 64% of the risks from a survival model fitted to the PPS data for the pembrolizumab plus chemotherapy (with or without bevacizumab) arm of KEYNOTE-826,³³ and 36% of the risks from a survival model fitted to the PPS data for the chemotherapy (with or without bevacizumab) arm in KEYNOTE-826.

The company fitted six standard parametric survival models to the IPD for PPS from KEYNOTE-826³³ to inform PPS2 in the economic model. The survival distributions were fitted separately to the data for each treatment group. These included the exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma distributions. AIC and BIC statistics for the fitted parametric survival distributions for PPS for both treatment groups (denoted PPS2 in the economic model) are presented in Table 22. The empirical (smoothed) and modelled hazard plots for each treatment group are presented in Figure 19 and Figure 20. The Kaplan-Meier survival functions and the parametric survival model predictions for PPS for the pembrolizumab plus chemotherapy (with or without bevacizumab) and chemotherapy (with or without bevacizumab) alone groups are shown in Figure 21 and Figure 22, respectively.

The company's model selection process for transitions from the PD2 state to Dead included consideration of: (i) goodness-of-fit statistics (AIC and BIC) and (ii) visual fit and (iii) whether the selected parametric survival models resulted in a mean OS estimate for pembrolizumab plus chemotherapy which was greater than that for chemotherapy alone and whether the curves did not cross (reflecting the NICE Appraisal Committee's conclusions in TA885⁹). The CS¹ also states that based on the recommendation in TSD 14,⁴³ the same model form was applied to both treatment groups. Clinical input regarding plausibility was not used to inform model selection; however, the company's clarification response¹⁷ (question B14) states that the selected models were agreed by the company, the EAG and the NICE Appraisal Committee in TA939.¹⁰

The company selected the generalised gamma model for PPS in both treatment groups because this distribution: (a) had the lowest AIC value; (b) had the best visual fit to the data and (c) resulted in an estimate of PPS which was longer for pembrolizumab plus chemotherapy than chemotherapy alone and the curves did not cross. The CS¹ does not report any sensitivity analyses in which alternative parametric survival distributions are used to model PPS (see Section 4.2.6).

Table 22: AIC and BIC statistics, PPS, KEYNOTE-826, both treatment groups

Distribution	Pembrolizumab + chemotherapy +/- bevacizumab		Chemotherapy +/- bevacizumab	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Gompertz				
Log-normal				
Log-logistic				
Generalised gamma (base case)				

*AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold.*

Figure 19: Smoothed empirical and modelled hazards, PPS, KEYNOTE-826, pembrolizumab plus chemotherapy (with or without bevacizumab) group (reproduced from clarification response, Figure 1)

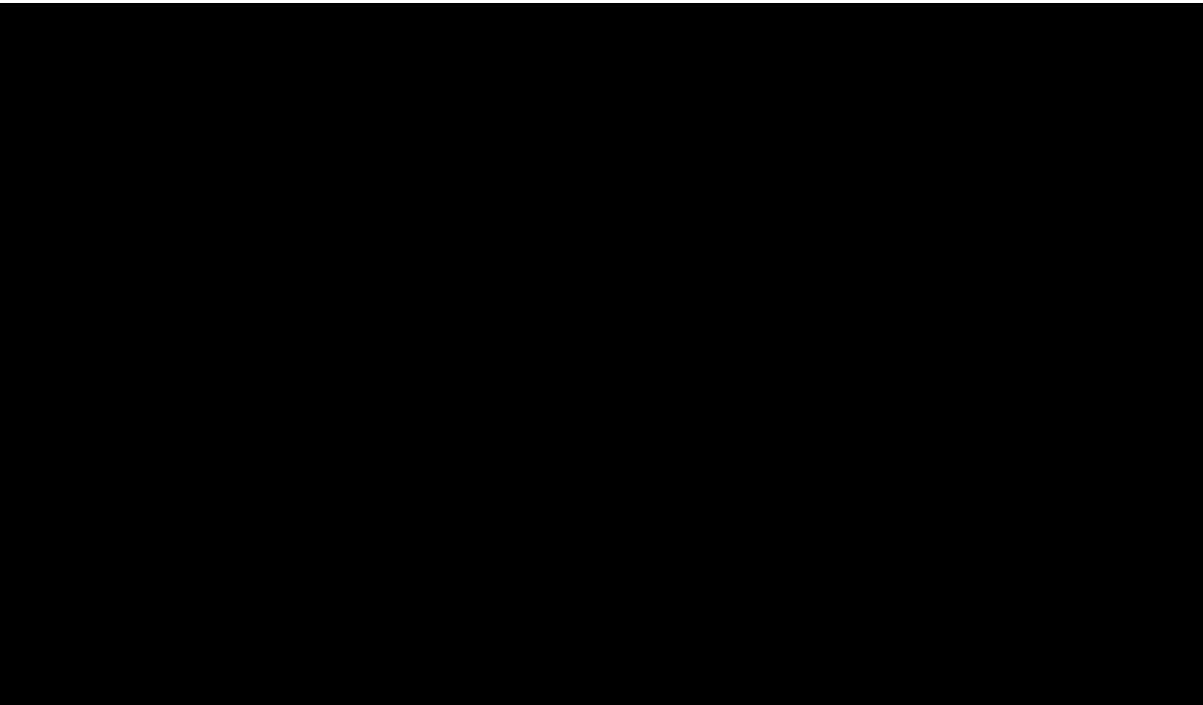


Figure 20: Smoothed empirical and modelled hazards, PPS, KEYNOTE-826, chemotherapy (with or without bevacizumab) group (reproduced from clarification response, Figure 2)

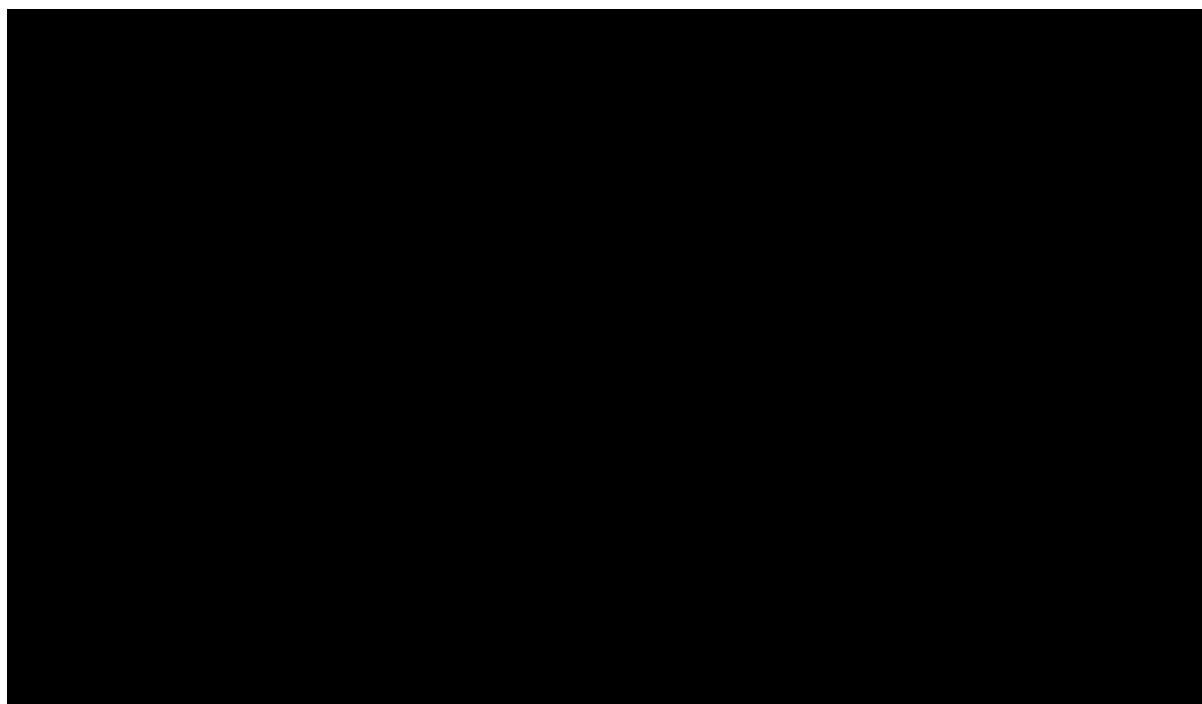


Figure 21: Observed Kaplan-Meier plot and modelled survival distributions, PPS, KEYNOTE-826, pembrolizumab plus chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)



KM - Kaplan-Meier; PPS - post-progression survival

Figure 22: Observed Kaplan-Meier plot and modelled survival distributions, PPS, KEYNOTE-826, chemotherapy (with or without bevacizumab) group (generated by the EAG using the company's original model)

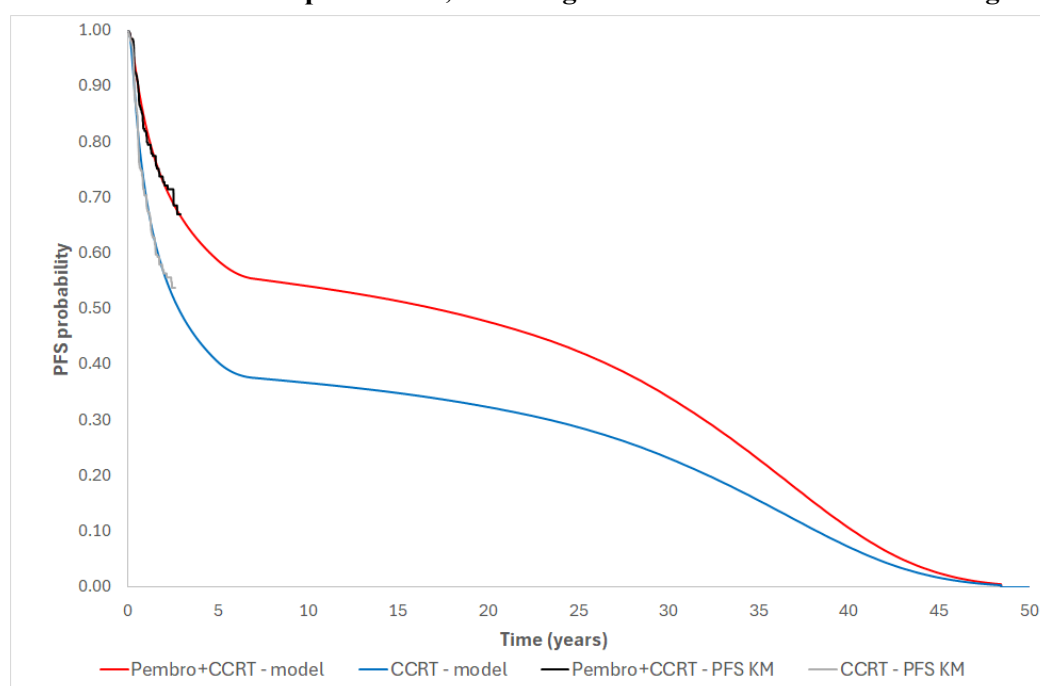


KM - Kaplan-Meier; PPS - post-progression survival

Model-predicted PFS and OS

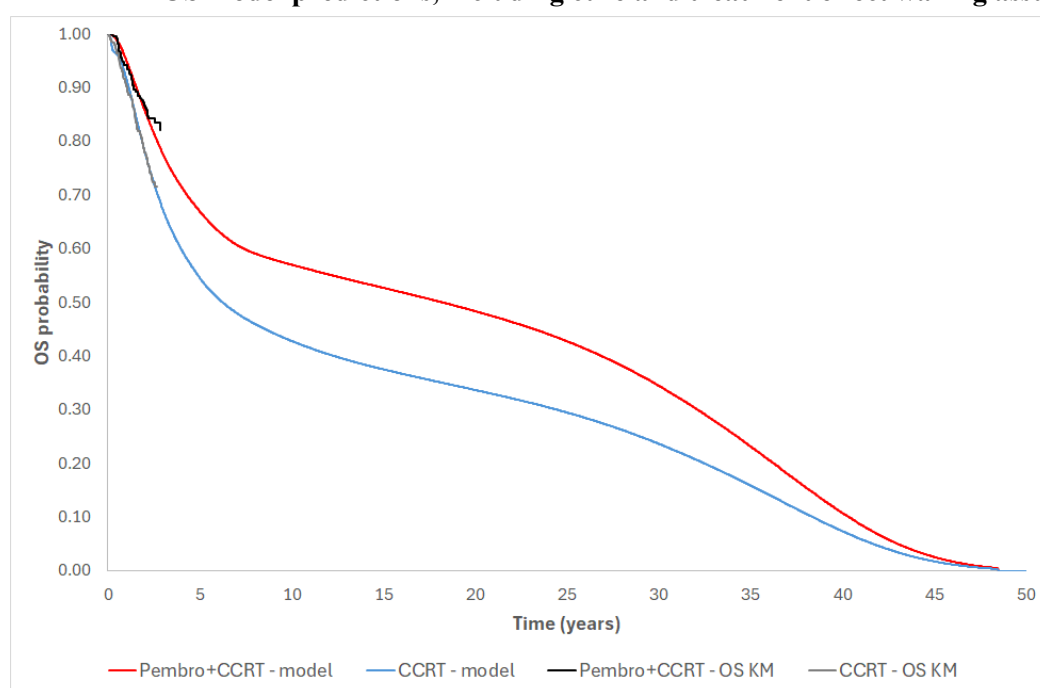
Within the company's economic model, PFS on first-line therapy is modelled as a function of TTP and PFS, based on the fitted parametric survival models and assumptions relating to cure and treatment effect waning for pembrolizumab. The Kaplan-Meier function for PFS in KEYNOTE-A18¹⁴ and aggregate modelled PFS predictions generated by the company's economic model are shown in Figure 23. OS is modelled as a function of all of the transition probabilities and assumptions relating to cure, treatment effect waning for pembrolizumab and the distribution of subsequent-line treatments. The Kaplan-Meier function for OS in KEYNOTE-A18 and aggregate modelled OS predictions generated by the company's original model are shown in Figure 24. The model predicts that the pembrolizumab plus CCRT generates a large, sustained improvement in PFS and OS compared to CCRT alone.

Figure 23: Observed Kaplan-Meier PFS from KEYNOTE-A18 (IA2) and company's aggregated PFS model predictions, including cure and treatment effect waning assumptions



KM - Kaplan-Meier; PFS - progression-free survival; CCRT - concurrent chemoradiotherapy; Pembro - pembrolizumab

Figure 24: Observed Kaplan-Meier OS from KEYNOTE-A18 (IA2) and company's aggregated OS model predictions, including cure and treatment effect waning assumptions



KM - Kaplan-Meier; OS - overall survival; CCRT - concurrent chemoradiotherapy; Pembro - pembrolizumab

4.2.3.2 Health-related quality of life

CS Appendix G¹⁵ reports the methods and results of an SLR conducted to identify studies reporting health state utility values for patients with LACC. The review identified only one study which reported EQ-5D utility values which was based in Thailand.⁴⁴ This study was not considered relevant for

inclusion in the model. An update of this SLR conducted by the company in 2025 did not identify any other relevant studies (see clarification response,¹⁷ question B18). Instead, health state utility values for the PF and PD1 health states were informed by EQ-5D-5L data collected in KEYNOTE-A18¹⁴ (mapped to the 3L version), whereas the utility value for the PD2 health state was estimated by applying a utility decrement derived from KEYNOTE-826³³ to the utility value for the PD1 health state from KEYNOTE-A18. A disutility value associated with AEs was estimated using a linear mixed-effects regression model fitted to the EQ-5D data from KEYNOTE-A18. The utility values used in the company's model are summarised in Table 23. All utility values within the economic model are adjusted for increasing age based on the EQ-5D-3L estimates for the UK general population (note – according to the CS, this was done using estimates reported by Hernández Alava *et al.*⁴⁵ but the executable model uses older estimates from Ara and Brazier⁴⁶). The company's approach to estimating health state utility values and AE-related disutility is described in further detail below.

Table 23: Utility values applied in the company's base case model (adapted from CS, Table 41)

State	Utility value	SE	Source
PF	██████	██████	Raw mean PF utility from KEYNOTE-A18 (IA2) ¹⁴
PD1	██████	██████	Raw mean PD utility from KEYNOTE-A18 (IA2) ¹⁴
PD2	██████	N/a	Utility decrement of progression from KEYNOTE-826 CPS ≥ 1 population ³³ (██████; i.e., the difference between PF and PD utility) was applied to the raw mean PD utilities from KEYNOTE-A18 (IA2). ¹⁴
Disutility Grade ≥ 3 AEs	██████	██████	Based on the progression-based mixed-effects model using KEYNOTE-A18 data (IA2), ¹⁴ with AE and progression status as covariates

PF - progression-free; PD - progressed disease; PD1 - first disease progression; PD2 - second disease progression; AE - adverse event; CPS - combined positive score; SE - standard error; IA2 - Interim Analysis; N/a - not applicable

Health state utility values - PF and PD1 health states

HRQoL data were collected in KEYNOTE-A18¹⁴ using the EQ-5D-5L instrument. The data used in the company's economic model reflect the subset of the trial population with FIGO 2014 Stage III to IVA LACC who completed at least one EQ-5D-5L questionnaire at IA2 (545 patients, 7,574 EQ-5D-5L assessments). The data were mapped onto the EQ-5D-3L using the algorithm reported by Hernández-Alava *et al.*⁴⁷

Utility values for the PF and PD1 health states were estimated using two approaches: raw means and linear mixed-effects regression models. The raw means approach was used to inform the base case analysis, whereby utility values were calculated as raw averages of EQ-5D measurements in the PF and PD states (i.e., patients with longer PFS contributed more measurements to the PF utility estimate than patients with shorter PFS). The CS¹ states that the estimated utility value for the PD1 state of ██████ has external validity given its similarity to the estimated utility value of ██████ for patients who were progression-free in KEYNOTE-826.³³

Health state utility values - PD2 health state

Owing to the limited data on patients experiencing a second progression event (PD2) at IA2 in KEYNOTE-A18,¹⁴ the utility estimates from the CPS ≥ 1 population in KEYNOTE-826³³ were used to inform the company's base case analysis. The company estimated a utility decrement between PF and PD of [REDACTED] from KEYNOTE-826 and applied this decrement to the utility value for the PD1 state derived from KEYNOTE-A18; this resulted in an estimated utility value for the PD2 state of [REDACTED] (i.e., [REDACTED] minus [REDACTED]). A scenario analysis was conducted using only KEYNOTE-A18 data, assuming equivalent utility for the PD1 and PD2 states (i.e., no further utility decrement from PD1 to PD2) as a simplifying assumption (see Section 4.2.6).

Company's sensitivity analysis - time-to-death utility values

The company explored the use of time-to-death utility values in scenario analyses. The values used in this analysis can be found in Table 59 (Appendix 3); the results of this analysis are presented in Section 4.2.6.

Disutility associated with AEs

The company's model includes QALY losses associated with Grade ≥ 3 AEs occurring in at least 5% of patients in either treatment arm of KEYNOTE-A18.¹⁴ Grade ≥ 2 diarrhoea was also included in the model due to its high management costs. The model incorporates the expected QALY losses related to AEs by multiplying the disutility for each AE by its respective duration and the per-model cycle probability of experiencing each AE. AE incidence was considered separately for Year 1 and Year 2. The model assumes that no AEs persist beyond Year 2, as the maximum treatment duration for first-line therapy is 2 years. Both the incidence and duration of each individual AE were taken from KEYNOTE-A18. The model applies the same regression-based disutility estimate of [REDACTED] to all included AEs, derived from a linear mixed-effects regression model (Model 1a, progression-based), which included AEs as the only covariate. Further details of the mixed-effects regression models fitted by the company are summarised in Appendix 3.

The resulting expected values were summed across all AEs to estimate the overall QALY loss which is applied in each model cycle over the first 2 years, conditional on PF health state occupancy. AE frequencies, AE durations and estimated disutility values are summarised in Table 24.

Table 24: QALY losses associated with AEs included in the company's model

AE	Utility decrement	Duration (weeks)	Weekly probability of Grade ≥ 3 AEs, Year 1		Weekly probability of Grade ≥ 3 AEs, Year 2		Source
			Pembro plus CCRT	CCRT alone	Pembro plus CCRT	CCRT alone	
Anaemia	■	■	■	■	■	■	KEYNOTE -A18 (IA2, DCO January 2024) ¹⁴
White blood cell count decreased	■	■	■	■	■	■	
Neutrophil count decreased	■	■	■	■	■	■	
Lymphocyte count decreased	■	■	■	■	■	■	
Leukopenia	■	■	■	■	■	■	
Neutropenia	■	■	■	■	■	■	
Lymphopenia	■	■	■	■	■	■	
Hypokalaemia	■	■	■	■	■	■	
Diarrhoea (Grade ≥ 2)	■	■	■	■	■	■	
Total QALY losses due to AEs			0.00042	0.00038	0.00002	0.00001	

QALY - quality-adjusted life-year; AE - adverse event; CCRT - concurrent chemoradiotherapy; DCO - data cut-off

4.2.3.3 Resource use and costs

The model includes costs associated with: (i) drug acquisition (first-and subsequent-line treatments) and administration; (ii) monitoring; (iii) disease management; (iv) the management of AEs; (v) PD-L1 testing and (vi) end-of-life care. The costs applied in the economic model are summarised in Table 25; further details are provided in the subsequent sections. It should be noted that the original version of the company's executable model includes some errors relating to costs; the text below relates to the cost assumptions as described in the CS.¹ Model errors are discussed in detail in Section 4.3.5 (critical appraisal point 1).

Table 25: Summary of costs applied in the company's model, exclude PAS discount for pembrolizumab

Cost component	Pembrolizumab plus CCRT	CCRT alone
Acquisition costs (first-line treatment) - per treatment cycle (including list price of pembrolizumab – see CS Appendix J for details of PAS)	Pembrolizumab Q3W: £5,260 Pembrolizumab Q6W: £10,520	Cisplatin: £28 EBRT: £7,840 Brachytherapy: £15,692
Administration and monitoring costs (first-line treatment) - per treatment cycle	Cisplatin: £28 EBRT: £7,840 Brachytherapy: £15,692 Pembrolizumab Q3W: £202 Pembrolizumab Q6W: £152	Cisplatin: £152
Acquisition costs (subsequent treatments) - once-only costs (including list price of pembrolizumab – see CS Appendix J for details of PAS)	Second-line (PD1), early progressors: [REDACTED] Second-line (PD1), late progressors: [REDACTED] Third-line (PD2): [REDACTED]	Second-line (PD1): [REDACTED] Third-line (PD2): [REDACTED]
Administration and monitoring costs (subsequent treatments) - once-only costs	Second-line (PD1), early progressors: [REDACTED] Second-line (PD1), late progressors: [REDACTED] Third-line (PD2): [REDACTED]	Second-line (PD1): [REDACTED] Third-line (PD2): [REDACTED]
Disease management costs - per model cycle	PF (Years 0-2): £23 PF (Years 2-5): £15 PD1: £78 PD2: £43	
AE management costs - per model cycle	Year 1: £19.13 Year 2: £0.78	Year 1: £17.10 Year 2: £0.37
PD-L1 testing costs	£36	
End-of-life care costs	£7,429	

PAS - Patient Access Scheme; CCRT - concurrent chemoradiotherapy; EBRT - external beam radiotherapy; Q3W - every 3 weeks; Q6W - every 6 weeks; PD1 - first post-progression; PD2 - second post-progression; PF - progression-free; AE - adverse event; PD-L1 - programmed death-ligand 1

Drug acquisition costs and radiotherapy fraction costs in the first-line setting

The total costs of drug acquisition and radiotherapy in the first-line setting are summarised in Table 26. All drug costs were applied as costs per treatment cycle. The cost of EBRT was applied as a weekly cost per model cycle up to maximum of 7 model cycles whereas the cost of brachytherapy was applied as a one-off cost to patients who discontinue EBRT in each model cycle. The original model contains a programming error around brachytherapy costs (see Section 4.3.5) which was corrected in the company's updated model (see Section 5.1.1). Within the economic model, the total acquisition costs of drugs and radiotherapy were calculated using the empirical Kaplan-Meier function for TTD from IA2 of KEYNOTE-A18¹⁴ (see Figure 25). The EAG notes that the company's original model uses the same Kaplan-Meier TTD estimates for cisplatin and radiotherapy in both the intervention and comparator groups. This was corrected in the company's updated model using arm-specific Kaplan-Meier TTD data (see Section 5.1.1). The model assumes an RDI of 100% for all treatment components in both treatment groups. The model assumes a maximum treatment duration of 20 model cycles (up to 2 years) for pembrolizumab and 7 model cycles (7 weeks) for both cisplatin and radiotherapy. The EAG

notes that TTD is not structurally linked to any clinical outcomes in the model (i.e., if all patients die in the first weekly model cycle, the net acquisition costs remain unchanged).

The list price per vial of 100mg pembrolizumab of £2,630 was taken from the British National Formulary (BNF).³⁷ The company has an agreed PAS for pembrolizumab; the cost per vial including the PAS discount can be found in CS Appendix J.¹⁵ Unit costs of cisplatin of £3.67 (10mg), £19.69 (50mg) and £37.34 (100mg) were taken from the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).³⁸ Unit costs for the preparation and delivery of EBRT and brachytherapy were taken from the NHS Cost Collection 2023/24;³⁹ the costs per fraction of EBRT and brachytherapy were assumed to be £1,194 and £1,435 for preparation, and £266 and £3,564 for delivery, respectively. The duration of radiotherapy was based on the KEYNOTE-A18 protocol;³⁰ the total number of administrations and dose per radiotherapy fraction were taken from BGCS guidelines.¹¹

In the first-line setting, no vial sharing was assumed for pembrolizumab or cisplatin. To account for expected drug wastage due to variability in body weight (or BSA) and the use of non-divisible vial sizes, the company applied the following approach to estimate the costs of pembrolizumab and cisplatin.

- (a) To calculate weight-based (or BSA-based) doses, the company assumed a log-normal distribution of body weight (or BSA), with distribution parameters derived using the method of moments applied to the reported mean and the standard error (SE) from KEYNOTE-A18.¹⁴
- (b) Different dosing bands were generated based on all feasible combinations of available vial sizes.
- (c) The proportions of patients falling into each dosing band were calculated for both the intervention and comparator groups based on a log-normal distribution.
- (d) These proportions of patients in each dosing band were applied to weight vial requirements, and the weighted vial counts were multiplied by the corresponding unit costs to derive the mean drug unit cost per treatment cycle.

Table 26: Summary of drug acquisition and radiotherapy costs included in the company's model, excludes PAS discount for pembrolizumab, first-line setting

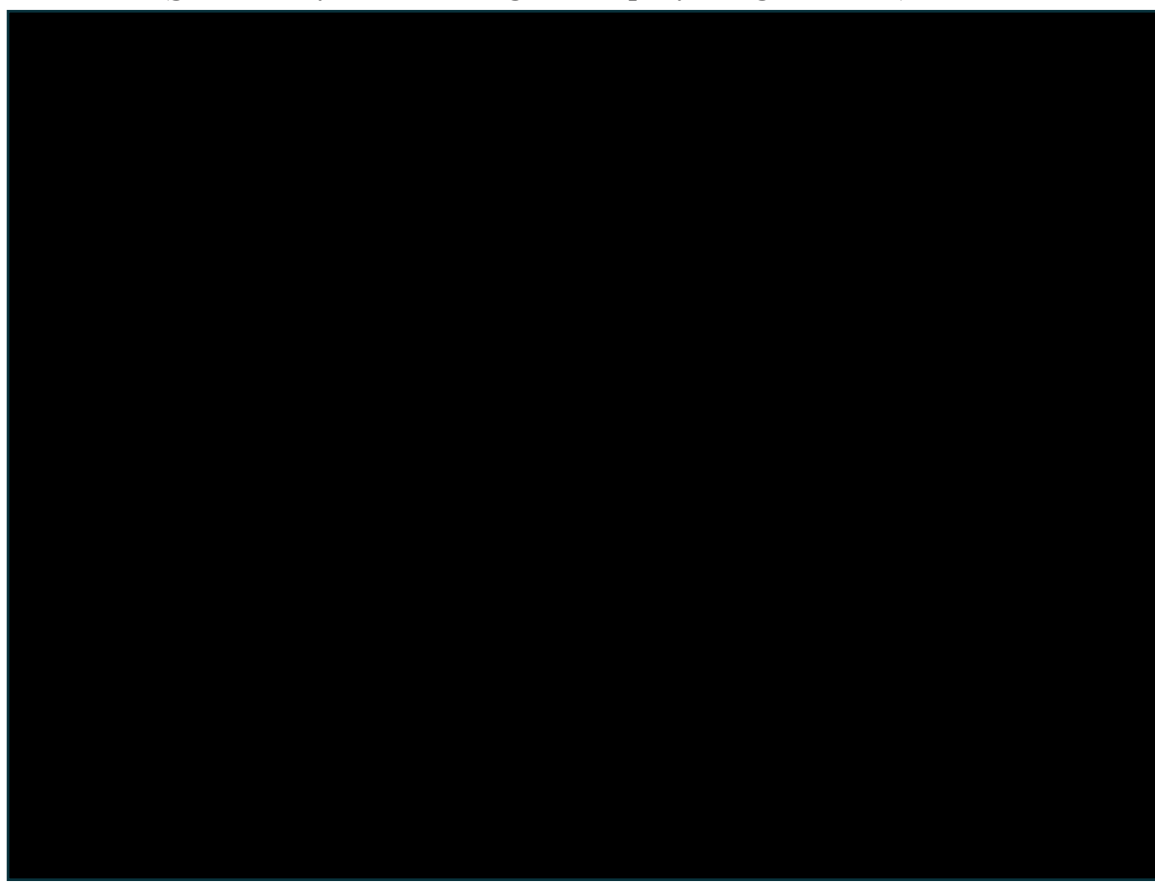
	Admin. Route	Dose per admin	Dosing schedule (weeks)	RDI	Criteria for discontinuation	Cost per treatment cycle	Cost per weekly model cycle	Source
Pembrolizumab Q3W (list price) [†]	IV	200mg	3	100%	Maximum of 2 years, progression or death	£5,260	N/a	BNF 2024 ³⁷
Pembrolizumab Q6W (list price) [†]	IV	400mg	6	100%	Maximum of 2 years, progression or death	£10,520	N/a	BNF 2024 ³⁷
Cisplatin	IV	40mg/m ²	1	100%	Maximum of 7 model cycles, progression or death	£28	N/a	eMIT 2024 ³⁸
EBRT*	-	45 Gy (1 fraction for preparation and 25 fractions for delivery)	5.71	100%	Maximum of 40 days, progression or death	£7,840	£1,372	NHS Cost Collection 2023/24 ³⁹
Brachytherapy*	-	40-45 Gy (1 fraction for preparation and 4 fractions for delivery)	1.43	100%	Maximum of 10 days, progression or death	£15,692	N/a	NHS Cost Collection 2023/24 ³⁹

RDI - relative dose intensity; Q3W - every 3 weeks; Q6W - every 6 weeks; IV - intravenous; N/a - not applicable; EBRT - external beam radiotherapy; Gy - Gray; BNF - British National Formulary; eMIT - electronic Market Information Tool

** Cost includes both the preparation and delivery of radiotherapy*

† Details of the PAS for pembrolizumab can be found in CS Appendix J¹⁵

Figure 25: Kaplan-Meier for TTD for pembrolizumab, cisplatin and EBRT, KEYNOTE-A18, (generated by the EAG using the company's original model)



KM - Kaplan-Meier; TTD - time to discontinuation

Note: The same TTD functions for cisplatin and EBRT are applied to each treatment group in the model

Drug administration and monitoring costs in the first-line setting

Table 27 summarises the drug administration and monitoring costs applied in the first-line setting. The company's model assumes that drugs and EBRT are administered in an outpatient setting. Unit costs were taken from the NHS Cost Collection 2023/24.³⁹ In the pembrolizumab plus CCRT group, the cost of complex chemotherapy delivery was applied for the administration of pembrolizumab Q3W and the cost of simple chemotherapy delivery was applied for the administration of pembrolizumab Q6W. As cisplatin is delivered concurrently with pembrolizumab, the model assumes no additional administration costs for cisplatin in the pembrolizumab plus CCRT group. In the CCRT alone group, the cost of simple chemotherapy delivery was applied for the administration of cisplatin. These costs were applied as one-off costs in each treatment cycle, conditional on the probability of being alive and remaining on treatment (based on the TTD function).

Patients in the pembrolizumab plus CCRT group are assumed to undergo monitoring via a blood test in each treatment cycle and a CT scan every 12 weeks that the patient remains on treatment. A one-off MRI scan was also assumed 3 months after the last dose of radiotherapy in both treatment groups.

Table 27: Drug administration and monitoring costs, first-line treatments

Cost type	Component	Unit cost per treatment cycle (unless otherwise stated)		Source
		Pembrolizumab plus CCRT	CCRT alone	
Administration costs	Complex chemotherapy	Q3W: £202	N/a	NHS Cost Collection 2023/24 ³⁹
	Simple chemotherapy	Q6W: £152 Cisplatin: £0	Cisplatin: £152	
Monitoring costs	Blood tests	£8	N/a	
	CT tests (per model cycle)*	£12	N/a	
	MRI tests (applied as one-off costs at model cycle 20)‡	£171	£171	

CCRT - concurrent chemoradiotherapy; Q3W - every 3 weeks; Q6W - every 6 weeks; CT - computed tomography; MRI - magnetic resonance imaging; N/a - not applicable

* A CT scan is assumed to be given every 12 weeks during pembrolizumab treatment. Weekly model cycle costs were estimated and applied as a function of pembrolizumab TTD.

‡ Applied to patients remaining progression-free at cycle 20

Drug acquisition costs for subsequent-line treatments

Amongst those patients who have experienced a first progression event, 80% in both the intervention and comparator groups are assumed to receive active treatment and 20% receive no further active treatment. All early progressors in the intervention group (those who experience first progression < 2.5 years of initial treatment with pembrolizumab) who receive active treatment are assumed to receive chemotherapy with or without bevacizumab. For late progressors in the intervention group (those who experience first progression ≥ 2.5 years of initial treatment with pembrolizumab) and all progressors in the comparator group, 80% are assumed to receive further active treatment, 64% of whom receive pembrolizumab plus chemotherapy with or without bevacizumab and 36% receive chemotherapy with or without bevacizumab. Chemotherapy options include paclitaxel and carboplatin or cisplatin. Following second progression, all patients are assumed to be treated with paclitaxel as third-line therapy. The distributions of subsequent treatments (adjusted for the proportion of patients receiving active treatment) are summarised in Table 28.

Table 28: Distribution of subsequent treatments applied in the company's model

Treatment group	Component	Pembrolizumab plus CCRT (early progressors)	Pembrolizumab plus CCRT (late progressors)	CCRT alone
Second-line treatment				
No treatment	-	20.00%	20.00%	20.00%
Active treatment*	Pembrolizumab	0.00%	51.20%	51.20%
	Paclitaxel			
	Carboplatin			
	Bevacizumab			
	Cisplatin			
Third-line treatment				
Active treatment	Paclitaxel	100%	100%	100%

CCRT - concurrent chemoradiotherapy

*Adjusted based on the 80% of patients receiving active treatment

The total drug acquisition costs applied in both the second-and third-line settings are summarised in Table 29. As TTD estimates for each subsequent treatment component were unavailable, expected costs were estimated as the product of the drug acquisition cost per month, the mean treatment duration (based on KEYNOTE-826,^{33, 36} clinical input and assumptions) and the proportion of patients receiving each corresponding treatment component (see Table 28). An RDI of 100% was assumed for all subsequent-line treatment components in the model. Unit costs were taken from the BNF³⁷ and eMIT,³⁸ and the expected costs were applied as once-only costs to all patients at the point of progression to PD1 or PD2. The model assumes that vial sharing is permitted for all drugs used as subsequent-line therapy, except for pembrolizumab and cisplatin.

Table 29: Drug acquisition costs of active subsequent-line treatments, excludes PAS discount for pembrolizumab

	Admin route	Dose per admin	Dosing schedule (weeks)	RDI	Mean treatment duration (months)	Cost per treatment cycle	Cost per month	Total expected costs	Source of unit cost
Second-line treatment (following first progression)									
Pembrolizumab	IV	200mg	3	100%	*****	£5,260	£7,624	£12,719	BNF 2024 ³⁷
Paclitaxel	IV	175mg/m ²	3	100%	*****	£32	£46		eMIT 2024 ³⁸
Carboplatin	IV	750mg	3	100%	*****	£39	£56		eMIT 2024 ³⁸
Bevacizumab	IV	15mg/kg	3	100%	*****	£2,187	£3,170		BNF 2024 ³⁷
Cisplatin	IV	40mg/m ²	1	100%	*****	£25	£110		eMIT 2024 ³⁸
Third-line treatment (following second progression)									
Paclitaxel	IV	80 mg/m ²	1	100%	*****	£14	£63	£63	eMIT 2024 ³⁸
Total once-only cost for second-line treatments: Early progressors*								£12,719	
Total once-only cost for second-line treatments: Late progressors*								£12,719	
Total once-only cost for second-line treatments: All progressors from CCRT group*								£12,719	
Total once-only cost for third-line treatments: All progressors*								£63	

Admin - administration; RDI - relative dose intensity; IV - intravenous; BNF - British National Formulary; eMIT - electronic Market Information Tool; CCRT - concurrent chemoradiotherapy

*Adjusted for the proportion of patients receiving each treatment component

Drug administration costs for subsequent-line treatments

Table 30 summarises the drug administration and monitoring costs applied to subsequent-line treatments. The model assumes that drugs are administered in an outpatient setting. Unit costs were taken from the NHS Cost Collection 2023/24.³⁹ The cost of complex chemotherapy delivery was applied to the administration of pembrolizumab and the cost of simple chemotherapy delivery was applied to the administration of other drugs. These costs were applied as one-off costs to all patients at the time of progression and were calculated as the product of the monthly cost, the mean treatment duration and the proportion of patients receiving each treatment component.

Table 30: Drug administration costs of subsequent treatments

	Mean treatment duration (months)	Cost per treatment cycle	Cost per month	Total expected costs	Source
Second-line treatment (following first progression)					
Pembrolizumab	***	£202	£292	***	NHS Cost Collection 2023/24 ³⁹
Paclitaxel	***	£152	£220	***	
Carboplatin	***	£152	£220	***	
Bevacizumab	***	£152	£220	***	
Cisplatin	***	£152	£661	***	
Third-line treatment (following second progression)					
Paclitaxel	***	£152	£661	***	NHS Cost Collection 2023/24 ³⁹
Total costs (once-only costs) for second-line treatments: early progressors*				***	
Total costs (once-only costs) for second-line treatments: late progressors*				***	
Total costs (once-only costs) for second-line treatments: progressors from CCRT group*				***	
Total costs (once-only costs) for third-line treatments: all progressors*				***	

BNF - British National Formulary; eMIT - electronic Market Information Tool; CCRT - concurrent chemoradiotherapy

* Adjusted for the proportion of patients receiving each component

Disease management costs

Table 31 summarises the per-cycle disease management costs for each alive health state in the company's model: PF in the first 2 years, PF between 2 to 5 years, PD1 and PD2. The resource use estimates were based on clinical input obtained by the company.⁴² Unit costs for each resource use component were taken from the NHS Cost Collection 2023/24.³⁹ The same disease management costs were applied in both the intervention and comparator groups of the model. Based on clinical expert opinion and the BGCS guidelines, patients who remain progression-free after 5 years are assumed to be discharged from regular follow-up care and incur no further disease management costs. Additionally,

the model assumes that all patients with disease progression incur a once-only cost of £276 (the unweighted mean cost of a CT, MRI and PET-CT scan) on entry into the PD1 and PD2 states.

Table 31: Disease management resource use and costs applied in the company's model

	Frequency per model cycle				Unit cost	Total cost per model cycle			
	PF (Year 0-2)	PF (Year 2-5)	PD1	PD2		PF (Year 0-2)	PF (Year 2-5)	PD1	PD2
CT scan*	0.01	0.01	0.08	0.13	£142	£1	£1	£12	£18
Blood test†	0.00	0.00	0.33	0.13	£8	£0	£0	£3	£1
PET-CT scan*	0.01	0.01	0.00	0.00	£630	£6	£6	£0	£0
Oncology appointment‡	0.04	0.02	0.33	0.13	£191	£8	£4	£64	£24
Consultant-led phone call‡	0.04	0.02	0.00	0.00	£173	£7	£4	£0	£0
Total cost						£23	£15	£78	£43

PF - progression-free; PD1 - first post-progression; PD2 - second post-progression; CT - computed tomography; PET - positron emission tomography

* A CT (50%) or PET-CT (50%) scan was assumed to be performed annually in PF state. A CT scan (100%) was assumed to be performed every 12 weeks in PD1 and every 8 weeks in PD2.

† A blood test (100%) was assumed every 3 weeks in PD1 and every 8 weeks in PD2.

‡ An in-person oncology appointment (50%) or consultant-led phone call (50%) was assumed to take place once every 12 weeks in the PF state. An in-person oncology appointment (100%) was assumed every 3 weeks in PD1 and every 8 weeks in PD2.

AE management costs

Table 32 summarises the frequency of AEs and the costs of managing each event. AE frequencies were based on Grade ≥ 3 events occurring in $\geq 5\%$ of patients in either treatment arm of KEYNOTE-A18 (IA2).¹⁴ Unit costs were estimated as weighted non-elective short-stay costs, taken from the NHS Cost Collection 2023/24.³⁹ AE management costs are applied as per-cycle costs to all patients in the PF state over the first two years; subsequently, AE management costs are assumed to be zero in both treatment groups. The expected costs per 1-week model cycle were estimated to be £19.13 (pembrolizumab plus CCRT) and £17.10 (CCRT alone) in Year 1 and £0.78 and £0.37 in Year 2. AEs associated with subsequent treatments are not included in the company's model.

Table 32: AE frequencies and unit costs

AE	Frequency per model cycle (Year 1)		Frequency per model cycle (Year 2)		Unit cost	Total costs per model cycle (Year 1)		Total costs per model cycle (Year 2)	
	Pembrolizumab plus CCRT	CCRT alone	Pembrolizumab plus CCRT	CCRT alone		Pembrolizumab plus CCRT	CCRT alone	Pembrolizumab plus CCRT	CCRT alone
Anaemia	████	████	████	████	£620	████	████	████	████
White blood cell count decreased	████	████	████	████	£561	████	████	████	████
Neutrophil count decreased	████	████	████	████	£561	████	████	████	████
Lymphocyte count decreased	████	████	████	████	£561	████	████	████	████
Leukopenia	████	████	████	████	£696	████	████	████	████
Neutropenia	████	████	████	████	£696	████	████	████	████
Lymphopenia	████	████	████	████	£696	████	████	████	████
Hypokalaemia	████	████	████	████	£584	████	████	████	████
Diarrhoea	████	████	████	████	£567	████	████	████	████
Total costs per weekly model cycle per patient						£19.13	£17.10	£0.78	£0.37

AE - adverse event; CCRT - concurrent chemoradiotherapy

PD-L1 testing costs

The company's model includes the costs of one-off PD-L1 testing for all patients at the point of first progression, including those who would not receive pembrolizumab or any other active subsequent therapy. The cost was estimated to be £36.20 based on the NHS Cost Collection 2023/24 (histopathology and histology, currency code DAPS02).³⁹

End-of-life care costs

The cost of end-of-life care was estimated to be £7,429 based on a research report by the Nuffield Trust on the costs of care in the last three months of life for: (i) patients with cancer diagnosis, (ii) patients without cancer diagnosis, and (iii) all patients (Georghiou and Bardsley⁴¹). This source has been used in several previous NICE TAs.⁴⁸⁻⁵² The cost of end-of-life care is applied as a once-only cost for all patients upon entry into the Dead state.

4.2.4 Model evaluation methods

The CS¹ presents ICERs for pembrolizumab plus CCRT versus CCRT alone using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo samples. The results of the probabilistic sensitivity analysis (PSA) are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). All model results presented in the CS include the PAS-discounted price for pembrolizumab and the list prices for other treatments. All ICERs presented in the CS apply a decision modifier of 1.0 which is consistent with estimates obtained using the York QALY Shortfall Calculator⁵³ and the comparator QALY estimates from the company's base case model.

The CS¹ presents the results of deterministic sensitivity analyses (DSAs) using a tornado plot. The CS also presents the results of 25 scenario analyses which explore the impact of: applying a shorter (35-year) time horizon; applying discount rates of 1.5%; excluding end-of-life care costs; assuming alternative utility and disutility values; excluding treatment effect waning assumptions; using the Gompertz distributions for PFS and TTP to model transitions out of the PF state; using 1- and 2-knot RCS models for PFS and TTP to model transitions out of the PD1 state; applying alternative cure proportions and time points; assuming 6-monthly General Practitioner (GP) visits after 5 years in the PF state and applying multipliers of 3.0 and 1.5 to estimate OS for patients who do not receive active second-line treatment.

4.2.5 Company's original model cost-effectiveness results

Company's central estimates of cost-effectiveness

Table 33 presents the central estimates of cost-effectiveness generated using the company's original submitted model. All ICERs include the PAS for pembrolizumab and a decision modifier of 1.0. The

probabilistic version of the model suggests that pembrolizumab plus CCRT is expected to generate an additional 1.99 discounted QALYs at an additional cost of [REDACTED]. The corresponding ICER is [REDACTED] per QALY gained. The deterministic version of the model results in a slightly lower ICER of [REDACTED] per QALY gained.

Table 33: Company's base case results, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated by the EAG using the company's original model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Pembrolizumab plus CCRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.99	[REDACTED]	[REDACTED]
CCRT	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
Deterministic model							
Pembrolizumab plus CCRT	*****	*****	*****	*****	2.05	*****	*****
CCRT	*****	*****	*****	-	-	-	-

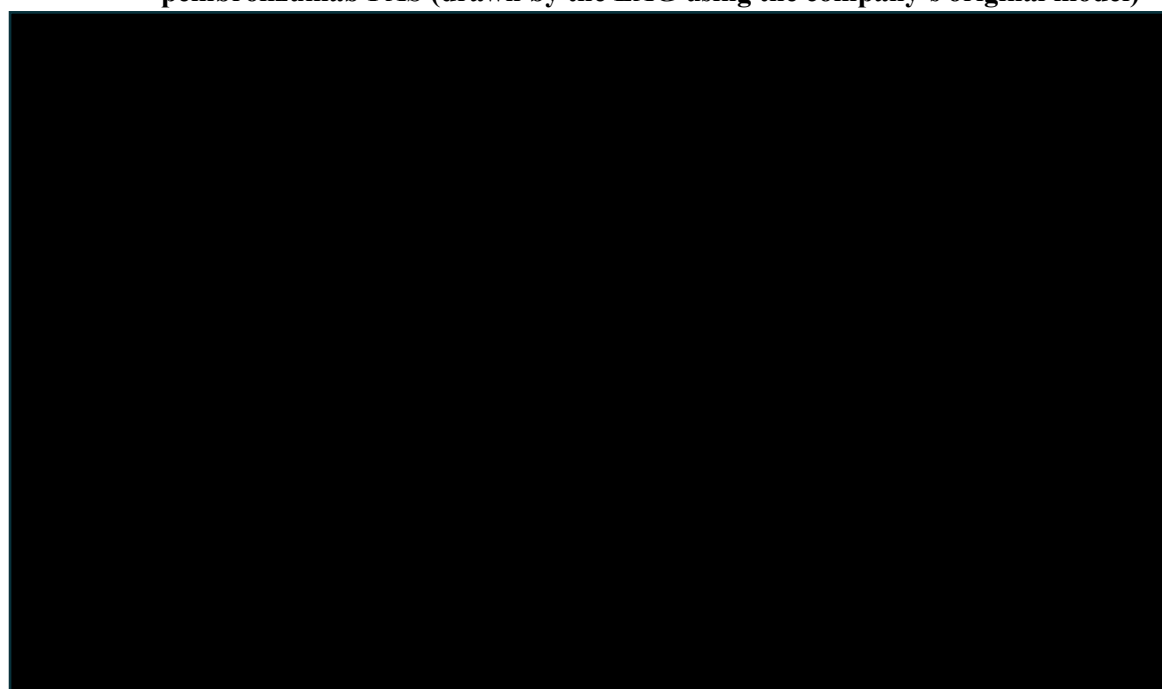
CCRT - concurrent chemoradiotherapy; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

*Undiscounted

Company's PSA results

The results of the company's PSA are presented as a cost-effectiveness plane in Figure 26 and as CEACs in Figure 27. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that pembrolizumab plus CCRT generates more net benefit than CCRT alone is expected to be approximately [REDACTED] and [REDACTED], respectively.

Figure 26: Cost-effectiveness plane, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (drawn by the EAG using the company's original model)



CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; EAG - External Assessment Group; QALY - quality-adjusted life year

Figure 27: Cost-effectiveness acceptability curves, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (drawn by the EAG using the company's original model)

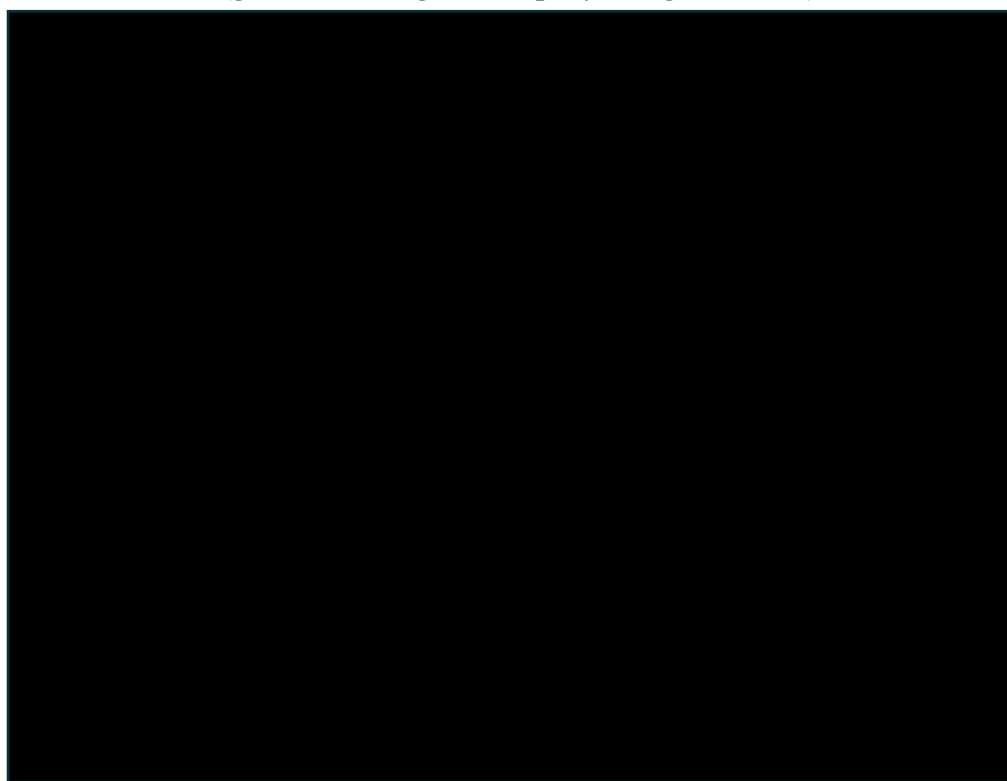


CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; EAG - External Assessment Group

Company's DSA results

Figure 28 presents the results of the company's DSAs using a tornado plot. The company's DSAs indicate that the results are not particularly sensitive to any of the parameters tested. Across all DSAs, the ICER for pembrolizumab plus CCRT versus CCRT ranges from [REDACTED] to [REDACTED] per QALY gained.

Figure 28: Tornado plot, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated using the company's original model)



PAS - Patient Access Scheme; OWSA - one-way sensitivity analysis; ICER - incremental cost-effectiveness ratio; CCRT - concurrent chemoradiotherapy; EOL - end-of-life; KNA18 - KEYNOTE-A18

Company's scenario analyses

Table 34 presents the results of the company's scenario analyses. The analyses indicate that the ICER is sensitive to the discount rates for health outcomes and costs. Across all of the scenario analyses tested, the ICER for pembrolizumab plus CCRT versus CCRT ranges from [REDACTED] per QALY gained (Scenario S2, discount rates = 1.5%) to [REDACTED] per QALY gained (Scenario S19, cure assumption removed).

Table 34: Company's scenario analysis results, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated by the EAG using the company's original model)

Scenario no.	Scenario description	Inc. QALYs	Inc. Costs	ICER
-	Company's base case (deterministic)	2.05	*****	*****
S1	35-year time horizon	1.99	*****	*****
S2	Discount rates = 1.5%	2.79	*****	*****
S3	Exclude end of life care costs	2.05	*****	*****
S4	Time to death utility values	1.99	*****	*****
S5	Utility values based on multivariate linear regression	2.01	*****	*****
S6	Exclude AE-related disutility values	2.05	*****	*****
S7	Apply same utility in PD1 and PD2 states (utility value = █████, from KEYNOTE-A18)	2.04	*****	*****
S8	Exclude age-adjustment of utility values	2.23	*****	*****
S9	Exclude treatment effect waning for pembrolizumab at first- and second-line treatment	1.83	*****	*****
S10	PF Pembrolizumab plus CCRT PFS/TTP distributions = Gompertz	1.93	*****	*****
S11	PF CCRT PFS/TTP distributions = Gompertz	1.81	*****	*****
S12	PF Pembrolizumab plus CCRT and CCRT PFS/TTP distributions = Gompertz	1.68	*****	*****
S13	PD1 PFS/TTP distribution = 2-knot hazard RCS (both treatment groups)	2.03	*****	*****
S14	PD1 PFS/TTP distribution = 1-knot hazard RCS (both treatment groups)	2.07	*****	*****
S15	Pembrolizumab arm PPS weighted to account for pre- and post- 2.5-year re-challenge	2.06	*****	*****
S16	Final cure proportion at 7 years = 50%	1.88	*****	*****
S17	Cure time point starts at 3 years and ends at 5 years	2.02	*****	*****
S18	Cure time point starts at 7 years and ends at 9 years	1.95	*****	*****
S19	Cure assumption removed	1.71	*****	*****
S20	Cure and treatment effect waning assumptions removed	1.75	*****	*****
S21	Include 6 monthly GP visits after 5 years in the PF state	2.05	*****	*****
S22	No treatment multiplier = 3.0	2.06	*****	*****
S23	No treatment multiplier = 1.5	2.05	*****	*****
S24	Assume 10% of patients receive no 2L treatment after progression	1.99	*****	*****
S25	SMR = 1.0	2.11	*****	*****

CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; EAG - External Assessment Group; S - scenario; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; AE - adverse event; PF - progression-free; PD - progressed disease; PFS - progression-free survival; TTP - time to progression; RCS - restricted cubic spline; GP - General Practitioner; SMR - standardised mortality ratio

* The ICER reported in the CS is slightly lower at █████ per QALY gained

4.3 Critical appraisal of the company's original economic analyses

This section presents the EAG's critical appraisal of the company's original economic model (based on KEYNOTE-A18¹⁴ IA2), as described in the CS.¹ Section 4.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 4.3.2 describes the EAG's verification of the company's model. Section 4.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 4.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.⁵⁴ Section 4.3.5 presents the main issues identified during the EAG's critical appraisal of the company's model.

Following the clarification round, the company submitted an updated version of the economic model which included substantial revisions, most notably, the use of a wider set of parametric survival models fitted to updated PFS and TTP data from the Final Analysis data-cut of KEYNOTE-A18.²¹ This updated model is summarised and critiqued separately in Section 5.1.

4.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's original submitted economic analysis and the underlying model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.^{55, 56}
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS¹ and the company's executable model.
- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

4.3.2 Model verification

Table 35 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. The results obtained from the EAG's rebuilt model

are very similar to those generated using the company's model. However, the EAG's double-programming exercise led to the identification of several minor programming errors; these issues are discussed in detail in Section 4.3.5 (critical appraisal point 1).

Table 35: Comparison of results generated using the company's original model and the EAG's double-programmed model, includes pembrolizumab PAS, includes decision modifier of 1.0, excludes correction of errors, deterministic

Option	Company's original model				EAG's double-programmed model			
	LYGs	QALYs	Costs	ICER	LYGs	QALYs	Costs	ICER
Pembrolizumab plus CCRT				-				-
CCRT alone				-				-
Incremental		2.05				2.05		

EAG - External Assessment Group; PAS - Patient Access Scheme; CCRT - concurrent chemoradiotherapy; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

4.3.3 Correspondence between model inputs and original source data

The EAG checked the input parameter values of the company's original model against their original sources. The coefficients of the standard parametric survival models and RCS models used to estimate the transition probabilities were generated from analyses of IPD from KEYNOTE-A18¹⁴ and KEYNOTE-826.³³ These data were not made available to the EAG, and as such, the EAG could not verify that these analyses have been undertaken appropriately. In addition, the mean treatment durations of subsequent-line treatments were based on KEYNOTE-826; with the exception of pembrolizumab and bevacizumab which were taken from Colombo *et al.*,³⁶ these values were redacted in the TA939 committee papers¹⁰ and therefore the EAG could not verify their accuracy. The EAG was able to identify most of the model parameters except for mean body weight, mean BSA, the proportion of patients receiving carboplatin as second-line therapy and AE frequencies.

4.3.4 Adherence of the company's original model to the NICE Reference Case

Table 36 summarises the extent to which the company's economic model adheres to the NICE Reference Case.⁵⁴ The EAG does not believe that the company's base case model is subject to any major deviations. However, the EAG notes that whilst the final NICE scope lists three potential subgroups, economic subgroup analyses are neither presented nor discussed in the CS.¹ The EAG also notes that the company has conducted an additional DCEA of pembrolizumab plus CCRT for the treatment of LACC; this analysis is discussed separately in Section 5.3.2.

Table 36: Adherence of the company's original model to the NICE Reference Case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is in line with the final NICE scope. ¹³ Economic subgroup analyses are not presented.
Comparator(s)	As listed in the scope developed by NICE	The comparator included in the economic analysis is in line with the final NICE scope. ¹³
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	Costs include those borne by the NHS and PSS.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for pembrolizumab plus CCRT versus CCRT alone.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 50-year (lifetime) time horizon.
Synthesis of evidence on health effects	Based on systematic review	TTP and PFS outcomes for both treatment groups were informed by KEYNOTE-A18 (IA2) ¹⁴ which is the pivotal trial of pembrolizumab identified from the company's SLR. Outcomes for the PD1 and PD2 health states were based on the data from KEYNOTE-826 (CPS ≥ 1 subgroup). ³³ The EAG considers these data sources to be relevant to the decision problem.
Measuring and valuing health	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health state utility values are based on EQ-5D-3L estimates from KEYNOTE-A18 ¹⁴ (mapped from the 5L version) and values from KEYNOTE-826 ³³ (the pivotal trial used to inform TA939 ¹⁰).
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Disutility associated with AEs are based on the regression coefficient from a mixed-effects linear regression model fitted to KEYNOTE-A18 data.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied in the company's base case analysis. The CS ¹ includes details regarding the results of a distributional cost-effectiveness analysis of pembrolizumab plus CCRT for LACC. This type of analysis does not form part of the NICE Reference Case ⁵⁴ and is discussed separately in Section 5.3.2.
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	Drug costs are valued at current prices. Other resource costs are valued using estimates from the NHS Cost Collection 2023/24 ³⁹ and the PSSRU. ⁴⁰

Element	Reference case	EAG comments
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

TTP - time to progression; PFS - progression-free survival; NHS - National Health Service; PSS - Personal Social Services; PSSRU - Personal Social Services Research Unit; QALY - quality-adjusted life year; EQ-5D-3L - Euroqol 5-Dimensions (3-level); NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; HRQoL - health-related quality of life; CCRT - concurrent chemoradiotherapy; LACC - locally advanced cervical cancer; IA2 - Interim Analysis 2

4.3.5 Main issues identified from the EAG's critical appraisal of the company's original model

Box 1 summarises the main issues identified from the EAG's critical appraisal of the company's original economic model. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified from the EAG's critical appraisal of the company's original model

- (1) Model errors and other minor issues
- (2) Uncertainty around survival modelling of data from KEYNOTE-A18 (IA2)
- (3) Concerns regarding the approach used to derive transition probabilities
- (4) Uncertainty around cure and treatment waning assumptions in first- and second-line settings
- (5) Uncertainty around the use and outcomes of pembrolizumab re-challenge
- (6) Uncertainty around survival benefits of subsequent-line treatments
- (7) Issues relating to health state utility values
- (8) Issues relating to costs

(1) Model errors and other minor issues

The EAG's double-programming exercise and additional cell checking revealed several minor errors in the company's original executable model. These errors are described below. With the exception of issues (c) and (d-v to vi), these errors were identified before the EAG submitted the clarification letter to NICE. As part of its clarification response,¹⁷ the company provided an updated version of the model which addresses some but not all of these errors (see Section 5.1).

(a) Errors related to general population mortality risks

- (a-i) The company's model includes an outdated life table for females in the UK.³⁵ The EAG considers it more appropriate to use the life table for females in England.⁵⁷
- (a-ii) The model includes a one-cycle lag in the calculations of general population mortality risks.
- (a-iii) In the model trace worksheets, the transition probabilities for the risks of progression and death from the PD1 and PD2 states are adjusted by general population mortality risks conditional on patient age, assuming that patients enter the PD1 and PD2 sub-models in the first model cycle. This approach is incorrect because the risks of progression and death should be constrained using the general population mortality risk relevant to the age at which patients enter each of the PD sub-models.

(b) Errors related to transition probabilities

- (b-i) The calculations of per-cycle transition probabilities based on the PPS data from KEYNOTE-826³³ (worksheet “KN-826 PPS”) include a programming error starting from model cycle 2,087, whereby due to an incorrect cell reference, the per-cycle probability of death in PD2 erroneously increases in all subsequent cycles.
- (b-ii) The calculations of transition probabilities from PD2 to Dead in the model trace worksheets include a programming error resulting in all patients being assigned to the Dead state several cycles earlier than the final model cycle.
- (b-iii) Within the model trace for the pembrolizumab plus CCRT group, the per-cycle transition probability of TTP2 for late progressors is erroneously constrained by the per-cycle probability of PFS rather than the general population mortality risk.

(c) Errors related to utility values

Contrary to the model description provided in Section 3.4.1 of the CS,¹ the company’s model erroneously includes general population utility adjustments based on Ara and Brazier⁴⁶ rather than Hernández Alava *et al.*⁴⁵

(d) Errors related to costs

- (d-i) Within the model, the same TTD data are used to calculate the drug acquisition and administration costs in both the pembrolizumab plus CCRT and CCRT alone groups. The EAG considers that the TTD estimates should be based on data for the respective groups in KEYNOTE-A18.¹⁴
- (d-ii) The model includes a once-only cost of brachytherapy of £15,692; this cost is applied to patients who discontinue EBRT. The model includes a programming error which results in the one-off costs of brachytherapy not being applied to all patients, thereby leading to an underestimation of radiotherapy costs in both treatment groups.
- (d-iii) Within the model trace worksheets, PD-L1 testing costs are applied to all patients who progress, regardless of their subsequent treatment options. The EAG believes that patients who are not eligible for pembrolizumab should not incur the costs of PD-L1 testing after their first progression event.
- (d-iv) Drug acquisition costs for cisplatin, paclitaxel and carboplatin were taken from an outdated version of eMIT. The EAG considers that the model should reflect the most recent version of eMIT.
- (d-v) The CS¹ states that the end-of-life care cost was inflated from £6,207 to current prices using inflation indices from PSSRU 2023. However, the EAG was unable to identify the reported end-of-life care cost in Georghiou and Bardsley.⁴¹ In addition, the inflation indices should have been taken from PSSRU 2024.⁴⁰

- (d-vi) Drug administration costs related to cisplatin were excluded for the pembrolizumab plus CCRT group, based on the assumption that these were covered by the administration costs of pembrolizumab when given concurrently. However, cisplatin is administered weekly for the first 7 weeks while pembrolizumab is given every 3 weeks. The EAG therefore considers that the company's model underestimates the administration costs of cisplatin for several weeks.

(e) Errors related to PSA

Within the PSA, uncertainty around the AE-related disutility is not sampled. In addition, the subsequent treatment distributions among late progressors from the intervention group and all progressors from the comparator group are sampled independently in the PSA, thereby producing slightly inconsistent results.

(f) Other minor issues

- (f-i) The company's model includes the functionality to apply half-cycle correction, but this is excluded from the base case analysis. The EAG believes that half-cycle correction should be included. This issue is minor because the cycle length is short (1 week).
- (f-ii) Within the model, the weighted survival model for PPS2 in the pembrolizumab plus CCRT group is underestimated as it ignores the effect of pembrolizumab in the late progressor group (the parameter named 'p_PD2_pembro_hist_int' [contained in worksheet "Controls", cell I171] is set to zero).
- (f-iii) The model calculates the per-cycle QALY loss associated with AEs based on the overall frequency of events in the ITT population of KEYNOTE-A18¹⁴ in Year 1 and Year 2. However, in the model trace, the per-cycle QALY loss is applied only to those patients who remain progression-free in each model cycle. The same issue also applies to the AE management costs. This approach underestimates the overall incidence of AEs observed in the trial and their associated QALY losses and costs.
- (f-iv) Regarding the price of bevacizumab, the company used the prices of the originator product rather than biosimilars. The EAG believes that would be more appropriate to include the lowest price of bevacizumab biosimilars in the model.
- (f-v) The model does not account for drug wastage when calculating drug acquisition costs for subsequent-line treatments with body weight- or BSA-based dosing.
- (f-vi) The model does not account for AEs related to subsequent-line treatments in terms of QALY losses or AE management costs. This likely results in the slight underestimation of total QALYs and costs in both treatment groups.
- (f-vii) The model assumes that end-of life care costs are incurred by all patients, including those patients who die after being cured (i.e., after Years 5-7). The EAG believes that end-of-life care costs

incurred by patients who are assumed to be cured of LACC reflect future unrelated costs and that these should not be included in the model.

The company's clarification response¹⁷ (questions B23, B26, B35-B36, B38, B40, B42, B44-B46 and B49) acknowledges that issues (a), (b), (d) and (e) were programming errors in the original model, and these were addressed in the updated version of the company's model provided as part of its clarification response. The company agreed with the EAG that issues (f-ii)-(f-vii) were minor, and addressed some of these (f-iv)-(f-vi) in the updated model (see clarification response,¹⁷ questions B19, B20, B27, B33, B34, B43 and B47). The results of the company's updated (post-clarification) model are summarised separately in Section 5.1.2.

(2) Uncertainty around survival modelling of data from KEYNOTE-A18 (IA2)

The EAG has several concerns regarding the parametric survival modelling presented in the CS.¹ These concerns are discussed below in terms of the general considerations around model fitting and selection set out in NICE DSU TSDs 14 and 21.^{43, 58}

(a) Use of independent models fitted to data for each treatment group

The company fitted parametric survival models separately to the data for each treatment group in KEYNOTE-A18.¹⁴ The CS¹ highlights that it is generally unnecessary to use jointly fitted models (i.e., models which include a treatment-indicating covariate) when IPD are available.⁴³ Figure 12 of the CS presents a plot of Schoenfeld residuals for PFS, although this plot is not discussed in the text of the CS. Nevertheless, the EAG agrees that the use of independently fitted models is appropriate.

(b) Range of models assessed

The company's survival analysis of PFS and TTP data from KEYNOTE-A18 (IA2)¹⁴ reported in the CS¹ is limited to the use of standard parametric survival models. More flexible models such as RCS distributions were not fitted to the data from KEYNOTE-A18 IA2 (although RCS models were fitted to PFS and TTP data from KEYNOTE-826³³). In addition, whilst the economic model includes structural assumptions of cure in both the pembrolizumab plus CCRT and CCRT alone groups, the CS does not mention the use of MCMs to estimate cure fractions using the KEYNOTE-A18 data. The EAG considers that the use of more flexible models may have been better able to capture the underlying shape of the hazard functions for PFS and TTP in KEYNOTE-A18.

(c) Statistical and visual goodness-of-fit

Section 3.3.2.1 of the CS¹ states that amongst the range of standard parametric survival models fitted, only the Gompertz and generalised gamma distributions fitted the observed data well (shown previously in Figure 9 and Figure 10). Amongst the range of fitted models, the generalised gamma distribution

provided the best statistical fit to the data for pembrolizumab plus CCRT and CCRT alone in terms of both AIC and BIC (Table 18 and Table 19). However, The EAG disagrees that these models provide a good representation of the available Kaplan-Meier estimates of PFS and TTP and notes that more flexible models may have provided a better fit to the data.

(d) Consideration of nature of hazards

Section 3.3.2 of the CS¹ states that, amongst other factors, the company's model selection process for PFS and TTP in KEYNOTE-A18 (IA2)¹⁴ included consideration of the underlying hazard functions. The CS presents hazard plots for PFS and TTP data from KEYNOTE-826³³ (used to estimate transition probabilities for the PD1 and PD2 health states) but does not present or discuss hazard plots for PFS and TTP data from KEYNOTE-A18 (used to estimate transition probabilities for the PF health state). Based on the information presented in the CS, it is unclear whether or how the company used hazard plots to inform parametric survival model selection for the KEYNOTE-A18 data. It is also unclear whether the hazard functions for PFS and TTP based on the generalised gamma distribution reflect the underlying empirical hazards in KEYNOTE-A18 at IA2.

(e) Consideration of long-term clinical plausibility

The CS¹ states that clinicians who attended the 2024 advisory board meeting confirmed that the generalised gamma model with a 5-7 year cure point provided the most plausible long-term PFS estimates.⁴² The minutes of this meeting contain very limited details pertaining to the views of the clinical experts or what questions were asked e.g., whether the clinicians were asked to select a preferred model from the set of candidate models, and/or whether they were asked to provide expectations of long-term PFS for pembrolizumab plus CCRT and CCRT alone. The company's clarification response¹⁷ (question B12) explains that the clinical advisors were presented with a range of fitted parametric survival models with different cure assumptions applied, but excluding the impact of treatment effect waning for pembrolizumab. The company's clarification response states that the generalised gamma PFS model was "*the most representative of their clinical experience and expectation.*" However, it is possible that flexible parametric survival models may have also provided clinically plausible long-term PFS projections. The company's clarification response¹⁷ (question B16) states that no clinical input was sought by the company regarding the plausibility of the modelled long-term OS predictions.

The EAG sought the views of its clinical advisors regarding the plausibility of the company's selected models for PFS based on the KEYNOTE-A18 (IA2) data.¹⁴ The EAG also sought the views of its clinical advisors regarding the plausibility of the aggregate OS functions predicted by the company's model. As noted in Section 4.2.3, modelled PFS and TTP in KEYNOTE-A18 are adjusted to account for the company's assumptions regarding effect waning and cure, whereas modelled OS is a function

of data on PFS and TTP in KEYNOTE-A18, PFS, TTP and PPS in KEYNOTE-826,³³ as well as assumptions regarding cure, treatment effect waning and subsequent treatment pathways. The EAG did not seek the views of its clinical advisors regarding the plausibility of the models fitted to the PFS and TTP data from KEYNOTE-826 because the selected distributions used in the company's original model are consistent with the preferred distributions used in the final economic model which informed TA939.¹⁰

Both of the EAG's clinical advisors commented that they would expect the vast majority of patients who remain alive and progression-free at 5-7 years to be unlikely to progress/relapse; this provides some support for the cure assumptions applied in the company's model which result in the adjusted PFS functions for both treatment groups flattening out in the longer-term (see Figure 23). In addition, both of the EAG's clinical advisors commented that the radiation therapy given in KEYNOTE-A18¹⁴ was not optimised and that a higher total dose would be given in current UK practice (a minimum total dose of 85 Gy, with a usual dose being around 90-95 Gy). As a consequence, the clinical advisors commented that the Kaplan-Meier estimates for PFS in both treatment groups in KEYNOTE-A18 would likely have been higher had patients received optimised radiation therapy based on current UK practice.

The EAG's first clinical advisor noted that there is considerable uncertainty around long-term outcomes for pembrolizumab plus CCRT in the Stage III-IVA LACC population due to the limited duration of follow-up at IA2 in KEYNOTE-A18.¹⁴ They commented that it is difficult to estimate what proportion of patients would remain progression-free in the longer-term because there are only limited follow-up data after patients have completed 2 years of pembrolizumab treatment, and it is currently unknown whether the effect of pembrolizumab would be maintained or diminish after completing treatment. The clinical advisor emphasised the importance of having access to longer-term data on PFS to inform the model assumptions. They also considered the model-predicted PFS gain at Year 7 for pembrolizumab plus CCRT versus CCRT alone (a difference of approximately ■ based on IA2) to be "*very optimistic*." The clinical advisor also commented that whilst the model-predicted OS might be plausible, the magnitude of the OS gain for pembrolizumab plus CCRT is difficult to estimate given the short follow-up at IA2. They stated that it is possible that the gap between the modelled OS functions could diminish, but that longer-term data would be required to determine this. The EAG's second clinical advisor stated that amongst the standard parametric models fitted to the PFS data, they preferred the more optimistic generalised gamma and Gompertz distributions for both the pembrolizumab plus CCRT and CCRT alone groups. With respect to model-predicted OS, the clinical advisor considered the shape of the OS models to be plausible but agreed that follow-up at IA2 was short, thereby leading to uncertainty.

EAG's conclusions regarding the company's survival analysis

The EAG believes that the analysis of PFS and TTP data from IA2 of KEYNOTE-A18¹⁴ presented in the CS¹ is limited due to the following issues: (i) the company's survival analysis included only consideration of standard parametric survival models; (ii) none of the fitted standard parametric models provide a good representation of the observed PFS or TTP data in both treatment groups and (iii) it is unclear whether the company used the modelled and empirical hazard functions for PFS/TTP to inform model selection. More flexible models may have provided a better representation of the underlying hazards and may have provided clinically plausible extrapolations beyond the observed data. Longer-term data are required to reduce uncertainty around the magnitude of the absolute and relative benefit of pembrolizumab plus CCRT on PFS and OS.

As noted in Section 4.2, following the clarification round, the company provided an updated economic model which includes the use of a wider set of parametric survival models (including RCS models) fitted to longer-term data from the Final Analysis data-cut of KEYNOTE-A18.^{16, 21} These updated survival analyses are summarised and critiqued separately in Section 5.1. Updated PFS, TTP and OS data from the Final Analysis data-cut are presented in Appendix 1 and 2.

(3) Concerns regarding the approach used to derive transition probabilities

The company's model includes transition probabilities derived from parametric survival models fitted to data on PFS and TTP from KEYNOTE-A18¹⁴ and KEYNOTE-826³³ (previously described in Section 4.2.2). Given that PFS is a composite end point which is comprised of two events (progression and death prior to progression), the EAG believes that the derivation of transition probabilities from survival models fitted to data from both trials should have been undertaken using competing risks approach.⁵⁹ This would have involved reprocessing the PFS data to censor the event not of interest (resulting in separate datasets for TTP censoring for death events and pre-progression mortality [PPM] censoring for progression events) and calculating the proportion of the joint hazard attributable to each cause-specific hazard k . However, this approach has not been adopted in the company's model.

During the clarification round, the EAG asked the company why a competing risks approach had not been used in the model (see clarification response,¹⁷ question B3). The company's response argues that very few death events occurred in KEYNOTE-A18 which would have increased uncertainty due to the sparseness of the data. The company's response also states that the approach adopted in the current appraisal was previously accepted in TA939.¹⁰ The EAG notes that the company's approach does not resolve issues relating to sparseness of the data and that it may mischaracterise event risks over time, thereby leading to biased predictions of long-term OS. The EAG notes that the company's original model provides OS predictions which appear consistent with the data from KEYNOTE-A18 at IA2.

However, this is not the case with respect to the company's updated (post-clarification) model, whereby the transition probabilities had to be recalibrated due to the poor fit between the modelled aggregate OS and the observed OS data from the Final Analysis data-cut of KEYNOTE-A18 (see Section 5.1 and Appendix 2, Figure 65).

(4) Uncertainty around cure and treatment waning assumptions

The company's model includes structural assumptions relating to cure (following first-line treatment with either pembrolizumab plus CCRT or CCRT alone only) and treatment effect waning (following first- and second-line treatment with pembrolizumab). The EAG's concerns regarding these assumptions are discussed below.

(a) Uncertainty surrounding the company's cure assumptions

The EAG believes that the structural assumptions of cure applied in the company's model are uncertain given the limited follow-up at IA2 in KEYNOTE-A18.¹⁴ The EAG's clinical advisors commented that the majority of patients who progress do so within two years, and very few recurrences occur beyond five years. However, the duration of follow-up at IA2 in KEYNOTE-A18¹⁴ is short: the maximum follow-up duration is around 38 months for PFS and 41.5 months for OS. The CS¹ acknowledges this uncertainty and explains that no external data are available to inform the cure assumptions for patients with LACC: *"The company were unable to identify the sort of very long term epidemiological data that would allow this [the proportion of patients who are cured] to be calculated but suspect that no observational study would have long enough follow up since the introduction of modern radiotherapy techniques"* (CS,¹ page 77). The EAG notes that one approach for estimating the proportion of patients who would be cured following treatment would involve fitting MCMs to estimate cure fractions. However, this approach is not mentioned in the CS and it is unclear whether any estimated cure fractions would be reliable given the limited duration of follow-up at IA2.

The CS¹ reports several scenario analyses which alter the cured proportion, the cure time points or which remove the cure assumptions altogether (see Table 34, Scenarios S16 to S20). The ICER for pembrolizumab plus CCRT [REDACTED]. This indicates that whilst uncertain, the cure assumptions are not key drivers of cost-effectiveness in the company's original model. However, it should be noted that when the cure assumption is removed, the model predictions of OS are driven by the generalised gamma PFS and TTP models; these models provide a poor fit to the observed data and therefore the results of the scenario analysis should be interpreted with caution.

During the clarification process, the EAG asked the company to fit MCMs to the available data on PFS and TTP from KEYNOTE-A18¹⁴ (see clarification response,¹⁷ question B11). However, the company's

response states that: “*due to prioritising analyses that would be incorporated into the health economic model, we [the company] did not have time to produce these analyses.*” The EAG notes that it remains unclear whether cure fractions could be estimated using the data from IA2 or the Final Analysis data-cut of KEYNOTE-A18 and the extent to which pembrolizumab plus CCRT may lead to cure remains uncertain. The company’s clarification response includes plots of empirical (smoothed) hazard functions for PFS, TTP and OS for both treatment groups based on the Final Analysis data-cut of KEYNOTE-A18 (see Appendix 2, Figure 37 to Figure 42). These plots indicate that the hazards for PFS and TTP in both treatment groups are decreasing at later time points; however, the hazard function for OS appears to be decreasing in the CCRT alone group, but increasing in the pembrolizumab plus CCRT group. This observed hazard function for OS in the pembrolizumab plus CCRT group is not consistent with the hazard function for an MCM (which will decrease over time as the mix of surviving patients is predominated by those who are cured). It is likely that additional follow-up beyond the Final Analysis DCO would be required to observe a decreasing hazard of OS in the pembrolizumab plus CCRT group.

(b) Uncertainty surrounding the company’s treatment effect waning assumptions

The company’s model includes assumptions of treatment effect waning for pembrolizumab in both the first- and second-line settings. The CS¹ states: “*While MSD does not endorse the application of treatment effect waning in patients that have received immunotherapy, within this submission it has been explored in the base case due to precedent in past NICE appraisals, particularly the assumptions agreed by the committee.*” The EAG’s clinical advisors stated that, due to the short follow-up at IA2 in KEYNOTE-A18,¹⁴ it is unclear whether the treatment effect of pembrolizumab would be maintained or reduced over time. However, one of the EAG’s clinical advisors commented that the risks of progression after 5-7 years are expected to be very low for CCRT alone; this limits the impact of the treatment effect waning assumptions for pembrolizumab plus CCRT in the first-line setting (because the baseline risk of progression for CCRT alone is expected to be close to zero by Year 7).

The scenario analyses presented in the CS¹ indicate that removing the treatment effect waning assumption for pembrolizumab plus CCRT leads to a small increase in the ICER (see Table 34, Scenario S9). However, these assumptions are not key drivers of the ICER in the company’s original model.

(5) Uncertainty around the use and outcomes of pembrolizumab re-challenge

The company’s model includes an assumption that patients who receive first-line treatment with pembrolizumab plus CCRT and progress at least 6 months after completing pembrolizumab treatment (i.e., at least 2.5 years after initiating first-line treatment) can be re-challenged with pembrolizumab (in combination with chemotherapy, with or without bevacizumab) in the second-line setting. The CS¹

states that the 2.5-year time point for pembrolizumab re-challenge: “...is due to the fact the NHS does not currently commission immunotherapy rechallenge if patients progression while on immunotherapy or for 6 months after successful completion of a course of immunotherapy” (CS, page 112). At IA2 in KEYNOTE-A18, only █ patients (████) in the intervention group had received pembrolizumab as a subsequent-line therapy” (see CS, Table 18). The CS does not provide any further information to support the assumption that pembrolizumab re-challenge for patients with progressed LACC would be commissioned by NHSE. The EAG also notes that the company’s model assumes that PFS and TTP outcomes for patients who are re-challenged with pembrolizumab are identical to those for patients who are pembrolizumab-naïve and who receive pembrolizumab at second-line – this assumption is likely to be optimistic.

The EAG’s clinical advisors’ views were broadly similar regarding whether they would re-challenge with pembrolizumab. One clinical advisor stated that they may not be permitted to re-challenge patients with pembrolizumab because there are no data to support its efficacy and safety in this setting. However, they stated that despite this absence of evidence, they might consider pembrolizumab re-challenge for some late progressors who had achieved a complete response in the first-line setting, although they also stated that other treatment options might be considered instead. The other clinical advisor commented that treatment options at second-line are limited and so they may be willing to re-challenge with pembrolizumab despite the uncertainty around its effectiveness. However, they stated that caution is needed due to the lack of evidence. Both clinical advisors agreed that they would expect outcomes for patients who are re-challenged with pembrolizumab to be less favourable (i.e., a lower response rate and a shorter duration of response) than for patients who have not previously received pembrolizumab. The EAG believes that further information is needed from NHSE to determine whether pembrolizumab re-challenge for patients with progressed LACC would be commissioned in NHS practice. Further clinical studies are required to determine the effectiveness and safety of pembrolizumab re-challenge.

Despite these uncertainties, scenario analyses undertaken by EAG indicate that removing pembrolizumab re-challenge from the model has only a moderate impact on the ICER (see Section 5.2).

(6) Uncertainty around survival benefits of subsequent-line treatments

Owing to the limited study follow-up in KEYNOTE-A18,¹⁴ all transition probabilities for patients who survive their first progression event are informed by KEYNOTE-826.³³ The EAG believes that the need to rely on external data from KEYNOTE-826 – rather than within-trial data from KEYNOTE-A18 – leads to uncertainty. The validity of the transition probabilities derived from external data is dependent on a strong assumption of exchangeability between patients in KEYNOTE-A18 at the time of progression and those at baseline in KEYNOTE-826.

In the company's model, 80% of patients in PD1 are assumed to receive subsequent treatment and their PPS is modelled using a weighted survival approach drawing on both arms of KEYNOTE-826³³ (see Table 17). The EAG considers the second-line treatment distributions used in the model to be broadly reasonable, although the EAG's clinical advisors commented that they would expect more than 64% of patients to receive pembrolizumab in clinical practice. However, the EAG remains somewhat concerned about the population exchangeability assumption, as outlined below.

KEYNOTE-826 subgroups

In the company's original model, post-progression transition probabilities are modelled using the KEYNOTE-826 CPS ≥ 1 subgroup.³³ Following the clarification process, the company's updated base case analysis¹⁶ further restricted the data set to KEYNOTE-826 patients with a CPS of ≥ 1 who had received prior CRT (see Section 5.1). The EAG considers limiting to the KEYNOTE-826 data to the CPS ≥ 1 subgroup to be reasonable, as over [REDACTED] of the patients in KEYNOTE-A18 had a CPS of ≥ 1 . The EAG also considers the additional restriction to the prior CRT subgroup in the company's updated model to be theoretically appropriate given the focus on patients receiving CCRT as first-line treatment (i.e., the KEYNOTE-A18 control arm).

However, in the company's updated analysis, the use of the KEYNOTE-826 data³³ leads to a poor concordance between modelled OS and KEYNOTE-A18 OS at the Final Analysis DCO,²¹ necessitating calibration of the final model (see Section 5.1). This remains the case when the CPS ≥ 1 subgroup data (not restricted by prior CRT) are used. The EAG notes that there are potential differences in CRT practice between the two studies: all KEYNOTE-826 patients completed CRT before November 2018, whereas KEYNOTE-A18 patients initiated CCRT from May 2020. The EAG's clinical advisors commented that the CCRT dose and delivery mode may potentially influence OS; however, without more granular data on radiotherapy regimens used in KEYNOTE-826, it remains uncertain whether effects observed in KEYNOTE-826 are generalisable to KEYNOTE-A18 subsequent-treatment effects.

Further, the EAG notes that prior treatment was not a randomisation stratification factor in KEYNOTE-826;³³ hence, restricting the data set to patients who had received prior CRT may compromise randomisation. Nevertheless, the company's model uses weighted transition probabilities derived from both arms of KEYNOTE-826 to model subsequent treatment within each KEYNOTE-A18 treatment group.¹⁴ Accordingly, arm-level exchangeability within the restricted KEYNOTE-826 subgroup is less critical. Rather, the key question is whether the outcomes weighted by the subsequent treatment distribution applied in the model are generalisable to the KEYNOTE-A18 population at progression. According to the company's clarification response¹⁷ (question A6), baseline characteristics are broadly similar between arms within the KEYNOTE-826 CPS ≥ 1 with prior CRT subgroup, thereby enabling a

comparison of KEYNOTE-A18 at-progression characteristics with the overall (non-arm-specific) restricted KEYNOTE-826 subgroup in order to assess exchangeability. The EAG details these additional considerations in assessing population exchangeability in addition to CCRT below.

Patient characteristics in KEYNOTE-A18 at progression versus KEYNOTE-826 at baseline

The EAG compared the characteristics of patients in KEYNOTE-A18²¹ (those with FIGO 2014 Stage III–IVA who had subsequent therapy) with KEYNOTE-826 (CPS $\geq$ 1)³³ based on information provided in the company’s response to clarification question A6.¹⁷ However, the same conclusions also hold for the KEYNOTE-826 CPS $\geq$ 1 with prior CRT subgroup (as used in the company’s updated model; see Section 5.1). Given the limited post-progression data available from KEYNOTE-A18, the only time-varying factor available was ECOG PS recorded at the closest time point to progression (on or before the date of progression).

ECOG PS distributions were broadly similar between KEYNOTE-A18²¹ at progression and KEYNOTE-826³³ at baseline; only one KEYNOTE-A18 patient had an ECOG PS of 2 at progression (see clarification response,¹⁷ question A6). The EAG’s clinical advisors stated that subsequent therapy is typically offered to patients with an ECOG PS of 0-1 and may be considered for selected patients with ECOG PS 2, thereby supporting comparability based on this factor. The EAG considers that ECOG PS in KEYNOTE-A18 at progression broadly reflects clinical practice and that KEYNOTE-826 broadly reflects the KEYNOTE-A18 population at progression with respect to ECOG PS. However, because ECOG PS in KEYNOTE-A18 was recorded closest to—but prior to or on the date of—progression, ECOG PS at progression could potentially be slightly worse; KEYNOTE-826 may therefore represent a marginally fitter cohort, although the EAG that considers any imbalance between the populations is likely to be small.

The EAG also notes some uncertainty about the comparability of initial disease staging between KEYNOTE-A18²¹ and KEYNOTE-826,³³ which may affect prognosis. KEYNOTE-826 assessed stage at diagnosis using FIGO 2009 (~50% Stage I–II), whereas the target population for the current appraisal relates to FIGO 2014 Stage III–IVA. The EAG’s clinical advisors commented that the differences between FIGO 2009 and FIGO 2014 are minor, with staging definitions being largely consistent. For instance, Stage IV in FIGO 2009 required biopsy confirmation of carcinoma extension beyond the true pelvis or mucosal involvement of the bladder and/or rectum, whereas FIGO 2014 does not explicitly require biopsy confirmation. Thus, when considering initial staging, KEYNOTE-826 likely included more patients who would have been diagnosed at FIGO 2014 Stage I–II, whereas the KEYNOTE-A18 III-IVA subgroup comprised only patients with *de novo* Stage III–IVA. In addition, most KEYNOTE-826 participants (■■■■) entered the trial with metastatic, or persistent/recurrent disease with distant

metastases. Because information on local and distant metastases was not available for KEYNOTE-A18 patients at the point of progression, this limits the ability to compare against the KEYNOTE-826 population.

Baseline patient age was similar across KEYNOTE-A18²¹ (FIGO 2014 III-IVA subgroup, mean: 50.5 years) and KEYNOTE-826 (CPS ≥ 1 subgroup, mean: 51.0 years; CPS ≥ 1 with prior chemoradiation subgroup: 50.4 years).³³ However, age would increase by the time of progression in KEYNOTE-A18; therefore, KEYNOTE-826 technically represents a slightly younger cohort than KEYNOTE-A18 at progression. KEYNOTE-826 included a higher proportion of White and European patients, which is more reflective of UK practice. Nevertheless, the EAG's clinical advisors suggested that ethnicity alone is unlikely to modify the treatment effect.

Other baseline characteristics that do not change over time appear broadly comparable between KEYNOTE-A18²¹ and KEYNOTE-826³³ (specifically the majority of patients have squamous histology). Nonetheless, given limited post-progression data in KEYNOTE-A18 and the potential for unmeasured prognostic differences, there remains residual uncertainty about population exchangeability.

No subsequent treatment subgroup following progression

In the model, 20% of progressed patients (in PD1) are assumed not to receive subsequent therapy and may transition only to death. Because all KEYNOTE-826³³ patients received active treatment (precluding a like-for-like mapping to KEYNOTE-A18²¹ patients receiving no subsequent treatment), the company's model applies a multiplier of 2.0 to the KEYNOTE-826 chemotherapy-arm survival for the transition from PD1 to Death. The EAG considers this general approach to be pragmatic given the absence of data. However, one of the EAG's clinical advisors commented that patients who do not receive subsequent therapy are expected to have a poorer prognosis and indicated a preference for a multiplier of 3. In KEYNOTE-A18, however, ECOG PS closest to progression showed a slightly higher proportion with an ECOG PS of >0 among recipients than non-recipients (████ vs █████), while ECOG PS of >1 was rare in both groups █████ Given the EAG's advisors' view that ECOG PS 0 and 1 are broadly similar prognostically, the EAG considers the use of a multiplier greater than 1 to be reasonable.

EAG's conclusions regarding exchangeability

Overall, the EAG considers the KEYNOTE-826 CPS ≥ 1 with prior CRT subgroup³³ to be broadly comparable —on measured prognostic factors— to the FIGO 2014 Stage III–IVA population in KEYNOTE-A18²¹ at progression, and considers the principle of using subgroup KEYNOTE-826 data to be reasonable. However, unmeasured prognostic differences leave the overall uncertainty

unquantifiable. The principal outstanding concern is whether prior CRT practice in KEYNOTE-826 is comparable to that in the KEYNOTE-A18 control arm as well as reflecting current clinical practice. The EAG is unable to determine the precise cause of the discrepancy between the company's updated uncalibrated OS and KEYNOTE-A18 OS (see Section 5.1). Whilst this poor fit may be a result of limitations in population exchangeability given unmeasured prognostic factors, it may also be a consequence of other factors, including the misspecification of survival models used to estimate transition probabilities and/or the incorrect handling of competing risks.

(7) *Issues relating to health state utility values*

Health state utility values within the company's economic model are informed by EQ-5D-5L data collected in the KEYNOTE-A18 and KEYNOTE-826 trials^{14, 33} (mapped to the 3L version). The disutility associated with AEs was also based on EQ-5D data from KEYNOTE-A18. The EAG's clinical advisors suggested that HRQoL is likely to be similar between the treatment groups; hence, the EAG agrees with the company's decision to apply treatment-independent utility values. The EAG considers the company's base case progression-based utility set broadly acceptable but notes some minor issues below.

Data completeness

The utility data from KEYNOTE-A18¹⁴ came from a subset of patients who completed at least one EQ-5D-5L questionnaire. Eight percent of patients had missing EQ-5D responses (see clarification response,¹⁷ question B21). Missing data may introduce bias, although the EAG considers this bias to be small if the data are missing at random across arms.

Mixed use of raw-mean and regression-based utilities from KEYNOTE-A18

Although the company estimated the disutility associated with AEs in KEYNOTE-A18¹⁴ using regression analysis, it did not apply regression-adjusted utilities in the PF and PD health states, instead choosing to rely on raw mean pre- and post-progression utility values (PF: [REDACTED]; PD1: [REDACTED]). The EAG considers this approach to be inconsistent but believes any impact on the ICER would likely be small if the PF and PD1 utilities were also derived from the KEYNOTE-A18 regression analysis (PF: [REDACTED]; PD1: [REDACTED]) given the scale of differences.

Utility estimates from KEYNOTE-826

The EAG cautions against relying on KEYNOTE-826³³ utility data for PD2 utility in the model. Specifically, for PD2 utility the company applied the PF→PD decrement from KEYNOTE-826 to PD1 utility from KEYNOTE-A18,¹⁴ yielding a PD2 utility of [REDACTED]; however, the EAG's clinical advisors commented that utility is likely to be lower than this estimate.

AE disutility

The EAG notes that the company's approach of applying QALY losses conditional on the probability of being alive and progression-free is unconventional as it underestimates the impact of overall QALY losses due to AEs. Further, it appears that AEs included in the regression model may have occurred both before and after disease progression in KEYNOTE-A18¹⁴ and could therefore include some AEs related to subsequent treatments. Owing to time constraints, the company did not incorporate AEs from subsequent treatments into the updated model (see clarification response,¹⁷ question B20). Nevertheless, this limitation is unlikely to substantially affect the ICER, given that QALY losses from subsequent treatments are likely to be small. In addition, the company did not model event-specific AE-related disutilities – the company's clarification response (question B19) states that there are a lack of AE-specific utility values available and notes that the company's current approach has also been used in previous appraisals (TA1017 and TA1037).^{60, 61} The EAG acknowledges the company's response, but believes that this leads to further uncertainty around the impact of event-specific AE-related disutility.

Overall, the EAG considers the utility values applied in the company's base case model to be broadly reasonable. However, the PD2 utility is likely overestimated, and uncertainty remains regarding the modelling of AE-related disutility.

(8) Issues relating to costs

The EAG's critical appraisal identified three minor issues relating to the costs applied in the company's original model. These are discussed below.

Assumption of 100% RDI

The model assumes that the RDI for all drugs is 100%. The EAG does not believe that this assumption reflects the experience of the KEYNOTE-A18 or KEYNOTE-826 trials.^{14, 33} The company's clarification response¹⁷ (question B24) states that an RDI of 100% was not observed in KEYNOTE-A18 and the company's response reports the percentages of actual versus expected numbers of doses of pembrolizumab and cisplatin from KEYNOTE-A18. The company's response also states: "*We have now included [in the updated post-clarification model] the actual number of cycles of subsequent treatments received in KEYNOTE-826 and so a relative dose intensity adjustment is not needed.*" The EAG considers that the company's approach to incorporate the actual mean treatment cycles observed in the clinical studies does not adequately address the issue relating to RDI. RDI is defined as the ratio of the delivered dose intensity to the planned (referenced) dose intensity.^{62, 63} Delivered dose intensity is estimated as the actual total dose delivered divided by the actual total duration to complete therapy. Planned dose intensity is estimated as the total expected dose to be delivered divided by total expected treatment duration. Although the company's updated approach of using the observed mean treatment cycles for each treatment (clarification response, question B24) better represents the study data, the

EAG considers that it still does not fully reflect the RDI as the observed cumulative dosage (total volume administered) of each drug is also required to calculate RDI. However, the EAG believes that this is unlikely to have a significant impact on the cost-effectiveness results.

Distribution of subsequent therapies

The company's model assumes that 64% of late progressors in the intervention group and all progressors in the CCRT alone group who receive active treatment are treated with pembrolizumab plus chemotherapy with or without bevacizumab. The EAG's clinical advisors commented that the proportion of patients who receive pembrolizumab at second-line is likely to be higher in NHS practice. As the proportion of pembrolizumab use at second-line remains uncertain, the EAG has explored the impact of assuming higher proportion in sensitivity analyses and notes that this has only a minimal impact on the ICER (see Section 5.2).

Overestimation of administration costs related to the subsequent treatments

The company's model estimates the administration costs of subsequent treatments as the product of the monthly cost, the mean treatment duration for each regimen component and the proportion of patients receiving each regimen component. As most treatments are administered concurrently every 3 weeks, except for cisplatin which is given weekly, the EAG considers that the company's approach likely overestimates administration costs because each regimen component cost is treated as being mutually exclusive (this is inconsistent with the approach applied for administration costs for first-line treatments in the model and TA939¹⁰). The EAG explored the impact of addressing this issue and found that it was likely to have only a minimal impact on the ICER (results not shown here).

Assumption that all drug administration takes place in an outpatient setting

The company's model assumes that all drugs (and EBRT) are administered in an outpatient setting. However, some centres may administer chemotherapy as a day-case rather than outpatient procedure. The proportion of centres using each approach is unknown. The EAG notes that applying day-case costs for drug administration increases the company's base case ICER for pembrolizumab plus CCRT by less than £1,000.

PD-L1 testing costs

The company's model assumes that all patients who have experienced a first progression event and who receive subsequent active treatment incur PD-L1 testing costs. The EAG's clinical advisors stated that PD-L1 testing is not routinely done following disease progression as most progressed patients are likely to be PD-L1 positive (and some patients undergo PD-L1 testing earlier in the treatment pathway). However, the EAG notes that additional testing of the company's model indicates that this cost is not a key driver of the ICER (see Section 5.2).

5. COMPANY'S UPDATED MODEL RESULTS AND EAG'S EXPLORATORY ANALYSES

This chapter summarises the company's updated (post-clarification) model and presents the methods and results of the EAG's exploratory analyses. Section 5.1 summarises the methods results of the company's updated model, including a critique by the EAG. Section 5.2 summarises the methods and results of the EAG's exploratory analysis undertaken using the company's updated model. Section 5.3 presents a discussion around decision modifiers. Section 5.4 includes details regarding confidential price discounts available for subsequent-line drugs included in the company's model. Section 5.5 summarises the conclusions of the economic analyses presented by the company and the EAG.

5.1 Company's updated economic model and results

5.1.1 Company's updated base case analyses

Following the clarification round, the company submitted an updated version of its economic model. The company's updated model includes substantial revisions, most notably, the inclusion of updated data from the Final Analysis data-cut of KEYNOTE-A18²¹ (DCO 7th January 2025) and the use of flexible RCS models fitted to the updated PFS and TTP data from this data-cut. The company's addendum to the CS,¹⁶ which was provided alongside its clarification response,¹⁷ reports the results of two updated base case analyses: (i) an updated 'primary base case analysis' informed by investigator-assessed PFS/TTP data from KEYNOTE-A18 and (ii) an updated 'secondary base case analysis' informed by BICR-assessed PFS/TTP data from KEYNOTE-A18. Key tables and figures relating to the company's updated survival analysis and the updated parameters of its primary base case model can be found in Appendix 2. The key changes applied in the company's updated post-clarification model are summarised below.

Transition probabilities out of the progression-free state (PF to PF, PF to PDI and PF to Dead)

The company estimated transition probabilities out of the PF state separately according to whether PFS/TTP was assessed by investigators or BICR. For its updated primary base case analysis (investigator-assessed PFS/TTP), the company fitted both RCS models and standard parametric survival models to the data on PFS and TTP from the Final Analysis data-cut of KEYNOTE-A18.²¹ For its primary base case analysis, the company selected the 1-knot odds RCS model for both PFS and TTP, including assumptions of cure and treatment effect waning. For its secondary base case analysis, the company used BICR-assessed PFS and TTP from the Final Analysis data-cut of KEYNOTE-A18. For this analysis, the company fitted only standard parametric survival models. The generalised gamma model, including assumptions of cure and treatment effect waning for pembrolizumab, was selected for inclusion in the company's secondary base case analysis.

Transition probabilities out of the first post-progression state (PD1 to PD1, PD1 to PD2 and PD1 to Dead)

As described in Section 4.2.3.1, the company's original survival analysis of KEYNOTE-826³³ including fitting both RCS models and standard parametric survival models to the available PFS and TTP data for the CPS ≥ 1 subgroup. Within the company's updated base case analyses, RCS models were fitted to the data on TTP and PFS for the subgroup of patients in KEYNOTE-826 with CPS ≥ 1 and prior CRT, to better align with the model population following progression. The company's updated primary and secondary base cases analyses use the 2-knot odds RCS model fitted to the KEYNOTE-826 subgroup data, including an assumption of treatment effect waning for pembrolizumab.

The company's clarification response¹⁷ and addendum¹⁶ highlight that the updated economic model substantially underestimates OS in the pembrolizumab plus CCRT group, whereas model-predicted OS for the CCRT alone group is reasonably accurate within the observed period of KEYNOTE-A18.¹⁴ In order to address this issue, the company used a calibration approach which down-weights the weighted transition probabilities in the PD1 sub-model for two years (although the company's addendum refers to four years); beyond this time point, uncalibrated transition probabilities are applied. The calibration factors applied to the first-line pembrolizumab plus CCRT and CCRT alone groups are 0.45 and 0.85 in the primary base case, and 0.44 and 0.54 in the secondary base case. These calibration factors temporarily slow down progressions out of the PD1 state, thereby resulting in a higher aggregate modelled OS curve. Comparisons of observed investigator-assessed PFS and OS from the Final Analysis of KEYNOTE-A18²¹ and model-predicted investigator-assessed PFS and OS (with and without calibration) generated by the company's updated economic model are shown in Appendix 2, Figure 63 and Figure 65).

Transition probabilities out of the second post-progression state (PD2 to PD2 and PD2 to Dead)

Transition probabilities for the PD2 state were estimated using standard parametric survival models fitted to the data on PPS from the KEYNOTE-826 CPS ≥ 1 prior CRT subgroup.³³ The log-normal distribution was selected for both treatment groups for inclusion in the company's updated base case analyses.

Other amendments to model parameters

Based on the Final Analysis of KEYNOTE-A18,²¹ the company's model also includes updated utility values for the PF and PD1 health states, an updated AE-related disutility value, updated AE frequencies related to first-line treatments and updated unit costs of cisplatin, paclitaxel and carboplatin. The mean treatment duration of each subsequent-line therapy was also updated to align with the data from the CPS ≥ 1 with prior CRT subgroup of KEYNOTE-826³³ by incorporating the observed number of

treatment cycles in the study. The values of these updated model parameters can be found in Appendix 2, Table 52 to Table 57.

Correction of model errors and other minor issues

The company's updated model includes the correction of some of the programming errors and other minor issues discussed in Section 4.3.5. The company's updated model includes the following amendments:

- The correction of model errors (see Section 4.3.5, critical appraisal point 1, Issues a-i, a-ii, b, d-i, d-ii, d-iii, d-iv and e).
- Additional functionality to undertake scenario analysis which excludes the calibration factors.
- Additional functionality to undertake scenario analysis which applies the price of the least expensive biosimilar to bevacizumab.
- Additional functionality to undertake scenario analysis which removes end-of-life care costs for patients who remain progression-free after Year 7.

The EAG scrutinised the company's updated economic model and identified some additional minor errors. These errors have been corrected as part of the EAG's preferred analysis (see Section 5.2).

- i. Executable model, worksheet "KN-826 TTP Splines". When applying a calibration factor to the weighted transition probabilities for late progressors in the intervention group and all progressors in the comparator group, the formulae erroneously reference cell E36 instead of cell E136 for capping the calibration factor at two years.
- ii. Whilst the company's addendum¹⁶ states that the calibration factors were applied for four years, the executable model applies the calibration factors for two years.
- iii. Regarding the end-of-life care costs for cured patients, the company's clarification response¹⁷ (question B33) states that: "*In line with NICE's position to exclude "Future Unrelated Costs" (e.g. section 4.4.11 of the manual but also discussed in position statements over the years), this now presents the company's base-case...*". However, the company's updated base case model includes end-of-life care costs for all patients at the point of death. In addition, whilst the company has included additional functionality to exclude these costs from the model, the model erroneously excludes them for all patients, yet the cured proportion is 95% (rather than 100%).

5.1.2 Company's updated model results

Company's central estimates of cost-effectiveness (company's updated model)

Table 33 presents the central estimates of cost-effectiveness generated using the company's updated (post-clarification) primary base case analysis (informed by investigator-assessed PFS and TTP from KEYNOTE-A18).²¹ All ICERs include the PAS for pembrolizumab and a decision modifier of 1.0. The

probabilistic version of the model suggests that pembrolizumab plus CCRT is expected to generate an additional 1.24 discounted QALYs at an additional cost of [REDACTED]. The corresponding ICER is [REDACTED] per QALY gained. The deterministic version of the model results in a slightly higher ICER of [REDACTED] per QALY gained. These ICERs are substantially higher than those generated using the company's original model (Section 4.2.6; company's original probabilistic base case ICER = [REDACTED] per QALY gained; company's original deterministic base case ICER = [REDACTED] per QALY gained).

Table 37: Company's updated base case results, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated by the EAG using the company's updated model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Pembrolizumab plus CCRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.24	[REDACTED]	[REDACTED]
CCRT				-	-	-	-
Deterministic model							
Pembrolizumab plus CCRT	*****	*****	*****	***	1.21	*****	*****
CCRT	*****	*****	*****	-	-	-	-

CCRT - concurrent chemoradiotherapy; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

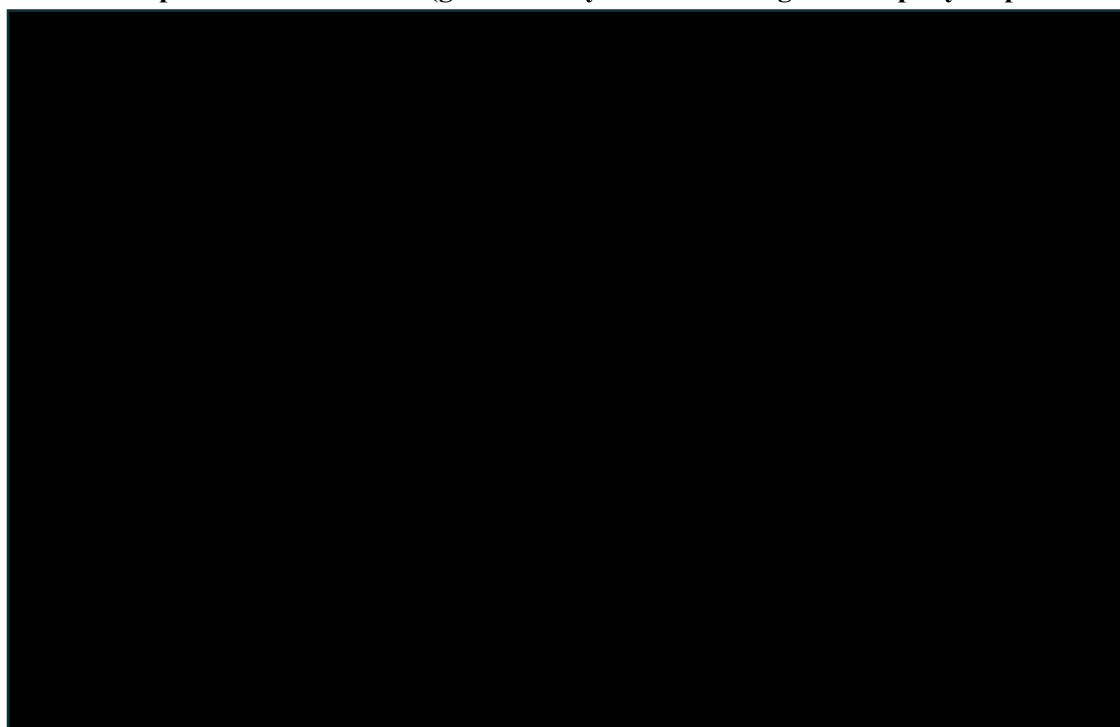
* Undiscounted

† Generated by re-running the company's PSA

Company's PSA results (company's updated model)

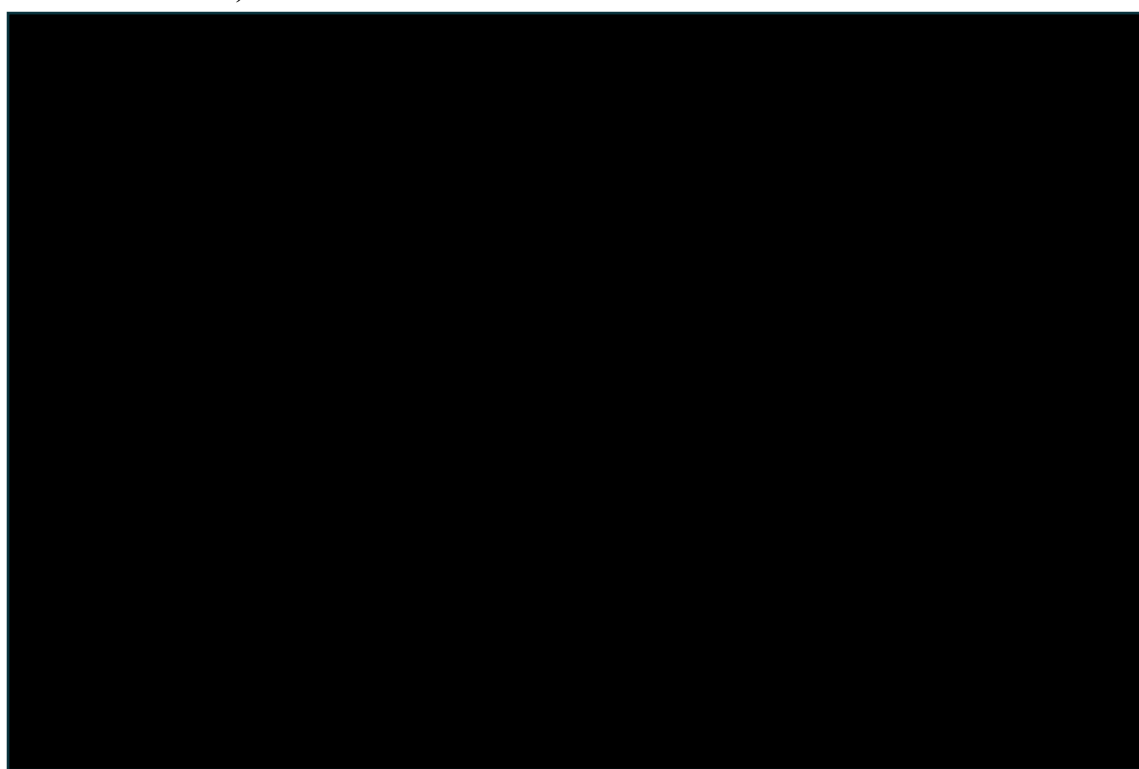
The results of the company's updated PSA are presented as a cost-effectiveness plane in Figure 26 and as CEACs in Figure 27. Assuming WTP thresholds of £20,000 and £30,000 per QALY gained, the probability that pembrolizumab plus CCRT generates more net benefit than CCRT is expected to be approximately [REDACTED] and [REDACTED], respectively.

Figure 29: Cost-effectiveness plane, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated by the EAG using the company's updated model)



CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; EAG - External Assessment Group; QALY - quality-adjusted life year

Figure 30: Cost-effectiveness acceptability curves, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated by the EAG using the company's updated model)

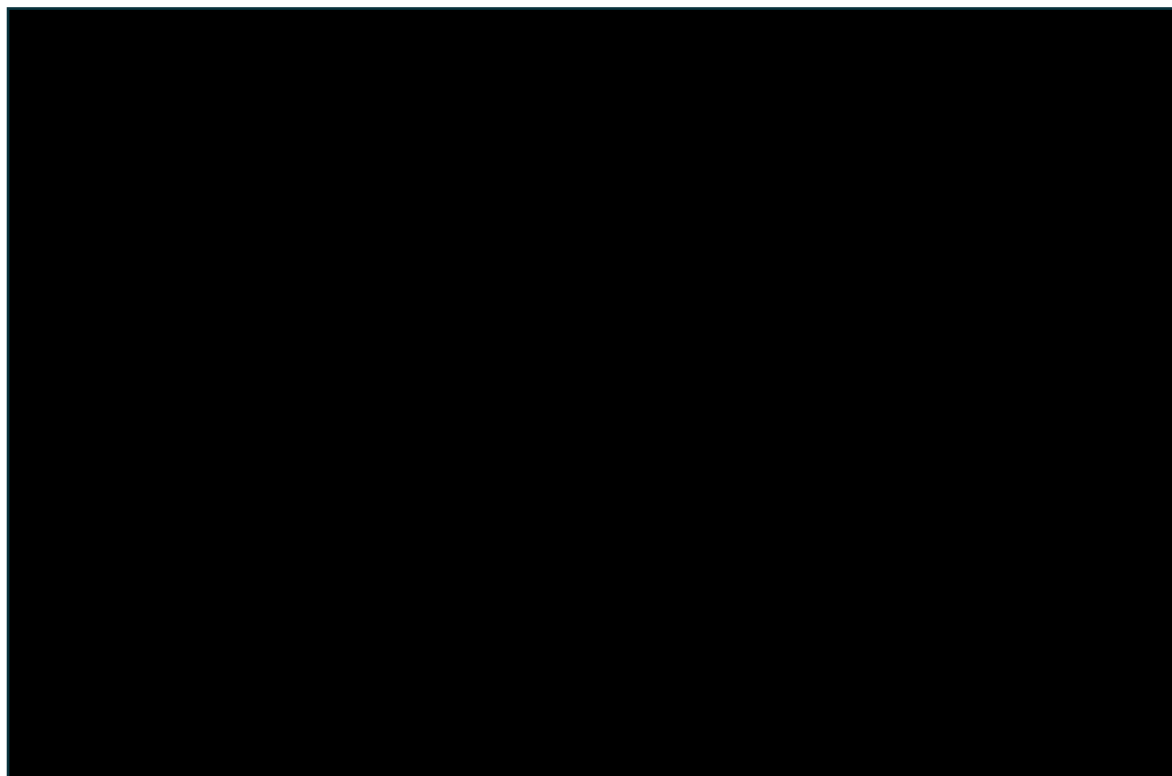


CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; EAG - External Assessment Group

Company's DSA results (company's updated model)

Figure 28 presents the results of the company's updated DSAs using a tornado plot. Similar to the company's original model analyses, the DSAs indicate that the ICER is not particularly sensitive to any of the parameters tested. Across all DSAs, the ICER for pembrolizumab plus CCRT versus CCRT ranges from [REDACTED] to [REDACTED] per QALY gained.

Figure 31: Tornado plot, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (generated using the company's updated model)



CRT/CCRT - concurrent chemoradiotherapy; PAS - Patient Access Scheme; PD1 - Progressed Disease 1; ICER - incremental cost-effectiveness ratio

Company's scenario analyses (company's updated model)

Table 38 presents the results of the company's scenario analyses using the company's updated model. The analyses indicate that the ICER is particularly sensitive to: (i) the cure and treatment effect waning assumptions; (ii) the use of the generalised gamma distribution for PFS and TTP data from KEYNOTE-A18²¹ (rather than the 1-knot odds RCS model) and (iii) the application of discount rates of 1.5% for health outcomes and costs. Across the range of scenarios tested, the ICER for pembrolizumab plus CCRT versus CCRT ranges from [REDACTED] per QALY gained (Scenario 2, use of generalised gamma models for PFS/TTP in KEYNOTE-A18) to [REDACTED] per QALY gained (Scenario 1, cure and treatment effect waning assumptions removed). The company's secondary base case analysis based on BICR-assessed PFS/TTP indicates a lower ICER of [REDACTED] per QALY gained.

Table 38: Company's scenario analysis results, pembrolizumab plus CCRT versus CCRT, includes pembrolizumab PAS (adapted from the company's addendum)

No.	Scenario	Inc. QALYs	Inc. Costs	ICER
-	Company's primary base case (investigator-assessed PFS/TTP)	1.209	*****	*****
-	Company's secondary base case (BICR-assessed PFS/TTP)	1.715		
1	Remove cure and treatment effect waning assumptions	0.836		
2	Both arms KEYNOTE-A18, PFS/TTP - generalised gamma	1.528		
3	Exclude pembrolizumab treatment waning (first- and second-line)	0.956		
4	Discount rates = 1.5%	1.606	*****	*****
5	Both arms KEYNOTE-A18 PFS/TTP 1-knot hazard RCS	1.115	*****	*****
6	Cure starting at 3 years and finishing at 5 years	1.283	*****	*****
7	Exclude utility adjustment based on age	1.304		
8	Remove cure assumption	1.180		
9	10% of patients get no further treatment after progressing	1.111		
10	35-year time horizon	1.172		
11	Cure starting at 7 years and finishing at 9 years	1.184	*****	*****
12	Utilities based on time until death	1.177	*****	*****
13	Cure proportion = 50%	1.195		
14	Utilities based on multivariate regression	1.180		
15	Remove the background mortality SMR	1.236		
16	Exclude end-of-life cost	1.209		
17	No treatment HR = 1.5	1.200	*****	*****
18	PD2 utility value equal to PD1 utility value (utility =)	1.202		
19	Replacing the cost of bevacizumab with biosimilars	1.209		
20	No treatment HR = 3.0	1.216		
21	Weighting PPS curve by the implied weighted average of pre and post 2.5-year progressors in the pembrolizumab group	1.215		
22	Exclude AE disutility	1.213	*****	*****
23	6 monthly GP visit post 5 years PFS	1.209	*****	*****
24	Subsequent pembrolizumab use set equal to trial (in pembrolizumab plus CCRT arm, in CCRT arm). Calibration factors 0.51 and 0.70.*	1.257		

CCRT - concurrent chemoradiotherapy; Inc. - incremental; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BICR - Blinded Independent Central Review; PFS - progression-free survival; TTP - time to progression; RCS - restricted cubic spline; SMR - standardised mortality ratio; HR - hazard ratio; PD - progressed disease; PPS - post-progression survival

* This scenario assumes that of early progressors and late progressors receive pembrolizumab. This is inconsistent with the company's model assumptions regarding eligibility for pembrolizumab re-challenge

5.1.3 EAG's critique of the company's updated economic model

This section provides a brief commentary from the EAG on the company's updated primary base case model informed by data on investigator-assessed PFS/TTP from the Final Analysis data-cut of KEYNOTE-A18.²¹ Table 39 summarises the data sets and parametric models used to inform the company's original base case model presented in the CS¹ and its updated primary base case model following the clarification.¹⁶

Table 39: Summary of key changes applied in company's updated model

Dataset, end point(s)	Original model	Updated model
KEYNOTE-A18 ^{14, 21} PFS/TTP	Generalised gamma model fitted to data from IA2	1-knot odds RCS model fitted to data from Final Analysis
KEYNOTE-826 ³³ PFS/TTP	3-knot hazards RCS model fitted to data from Final Analysis, CPS ≥ 1 subgroup	2-knot odds RCS model fitted to data from Final Analysis, CPS ≥ 1 with prior CRT subgroup
KEYNOTE-826 ³³ PPS	Standard generalised gamma model fitted to data from Final Analysis, CPS ≥ 1 subgroup	Standard log-normal model fitted to data from Final Analysis, CPS ≥ 1 with prior CRT subgroup

PFS - progression-free survival; TTP - time to progression; PPS - post-progression survival; IA2 - Interim Analysis 2; RCS - restricted cubic spline; CRT - chemoradiotherapy; CPS - combined positive score

KEYNOTE-A18, Final Analysis DCO, PFS and TTP models

The company selected the 1-knot odds RCS model for PFS and TTP in both treatment groups in its primary base case analysis, based on the Final Analysis of KEYNOTE-A18.²¹

In general, the RCS models with 1 or 2 knots provide the best statistical fit to the PFS and TTP data based on AIC and BIC in both groups, regardless of which scale the models were fitted on (see Appendix 2, Table 47 and Table 48).

When considering the modelled and smoothed empirical hazard functions for PFS, there is little basis for choosing between the RCS models with 1 or 2 knots in the CCRT alone group; the RCS models with 3 knots feature a higher hazard peak at around 35 weeks which is not reflected in the observed data for CCRT alone (see Appendix 2, Figure 44). In the pembrolizumab plus CCRT group, none of the models appear to fully reflect the decreasing slope of the smoothed empirical hazard function for PFS (see Appendix 2, Figure 43). However, the EAG acknowledges that the shape of the smoothed hazard function may be sensitive to the bandwidth used for smoothing. The EAG also notes that a direct comparison of observed and modelled hazards over the full study period was not possible because the company's modelled hazard plots are truncated at around 140 weeks (RCS models for PFS and TTP; Appendix 2, Figure 43 to Figure 46). In contrast, the company's plots of the raw and smoothed empirical hazards for PFS and TTP extend to around 220 weeks and were presented separately (EAG Appendix 2, Figure 37 to Figure 40). For TTP, all of the RCS models appear to provide a good representation of the smoothed empirical hazard function in the CCRT alone group, but again none of the models appear to fully reflect the pattern of decreasing hazards in the observed data for the pembrolizumab plus CCRT group (see Appendix 2, Figure 45 and Figure 46).

All RCS models provide a similar visual fit to PFS and TTP within the observed period; the fit is better for the CCRT alone group than the pembrolizumab plus CCRT group (see Appendix 2, Figure 47 to

Figure 50). Amongst the set of spline models fitted, the odds 1-knot RCS model provides the most optimistic projection of long-term PFS and TTP for the pembrolizumab plus CCRT group and the second-most optimistic projection for the CCRT alone group. The EAG notes that the 1-knot odds RCS models provide a better fit to the Kaplan-Meier estimates at the Final Analysis DCO and a more favourable long-term prediction of PFS/TTP for the CCRT group compared to the company's original model (the generalised gamma distribution fitted to data from IA2, Figure 9 to Figure 12).

The company's addendum¹⁶ states that the company did not seek additional clinical input to inform model selection based on the RCS distributions fitted to the updated data from the Final Analysis DCO. The EAG's clinical advisors considered the predictions of PFS and OS based on the updated models to be reasonable, but noted that longer-term data would be required to have greater confidence in the overall model predictions.

KEYNOTE-826, CPS ≥ 1 with prior CRT subgroup, PFS and TTP models

The company selected the 2-knot odds RCS model for PFS and TTP in both treatment groups of the prior CRT subgroup of KEYNOTE-826.³³

The 2-knot odds RCS model is one of the best-fitting RCS models based on AIC and BIC for PFS and TTP in both treatment groups (see Appendix 2, Table 49 and Table 50).

With respect to the hazard functions, the 2-knot odds RCS model provides a good representation of the PFS hazards for both groups (see Appendix 2, Figure 51 and Figure 52). The model also approximates the hazard function for TTP in the pembrolizumab plus chemotherapy (with or without bevacizumab) group; the same is not true for the chemotherapy (with or without bevacizumab) group, as none of the models follow the decreasing pattern of indicated by the smoothed empirical hazard function (see Appendix 2, Figure 53 and Figure 54). The EAG notes that the shape of the smoothed hazard may be sensitive to the bandwidth applied. Nonetheless, the peak of the modelled hazard lies outside of the 95% CI of the smoothed hazard between approximately Week 20 and Week 50 for the chemotherapy (with or without bevacizumab) group (see Appendix 2, Figure 54). Although the model captures the downward trend in later follow-up reasonably well, the slope after Week 50 is less steep than the smoothed hazard, suggesting a slightly optimistic long-term TTP projection.

The visual fit of the 2-knot odds RCS models to the PFS and TTP data from KEYNOTE-826³³ is generally good (see Appendix 2, Figure 55 to Figure 58). The company's addendum¹⁶ (page 84) states that: "*Due to time constraints clinical validation was unable to be sought on the estimated outcomes of this subgroup of the KEYNOTE-826 trial. As such selections have been based on statistical fit. We note that the implied plateaus are morphologically similar to those validated in TA939.*" The EAG notes

that these implied plateaus may not be directly transferable to the $\text{CPS} \geq 1$ with prior CRT subgroup because the data reflect a different population to that considered in TA939.¹⁰

The EAG's clinical advisors considered the 2-knot odds RCS models selected for inclusion in the updated model to be reasonable.

KEYNOTE-826, $\text{CPS} \geq 1$ with prior CRT subgroup, PPS models

The company selected the standard log-normal distribution to represent PPS within the $\text{CPS} \geq 1$ prior CRT subgroup of KEYNOTE-826.³³

The log-normal model was preferred by the company because the generalised gamma distribution results in a longer tail in the prior CRT subgroup (see EAG Appendix 2, Figure 61 and Figure 62); this trend was not apparent in the broader $\text{CPS} \geq 1$ subgroup. The EAG's clinical advisors commented that there is uncertainty around long-term survival for these patients.

Aggregate model-predicted OS (including calibration)

As noted in Section 5.1.1, the company's updated base case model does not provide a good representation of observed OS from the Final Analysis data-cut of KEYNOTE-A18.²¹ As such, the company elected to apply calibration factors to the weighted transition probabilities estimated from KEYNOTE-826³³ for the first 2 years after entering the PD1 state – this approach forces the model-predicted OS to be similar to the observed OS in KEYNOTE-A18. This is a new problem which was not evident in the original version of the company's model based on data from IA2.^{1, 14} The EAG believes that this discrepancy may be a consequence of one or more of the following factors: (i) the company's decision not to properly account for competing risks in the derivation of progression and death risks; (ii) the misspecification of one or more of the survival models used to inform any of the transition probabilities which inform OS, or (iii) the use of post-progression data from KEYNOTE-826 which may not be fully representative of the progressed population in KEYNOTE-A18. The EAG considers the company's calibration approach to be a potentially pragmatic solution, but notes that the need to force the model to better predict OS is far from ideal and that the resulting OS extrapolation obtained from the calibrated model should be interpreted with caution.

Company's secondary base case BICR-assessed PFS/TTP

The company's addendum¹⁶ includes a secondary base case analysis which uses data on BICR-assessed PFS/TTP instead of investigator-assessed PFS/TTP in KEYNOTE-A18.²¹ The company's addendum states that this analysis has been conducted to assess uncertainty, and highlights that the primary end point in KEYNOTE-A18 included BICR-assessed PFS before this was amended to include investigator-assessed PFS. Unlike the analyses of investigator-assessed PFS/TTP described above, the company's

new analyses of BICR-assessed PFS/TTP are limited to standard parametric survival models and in some cases none of the models provide an adequate fit to the data (e.g., the fit of all standard models to TTP for the chemotherapy group is particularly poor). Flexible parametric models have not been considered. The EAG also notes that the data from KEYNOTE-826 reflect investigator-assessed PFS and TTP; hence, using BICR-assessed PFS and TTP from KEYNOTE-A18 would lead to inconsistency between the data sets used to inform the event risks for first- and subsequent-line treatments in the economic model. The EAG does not believe that there is a sufficient justification for considering BICR-assessed PFS/TTP as a base case analysis and therefore this analysis is not discussed in detail in this EAG report.

Other amendments applied within the company's updated model

The company's updated model includes the correction of most of the errors in the company's model which were identified by the EAG.¹⁷ Whilst the company has not been able to fully address all of the issues listed in the EAG's clarification letter, none of these remaining issues are expected to have a significant impact on the ICER.

EAG's conclusions on the company's updated model

The EAG believes that the parametric survival models selected for inclusion in the company's updated primary (investigator-assessed PFS/TTP) base case analysis are reasonable. In particular, the EAG believes that the RCS models provide an improved representation of the hazards for PFS in KEYNOTE-A18,²¹ particularly in the CCRT alone group. However, because the company has not obtained clinical input around the plausibility of PFS, TTP and aggregate modelled OS to inform parametric model selection using the Final Analysis data-cut of KEYNOTE-A18, there is considerable uncertainty regarding the long-term model predictions. Similarly, the company has not obtained additional clinical input regarding the plausibility of the RCS models fitted to the KEYNOTE-826 CPS ≥ 1 with prior CRT subgroup data.³³ Further clinical input would be valuable in determining the plausibility of the updated model predictions of PFS and OS in both treatment groups. The EAG remains concerned that whilst the model includes assumptions of cure in both treatment groups, the company has not attempted to fit MCMs to the Final Analysis data set of KEYNOTE-A18; hence, it remains unclear whether cure fractions could be reliably estimated using the available data from the Final Analysis data-cut. As OS is modelled as a function of the transition probabilities, the calibration factors, together with structural assumptions about cure, treatment effect waning and subsequent treatment distributions, the results of the company's updated base case model should be considered highly uncertain.

5.2 EAG's exploratory analyses

5.2.1 EAG's exploratory analysis - methods

As discussed in Section 5.1.3, the EAG believes that the changes applied in the company's updated model are generally appropriate, including the use of PFS and TTP from the updated Final Analysis data-cut of KEYNOTE-A18,²¹ the application of RCS models to these updated data, and the updates applied to other model parameters (see Appendix 2). However, the EAG considers that the need to calibrate the weighted transition probabilities to force aggregate modelled OS to fit the observed OS data from KEYNOTE-A18 leads to unresolvable uncertainty. As such, the EAG's preferred analysis is very similar to the company's updated primary base case model and includes only the correction of the additional minor errors detailed in Section 5.1.1. The EAG also undertook additional sensitivity analyses to explore other areas of uncertainty which were not already addressed in the company's addendum.¹⁶

The EAG's exploratory analyses were undertaken using the updated model provided as part of the company's clarification response.¹⁷ All analyses were undertaken using the deterministic version of the model. The results of the EAG's preferred analysis are presented using both deterministic and probabilistic versions of the model.

All analyses were undertaken by one modeller and checked by a second modeller. All results presented in this section include the PAS discount for pembrolizumab and a decision modifier of 1.0. The results of the analyses including price discounts for bevacizumab are provided in a separate confidential appendix to this EAG report.

EAG's preferred analysis

EAG: Correction of errors and other minor issues

The following corrections were applied to the company's updated model within a single combined analysis:

- (a) Half-cycle correction was included.
- (b) The programming error relating to the application of the calibration factors, as detailed in Section 5.1.1, was corrected.
- (c) Age-adjusted general population utility values were updated to use EQ-5D-3L estimates for the UK reported by Hernández Alava *et al.*⁴⁵
- (d) The end-of-life care cost was amended to use the per-patient estimated costs in the last three months of life for patients with a cancer diagnosis from Georgiou and Bardsley, 2014⁴¹ and the net cost was inflated to 2024 prices using PSSRU 2024.⁴⁰
- (e) The administration cost of cisplatin was included for the pembrolizumab plus CCRT group during the weeks when it was not covered by pembrolizumab administration.

EA1 reflects the EAG's preferred analysis and results are presented using both deterministic and probabilistic versions of the model (EA1a and EA1b, respectively).

EAG's additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic version of the EAG's preferred model (EA1a).

- *ASA1a-d: Alternative RCS models for PFS and TTP.* The model was re-run using alternative RCS models (1-knot normal, 2-knot hazard, 2-knot odds and 2-knot normal) for PFS and TTP based on KEYNOTE-A18.²¹ The same functional form was applied for both treatment groups. These analyses were conducted using existing functionality in the company's updated model.
- *ASA2: Alternative subgroup from KEYNOTE-826.* This analysis was conducted based on PFS, TTP and PPS data for the CPS ≥ 1 population from KEYNOTE-826 (not restricted by prior CRT).³³ PFS and TTP were modelled using the 3-knot hazard RCS model, and PPS was modelled using the standard generalised gamma distribution. The calibration factors were also adjusted accordingly: 0.48984 for pembrolizumab plus CCRT group and 0.73426 for CCRT alone group. The calibration factors were re-estimated using the Excel Solver add-in to minimise the sum squared error between the model-predicted OS and directly-fitted OS using the generalised gamma distribution applied to the KEYNOTE-A18 Final Analysis data-cut²¹ (weighted by number of risk).
- *ASA3: Exclusion of the calibration factors for OS.* This analysis explores the impact of excluding calibration of the weighted transition probabilities for PFS and TTP based on the data from KEYNOTE-826.
- *ASA4: Application of the calibration factors for four years.* This analysis applies the calibration factors for PFS and TTP (based on the data from KEYNOTE-826³³) for four years (rather than two years) as this appears to reflect the company's intended approach, as described in its addendum to the CS.¹⁶
- *ASA5: Alternative pembrolizumab-treated proportion following first progression event.* Based on advice from the EAG's clinical advisors, this analysis explores the assumption that 80% of patients would receive pembrolizumab following disease progression, compared with 64% applied in the company's base case analysis. This excludes early progressors in the intervention group.
- *ASA6: Exclusion of pembrolizumab re-challenge.* This analysis assumes that patients who progress after first-line treatment with pembrolizumab plus CCRT would not be re-challenged with pembrolizumab following disease progression.
- *ASA7: Exclusion of PD-L1 testing costs.* This analysis excludes the costs of PD-L1 testing after disease progression.

- *ASA8: Removal of the cure warm-up period.* This analysis removes the cure warm-up period for both treatment groups. Patients are assumed to be cured after 7 years in both groups.
- *ASA9: No additional treatment effect for pembrolizumab vs chemotherapy in late progressors.* This analysis assumes that the treatment effect for pembrolizumab wanes immediately after the first model cycle in late progressors who are re-challenged with pembrolizumab following first disease progression.
- *ASA10: Alternative utility value for PD2 state.* This analysis was undertaken to examine whether the utility value applied in the PD2 state has a marked impact on the ICER for pembrolizumab plus CCRT. The analysis applies an arbitrary 50% reduction to the utility value for the PD2 state (PD2 utility = [REDACTED]).

5.2.2 EAG's exploratory analysis - results

EAG's preferred analysis results

The results of the EAG's preferred analysis of pembrolizumab plus CCRT versus CCRT alone are presented in Table 40. All ICERs apply a decision modifier of 1.0 (i.e., no QALY weighting). As shown in the table, the correction of remaining model errors and other minor issues in the company's updated model slightly reduces the ICER compared to the company's base case estimate. The EAG's preferred analysis suggests a probabilistic ICER of [REDACTED] per QALY gained (EA1b). The deterministic version of the model suggests a slightly lower ICER of [REDACTED] per QALY gained (EA1a).

Table 40: EAG's preferred analysis, including PAS discounts of pembrolizumab

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated primary base case (post-clarification), deterministic							
Pembrolizumab plus CCRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.21	[REDACTED]	[REDACTED]
CCRT alone	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
EA1a: EAG-preferred analysis, deterministic							
Pembrolizumab plus CCRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.24	[REDACTED]	[REDACTED]
CCRT alone	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-
EA1b: EAG-preferred analysis, probabilistic							
Pembrolizumab plus CCRT	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.24	[REDACTED]	[REDACTED]
CCRT alone	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-	-

CCRT - concurrent chemoradiotherapy; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

* Undiscounted

† Generated by re-running the company's PSA

EAG's additional sensitivity analysis results

The results of the EAG's additional sensitivity analyses are presented in Table 41. As shown in the table, the ICER is sensitive to choice of RCS model applied to the PFS and TTP data from KEYNOTE-

A18.²¹ (ASA2) and to the exclusion of the calibration factors applied to the weighted transition probabilities in the PD1 state (ASA3). The model is not particularly sensitive to any of the other scenarios tested.

Table 41: EAG's additional sensitivity analysis, including PAS discount of pembrolizumab

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA1a: EAG-preferred analysis, deterministic							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.24	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA1a: PFS, TTP = 1 knot normal RCS model							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.41	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA1b: PFS, TTP = 2 knot hazard RCS model							
Pembrolizumab plus CCRT	*****	*****	*****	*****	0.92	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA1c: PFS, TTP = 2 knot odds RCS model							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.03	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA1d: PFS, TTP = 2 knot normal RCS model							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.12	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA2: KEYNOTE-826 CPS$\geq$1 subgroup, PFS, TTP = 3-knot hazard RCS model, PPS = generalised gamma model, calibration factors 0.49 and 0.73							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.23	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA3: Exclusion of the calibration factors for OS							
Pembrolizumab plus CCRT	*****	*****	*****	*****	0.93	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA4: Application of the calibration factors for four years							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.35	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA5: Pembrolizumab-treated proportion following disease progression = 80%							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.12	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA6: Exclusion of pembrolizumab re-challenge							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.07	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA7: Exclusion of PD-L1 testing costs							

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.24	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA8: Removal of the cure warm-up period							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.22	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA9: No additional treatment effect for pembrolizumab vs chemotherapy in late progressors							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.07	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-
ASA10: 50% reduction in utility value for PD2 state (utility value = *****)							
Pembrolizumab plus CCRT	*****	*****	*****	*****	1.27	*****	*****
CCRT alone	*****	*****	*****	-	-	-	-

ASA - additional sensitivity analysis; EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PFS - progression-free survival; TTP - time to progression; RCS - restricted cubic spline; CPS - combined positive score; PD-L1 - programmed death-ligand 1; CCRT - concurrent chemoradiotherapy, PD2 - second disease progression

* Undiscounted

5.3 Decision modifiers

5.3.1 Severity modifier

The economic analysis applied in the CS¹ includes a severity modifier of 1.0 (i.e., no QALY weighting is applied). Based on the characteristics of the KEYNOTE-A18 population (mean age = 51.5 years; 100% female¹⁴) and the estimated QALYs in the comparator group of the model, the York QALY Shortfall Calculator suggests an absolute QALY shortfall of [REDACTED] and a proportional QALY shortfall of [REDACTED]. The EAG agrees that a decision modifier of 1.0 is appropriate for pembrolizumab plus CCRT.

5.3.2 Health inequalities - distributional cost-effectiveness analysis

The CS¹ states that LACC is associated with substantial health inequalities in terms of incidence and patient outcomes. As part of its submission, the company presents the results of a DCEA⁶⁴ which estimates net health benefits (NHBs) by Index of Multiple Deprivation (IMD) quintiles for International Classification of Diseases Version 10 (ICD10) code C53 (“malignant neoplasm of the cervix uteri”), assuming a WTP threshold of £30,000 per QALY gained and a flat opportunity cost gradient across the IMD quintiles. The analysis was undertaken using the online Health Equity Impact calculator.⁶⁵ The company’s DCEA based on the original version of the economic model indicates that the use of pembrolizumab plus CCRT would result in positive NHBs for all IMD quintiles except for IMD 5 (least deprived). The EAG’s comments on the company’s original DCEA are summarised in Table 42. However, it should be noted that the inputs used in the company’s DCEA are not provided in the CS or its appendices and the EAG was unable to generate equivalent results to those presented in the CS using the online Health Equity Impact calculator; this precludes a detailed critique by the EAG.

Table 42: EAG comments on the company's DCEA using the original submitted model

Component of DCEA	NICE's preferred approach	EAG comments
Stratification of social groups	Based on IMD. This should be supported by rationale	The analysis is based on IMD quintiles. The population included in the DCEA is broader than the target population for the current appraisal as it includes all cases of cervical cancer, rather than FIGO 2014 Stage III-IVA LACC. The CS highlights this issue and states that a steeper gradient would be expected in the target population.
Uncertainty	Select sensitivity analyses. Full probabilistic analysis can be done but is not required	No scenario analyses are presented for factors which determine health inequality impacts e.g., disease prevalence and/or incremental health benefits. It is unclear if the DCEA has been conducted using the outputs of the deterministic or probabilistic version of the company's original model.
Uptake	Equal uptake across groups should be assumed. No change in uptake should be assumed, unless supported by robust evidence	Assumptions about uptake are not reported in the CS.
Health inequality aversion weights	Health inequality aversion weights should not be applied to QALYs	The application of health inequality aversion weights is not reported in the CS.
Health opportunity cost	Equally distributed across social groups with scenario analyses provided for alternative gradients	NHBs are presented according to three opportunity cost gradients - flat, moderate and steep. The share of opportunity costs in the moderate and steep scenarios are not reported in the CS.
Discounting	The same annual rate of 3.5% for both costs and health effects	Discount rates used in the DCEA are not reported in the CS.
Outputs	Net health benefit, total health benefit, and health opportunity costs should be presented for each IMD quintile	Results are presented in terms of NHB by IMD quintile, assuming a WTP threshold of £30,000 per QALY gained and a flat opportunity cost gradient. Other outputs e.g., total/gross health benefit and health opportunity costs are not reported in the CS. Weighted ICERs are not reported.

FIGO - International Federation of Gynecology and Obstetrics; IMD - Index of Multiple Deprivation; LACC - locally advanced cervical cancer; CS - company's submission; DCEA - distributional cost-effectiveness analysis; NHB - net health benefit; QALY - quality-adjusted life year

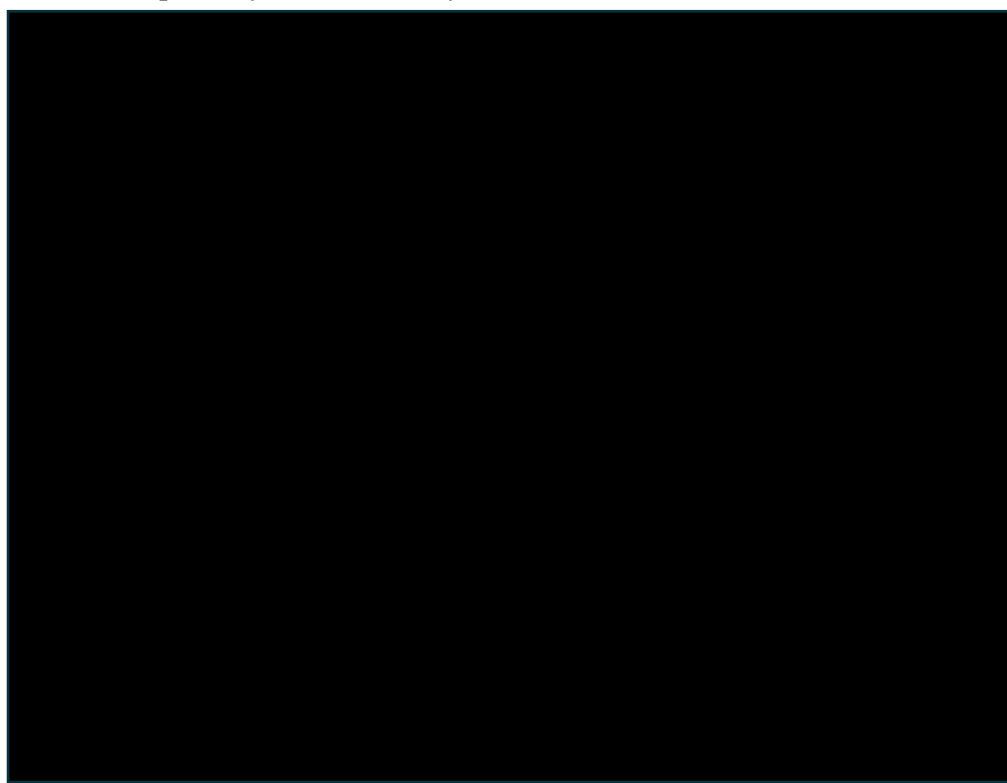
Following the clarification round, the company updated its DCEA to reflect a population size of [REDACTED] patients.¹⁶ The source of this alternative population size is not reported in the company's addendum¹⁶ and no further details are provided regarding inputs to the analysis. The company's addendum reports the 'net health inequality benefit', which is defined in the online calculator as "the modelled difference in net QALY benefit between the most and least deprived IMD group at population level";⁶⁵ no other

outcomes are presented. The EAG was able to replicate the estimates of net health inequality benefit reported in the company's addendum by using the online Health Equity Impact calculator⁶⁵ and guessing some of the inputs which had not been reported in the company's addendum. These results are summarised in Figure 32 and Table 43 for the company's updated primary base case analysis and Figure 33 and Table 44 for the company's updated secondary base case analysis.

Under the company's primary base case assumptions (based on investigator-assessed PFS), the net health inequality benefit is estimated to be ■ QALYs assuming a flat opportunity cost gradient, ■ QALYs assuming a moderate opportunity cost gradient and ■ QALYs assuming a steep opportunity cost gradient. When the health opportunity cost gradient is assumed to be flat, the NHB is positive only in the IMD1 (most deprived) quintile. The company's updated primary base case model suggests ■ NHBs across all IMD quintiles when the health opportunity cost gradient is assumed to be moderate or steep. Across all three health opportunity cost gradient scenarios, the equity-weighted ICER ■

Under the company's secondary base case assumptions (based on BICR-assessed PFS), the net health inequality benefit is estimated to be ■ QALYs assuming a flat opportunity cost gradient, ■ QALYs assuming a moderate opportunity cost gradient and ■ QALYs assuming a steep opportunity cost gradient. Across these three health opportunity cost gradient scenarios, the equity-weighted ICER ranges from approximately ■ per QALY gained when the Atkinson inequality aversion parameter is set to its maximum selectable value of 20.

Figure 32: Distribution of net health benefits across IMD quintiles using the company's updated primary base case analysis



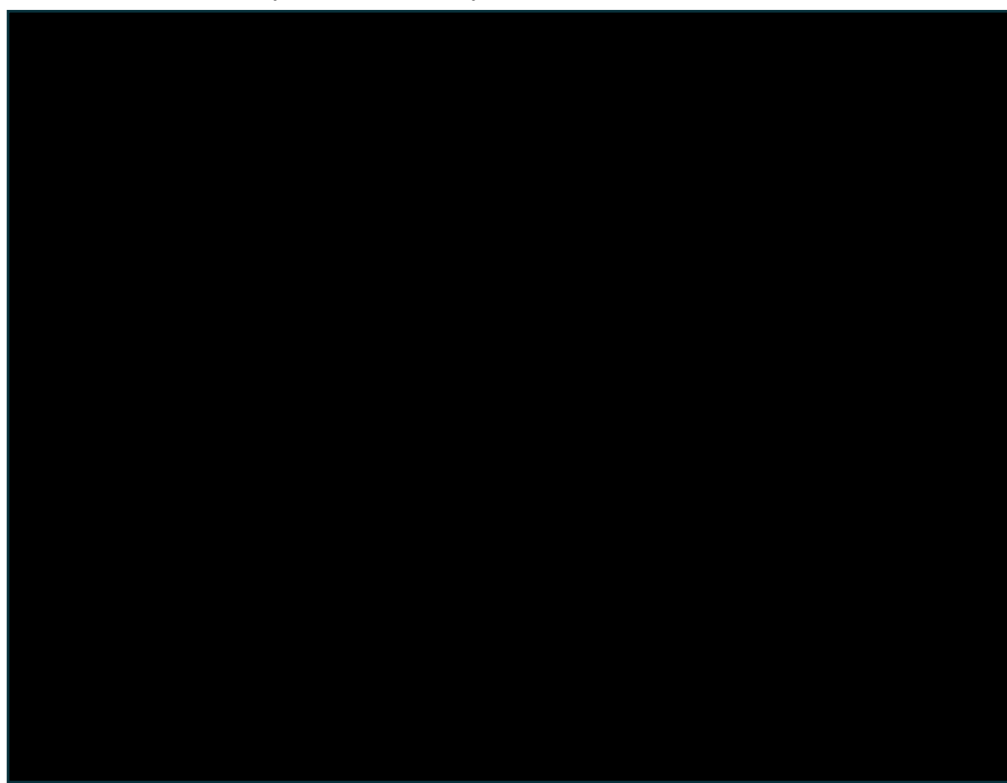
IMD - Index of Multiple Deprivation

Table 43: Summary results of DCEA using the company's updated primary base case

	IMD1	IMD2	IMD3	IMD4	IMD5	Total	Net health inequality benefit (QALYs)
Flat health opportunity cost							
Gross health benefit (QALYs)							
Opportunity costs (QALYs)							
Net health benefit (QALYs)							
Moderate health opportunity cost gradient							
Gross health benefit (QALYs)							
Opportunity costs (QALYs)	***	***	***	**	***	***	
Net health benefit (QALYs)	***	***	***	***	***	***	
Steep health opportunity cost gradient							
Gross health benefit (QALYs)							
Opportunity costs (QALYs)	***	***	***	**	***	***	
Net health benefit (QALYs)							

DCEA - distributional cost-effectiveness analysis; IMD - Index of Multiple Deprivation; QALY - quality-adjusted life-years

Figure 33: Distribution of net health benefits across IMD quintiles using the company's updated secondary base case analysis



IMD - Index of Multiple Deprivation

Table 44: Summary results of DCEA using the company's updated secondary base case

	IMD1	IMD2	IMD3	IMD4	IMD5	Total	Net health inequality benefit (QALYs)
Flat health opportunity cost							
Gross health benefit (QALYs)	■	■	■	■	■	■	■
Opportunity costs (QALYs)	■	■	■	■	■	■	
Net health benefit (QALYs)	■	■	■	■	■	■	
Moderate health opportunity cost gradient							
Gross health benefit (QALYs)	■	■	■	■	■	■	■
Opportunity costs (QALYs)	***	***	***	***	***	***	
Net health benefit (QALYs)	■	■	■	■	■	■	
Steep health opportunity cost gradient							
Gross health benefit (QALYs)	■	■	■	■	■	■	■
Opportunity costs (QALYs)	***	***	***	***	***	***	
Net health benefit (QALYs)	■	■	■	■	■	■	

DCEA - distributional cost-effectiveness analysis; IMD - Index of Multiple Deprivation; QALY - quality-adjusted life-years

5.3.3 Uncaptured benefits

With the exception of the distributional concerns described in Section 5.2.2, the CS¹ does not make a case that there are any other additional relevant benefits of pembrolizumab which have not been captured in the ICER.

5.4 Confidential comparator and subsequent treatment prices

The results of both the company's updated analyses and the EAG's exploratory analyses including PAS discounts for pembrolizumab and Medicines Procurement and Supply Chain (MPSC) prices for bevacizumab are provided in a separate confidential appendix to this EAG report. Table 1 of the confidential appendix provides details of the PAS price for pembrolizumab and the MPSC prices for the bevacizumab originator and biosimilars. The results of the company's updated primary base case analysis and scenario analyses are summarised in Table 2 and Table 3, respectively. The results of the EAG's preferred analysis and additional sensitivity analyses are presented in Table 4 and Table 5, respectively.

5.5 Discussion

The CS¹ presents an SLR of existing economic studies of treatments for adult patients (aged ≥ 18 years) with high-risk, LACC (Stage IB2–IVA). The SLR did not identify any UK economic evaluations of treatments for the target population of FIGO 2014 Stage III-IVA LACC.

The company's economic model assesses the cost-effectiveness of pembrolizumab plus CCRT versus CCRT alone for the treatment of adult patients with untreated high-risk FIGO 2014 Stage III-IVA LACC over a lifetime horizon from the perspective of the NHS and PSS. The company's original model uses a state-transition (semi-Markov) approach, informed by time-to-event data from IA2 of KEYNOTE-A18 (DCO 8th January 2024),¹⁴ as well as external data for post-progression outcomes from the Final Analysis of KEYNOTE-826 (CPS ≥ 1 subgroup).³³ The model includes four health states: (i) Progression-free; (ii) Progressed Disease 1; (iii) Progressed Disease 2 and (iv) Dead. The model includes an assumption that pembrolizumab re-challenge is permitted for patients who experience a first progression event at least 2.5 years after initiating first-line pembrolizumab (i.e., at least 6 months after completing first-line pembrolizumab treatment). A structural assumption of cure is applied in both treatment groups, whereby the predicted probabilities of progression are reduced by 0% at the end of Year 5, increasing approximately linearly to 95% by the end of Year 7. The model also includes an assumption of treatment effect waning for pembrolizumab when used in either the first- or second-line settings. Health state utility values and AE disutility are informed by EQ-5D data from KEYNOTE-A18 and KEYNOTE-826. Resource use estimates and unit costs are based on the KEYNOTE-A18 and KEYNOTE-826 trials, standard costing sources, literature and assumptions. The model includes a PAS for pembrolizumab in both the first- and second-line settings.

The probabilistic version of the company's original model results suggests that the ICER for pembrolizumab plus CCRT versus CCRT alone is [REDACTED] per QALY gained. The deterministic version of the model suggests a slightly lower ICER of [REDACTED] per QALY gained.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG's main concerns regarding the company's original model relate to: (i) uncertainty surrounding the magnitude of modelled treatment benefit on PFS and OS (including assumptions of cure) for pembrolizumab plus CCRT given the short follow-up duration at IA2 in KEYNOTE-A18,¹⁴ and (ii) the poor fit of the standard parametric survival models for PFS and TTP from KEYNOTE-A18 and the failure to explore the use of more flexible parametric survival models (e.g., RCS models and MCMs).

Following the clarification round, the company submitted an updated economic model which is informed by the Final Analysis data-cut of KEYNOTE-A18 (DCO 7th January 2025).^{16, 21} The amendments made within this updated model are substantial. The most notable changes to the company's updated primary base case model are: (i) the selection of 1-knot odds RCS models fitted to data on PFS and TTP from the Final Analysis data-cut of KEYNOTE-A18; (ii) the use of 2-knot odds RCS models fitted to data on PFS and TTP for the CPS ≥ 1 with prior CRT subgroup of KEYNOTE-826;³³ (iii) the inclusion of calibration factors applied to all post-progression transition probabilities out of the PD1 state which force the model-predicted OS to better fit the observed OS data from the Final Analysis data-cut of KEYNOTE-A18. The updated model also includes updated utility values, updated unit costs and the correction of several errors identified by the EAG at the clarification stage of the appraisal.

The probabilistic version of the company's updated model suggests that the ICER for pembrolizumab plus CCRT versus CCRT alone is [REDACTED] per QALY gained. The deterministic version of the updated model suggests a slightly higher ICER of [REDACTED] per QALY gained. These ICERs are markedly higher than the company's original ICERs because the Final Analysis data-cut of KEYNOTE-A18²¹ indicates a smaller absolute treatment benefit for pembrolizumab plus CCRT compared with the IA data-cut. The company's additional sensitivity analyses suggest that the updated model is particularly sensitive to: (i) the cure and treatment effect waning assumptions; (ii) the selection of alternative parametric survival models fitted to PFS and TTP from KEYNOTE-A18 and (iii) the use of BICR vs. investigator-assessed PFS/TTP.

The EAG scrutinised the company's updated model and checked the updated model inputs. The EAG is generally satisfied that the company's updated model addresses many of the limitations which were evident in the company's original economic analysis. However, the EAG notes that the long-term benefits of pembrolizumab plus CCRT remain uncertain, including the extent of its curative potential, which are hinged on assumptions that cannot be substantiated without longer-term data. Whilst the EAG requested that the company attempt to derive cure fractions using MCMs fitted to the PFS and TTP data

from the Final Analysis data-cut of KEYNOTE-A18,²¹ the company has not attempted to do this. The EAG also notes that the need to apply calibrated transition probabilities to force the model-predicted OS to fit the observed OS data from KEYNOTE-A18 is not ideal, and caution is advised in the interpretation of the updated calibrated model results.

The EAG undertook additional exploratory analyses using the company's updated model. The EAG's preferred model is very similar to the company's updated base case model, but includes a small number of additional error corrections. These corrections have only a negligible effect on the ICER. The probabilistic version of the EAG's preferred model leads to an ICER of [REDACTED] per QALY gained; this is slightly lower than the company's updated base case ICER. The EAG's additional sensitivity analyses indicate that the model is sensitive to the selection of alternative RCS models for PFS and TTP from KEYNOTE-A18²¹ and the removal of the calibration factors.

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7. APPENDICES

Appendix 1: Updated clinical results from the Final Analysis of KEYNOTE-A18

This appendix provides summary results from the Final Analysis of KEYNOTE-A18 which were provided as part of an additional addendum to the company's clarification response.¹⁷

This appendix contains the following data:

- Baseline patient characteristics in KEYNOTE-A18 - Table 45
- Updated summary of results from Final Analysis of KEYNOTE-A18 - Table 46
- Updated Kaplan-Meier plots of OS, investigator-assessed PFS and PFS2 - Figure 34, Figure 35 and Figure 36

Table 45: Baseline patient characteristics, KEYNOTE-A18, Stage III-IVA subgroup, Final Analysis (reproduced from company's clarification response addendum, Table 1)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	N	(%)	N	(%)	N	(%)
Participants in population	296		305		601	
Sex						
Female	296	100	305	100	601	100
Age (Years)						
< 65						
>= 65						
Mean						
SD						
Median						
Range						
Race						
American Indian or Alaska Native						
Asian						
Black or African American						
Multiple						
Native Hawaiian or Other Pacific Islander						
White						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Not Reported						
Geographic Region						
Asia Pacific						
EMEA						
North America						
Latin America						
Geographic Region 2						
North America						
Western Europe						
Rest of the World						
Age Group (Years)						
< 65						
65 - 74						
75 - 84						
85+						
Baseline ECOG						
0						
1						
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic						
No Positive Pelvic nor Para-Aortic						

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	N	(%)	N	(%)	N	(%)
Histology Subtype						
Non-squamous	1	100	1	100	2	100
Squamous	1	100	1	100	2	100
Planned Type of EBRT						
IMRT or VMAT	1	100	1	100	2	100
non-IMRT and non-VMAT	1	100	1	100	2	100
Planned Total Radiation Therapy Dose per (EQD2)						
< 70 Gy	1	100	1	100	2	100
>= 70 Gy	1	100	1	100	2	100
PD-L1 Status						
CPS <1	1	100	1	100	2	100
CPS >=1	1	100	1	100	2	100
Missing	1	100	1	100	2	100

CCRT - concurrent chemoradiotherapy; EMEA - Europe, the Middle East and Africa; ECOG - Eastern Cooperative Oncology Group; EBRT - external beam radiation therapy; IMRT - intensity modulated radiotherapy; VMAT - volumetric modulated arc therapy; PD-L1 - programmed death-ligand 1; CPS - combined positive score N - number

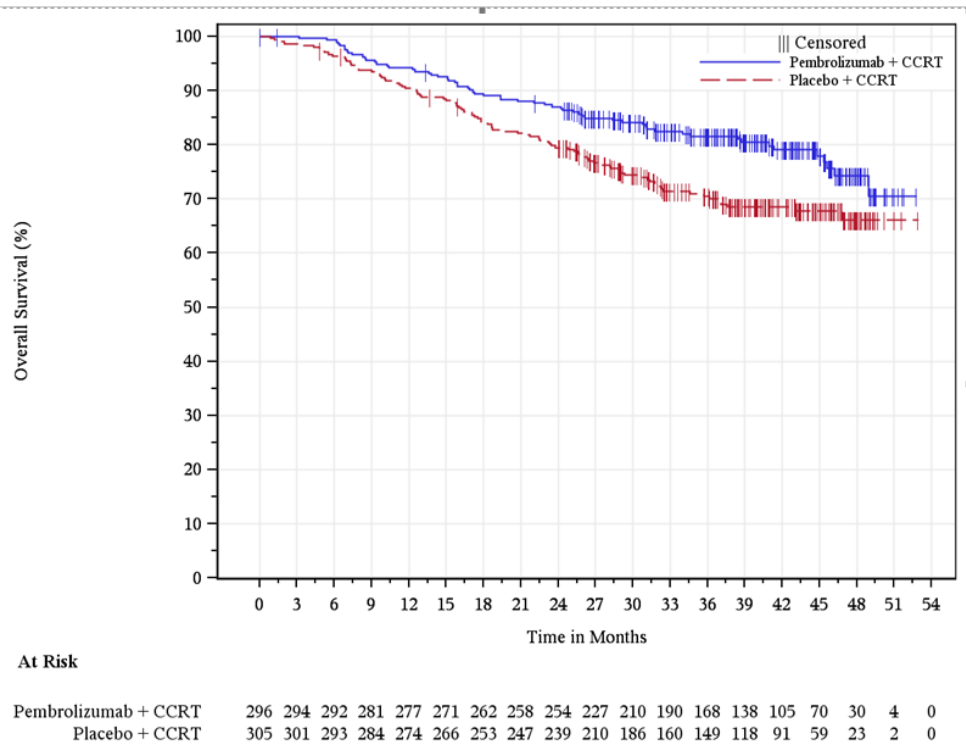
* EAG note: The baseline characteristics presented in CS Table 8 include minor differences from those presented in Table 1 of the addendum to the company's clarification response in terms of geographical region. The reasons for this are unclear.

Table 46: Summary of results of KEYNOTE-A18, FIGO 2014 Stage III-IVA subgroup, Final Analysis

End point		Pembrolizumab + CCRT	Placebo + CCRT	Effect estimate (95% CI, <i>p</i> -value)
Based on mITT population				
		(N=296)	(N=305)	
OS	OS events at Final Analysis N (%)			HR: 0.64 (0.46, 0.88; <i>p</i> =0.0031)
	Median OS, Months (95% CI)			
	OS rate at Month 24 (%) (95% CI)			
PFS	PFS events at Final Analysis, investigator-assessed N (%)			HR: 0.63 (0.48, 0.82; <i>p</i> =0.0002)
	Median PFS, investigator-assessed, Months (95% CI)			
	PFS rate at Month 24, investigator-assessed (%) (95% CI)			
	PFS events at Final Analysis, BICR N (%)		119 (39.0)	
	PFS rate at Month 24, BICR (%) (95% CI)			
ORR	N objective responses, BICR, ITT population			
	ORR, % (95% CI), BICR, ITT			
Based on participants with measurable disease at baseline				
		N=292	N=300	
ORR	Number of objective responses, investigator-assessed			
	ORR, % (95% CI), investigator-assessed			

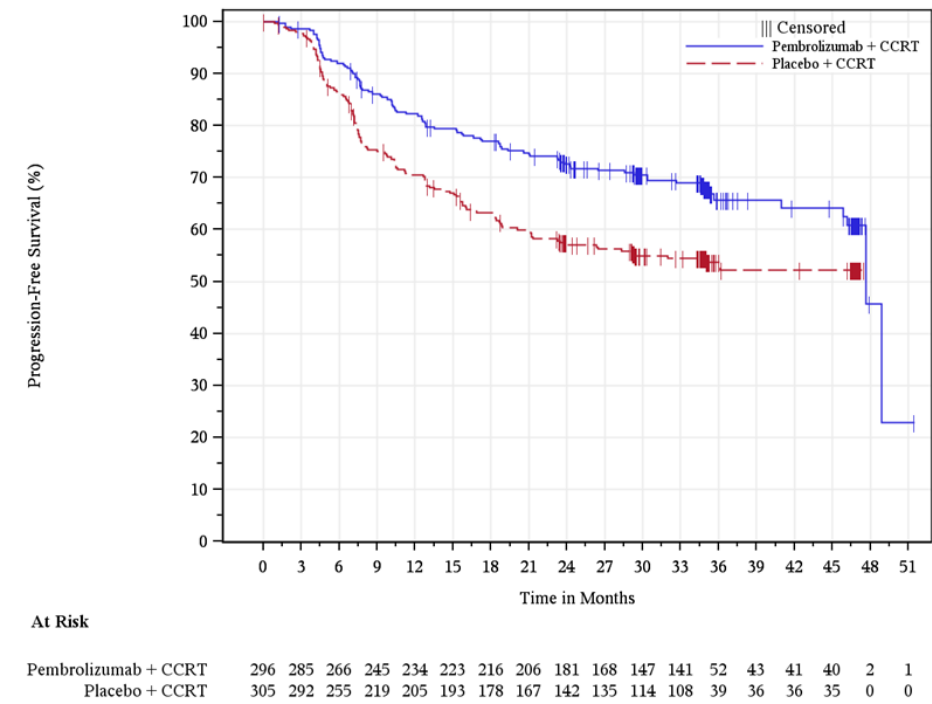
FIGO - International Federation of Gynecology and Obstetrics; IA2 - Interim Analysis 2; mITT - modified intention-to-treat; CI - confidence interval; OS - overall survival; PFS - progression-free survival; ORR - objective response rate; BICR - Blinded Independent Central Review; NR - not reported; N - number

Figure 34: Kaplan-Meier plot for overall survival, mITT population, Final Analysis (reproduced from company’s clarification response addendum, Figure 1)



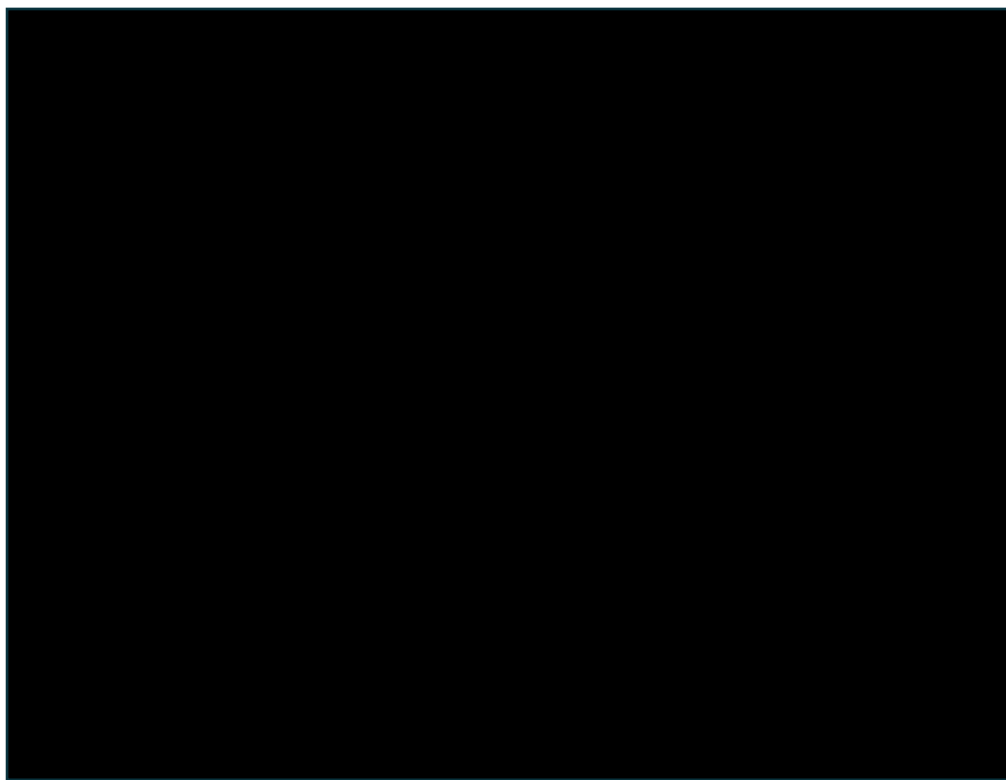
mITT - modified intention-to-treat; CCRT - concurrent chemoradiotherapy

Figure 35: Kaplan-Meier plot of progression-free survival (primary censoring rule) based on investigator assessment, mITT population, Final Analysis (reproduced from clarification response addendum, Figure 2)



mITT - modified intention-to-treat; CCRT - concurrent chemoradiotherapy

Figure 36: Kaplan-Meier plot of PFS after next-line treatment (PFS2), BICR assessment per RECIST 1.1, ITT population (reproduced from company's clarification response addendum, Figure 3)



BICR - blinded independent central review; RECIST - Response Evaluation Criteria in Solid Tumors; mITT - modified intention-to-treat; CCRT - concurrent chemoradiotherapy

Appendix 2: Updated time-to-event data and model parameters used in company's updated model

This appendix contains updated data from KEYNOTE-A18 and KEYNOTE-826 which are used in the company's updated (post-clarification) model.

The appendix contains the following data:

1. Hazard plots of PFS, TTP and OS based on KEYNOTE-A18 Final Analysis data-cut
 - Empirical and smoothed hazard plots of PFS, TTP and OS - Figure 37 to Figure 42
2. Updated survival analyses of PFS and TTP based on KEYNOTE-A18 Final Analysis data-cut (informing transitions out of the PF model health state)
 - AIC and BIC statistics for PFS and TTP - Table 47 and Table 48
 - Plots of smoothed empirical and RCS model hazards for PFS and TTP - Figure 43 to Figure 46
 - Kaplan-Meier plots and modelled survival estimates for PFS and TTP - Figure 47 to Figure 50
3. Updated survival analyses of PFS and TTP based on KEYNOTE-826 Final Analysis data-cut, CPS ≥ 1 with prior CRT subgroup (informing transitions out of the PD1 model health state)
 - AIC and BIC statistics for PFS and TTP - Table 49 and Table 50
 - Plots of smoothed empirical and RCS model hazards for PFS and TTP - Figure 51 to Figure 54
 - Kaplan-Meier plots and modelled survival estimates for PFS and TTP - Figure 55 to Figure 58
4. Updated survival analyses of PPS based on KEYNOTE-826 Final Analysis data-cut, CPS ≥ 1 with prior CRT subgroup (informing transitions out of the PD2 model health state)
 - AIC and BIC statistics for PPS - Table 51
 - Plots of smoothed empirical and model hazards PPS - Figure 59 and Figure 60
 - Kaplan-Meier plots and modelled survival estimates for PPS - Figure 61 and Figure 62
5. Model-predicted PFS and OS (with/without company's calibration)
 - Observed vs predicted PFS based on investigator-/BICR-assessed PFS - Figure 63 and Figure 64
 - Observed vs predicted OS based on investigator-/BICR-assessed PFS - Figure 65 and Figure 66
6. Utility values applied in the company's updated model
 - Utility and disutility values applied in the company's updated model - Table 52 and Table 53
7. Updated costs of active subsequent treatments
 - Updated tables of subsequent treatment duration and costs - Table 54 to Table 56
8. Updated AE management costs
 - Updated table of AE frequencies and management costs - Table 57

Hazard plots of PFS, TTP and OS based on KEYNOTE-A18 Final Analysis data-cut

Figure 37: Empirical and smoothed hazards, PFS, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



Figure 38: Empirical and smoothed hazards, PFS, KEYNOTE-A18, Final Analysis, CCRT alone

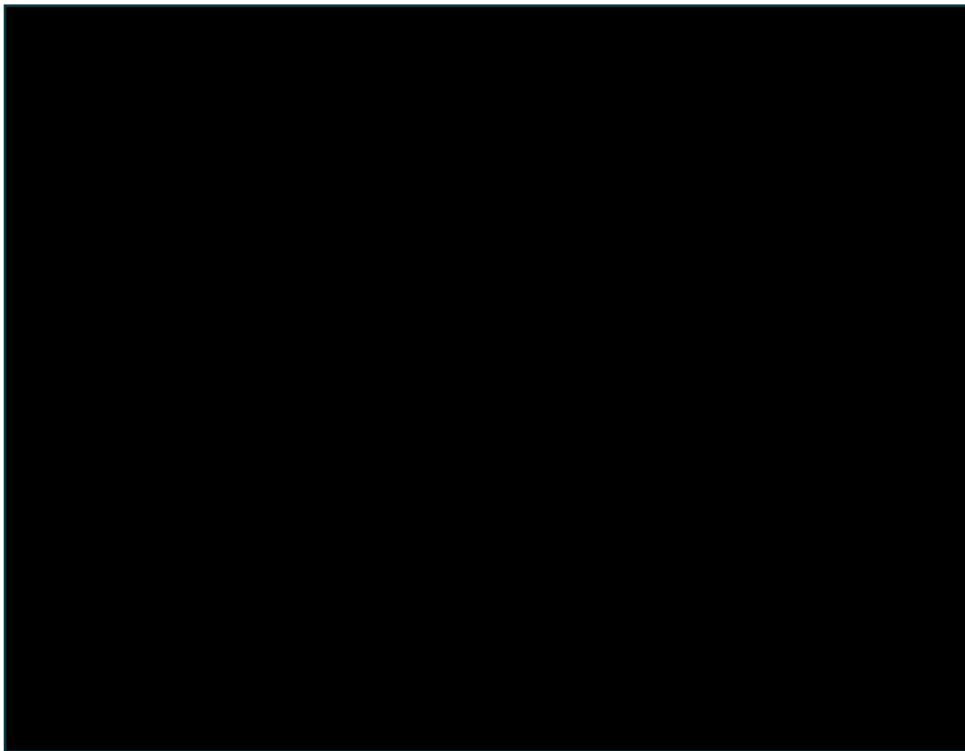


Figure 39: Empirical and smoothed hazards, TTP, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



Figure 40: Empirical and smoothed hazards, TTP, KEYNOTE-A18, Final Analysis, CCRT alone



Figure 41: Empirical and smoothed hazards, OS, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



Figure 42: Empirical and smoothed hazards, OS, KEYNOTE-A18, Final Analysis, CCRT alone



Updated survival analyses of PFS and TTP based on KEYNOTE-A18 Final Analysis data-cut (informing transitions out of the progression-free model health state)

Table 47: AIC and BIC statistics for spline models, PFS, KEYNOTE-A18, Final Analysis, both groups

AIC statistics											
Model	Pembrolizumab plus CCRT						CCRT alone				
	1-knot		2-knots		3-knots		1-knot		2-knots		3-knots
Hazard											
Odds											
Normal											
BIC statistics											
Model	Pembrolizumab plus CCRT						CCRT alone				
	1-knot		2-knots		3-knots		1-knot		2-knots		3-knots
Hazard											
Odds											
Normal											

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; PFS - progression-free survival; CCRT - concurrent chemoradiotherapy

Best-fitting model highlighted in bold. Note: The company's addendum reports AIC and BIC statistics as integer values, hence >1 model may be marked being the best fit

Table 48: AIC and BIC statistics for spline models, TTP, KEYNOTE-A18, Final Analysis, both groups

AIC statistics											
Model	Pembrolizumab plus CCRT						CCRT alone				
	1-knot		2-knots		3-knots		1-knot		2-knots		3-knots
Hazard											
Odds											
Normal											
BIC statistics											
Model	Pembrolizumab plus CCRT						CCRT alone				
	1-knot		2-knots		3-knots		1-knot		2-knots		3-knots
Hazard											
Odds											
Normal											

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; TTP - time to progression; CCRT - concurrent chemoradiotherapy

Best-fitting model highlighted in bold. Note: The company's addendum reports AIC and BIC statistics as integer values, hence >1 model may be marked being the best fit

Figure 43: Smoothed empirical and modelled hazard functions, PFS, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



Figure 44: Smoothed empirical and modelled hazard functions, PFS, KEYNOTE-A18, Final Analysis, CCRT alone



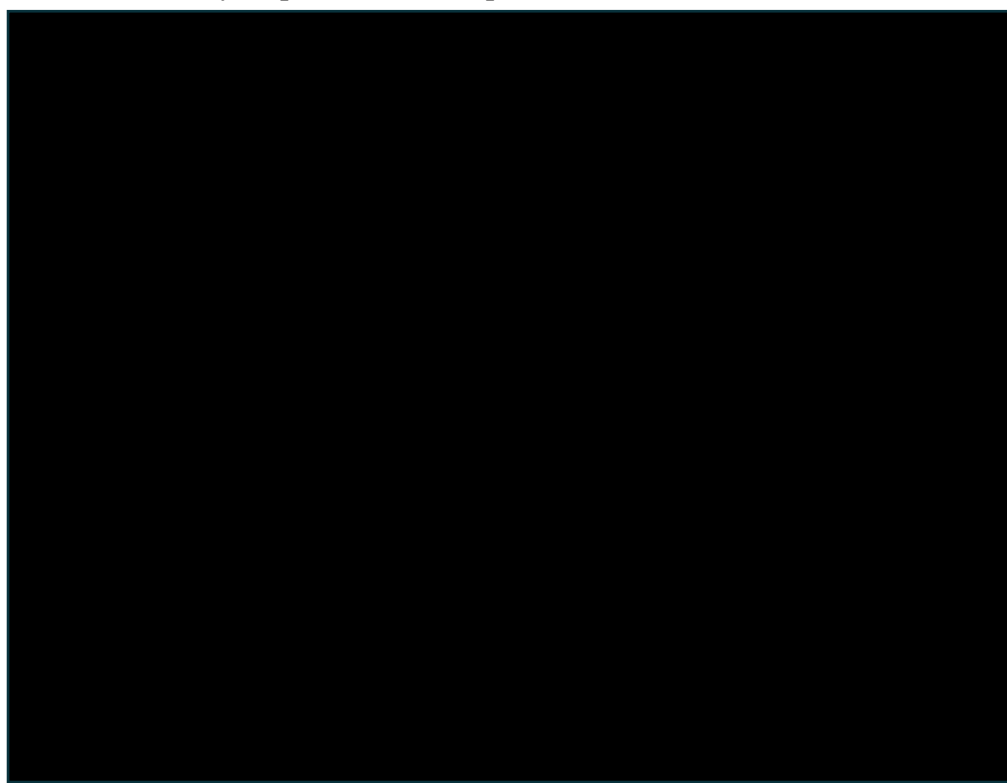
Figure 45: Smoothed empirical and modelled hazard functions, TTP, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



Figure 46: Smoothed empirical and modelled hazard functions, TTP, KEYNOTE-A18, Final Analysis, CCRT alone

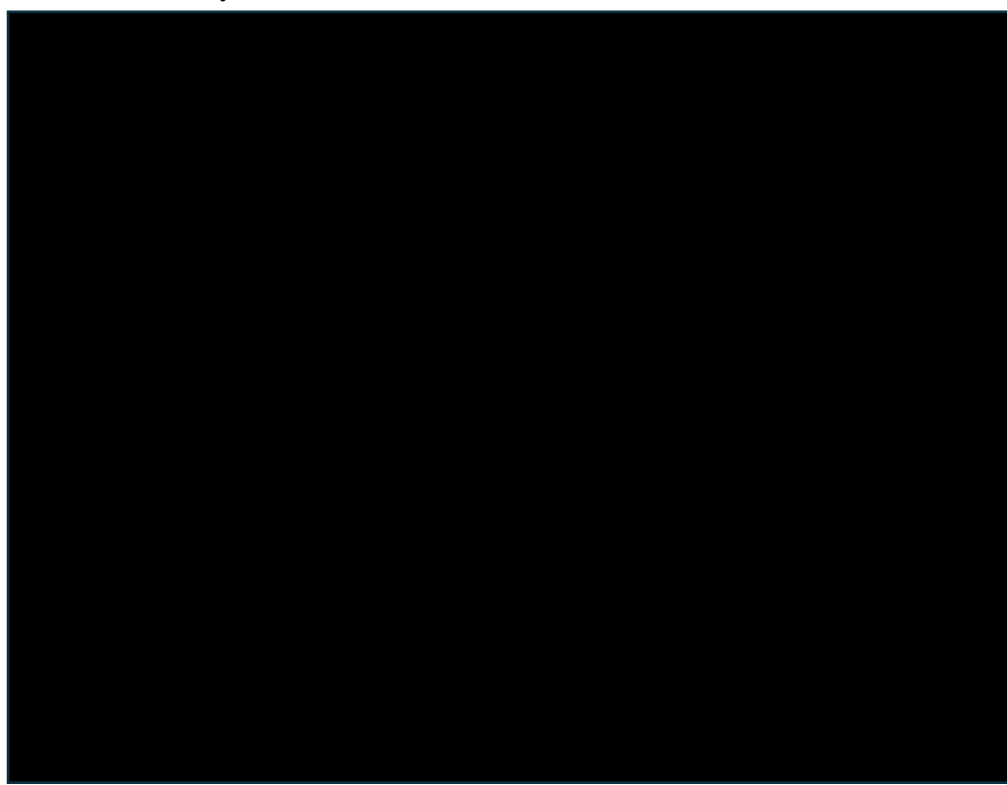


Figure 47: Kaplan-Meier plot and spline model predictions, PFS, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



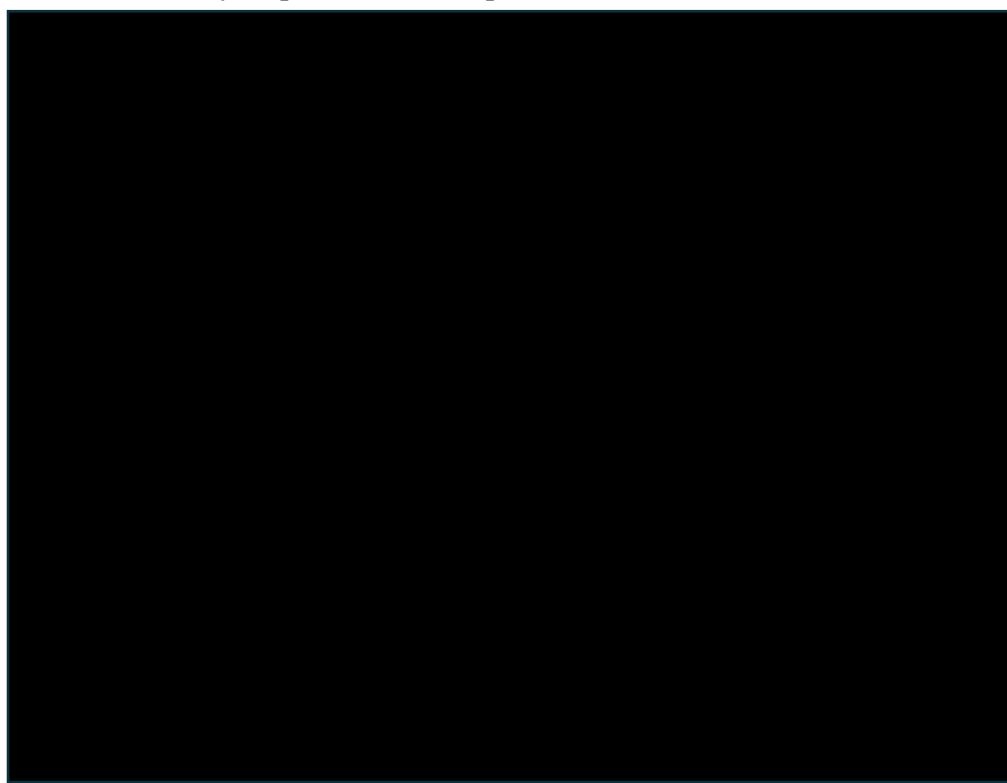
PFS - progression-free survival; k - knot; KM - Kaplan-Meier

Figure 48: Kaplan-Meier plot and spline model predictions, PFS, KEYNOTE-A18, Final Analysis, CCRT alone



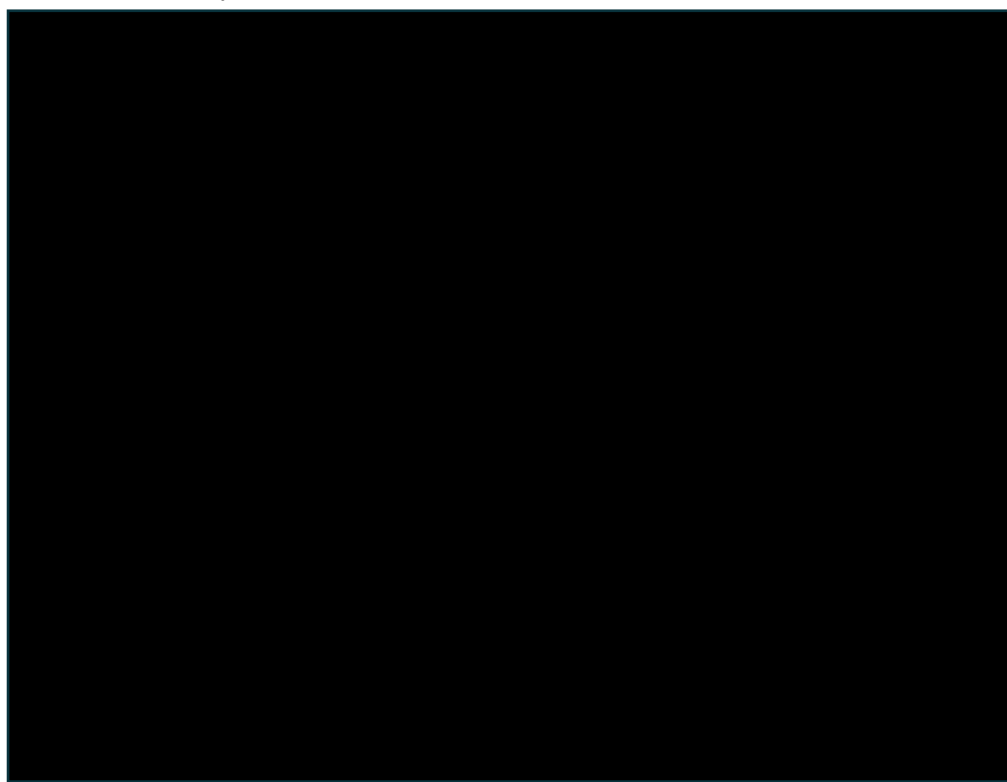
PFS - progression-free survival; k - knot; KM - Kaplan-Meier

Figure 49: Kaplan-Meier plot and spline model predictions, TTP, KEYNOTE-A18, Final Analysis, pembrolizumab plus CCRT



TTP - time to progression; k - knot; KM - Kaplan-Meier

Figure 50: Kaplan-Meier plot and spline model predictions, TTP, KEYNOTE-A18, Final Analysis, CCRT alone



TTP - time to progression; k - knot; KM - Kaplan-Meier

Updated survival analyses of PFS and TTP based on KEYNOTE-826 Final Analysis data-cut, CPS ≥ 1 with prior CRT subgroup (informing transitions out of the progressed disease 1 model health state)

Table 49: AIC and BIC statistics for spline models, PFS, KEYNOTE-826, prior CRT subgroup, Final Analysis, both groups

AIC statistics						
Model	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/-bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard						
Odds						
Normal						
BIC statistics						
Model	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/-bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard						
Odds						
Normal						

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CRT - chemoradiotherapy
Best-fitting model highlighted in bold. Note: The company's addendum reports AIC and BIC statistics as integer values, hence >1 model may be marked being the best fit

Table 50: AIC and BIC statistics for spline models, TTP, KEYNOTE-826, prior CRT subgroup, Final Analysis, both groups

AIC statistics						
Model	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/-bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard						
Odds						
Normal						
BIC statistics						
Model	Pembrolizumab + chemotherapy +/- bevacizumab			Chemotherapy +/-bevacizumab		
	1-knot	2-knots	3-knots	1-knot	2-knots	3-knots
Hazard						
Odds						
Normal						

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CRT - chemoradiotherapy
Best-fitting model highlighted in bold. Note: The company's addendum reports AIC and BIC statistics as integer values, hence >1 model may be marked being the best fit

Figure 51: Smoothed empirical and modelled hazard functions, PFS, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



Figure 52: Smoothed empirical and modelled hazard functions, PFS, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab



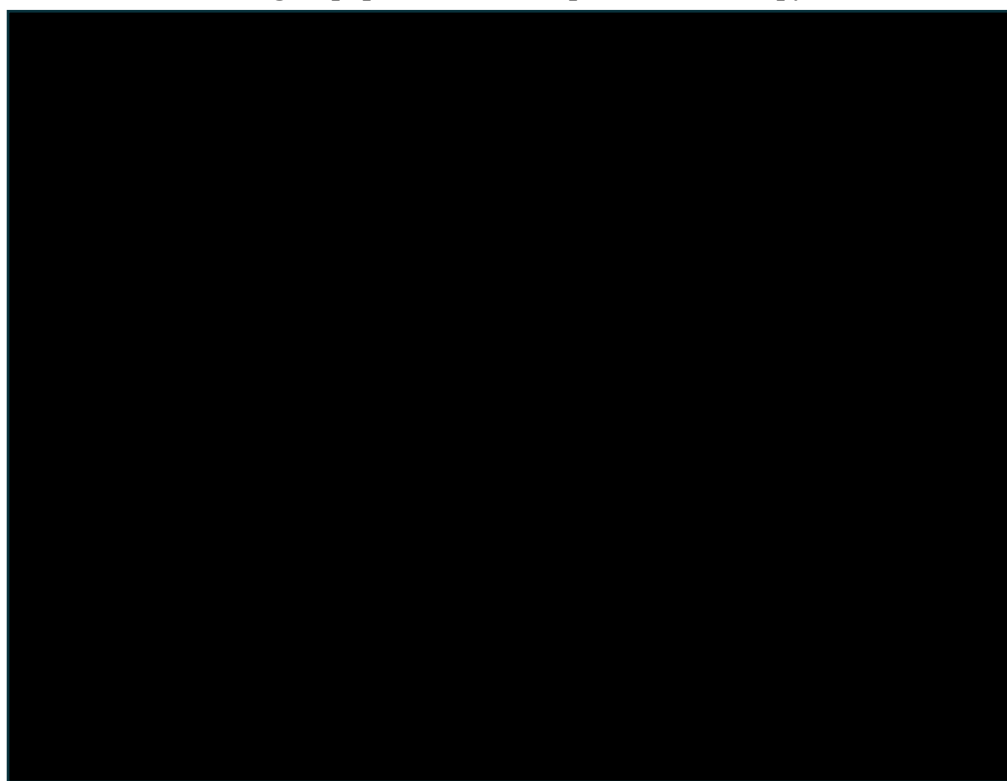
Figure 53: Smoothed empirical and modelled hazard functions, TTP, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



Figure 54: Smoothed empirical and modelled hazard functions, TTP, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab

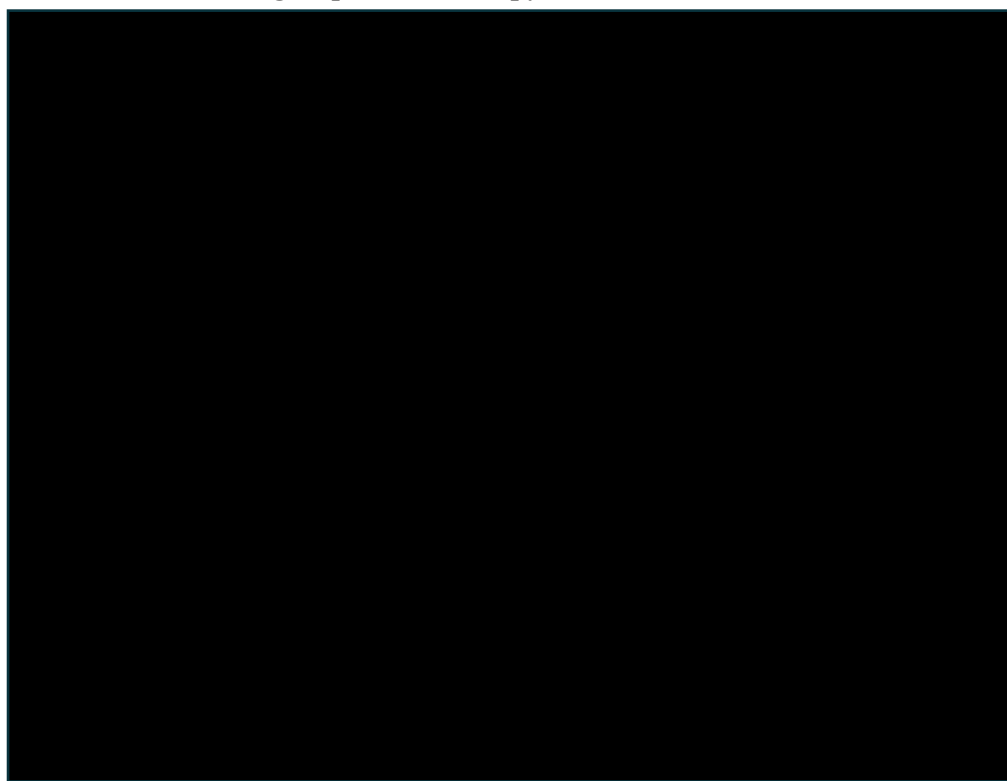


Figure 55: Kaplan-Meier plot and spline model, PFS, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



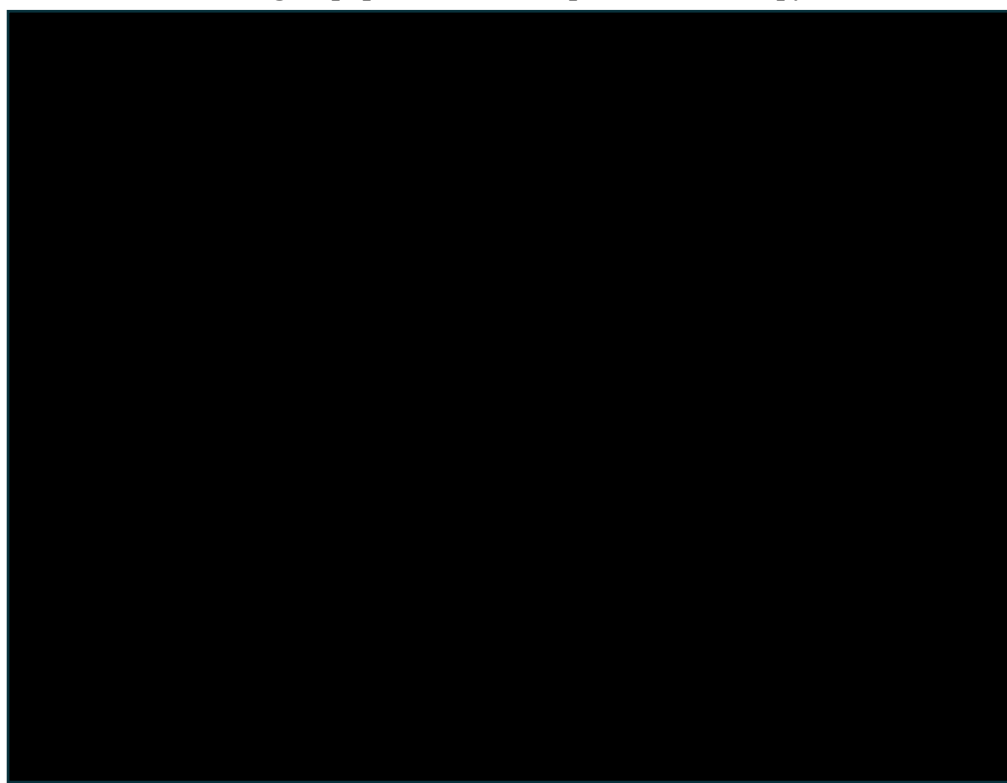
PFS - progression-free survival; k - knot; KM - Kaplan-Meier

Figure 56: Kaplan-Meier plot and spline model, PFS, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab



PFS - progression-free survival; k - knot; KM - Kaplan-Meier

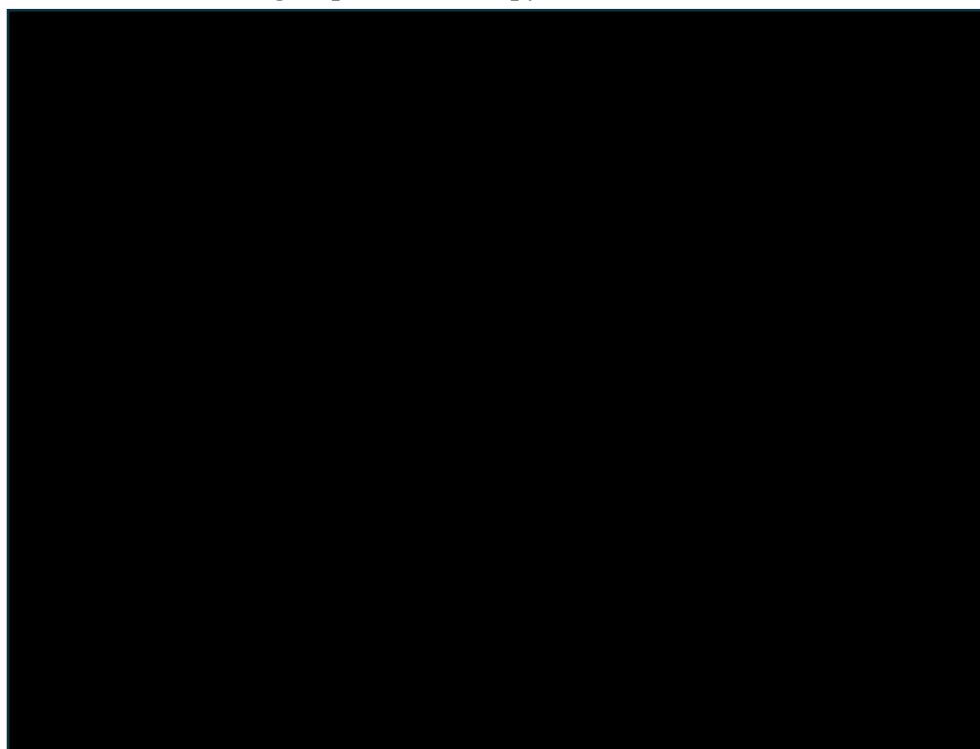
Figure 57: Kaplan-Meier plot and spline model, TTP, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



TTP - time to progression; k - knot; KM - Kaplan-Meier

The 1-knot normal RCS plot has been reproduced directly from the company's model but appears to be subject to an error.

Figure 58: Kaplan-Meier plot and spline model, TTP, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab



TTP - time to progression; k - knot; KM - Kaplan-Meier

Updated survival analyses of PPS based on KEYNOTE-826 Final Analysis data-cut, CPS ≥ 1 with prior CRT subgroup (informing transitions out of the progressed disease 2 model health state)

Table 51: AIC and BIC statistics for standard parametric models, PPS, KEYNOTE-826, prior CRT subgroup, Final Analysis, both groups

Model	Pembrolizumab + chemotherapy +/- bevacizumab		Chemotherapy +/- bevacizumab	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Gompertz				
Log-normal				
Log-logistic				
Generalized gamma				

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

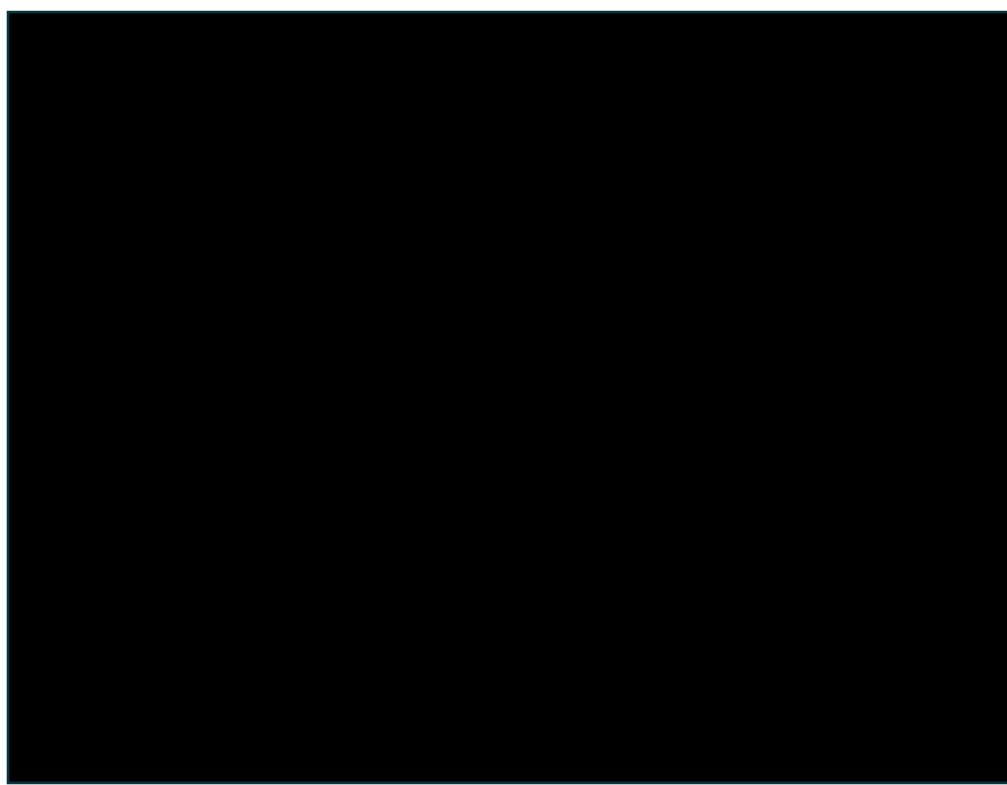
Figure 59: Smoothed empirical and modelled hazard functions, PPS, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



Figure 60: Smoothed empirical and modelled hazard functions, PPS, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab

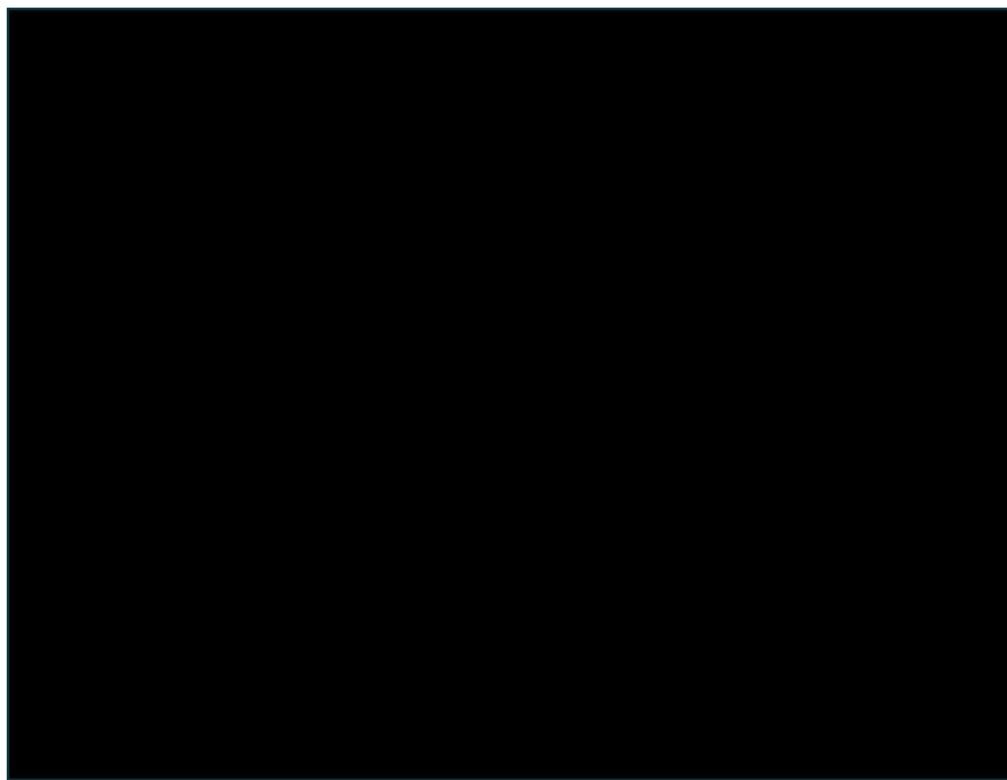


Figure 61: Kaplan-Meier plot and parametric survival model predictions, PPS, KEYNOTE-826, Final Analysis, prior CRT subgroup, pembrolizumab plus chemotherapy +/- bevacizumab



PPS - post-progression survival; KM - Kaplan-Meier

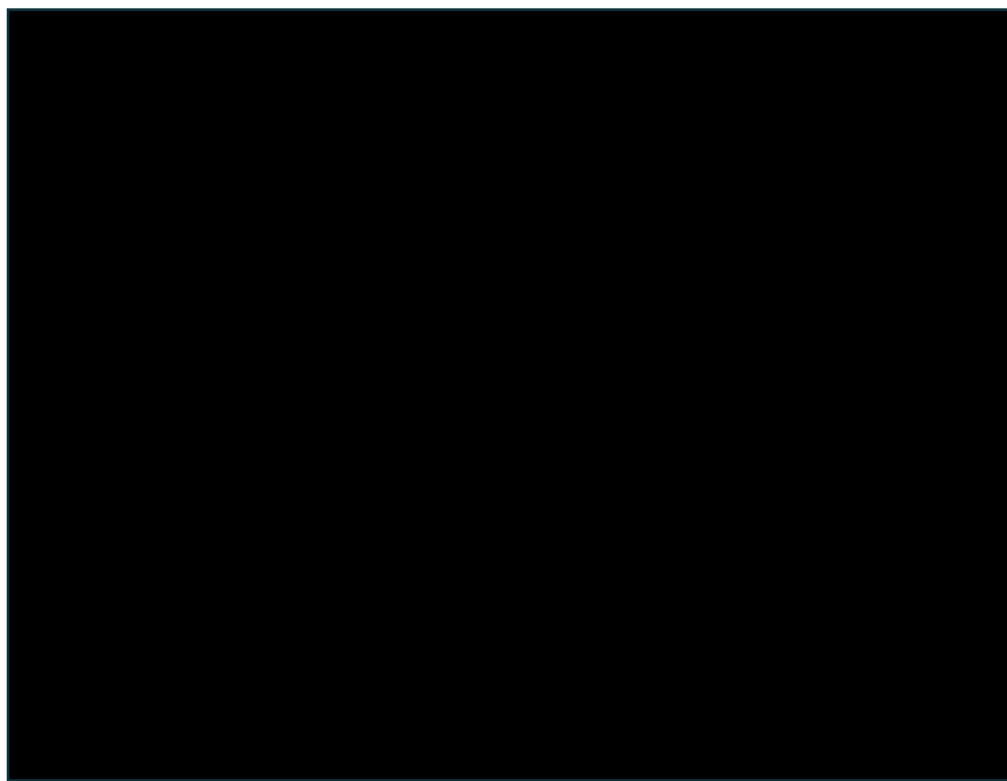
Figure 62: Kaplan-Meier plot and parametric survival model predictions, PPS, KEYNOTE-826, Final Analysis, prior CRT subgroup, chemotherapy +/- bevacizumab



PPS - post-progression survival; KM - Kaplan-Meie

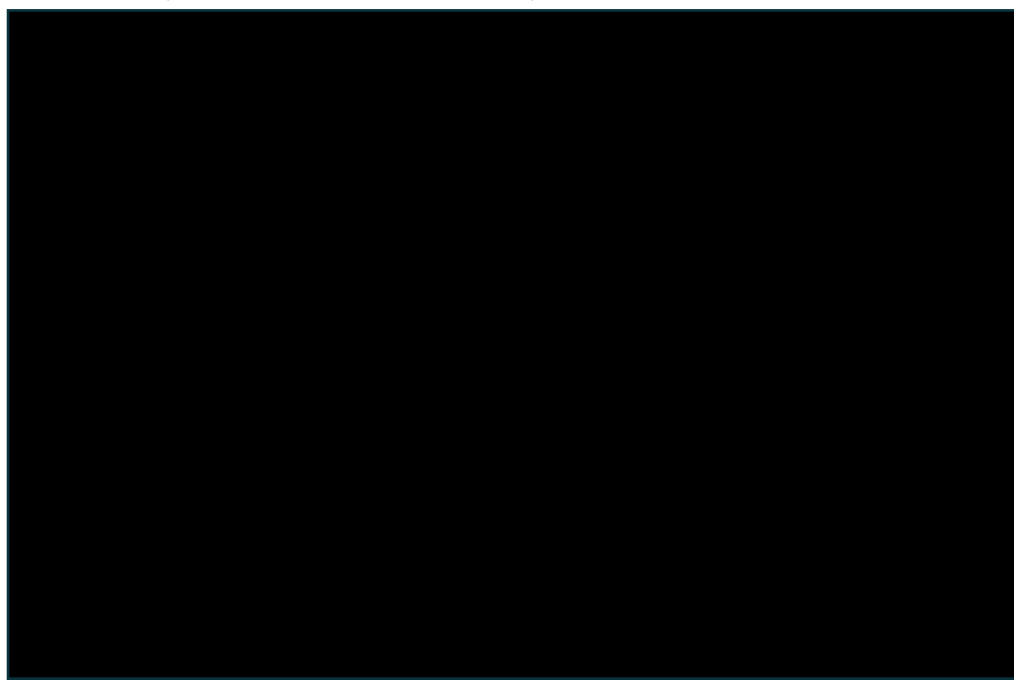
Model-predicted PFS and OS (with/without company's calibration)

Figure 63: Comparison of observed and model-predicted PFS, company's primary base case (based on investigator-assessed PFS)



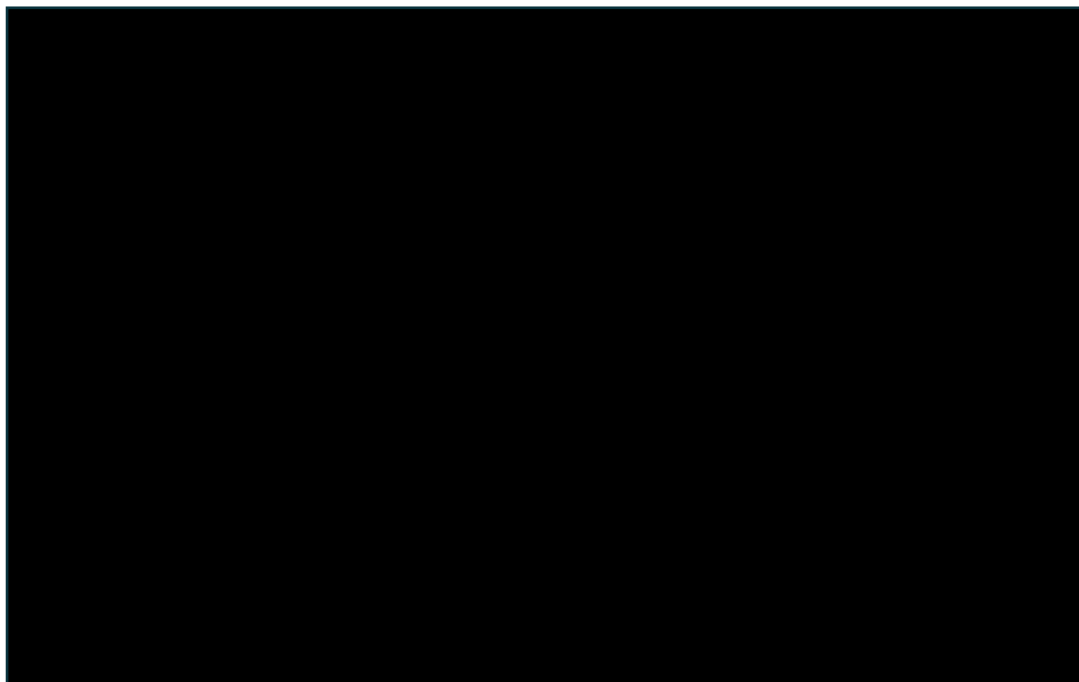
Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; FA - Final Analysis; PFS - progression-free survival; KM - Kaplan-Meier

Figure 64: Comparison of observed and model-predicted PFS, company's secondary base case (based on BICR-assessed PFS)



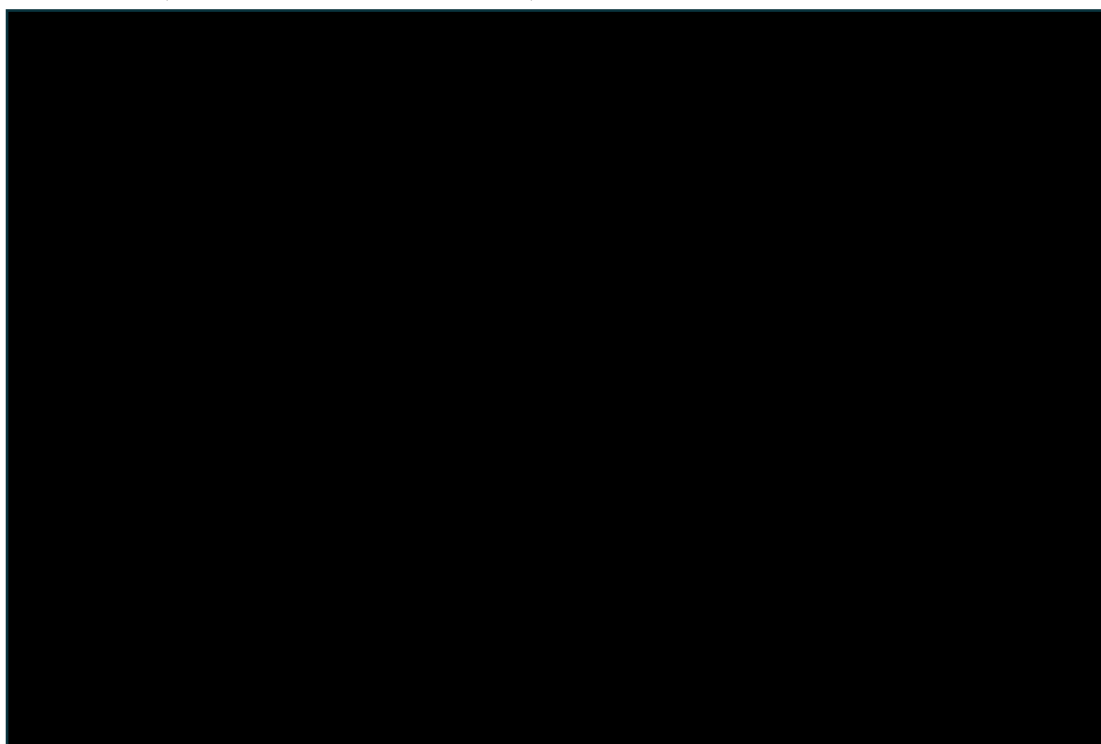
Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; FA - Final Analysis; PFS - progression-free survival; KM - Kaplan-Meier

Figure 65: Comparison of observed and model-predicted OS, company's primary base case (based on investigator-assessed PFS)



Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; FA - Final Analysis; OS - overall survival; KM - Kaplan-Meier

Figure 66: Comparison of observed and model-predicted OS, company's secondary base case (based on BICR-assessed PFS)



Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; FA - Final Analysis; OS - overall survival; KM - Kaplan-Meier

Utility values applied in the company's updated model

Table 52: Utility values applied in the company's updated model

State	Utility value	SE
PF		
PD1		
PD2		N/a
Disutility Grade ≥ 3 AEs		

PF - progression-free; PD1 - progressed disease 1; PD2 - progressed disease 2; AE - adverse event; SE - standard error; N/a - not applicable

Table 53: QALY losses associated with AEs included in the company's updated model

AE	Utility decrement	Duration (weeks)	Weekly probability of Grade ≥ 3 AEs, 0-12 months		Weekly probability of Grade ≥ 3 AEs, beyond 12 months		Source
			Pembro plus CCRT	CCRT alone	Pembro plus CCRT	CCRT alone	
Anaemia							KEYNOTE -A18 (DCO Jan 2025)
White blood cell count decreased							
Neutrophil count decreased							
Lymphocyte count decreased							
Leukopenia							
Neutropenia							
Lymphopenia							
Hypokalaemia							
Diarrhoea (Grade ≥ 2)							
Total QALY losses due to AEs			0.00051	0.00046	0.00003	0.00001	

QALY - quality-adjusted life-year; AE - adverse event; CCRT - concurrent chemoradiotherapy; DCO - data cut-off

Updated costs of active subsequent treatments

Table 54: Observed mean treatment cycles of each subsequent-line treatment in KEYNOTE-826 (CPS ≥ 1 with prior chemoradiotherapy subgroup)

Treatment	Observed mean treatment cycles from KEYNOTE-826 (CPS ≥ 1 with prior chemoradiotherapy subgroup)		Adjusted mean treatment cycles*	
	Pembrolizumab plus chemotherapy (with or without bevacizumab) group	Chemotherapy (with or without bevacizumab) group	Early progressors (pembrolizumab plus CCRT group)	Late progressors (pembrolizumab plus CCRT group) and all progressors (CCRT alone group)
Pembrolizumab		-	-	
Paclitaxel				
Carboplatin				
Bevacizumab				
Cisplatin				

CPS - combined positive score; CCRT - concurrent chemoradiotherapy

*based on the subsequent treatment distribution

Table 55: Updated drug acquisition costs of active subsequent-line treatments, excludes PAS discount for pembrolizumab

	Admin. Route	Dose per admin	Dosing schedule (weeks)	RDI	Cost per treatment cycle	Expected costs (pembrolizumab plus CCRT group)*		Expected costs (CCRT alone group)*	Source of unit cost
						Early progressors	Late progressors	All progressors	
<i>Second-line treatment (following first progression)</i>									
Pembrolizumab	IV	200mg	3	100%	£5,260	£1,260	£1,260	£1,260	BNF 2024 ³⁷
Paclitaxel	IV	175mg/m ²	3	100%	£20	£20	£20	£20	eMIT 2024 ³⁸
Carboplatin	IV	750mg	3	100%	£25	£25	£25	£25	eMIT 2024 ³⁸
Bevacizumab	IV	15mg/kg	3	100%	£2,319	£2,319	£2,319	£2,319	BNF 2024 ³⁷
Cisplatin	IV	40mg/m ²	1	100%	£32	£32	£32	£32	eMIT 2024 ³⁸
Total once -only costs for second-line treatments						£1,337	£1,337	£1,337	
<i>Third-line treatment (following second progression)</i>									
Paclitaxel	IV	80 mg/m ²	1	100%	£9				eMIT 2024 ³⁸

Admin. - administration; RDI - relative dose intensity; IV - intravenous; BNF - British National Formulary; eMIT - electronic Market Information Tool; CCRT - concurrent chemoradiotherapy

*Adjusted for the proportion of patients receiving each treatment component

Table 56: Updated drug administration costs of active subsequent-line treatments

	Cost per treatment cycle	Expected costs (pembrolizumab plus CCRT group)*		Expected costs (pembrolizumab plus CCRT group)* All progressors	Source
		Early progressors	Early progressors		
<i>Second-line treatment (following first progression)</i>					
Pembrolizumab	£202	*****	*****	*****	NHS Cost Collection 2023/24 ³⁹
Paclitaxel	£152	*****	*****	*****	
Carboplatin	£152	*****	*****	*****	
Bevacizumab	£152	*****	*****	*****	
Cisplatin	£152	*****	*****	*****	
Total once-only costs for second-line treatments		*****	*****	*****	
<i>Third-line treatment (following second progression)</i>					
Paclitaxel	£152				NHS Cost Collection 2023/24 ³⁹

BNF - British National Formulary; eMIT - Electronic Market Information Tool; CCRT - concurrent chemoradiotherapy

* Adjusted for the proportion of patients receiving each component

Updated AE management costs

Table 57: Updated AE frequencies and unit costs

AE	Frequency per model cycle (Year 1)		Frequency per model cycle (Year 2)		Unit cost	Total costs per model cycle (Year 1)		Total costs per model cycle (Year 2)	
	Pembrolizumab plus CCRT	CCRT alone	Pembrolizumab plus CCRT	CCRT alone		Pembrolizumab plus CCRT	CCRT alone	Pembrolizumab plus CCRT	CCRT alone
Anaemia					£620				
White blood cell count decreased					£561				
Neutrophil count decreased					£561				
Lymphocyte count decreased					£561				
Leukopenia					£696				
Neutropenia					£696				
Lymphopenia					£696				
Hypokalaemia					£584				
Diarrhoea					£567				
Total costs per weekly model cycle per patient						£19.18	£17.10	£0.89	£0.37

AE - adverse event; CCRT - concurrent chemoradiotherapy

Appendix 3: Additional details of estimation of health state utility values in the company's original model

In the linear mixed-effects regression modelling approach, random intercepts were applied to account for within-patient correlation due to repeated EQ-5D measurements. The company stated that this approach conceptually down-weights the contribution of long progression-free survivors with many observations, even though such patients are relevant over the entire time horizon of the economic model. For this reason, it was not preferred for the company's base case, but estimates from the regression modelling approach were included in scenario analyses.

Two sets of regression models were explored: one with progression status (PF vs PD) as the primary predictor, while the other using time-to-death (<30, 30–90, 90–180, 180–360, ≥ 360 days before death; the same intervals as in TA939¹⁰) as the primary predictor. Table 58 presents the two sets of regression models, with covariates added stepwise in addition to the primary predictors. Statistical significance was evaluated for each covariate, and model fit was assessed using AIC and BIC. In the progression-based models (Model 1a–1d), covariates were added sequentially: AEs; age + AEs; treatment arm + AEs; and treatment arm + age + AEs. In the time-to-death models (2a–2f), covariates were similarly added stepwise. Models 2c–2d included treatment as a covariate, and models 2e–2f extended these by adding a treatment $\times$ time-to-death interaction.

Table 58: Linear mixed effects regression models for estimating utilities from KEYNOTE-A18 (reproduced from CS Appendix L, Table 56)

Primary predictor	Model	Specification*	AIC	BIC
Progression status	1a	$Utility_{ij} = \beta_0 + \beta_1 Progression Status_{ij} + \beta_2 AE_{ij} + e_i$	████	████
	1b	$Utility_{ij} = \beta_0 + \beta_1 Progression Status_{ij} + \beta_2 Age_i + \beta_3 AE_{ij} + e_i$	████	████
	1c	$Utility_{ij} = \beta_0 + \beta_1 Progression Status_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + e_i$	████	████
	1d	$Utility_{ij} = \beta_0 + \beta_1 Progression Status_{ij} + \beta_2 Treatment_i + \beta_3 Age_i + \beta_4 AE_{ij} + e_i$	████	████
Time-to-death	2a	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 AE_{ij} + e_i$	████	████
	2b	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 Age_i + \beta_3 AE_{ij} + e_i$	████	████
	2c	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + e_i$	████	████
	2d	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 Treatment_i + \beta_3 Age_i + \beta_4 AE_{ij} + e_i$	████	████
	2e	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Time to death_{ij} * Treatment_i + e_i$	████	████
	2f	$Utility_{ij} = \beta_0 + \beta_1 Time to death_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Age_i + \beta_5 Time to death_{ij} * Treatment_i + e_i$	████	████

*i denotes individual and j denotes time when the EQ-5D-5L measures was taken

The company reported that in the progression-based models, progression status, ongoing grade 3+ AEs, and treatment arm were statistically significant predictors, but not age. The inclusion of treatment arm reduced model fit (Model 1c-1d), with higher AIC and BIC compared with the simpler model including only progression status and AEs (Model 1a), which the company therefore considered the best-fitting progression-based model.

In the time to death models, the company reported that only time to death intervals and ongoing grade 3+ AEs were significant, with treatment arm and age not being significant. The EAG noted, however, that treatment arm became significant once treatment × time-to-death interaction terms were included, as were all interaction terms (Models 2e–2f). The company considered the best-fitting time-to-death model to be the specification including time-to-death and ongoing AEs (Model 2a) given AIC/BIC values.

Based on these findings, the company selected the models that retained only the primary predictor (progression status or time to death) and ongoing grade 3+ AEs for use in scenario analyses (Model 1a

and Model 2a, respectively; Table 58). The EAG considered this reasonable but noted that the company appeared to apply the same AE coefficient from the progression-based model (Model 1a) in the time-to-death scenario analysis rather than the AE coefficient from Model 2a; however, the difference was minimal (~0.01). Further, the company's reported utility value for the time-to-death scenario analysis (Table 59) differed slightly from the value of its preferred model presented in CS Appendix L, Model 2a; however, the EAG considered this unlikely to have a substantial impact on the ICER.

Table 59: Summary of utility values for scenario analyses (reproduced from CS, Table 38)

Scenarios	State	Utility value: mean
Utilities based on KEYNOTE-A18, progression-based regression analysis	Progression-free	██████
	Progression	██████ (i.e., progression disutility: █████)
	360+ Days	██████
	270 - 359 Days	██████
Utilities based on KEYNOTE-A18, time to death regression analysis	180 - 269 Days	██████
	90 - 179 Days	██████
	30 - 89 Days	██████
	0 - 29 Days	██████
Assuming PD1 and PD2 utilities are equal, taken from the naïve means of PD utilities in KEYNOTE-A18	PD2	██████

SE - standard error; AE - adverse event

* In the company's regression model, days 180–356 were treated as one interval. Hence, the company applied 0.742 to days 270–359 and set 180–269 days to the same value.

Appendix 4: Instructions for implementing the EAG’s exploratory analyses

Instructions for implementing the EAG’s exploratory analyses using the EAG’s preferred model are provided in Table 60.

Table 60: Instructions for implementing the EAG’s exploratory analyses

Scenario		Instructions
EAG exploratory analysis (EA)	1	- Set I9 (<i>misc_HCC_text</i>) to “Yes” in the “Controls” worksheet - Set E6 (<i>fixcf?</i>) to “TRUE” in the “EAG EA” worksheet - Set E7 (<i>correct_genpoputility?</i>) to “TRUE” in the “EAG EA” worksheet - Set E8 (<i>correct_eol?</i>) to “TRUE” in the “EAG EA” worksheet - Set I73 (<i>drop_EOL_cure</i>) to “No” in the “Controls” worksheet - Set E10 (<i>fixcisplatinadmin?</i>) to “TRUE” in the “EAG EA” worksheet
EAG additional sensitivity analysis (ASA)	1a	- Set I100 (<i>drop_spline_KNA18_PFS</i>) to “k=1, scale = normal” in the “Controls” worksheet - Set J100 (<i>drop_spline_KNA18_PFS_comp</i>) to “k=1, scale = normal” in the “Controls” worksheet
	1b	- Set I100 (<i>drop_spline_KNA18_PFS</i>) to “k=2, scale = hazard” in the “Controls” worksheet - Set J100 (<i>drop_spline_KNA18_PFS_comp</i>) to “k=2, scale = hazard” in the “Controls” worksheet
	1c	- Set I100 (<i>drop_spline_KNA18_PFS</i>) to “k=2, scale = odds” in the “Controls” worksheet - Set J100 (<i>drop_spline_KNA18_PFS_comp</i>) to “k=2, scale = odds” in the “Controls” worksheet
	1d	- Set I100 (<i>drop_spline_KNA18_PFS</i>) to “k=2, scale = normal” in the “Controls” worksheet - Set J100 (<i>drop_spline_KNA18_PFS_comp</i>) to “k=2, scale = normal” in the “Controls” worksheet
	2	- Set I128 (<i>drop_KN826_pop</i>) to “CPS $\geq$ 1” in the “Controls” worksheet - Set I152 (<i>drop_spline_KN826_TTP</i>) to “k=3, scale = hazard” in the “Controls” worksheet - Set J152 (<i>drop_spline_KN826_TTP_comp</i>) to “k=3, scale = hazard” in the “Controls” worksheet - Set I195 (<i>drop_PSM_KN826_PPS_dist</i>) to “Generalised gamma” in the “Controls” worksheet - Set J195 (<i>drop_PSM_KN826_PPS_dist_comp</i>) to “Generalised gamma” in the “Controls” worksheet - Set K157 to “0.49” in the “Controls” worksheet - Set L157 to “0.73” in the “Controls” worksheet
	3	- Set E17 (<i>remove_cf?</i>) to “TRUE” in the “EAG EA” worksheet
	4	- Set E18 (<i>cfcap?</i>) to “TRUE” in the “EAG EA” worksheet
	5	- Set E19 (<i>diffpembro_perc?</i>) to “TRUE” in the “EAG EA” worksheet
	6	- Set E20 (<i>nopembrorechallenge?</i>) to “TRUE” in the “EAG EA” worksheet
	7	- Set E21 (<i>nopdl1test?</i>) to “TRUE” in the “EAG EA” worksheet
	8	- Set E22 (<i>nowarmup?</i>) to “TRUE” in the “EAG EA” worksheet
	9	- Set E23 (<i>nopemeffect?</i>) to “TRUE” in the “EAG EA” worksheet
	10	- Set E24 (<i>pd2utility?</i>) to “TRUE” in the “EAG EA” worksheet

Table 1 PFS probabilities at different time points

	2 year		5 year		10 year	
	Pembro+ CCRT	CCRT alone	Pembro+ CCRT	CCRT alone	Pembro+ CCRT	CCRT alone
EA1a: EAG-preferred analysis, deterministic	■	■	■	■	■	■
ASA1a: PFS, TTP = 1-knot normal RCS model	■	■	■	■	■	■
ASA1b: PFS, TTP = 2-knot hazard RCS model	■	■	■	■	■	■
ASA1c: PFS, TTP = 2-knot odds	■	■	■	■	■	■
ASA1d: PFS, TTP = 2-knot normal	■	■	■	■	■	■
ASA2: KEYNOTE-826 CPS $\geq$ 1 subgroup, PFS, TTP = 3-knot hazard RCS model, PPS = generalised gamma model, calibration factors 0.49 and 0.73	■	■	■	■	■	■

ASA - additional sensitivity analysis; EAG - External Assessment Group; PFS - progression-free survival; TTP - time to progression; RCS - restricted cubic spline; CCRT - concurrent chemoradiotherapy; CPS - combined positive score

Table 2 OS probabilities at different time points

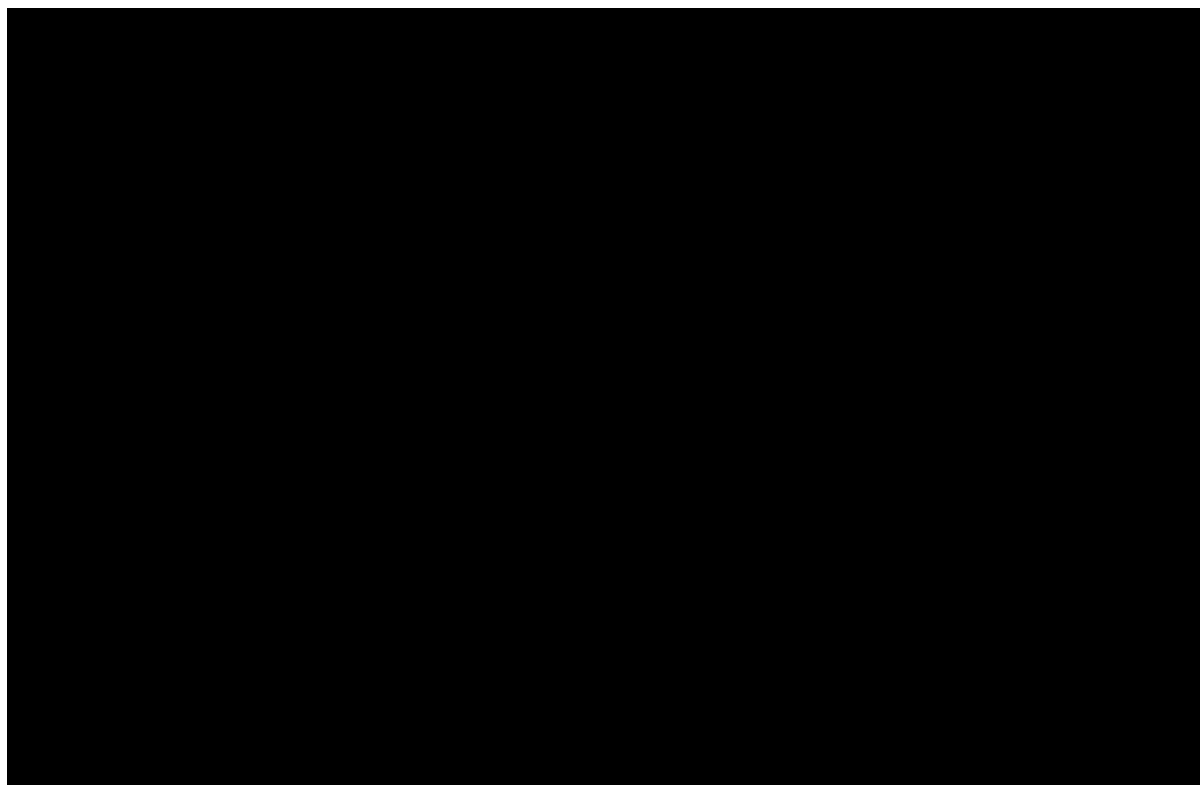
	2 year		5 year		10 year	
	Pembro+ CCRT	CCRT alone	Pembro+ CCRT	CCRT alone	Pembro+ CCRT	CCRT alone
EA1a: EAG-preferred analysis, deterministic	■	■	■	■	■	■
ASA1a: PFS, TTP = 1-knot normal RCS model	■	■	■	■	■	■
ASA1b: PFS, TTP = 2-knot hazard RCS model	■	■	■	■	■	■
ASA1c: PFS, TTP = 2-knot odds	■	■	■	■	■	■
ASA1d: PFS, TTP = 2-knot normal	■	■	■	■	■	■
ASA2: KEYNOTE-826 CPS $\geq$ 1 subgroup, PFS, TTP = 3-knot hazard RCS model, PPS = generalised gamma model, calibration factors 0.49 and 0.73	■	■	■	■	■	■
ASA3: Exclusion of calibration factors for OS	■	■	■	■	■	■
ASA4: Application of calibration factors for four years	■	■	■	■	■	■

ASA - additional sensitivity analysis; EAG - External Assessment Group; PFS - progression-free survival; OS: overall survival; TTP - time to progression; RCS - restricted cubic spline; CCRT - concurrent chemoradiotherapy; CPS - combined positive score

1. Impact of calibration factors (2 years vs 4 years vs no calibration)

Figure 1 shows the model-predicted OS with calibration factors applied for 2 years, 4 years and without calibration factors based on the EAG's preferred analysis (including error corrections). As shown in the plot, there is little difference in visual fit when applying the calibration for 2 years or 4 years, with the latter being slightly more optimistic. Neither of the calibration scenarios provide a particularly good representation of observed OS.

Figure 1 Comparison of observed and model-predicted OS



OS: overall survival; KM: Kaplan-Meier; CF: calibration factor

2. Share of opportunity cost applied in DCEA

On slide 33, there is a bullet point which reads “Share of opportunity costs in the moderate and steep scenarios not reported.” Table 1 shows the share of opportunity costs applied under the moderate and steep gradients using the DCEA simple R Shiny app. These are probably the same gradients applied in the company's original DCEA that we critiqued, but we couldn't replicate their original results for any scenario.

Table 1 Share of opportunity costs in DCEA (EAG's analysis)

	IMD1	IMD2	IMD3	IMD4	IMD5
Moderate gradient	23%	21%	21%	18%	17%
Steep gradient	26%	22%	22%	16%	14%

IMD: Index of Multiple Deprivation

3. Net Health Inequality Benefit

To clarify the concept, Net Health Inequality Benefit (NHIB) is the modelled difference in net QALY benefit between IMD1 and IMD5 at the population level by incorporating information on net QALY benefits of IMD2 to IMD4 using a simple linear regression model. If the health opportunity cost gradient is flat, the change in drug price does not affect NHIB. However, under moderate and steep gradients, drug price changes lead to larger QALY gaps.

Single Technology Appraisal

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 24 October 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Issue 1 Inclusion and referencing of pembrolizumab CAA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MSD request that all direct mentions of either the pembrolizumab CAA % or unit cost are removed from the EAG report, and that CS appendix J is referenced in its place	Pg 27, Table 25 (pg. 87), pg. 88, Table 26 (pg. 89) all include either the CAA % or unit cost, please can these be completely removed from the document or substituted for the list price if needed	MSD request that the details of the CAA are removed from the report to reduce the risk of unintentional data leaks and breach of confidentiality.	As requested, the EAG has removed details of the PAS discount and price from the EAG report. However, the EAG notes that this results in less transparency for the Appraisal Committee.

Issue 2 Reporting of subsequent treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Subsequent treatment costs, itemised by treatment, are presented alongside duration of treatment, as with Issue 1 this risks simple back calculation of the pembrolizumab PAS	Remove itemisation of subsequent treatment cost, reporting only total costs Redact the total subsequent treatment cost where it includes pembrolizumab PAS These relate to Table 29, Table 30	To reduce the risk of unintentional data leaks and breach of confidentiality While these are not direct references to the CAA price, public time on treatment data from KEYNOTE-826 could allow for relatively accurate	The EAG believes that removing itemised costs altogether will result in less transparency for the Appraisal Committee. Instead, the EAG has amended the reported figures to use the list price for pembrolizumab rather than the PAS

		estimates of the pembrolizumab CAA	price, where possible. The EAG has also updated the marking for the costs of second- and third-line therapies in Tables 25 and 29. Additional confidentiality marking for all subsequent-line therapies has been applied to Table 25, 29, 30, 55 and 56. The EAG has also corrected minor typographical errors in the third-line costs reported in Tables 25 and 29.

Issue 3 Description of MSD's assumption around immunotherapy rechallenge

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 120 "The company's economic model assumes that re-challenging with pembrolizumab is permitted	"The company's economic model assumes that re-challenging with pembrolizumab is permitted, <i>only 6 months after the successful</i>	Current wording does not fully capture MSD's position on the	The quoted text is on page 25. The EAG has amended the report to read: " <i>The company's</i>

(giving pembrolizumab to patients who have progressed after completing first-line treatment with pembrolizumab). The company's assumptions regarding treatment pathways and pembrolizumab re-challenge in the company's economic model are detailed in Section 4.2" MSD request that it is made clear that rechallenge is only assumed 6 months post successful completion of treatment (2 years + 6 months) as per NHS commissioning	completion of treatment (giving pembrolizumab to patients who have progressed after completing first-line treatment with pembrolizumab). The company's assumptions regarding treatment pathways and pembrolizumab re-challenge in the company's economic model are detailed in Section 4.2"	immunotherapy rechallenge assumption	<i>economic model assumes that re-challenging with pembrolizumab is permitted for patients who experience disease progression at least six months after completing first-line treatment with pembrolizumab."</i>

Issue 4 Description of details available from MSD's advisory board

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 69-70 "The CS does not mention whether the clinical	MSD request the comment is removed	Incorrect statement	The EAG agrees. The quoted text has been

experts who attended the 2024 advisory board meeting considered the modelled PFS predictions for the CCRT group to be plausible” In the CS, pgs 77-79 it is stated that clinicians were presented a range of scenarios, in which the generalised gamma, with cure between 5-7 years “provided the most plausible long term PFS estimates”			removed on page 69 and 109 and has replaced it with the following: <i>“The CS also states that the generalised gamma distribution was selected for PFS in the CCRT group because: (a) this distribution also provided a good visual fit to the KEYNOTE-A18 data and (b) it had the lowest AIC and BIC values in the CCRT group and (c) clinical experts who attended the 2024 advisory board meeting confirmed that the generalised gamma model including a 5-7 year cure point provided the most plausible estimates for CCRT alone.”</i>

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 25	Row “Acquisition costs (subsequent treatments) - once-only costs” is not marked as CIC	Mark as CiC	This has been marked for treatments including pembrolizumab, as described in the response above.
Table 29	All “Total once-only cost for second-line treatments” rows are currently not marked CIC	Mark as CiC	This has been marked for treatments including pembrolizumab, as

			described in the response above
Table 30	All “Total costs (once-only costs) for second-line treatments” rows are currently not marked CIC	Mark as CiC	This has been marked for treatments including pembrolizumab, as described in the response above

			contained in this section.