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Evidence Review Group's Report
Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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Contributions of authors

Mark Rodgers, Mark Corbett and Sumayya Anwer performed the critique of clinical evidence and co-authored sections 1, 2 and 3 of the report. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections. Helen Fulbright wrote the sections on the search strategies. Matthew Walton, Martin Njoroge, Sumayya Anwer and Robert Hodgson critiqued the company's model, and co-authored Sections 1, 4, 5 and 6 of report. Robert Hodgson took overall responsibility for the cost effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike's information criterion
APaT	All patients as treated
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BGCS	British Gynaecological Cancer Society
BNF	British National Formulary
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPS	Combined positive score
CR	Complete response
CS	Company submission
CSR	Clinical study report
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EoL	End-of-life
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
ERG	Evidence Review Group
FAD	Final appraisal determination
FDA	U.S. Food and Drug Administration
HRG	Healthcare resource group
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan-Meier
LS(M)	Least square (means)
MHRA	Medicines & Healthcare Products Regulatory Agency
NA	Not Applicable
N/A	Not Applicable

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	No response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PfC	Point for clarification
PFS	Progression-free survival
PICOS	Population, Intervention, Comparison, Outcomes, and Study design
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SD	Standard deviation
SD	Stable Disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
STA	Single technology appraisal
STM	State transition model
ToT	Time on treatment
TTD	Time to death
TTP	Time to progression
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1.	Applicability of the KEYNOTE-826 trial to the NHS population	2.2.1 and 3.2.2.1
2.	Immature overall survival data	3.2.3.1
3.	Uncertain relationship between progression-free survival and overall survival	3.2.1.3 and 4.2.2.1
4.	Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis	3.2.3.1
5.	Application of two-year stopping rule	2.3 and 4.2.6.1
6.	Appropriateness of state transition model	4.2.2.1
7.	Extrapolation of PFS	4.2.6.1
8.	Extrapolation of PPS	4.2.6.2
9.	Treatment waning effect for pembrolizumab	4.2.6.1
10.	Health state utilities	4.2.7.1
11.	Resource use	4.2.8
12.	Relevance of bevacizumab and availability of bevacizumab biosimilar	4.2.4
13.	End-of-life criteria	7

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The company's preferred extrapolation of PFS is based on a two-piece approach, the ERG prefers to use a single piece
- The company prefers to assume a differential PPS across treatment arms, the ERG prefers to assume a common (pooled) duration of PPS across treatment arms
- A lifetime treatment benefit is assumed by the company, whereas the ERG prefers the assumption of a 3-year treatment benefit to align with previous appraisals
- Time-to-death utilities are preferred by the company, yet the ERG considers there to be more conceptual validity to using progression-based utilities

- Time on treatment with pembrolizumab is capped at 24 months in the company's economic model, though the ERG prefers to use a 35-cycle cap in line with the KEYNOTE-826 trial
- The company model does not account for GP/nurse visits, blood-counts, and thyroid function tests costs, whereas the ERG prefers to include these costs
- The company model costs disutilities associated with Grade >3 events occurring in >5% of patients, the ERG model also includes Grade 1 and 2 AE's of special interest occurring in >5% of patients

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival
- Increasing overall survival

Overall, the technology is modelled to affect costs by:

- Its higher acquisition costs
- Its higher administration costs

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit for pembrolizumab (extrapolation of progression free survival)
- The size of the post-progression survival benefit for pembrolizumab (extrapolation of post-progression survival)
- Treatment waning
- Utility values applied in the model (time to death vs progression based)

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Applicability of the KEYNOTE-826 trial to the NHS population

Report section	2.2.1 and 3.2.2.1
Description of issue and why the ERG has identified it as important	Patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 were excluded from the KEYNOTE-826 trial. However, the ERG's advisors estimated that 20-30% of ECOG PS 2 patients would be eligible for systemic treatments in the NHS. Conversely, patients with ECOG PS 0 were over-represented in KEYNOTE-826 (56% of patients) compared with the ERG advisers' estimate for the relevant NHS population (10-15%). In the NHS, bevacizumab would not be continued for as many cycles as were observed in KEYNOTE-826 (where the number of cycles was unlimited). In KEYNOTE-826, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could have affected results to slightly favour pembrolizumab. Collectively, these issues mean that pembrolizumab may be less efficacious when used in an NHS setting, i.e. the KEYNOTE-826 results may be somewhat over-optimistic.
What alternative approach has the ERG suggested?	Not applicable.
What is the expected effect on the cost-effectiveness estimates?	The limited evidence adds uncertainty to the cost-effectiveness estimates. The ERG does not consider it appropriate to extrapolate results of the presented economic analysis to an ECOG 2 population.
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the proportion of ECOG 2 patients who receive systemic treatment. Evidence on the effectiveness of pembrolizumab in an ECOG 2 population; the ERG is unaware of any appropriate data sources.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Immature overall survival data

Report section	3.2.3.1
Description of issue and why the ERG has identified it as important	Overall survival (OS) data from KEYNOTE-826 are immature, with the median OS not being reached in the pembrolizumab group. This means that appropriate methods must be used for extrapolating and estimating longer-term OS data (see Issues 3 and 6).
What alternative approach has the ERG suggested?	Not applicable due to data immaturity.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The KEYNOTE-826 final trial analysis is anticipated in [redacted].

Issue 3 Uncertain relationship between progression-free survival and overall survival

Report section	3.2.1.3 and 4.2.2.1
Description of issue and why the ERG has identified it as important	In the company submission (CS), progression-free survival (PFS) is considered to be an appropriate surrogate for OS. However, it is unclear to what extent this is true; the CS does not robustly demonstrate that such an association exists, providing limited evidence based on clinical opinion and an analysis of KEYNOTE-826 . The ERG's clinical advisors do not believe that PFS is necessarily a reliable surrogate for OS in this population, noting that treatment can delay progression without extending survival. Extrapolation estimates of OS beyond the available trial data and into the longer-term are therefore highly uncertain.

What alternative approach has the ERG suggested?	The surrogate relationship between PFS and OS is a key assumption of the economic analysis, see issue 6.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The KEYNOTE-826 final trial analysis is anticipated in [redacted]. This may help validate whether observed improvements in PFS translate into OS benefits.

Issue 4 Pembrolizumab appears not to be efficacious in patients with metastases at their initial diagnosis

Report section	3.2.3.1
Description of issue and why the ERG has identified it as important	The subgroup of patients with metastases at initial diagnosis had statistically significantly worse PFS outcomes than patients without metastases at initial diagnosis. OS results were also notably different. This apparent lack of effect for PFS (in particular) and for OS was similar (in terms of hazard ratios) to that seen in the PD-L1 CPS <1 subgroup, which was excluded from the EMA's marketing authorisation.
What alternative approach has the ERG suggested?	Appropriate analysis of the metastatic subgroup in the economic model.
What is the expected effect on the cost-effectiveness estimates?	Unclear; apparent lack of efficacy in the metastatic population is likely to imply a higher ICER in this subgroup.
What additional evidence or analyses might help to resolve this key issue?	Appropriate analysis of the metastatic subgroup in the economic model. Clinical and/or expert opinion on the biological plausibility of a differential treatment effect.

Issue 5 Application of two-year stopping rule.

Report section	2.3 and 4.2.6.1
Description of issue and why the ERG has identified it as important	In KEYNOTE-826 a stopping rule was imposed limiting the maximum treatment duration to 35 cycles (about two years). It is unclear whether a stopping rule would be considered appropriate in clinical practice. The ERG, however, note a stopping rule has been applied in nearly all previous appraisals of pembrolizumab.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical validation of the appropriateness of a stopping rule.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6 Appropriateness of state transition model

Report section	4.2.2.1
Description of issue and why the ERG has identified it as important	The company's economic analysis uses a state transition model (STM). A key assumption of this approach is that is implies a surrogate relationship between PFS and OS. As discussed in Issue 3, there is limited evidence provided to support this assumption and uncertainty regarding the reliability of PFS as a surrogate. The ERG also notes that the model generates predictions that do not always align with the observed data and demonstrates a bias in favour of pembrolizumab. The ERG also has substantive concerns regarding the company's justification for the STM approach. The company's justification is founded on the extrapolations of time to progression (TTP) and PFS data, and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations.

	However, as discussed in Issue 7, it is unclear whether the TTP (PFS) extrapolations preferred by the company are clinically plausible. Alternative, more conservative, approaches to extrapolating TTP (PFS) do not result in TTP (PFS) crossing.
What alternative approach has the ERG suggested?	The ERG does not inherently object to a STM approach but is concerned about the clinical plausibility of model predictions. A partition survival model may be more appropriate if more mature OS data become available.
What is the expected effect on the cost-effectiveness estimates?	Using a partition survival approach (the alternative to a STM) would likely increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	The final cut analysis from KEYNOTE-826 (expected [redacted]) may resolve some of the uncertainty regarding the appropriateness of TTP (PFS) extrapolation and will help validate model predictions.

Issue 7 Extrapolation of PFS

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	The company's approach to extrapolating TTP and PFS uses a two-piece extrapolation approach which is justified on the basis of an observed inflection point in the TTP/PFS curve for pembrolizumab. The company considers this inflection point evidence of an emerging plateau and that observed hazards in the tail of the KM are indicative of an ongoing sustained decline in the risk of progression. This approach implies a very long tail to the survival function and result in the model predicting very substantial OS benefits. The ERG considers that this approach is potentially inappropriate given the immaturity of the data supporting the purported 'inflection point' in the TTP/PFS curve for pembrolizumab, and notes that this approach leads to substantive numbers of patients surviving beyond 5 years. While immunotherapies have historically been associated with durable response rates, the ERG considers there to be little evidence to support a paradigm shift in outcomes as modelled by the company.
What alternative approach has the ERG suggested?	The ERG considers a single-piece approach to be more reasonable given the limited OS evidence available.
What is the expected effect on the cost-effectiveness estimates?	Using a single-piece log-logistic model preferred by the ERG increases the ICER from £34,017 per QALY in the company's base-case to £71,907 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival estimates would help to determine the most appropriate approach to modelling TTP/ PFS. The final cut analysis from KEYNOTE-826 (expected [redacted]) may also help to resolve some of this uncertainty.

Issue 8 Extrapolation of PPS

Report section	4.2.6.2
Description of issue and why the ERG has identified it as important	The company's base-case model uses a single-piece generalised gamma model to predict post-progression survival (PPS). The ERG is concerned that this model results in overly optimistic estimates of survival with an overly long-tail. Treatment options in the second-line setting are extremely limited and it is unlikely that any patients would be alive beyond 3 years post progression. The company approach to modelling PPS also assumes a differential survival benefit across treatment arms with patients progressing on pembrolizumab assumed to have longer PPS. The available KM data, however, shows limited evidence to support this, assumption.
What alternative approach has the ERG suggested?	The ERG prefers to use a pooled PPS curve for both treatment arms and considers that more conservative parametric functions, such as the Weibull, provide more plausible predictions.
What is the expected effect on the cost-effectiveness estimates?	Pooling the PPS curves results in an increase in the ICER from £34,017 per QALY in the company base-case to £36,231 per QALY. Using the Weibull model in place of generalised gamma (assuming pooled PPS) results in an increase in the company base-case ICER to £34,832 per QALY.

What additional evidence or analyses might help to resolve this key issue?	Further exploration of the clinical plausibility of the company's base case assumptions would be useful. More mature data on PPS would also be useful to inform the most appropriate parametric model.

Issue 9 Including treatment waning effect for pembrolizumab

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	The company assumes a lifetime duration of the treatment effect associated with pembrolizumab. Evidence provided by the company to support this assumption is limited given the relatively short follow- up in KEYNOTE-826. The ERG considers that the application of a life-time treatment effect is highly uncertain and that insufficient evidence is available to substantiate this assumption. The ERG notes that previous appraisals of immunotherapies have applied a waning effect, in which mortality rates gradually return to those of the comparator therapy over a number of years following the discontinuation of treatment.
What alternative approach has the ERG suggested?	A benefit of treatment limited to between three and five years after discontinuation is preferred by the ERG. This aligns with committee preferences in several appraisals of immunotherapies.
What is the expected effect on the cost-effectiveness estimates?	When the duration of survival benefit is limited to three years (post treatment discontinuation), the ICER increases from £34,017 per QALY to £42,919 per QALY. When a five years limit is implemented the ICER increases to £38,823 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Uncertainties regarding long-term survival of patients receiving pembrolizumab may be resolved through additional follow-up in KEYNOTE-826. However, it is unlikely that data would be sufficiently mature following the expected [redacted] data cut to support a five-year survival benefit duration. More detailed analyses of long-term data from Phase III trials of other immunotherapies may provide supporting evidence for a durable treatment benefit.

Issue 10 Health state utilities

Report section	4.2.7.1
Description of issue and why the ERG has identified it as important	The approach taken by the company was to predict HRQoL by time to death (TTD). The ERG has conceptual issues with this approach as it relies on future death events to predict current HRQoL status. The ERG is also concerned that the TTD approach severs the link between progression and violates the accepted norm that progression status is major driver of HRQoL. Moreover, the TTD approach favours pembrolizumab and results in a treatment related utility benefit which has not been evidenced.
What alternative approach has the ERG suggested?	The ERG prefers the use of progression-based health state utilities estimated from KEYNOTE-826.
What is the expected effect on the cost-effectiveness estimates?	Using progression-based utilities increases the company base-case ICER from £34,017 in per QALY to £36,591 per QALY.
What additional evidence or analyses might help to resolve this key issue?	A comparison of the fit of the progression-based and TTD-based models would aid in determining which is statistically the most appropriate. Discussion and evidence on clinical plausibility of each approach would be useful. The company may also wish to amend their model structure to allow the mean utility for the cohort to be estimated on a per-cycle basis, to allow for the validation of predicted utility values over time.

Issue 11 Resource use

Report section	4.2.8
Description of issue and why the ERG has identified it as important	The ERG identified several issues relating to resource use. The most important related to the application of the stopping rule and the subsequent treatments modelled. The economic model applies a strict 24 month stopping rule. This does not fully align with KEYNOTE-826 where a 35-cycle limit was applied. This reduces the acquisition cost associated with pembrolizumab and severs the link between treatment costs and health effects. The ERG does not consider this reflective of

	practice and notes that previous NHS England policy permits patients to receive a full allocation of doses even when these fall outside the 24-month window. Modelled subsequent treatments do not utilise the distribution of therapies used in KEYNOTE-826, as the company consider that the treatments received by patients were not reflective of UK practice. The company's submission, however, provided only limited information on subsequent treatments received in KEYNOTE-826 and did not fully respond to clarification response on this point. Given the limited information provided, it is unclear if the company's base-case assumptions are appropriate. The ERG is also concerned about the subsequent treatments modelled. The ERG's clinical advisor raised concerns about the use of doxorubicin in this population and considered that paclitaxel would be used less frequently than assumed in the base-case.
What alternative approach has the ERG suggested?	Modelled time on treatment should align with KEYNOTE-826 and remove the 24-month cap imposed in the economic analysis. The ERG's preference would be to base the proportions of subsequent therapies received on the full data for each treatment arm from KEYNOTE-826.
What is the expected effect on the cost-effectiveness estimates?	Removing the time on treatment cap results in an increase in the ICER from £34,071 per QALY in the company base-case to £34,952 per QALY. The impact of alternative assumptions regarding subsequent treatment use is unknown.
What additional evidence or analyses might help to resolve this key issue?	Confirmation of the commissioning policy for pembrolizumab and the appropriateness of a 24-month vs 35-cycle time on treatment cap. Further information on the subsequent treatments received by patients in KENOTE-826 is necessary to inform the ERG preferred approach. It may also be appropriate to elicit additional UK clinical opinion on the composition of subsequent treatments used in NHS practice.

1.6 Other key issues: summary of the ERG's view

Issue 12 Relevance of bevacizumab and availability of bevacizumab biosimilar

Report section	4.2.4
Description of issue and why the ERG has identified it as important	NHS commissioning of bevacizumab did not follow the normal NICE process but instead was commissioned directly by NHS England. The cost-effectiveness of bevacizumab is therefore unknown. The ERG considers this commissioning route problematic as the cost-effectiveness of pembrolizumab may be influence by the cost-effectiveness of bevacizumab. The ERG also notes the availability of bevacizumab biosimilars. It is uncertain to what extent these are used in practice. The ERG, however, considers it realistic that a proportion of patients initiated on bevacizumab may be given a biosimilar product.
What alternative approach has the ERG suggested?	This ideally would be addressed by fully incremental analysis considering each of the four alternatives (doublet chemotherapy, doublet chemotherapy plus bevacizumab, doublet chemotherapy plus pembrolizumab, doublet chemotherapy plus bevacizumab and pembrolizumab). Reflect market share of biosimilars in the base-case analysis.
What is the expected effect on the cost-effectiveness estimates?	The impact of including bevacizumab as a comparator is difficult to quantify due to pembrolizumab's positioning as a combination therapy. Scenario analysis using biosimilar prices resulted in a small increase in the ICER from £34,017 to £34,056. This analysis is exclusive of commercial arrangements for comparator treatments.
What additional evidence or analyses might help to resolve this key issue?	Evidence to support appropriate comparisons is not available to resolve this issue. Resolution of this uncertainty may be partially addressed by considering subgroup analysis of KEYNOTE-826 stratifying by the investigator's decision to use bevacizumab.

	Further evidence of biosimilars in UK practice will help inform the appropriate base-case assumptions.

Issue 13 End-of-life criteria

Report section	7
Description of issue and why the ERG has identified it as important	The company considered the End of Life (EoL) criteria noting median survival is less than 24 months. The ERG notes that the EoL criteria are typically interpreted with respect to mean or average life-expectancy. This is in line with actuarial methods which use mean life-expectancy. It is also in line with decision making for cost-effectiveness, which is based on mean costs and QALYs. Mean OS predicted for the standard of care arm is 2.5 years using the company preferred assumptions and 2.08 using the ERG's preferred assumptions. These suggest that the EoL criteria are not met.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Determines maximum willingness to pay threshold.
What additional evidence or analyses might help to resolve this key issue?	Further validation of the projected survival is required to determine whether EoL criteria are met.

1.7 Summary of ERG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the ERG are described in Section 5.4. For further details of the exploratory and sensitivity analyses done by the ERG, see Section **Error! Reference source not found.**. The results of the ERG's exploratory analyses including the ERG's preferred base case are presented in Table 1 with probabilistic results for the ERG's preferred based case presented in Table 2

Table 1 ERG exploratory scenarios

Scenario	Technology	Incremental			ΔICER vs corrected BC
		Costs	QALYs	ICER	
ERG-corrected company base-case	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,021	-
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	SoC				
	Pembrolizumab	[redacted]	[redacted]	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	SoC				
	Pembrolizumab	[redacted]	[redacted]	£36,231	£2,209
2. b) Pooled survival curve for PPS using Weibull curve.	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,832	£811
3. a) Treatment waning for pembrolizumab between 3 and 5 years	SoC				
	Pembrolizumab	[redacted]	[redacted]	£42,919	£8,897
	SoC				

3. b) Treatment waning for pembrolizumab between 5 and 7 years	Pembrolizumab	[redacted]	[redacted]	£38,823	£4,802
4. Progression based utilities	SoC				
	Pembrolizumab	[redacted]	[redacted]	£36,591	£2,569
5. Subsequent therapy distribution from KEYNOTE-826	SoC				
	Pembrolizumab	[redacted]	[redacted]	£33,472	-£549
6. Full Pembro ToT KM curve used to calculate costs	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,952	£930
7. All patients receive biosimilar bevacizumab	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,056	£34
8. Bevacizumab maintenance treatment allowed	SoC				
	Pembrolizumab	[redacted]	[redacted]	£32,885	-£1,136
9. GP/nurse visits, blood-counts, and thyroid function tests costs	SoC				
	Pembrolizumab	[redacted]	[redacted]	£35,072	£1,051
10. All AEs of special interest occurring in more than 5% of patients modelled	SoC				
	Pembrolizumab	[redacted]	[redacted]	£34,220	£198
ERG preferred base-case (Scenarios 1, 2 (a), 3 (a), 4, 6, 9 & 10)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£95,529	£61,508

Table 2 ERG's alternative base-case analysis results (probabilistic)

Scenario	Technology	Total			Incremental		
		Costs	LYs	QALYs	Costs	QALYs	ICER
ERG-corrected company base-case (probabilistic)	SoC	[redacted]	2.11	[redacted]			
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£93,159

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report, the ERG has reviewed the clinical and cost-effectiveness evidence in the Company Submission (CS) in support of pembrolizumab (KEYTRUDA) with chemotherapy for treating recurrent, persistent or metastatic cervical cancer. The application for marketing authorization with the EMA in this indication is currently ongoing. EMA approval was received in March 2022[1] and MHRA approval was granted in May 2022.

In this section, the ERG critiques the company's proposed treatment pathway, positioning of pembrolizumab, and its definition of the decision problem when compared with the NICE scope.

2.2 Background

Pembrolizumab is a humanised monoclonal anti-PD-L1 antibody, which binds to the PD-1 receptor expressed by tumour cells and thus allows the patient's immune system to target and destroy these cells.

Section B.1.3 of the CS provides a brief and accurate overview of recurrent, persistent or metastatic cervical cancer, its aetiology, epidemiology, and prognosis.

2.2.1 Treatment pathway

The treatment pathway indicates that patients with an ECOG status of 0 or 1 receive systemic treatment and patients with a ECOG performance status (PS) >1 receive best supportive care or palliative radiotherapy. However, the British Gynaecological Cancer Society (BGCS) guidelines suggest that a proportion of women with ECOG PS 2 may also be considered for systemic treatment.[2] Clinical advice to the ERG suggests that 20-30% of patients undergoing systemic chemotherapy for recurrent, persistent or metastatic cervical cancer have ECOG PS 2 (see Section 3.2.2.1).

The systemic therapies in the proposed pathway (cisplatin or carboplatin with paclitaxel, with or without bevacizumab depending on patient risk factors) reflect clinical practice for a majority of UK patients. However, clinical advice to the ERG indicated that treatment choice is strongly guided by patient preference. This means that topotecan may be used occasionally, and platinum-based monotherapy may be used in some patients (~10%) who want to avoid paclitaxel-associated toxicity effects, such as hair loss.

Clinical advice to the ERG also suggested that the aim of treatment in this population is 'disease free' survival. Therefore, doublet therapy may not be initiated immediately in very fit patients, due to the burden of inconvenience and toxicity outweighing the limited potential for symptomatic or survival benefits. These patients may choose to start treatment only once their symptoms have worsened.

The ERG's clinical advisors agreed that over 50% of patients eligible for systemic chemotherapy would receive concomitant bevacizumab. Patients are considered eligible for bevacizumab on the basis of having better performance status, no significant comorbidities (e.g. hypertension), and low risk of bowel fistula formation.

The treatment pathway in the CS includes only first-line systemic therapy. BGCS guidelines state: "Second line treatment and beyond is dependent on the interval of progression since first line treatment in those patients with a good partial response with first line treatment and are more than 6 months out, rechallenging with platinum/paclitaxel could be considered. Mitomycin/5FU, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity but there is no standard of care. Response rates are universally poor and entry into clinical trials where possible to assess novel and immunotherapeutic agents should be strongly considered depending on patient's fitness and desires."[2] The ERG's clinical advisors suggested that fewer than half of patients with recurrent, persistent or metastatic disease would receive second-line treatment, and the choice of treatment in this group would be driven by clinician judgment alongside the BCGS recommendations.

2.2.2 Company's proposed positioning

The ERG agrees with the company's proposed positioning of pembrolizumab as first-line systemic therapy, in combination with chemotherapy (cisplatin or carboplatin plus paclitaxel) with or without bevacizumab. This is in line with BGCS guideline recommendations and the KEYNOTE-826 trial.

2.3 Critique of company's definition of decision problem

Table 3 summarises the decision problem as defined in the NICE scope and the CS.

The CS appropriately presents the results for the CPS (combined positive score) ≥1 trial subpopulation. This reflects the anticipated licence for pembrolizumab and constitutes 89% of the trial intention-to-treat (ITT) population.

The company seeks a recommendation for pembrolizumab in adults with untreated recurrent, persistent or metastatic cervical cancer, unrestricted by performance status. This matches the NICE scope and the granted licence indication. However, as noted in section 2.2.1, the KEYNOTE-826 trial that informs the CS included only patients with an ECOG PS of 0 or 1, whereas in practice around 20-30% of patients considered eligible for systemic therapy would have ECOG PS 2. In addition, the

proportion of patients with an ECOG PS 0 is substantially greater in the trial than seen in UK practice (see Section 3.2.2.1). Therefore (a) the trial population is likely to be fitter on average than the eligible UK treatment population and (b) the CS does not provide any evidence on the effects of pembrolizumab in eligible ECOG PS 2 patients.

KEYNOTE-826 permitted up to 35 cycles (approximately 2 years) of pembrolizumab (though participants who stopped treatment on achieving stable disease but subsequently experienced radiographic disease progression could receive up to 17 additional cycles (approximately 1 year)). However,

[redacted]

It states that

[redacted][3] The ERG's clinical advisors considered two years to be a reasonable treatment duration for pembrolizumab in this indication, given the absence of evidence on longer-term effects of immunotherapeutic agents. See Section 4.2 for further discussion of stopping rules.

The company's decision problem is restricted to platinum-based chemotherapy in combination with paclitaxel, with or without bevacizumab. The ERG's clinical advisors agreed this is the treatment most commonly used in practice. However, variations in disease presentation and patient preference mean that a small proportion of patients may receive topotecan or platinum-based monotherapy, as treatment options are limited.

The ERG's clinical advisors agreed that etoposide should be excluded as a comparator.

The ERG's clinical advisors noted that, if available, pembrolizumab might be preferred as an alternative to bevacizumab in patients with poorer performance status or risk factors for adverse outcomes. They added that the relative effects of adding pembrolizumab instead of bevacizumab to chemotherapy in patients eligible for either monoclonal antibody would also be of interest. However, KEYNOTE-826 was not designed to provide a randomised head-to-head comparison of chemotherapy plus pembrolizumab versus chemotherapy plus bevacizumab.

Outcomes in the company's decision problem match those in the NICE scope, with the addition of duration of response (DOR). The ERG agrees that these outcomes are all important for evaluating the effects of pembrolizumab in this indication. The ERG's clinical advisors noted that patients particularly value time without symptomatic disease. This preference, in combination with the limited survival benefits of currently available treatment for many patients, means that management often focuses on improving quality of life.

While overall survival (OS) was included as an outcome in the decision problem, it should be noted that OS data in the KEYNOTE-826 trial were immature, meaning that KEYNOTE-826 cannot currently provide a direct estimate of the effect of pembrolizumab on longer-term survival. In their justification for the economic model structure (CS p.81), the company states that "*UK clinical experts consulted for this appraisal confirmed that the trends in hazards observed for progression free survival (PFS) would be expected to become apparent for OS with longer-follow up*." Therefore, to estimate the effects of pembrolizumab on OS in the economic model, information on progression was used to inform mortality extrapolations (see Section 4.2.6 of the ERG report). However, the ERG's clinical advisors do not believe that progression-free survival (PFS) is necessarily a reliable surrogate for OS in this population: they noted that treatment can delay progression without extending survival.

Of the four subgroups in the NICE scope (histology, pelvic disease status, CPS of PD-L1 expression, tumour mutational burden), only CPS was considered in the KEYNOTE-826 trial. Randomisation was stratified by CPS, with the CPS≥1 population presented as the effectiveness analysis population in the CS, on the basis that this aligns with the licence for pembrolizumab (n.b. CPS≥10 and all-comer analysis sets from KEYNOTE-826 are available in figures 5 and 6 of the CS appendix). In response to a query from the ERG, the company stated that investigation of tumour mutational burden is a potential exploratory analysis for which no data are yet available (PfC A1). The KEYNOTE-826 clinical study report concluded "The treatment benefit of pembrolizumab plus chemotherapy with or without bevacizumab…was consistent across all the major subgroups tested in participants with persistent, recurrent, or metastatic cervical cancer *including by histology*". However, the ERG could not find any subgroup analysis based on histology, and none was provided in the CS or the company's response to points for clarification.

Subgroup analyses conducted in KEYNOTE-826 (and presented in the CS for the CPS≥1 population) were: metastatic disease at initial diagnosis, bevacizumab use, age (<65 or ≥65 years), race (white, all others), ECOG status (0 or 1). See Section 3.2.3.1 for further details.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with untreated recurrent, persistent or metastatic cervical cancer	The population was restricted to adults with untreated recurrent, persistent or metastatic cervical cancer and a CPS of PD-L1 expression score ≥1	Restriction by CPS is consistent with the licence.	KEYNOTE-826 included only patients with an ECOG status ≤1. Compared with the NHS setting, the trial population consequently overrepresented ECOG 0 status patients (56% vs 10-15%) and underrepresented ECOG 2 status patients (0% vs 20-30%). The trial population is therefore likely to be fitter on average than the eligible UK treatment population and provides no evidence on the effects of pembrolizumab in ECOG 2 status patients.
Intervention	Pembrolizumab in combination with paclitaxel and platinum-based chemotherapy (carboplatin or cisplatin) with or without bevacizumab	As per final scope	N/A	The intervention is consistent with the NICE scope. KEYNOTE-826 permitted up to 35 cycles (approximately 2 years) of pembrolizumab, though [redacted].
Comparator(s)	Platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel or topotecan or etoposide In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	Platinum chemotherapy (cisplatin or carboplatin) in combination with paclitaxel In addition, for people who would receive bevacizumab through the Cancer Drugs Fund: paclitaxel with platinum-based chemotherapy (carboplatin or cisplatin) with bevacizumab (15 mg/kg every 3 weeks)	Etoposide has been excluded from the list of comparators. Etoposide is used in small cell cervical cancer, a histology which is not covered by the KEYNOTE-826 trial. Cervical cancer is not included as an indication in the etoposide SmPC. Although it is acknowledged that TA183 approved the use of topotecan in combination with cisplatin for women with recurrent or stage IVB cervical cancer if they have not previously	The company's decision problem is restricted to platinum-based chemotherapy in combination with paclitaxel, with or without bevacizumab. The ERG's clinical advisors agreed this is the treatment most commonly used in practice. However, variations in disease presentation and patient preference mean that a small proportion of patients may receive

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			received cisplatin, topotecan has been excluded from the list of comparators: At the NICE scoping call held for this submission in December 2020, clinical experts in attendance did not report the use of topotecan in UK clinical practice. This was further confirmed at a recent advisory-board, in which clinicians confirmed that topotecan is not in use in the NHS in this indication Topotecan is not recommended by the BGCS guidelines for the treatment of advanced cervical cancer Bevacizumab is currently the preferred option for first-line treatment of advanced or metastatic cervical cancer in conjunction with chemotherapy. Topotecan was also rarely indicated prior to bevacizumab becoming available; the NICE FAD for TA183 states that '90–95% of women within the licensed population will have previously received cisplatin' Platinum-based monotherapy have also been excluded from the list of comparators to align with current treatment options recommended by the BGCS guidelines and clinician feedback.	topotecan or platinum-based monotherapy. The ERG's clinical advisors agreed that etoposide should be excluded as a comparator. The ERG's clinical advisors noted that the effects of adding pembrolizumab instead of bevacizumab to chemotherapy would be of interest. However, the KEYNOTE-826 trial does not include this as a randomised comparison. n.b. In table 1 of the CS, the "Decision problem addressed in the company submission" column incorrectly identifies "Platinum chemotherapy (cisplatin or carboplatin) alone" as a comparator included in the CS.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life Duration of response	Addition of the duration of response outcome to aid in capturing the most important health-related benefits of the Pembrolizumab in the patient population of interest.	Overall survival data were immature in the KEYNOTE-826 trial. The ERG's clinical advisors do not consider PFS to be a reliable surrogate for OS

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	As per final scope	N/A	The economic analysis is line with the reference case. See Table 11 for details. Confidential commercial arrangements for comparator treatments have not been accounted for in the company's analysis. The ERG presents analyses inclusive of these commercial arrangements in a confidential appendix to this report.
Subgroups to be considered	If the evidence allows the following subgroups will be considered based on: Histology (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and poorly differentiated carcinoma) Pelvic disease status (pelvic or locally recurrent cervical cancer and distant metastatic cervical cancer) CPS of PD-L1 expression (< 10, ≥ 10 and all-comers) Tumour mutational burden	This submission presents the subgroup analyses for the CPS ≥ 1 population	The company clarified that analyses of tumour mutational burden are not yet available. The absence of histology and pelvic disease status subgroups was not explicitly addressed.	CPS≥10 and all-comer analysis from KEYNOTE-826 were reported in the CS appendices. Subgroup analyses conducted in KEYNOTE-826 and presented in the CS were: metastatic disease at initial diagnosis, bevacizumab use, age (<65 or ≥65 years), race (white, all others), ECOG status (0 or 1). Though the KEYNOTE-826 mentioned the observed treatment effects being "…consistent across all the major subgroups tested in participants with persistent,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				recurrent, or metastatic cervical cancer *including by histology*", no histology subgroup data could be found among the provided materials.
Special considerations including issues related to equity or equality				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify all relevant evidence regarding the clinical efficacy and safety of first-line treatments for patients with recurrent, persistent or metastatic cervical cancer. Details of the review are reported in Appendix D of the CS. No network meta-analysis or indirect comparison was conducted – see Section 3.3.

3.1.1 Searches

The CS included searches to identify evidence on the efficacy and safety of first-line treatments for patients with recurrent, persistent or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix D.1.1 of the CS.

In response to the ERG's PfCs (C4-C7), the company provided additional search strategies and related information.

An appraisal of the literature searches is presented in Appendix 9.1

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review were presented in Table 2 of the CS Appendix document. The ERG considers these criteria to be appropriate to the decision problem. Two independent reviewers evaluated all titles and abstracts, and full-texts, which will have minimised the possibility of reviewer errors or bias affecting the selection process.

3.1.3 Critique of data extraction

The CS appendix stated that data were extracted "by two reviewers and reconciled by the third reviewer" so it appears likely that the process used will have limited the possibility of errors or bias affecting data extraction.

3.1.4 Quality assessment

Studies included in the systematic review were evaluated for risk of bias by two reviewers, using version 2 of the Cochrane risk of bias tool. The results were reported in Appendix D3 (p31); these were limited to judgements only, so the ERG asked the company (clarification question A17) to provide the details to justify the judgements made. The company responded with a table of very brief answers (e.g. yes, no, probably yes, etc) to signalling questions, which was insufficient to clarify this reporting issue. The ERG therefore looked for any risk of bias issues in the two trials used in the economic modelling: KEYNOTE-826 and GOG-240.[4] The ERG considered KEYNOTE-826 to be at

low overall risk of bias. The randomisation methods (interactive voice response system/integrated web response system) were robust. Blinding of patients, caregivers and outcome assessors appeared to be adequate, although few specific details were provided on how blinding was achieved (e.g. no details were presented on the similarity of appearance of pembrolizumab and placebo). In terms of patient attrition from the trial, nineteen patients withdrew consent in the placebo group compared with 13 in the pembrolizumab group; it was unclear how many of these patients were successfully followed up, but where survival data were missing the stated approach was to censor at the last known alive date. Although the risk of bias was low, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could have affected results to slightly favour pembrolizumab; the ERG's clinical advisor stated that patients with adenocarcinoma have poorer outcomes than patients with squamous cell carcinoma.

There is more uncertainty over the risk of bias in the GOG-240 trial.[4] Block randomisation was used and the methods of allocation concealment were not reported. Nevertheless, key baseline characteristics such as histology, performance status and age were well-balanced across groups. However, GOG-240[4] was an open-label trial with patients and caregivers not blinded to study treatments. It is unclear whether or not outcome assessors were blinded and to what extent the lack of blinding in this study may have biased the trial's results.

A discussion of the KEYNOTE-826 trial's applicability to the NHS was presented in Section B.2.13.1.1 of the CS (p71). The ERG's clinical advisor considered the trial population was broadly representative of NHS patients. The exception was that in KEYNOTE-826 patients with ECOG 2 performance status were excluded; the ERG's clinical advisor estimated that in the NHS around 20-30% of patients receiving a systemic therapy would have an ECOG status of 2.

3.1.5 Evidence synthesis

No evidence synthesis was conducted since only one eligible randomised trial of pembrolizumab (KEYNOTE-826) was identified in the systematic review and the company considered that the comparator evidence identified in other studies would not usefully add to the evidence provided in KEYNOTE-826 (see Section 3.3).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Trial design and methods

3.2.1.1 KEYNOTE-826

Section B.2.3 of the CS (p.28) summarises the design and methodology of the KEYNOTE-826 trial. Briefly, this was a randomised, double-blind, placebo-controlled, multinational trial comparing pembrolizumab plus chemotherapy (paclitaxel + cisplatin/carboplatin) with or without bevacizumab versus placebo plus chemotherapy with or without bevacizumab in adults with recurrent, persistent or metastatic cervical cancer.

Eligible patients were stratified by investigator's decision to use bevacizumab, PD-L1 status, and metastatic status at initial diagnosis, and randomised to receive either 200mg pembrolizumab or placebo every 3 weeks for up to 35 cycles.

Both treatment arms received paclitaxel and the investigator's choice of cisplatin or carboplatin every 3 weeks, with some participants receiving bevacizumab (15 mg per kg of body weight) at the investigator's discretion. Chemotherapy was limited to six-cycles, though patients who continued to benefit without unacceptable adverse events (AEs) could continue beyond this limit. There was no limit on the number of cycles of bevacizumab a patient could receive.

Treatment was planned to continue until radiographic disease progression, experience of unacceptable toxic effects, or the maximum number of cycles for each treatment component (see Section 3.2.1.3 for further details on treatment duration).

Primary endpoints were progression-free survival (PFS) based on RECIST 1.1 as assessed by investigator (see PfCs A11 and A12), and overall survival (OS). Secondary endpoints were objective response rate (ORR), duration of response (DOR), PFS rate at 12 months, patient-reported quality of life, safety and tolerability.

3.2.1.2 KEYNOTE-158

Section B.2.6.3 and Appendix F.2 of the CS briefly present results from KEYNOTE-158: a single-arm basket trial of pembrolizumab monotherapy in multiple advanced solid tumour types in a second line or later treatment setting. As this trial includes a very different treatment population (e.g. PFS 2.1 months vs 10.4 months in KEYNOTE-826) and does not align with the decision problem for this evaluation, it is not discussed further in the ERG report.

3.2.1.3 Points for critique

Use of interim analyses

The KEYNOTE-826 trial is ongoing. The CS presents data from the first planned interim analysis, with the CPS≥1 population followed up for a median of [redacted] The final trial analysis is anticipated [redacted].

The short follow-up period for the interim analysis means that a substantial proportion of data for some time-to-event outcomes were censored, with overall survival data in particular being immature. Section B.3.2.2 of the CS describes how the company's model uses the relatively more mature progression data to inform overall survival extrapolations. However, the ERG's clinical advisors did not entirely agree with the assertion that PFS is an appropriate surrogate for OS, noting that a proportion of patients in this population can experience delayed progression without an overall survival benefit (see Section 4.2.6.1).

Treatment duration

KEYNOTE-826 permitted a maximum of 35 treatment cycles of pembrolizumab (equivalent to around 24 months treatment duration) in the absence of disease progression or prohibitive toxicity. This was implemented as stopping rule in the model (see Section 4.2).

However, it should be noted that the current SmPC for pembrolizumab states "Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication)". While the maximum treatment duration in most pembrolizumab KEYNOTE trials was 35 cycles or 24 months, the SmPC does not explicitly mandate a stopping rule for cervical cancer.[5] The United States Prescribing Information (USPI) recommends treatment "until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months".[6]

In previous appraisals, pembrolizumab has mostly been recommended with a stopping rule (n=14/15), either explicitly in the recommendations (n=13) or in the marketing authorisation (n=1).[7-20]

Reported clinical effectiveness outcomes

The main body of the CS reports most primary and secondary endpoints specified in the KEYNOTE-826 protocol, with exploratory outcomes presented in the appendices (see Table 4). However, health related quality of life was an exception – the main body of the CS reports an exploratory measure (EuroQoL EQ-5D-5L) rather than the principal measure (EORTC QLQ-C30 global score) specified in the protocol. Section 3.2.3.1 of this ERG report therefore summarises the EORTC QLQ-C30 global score results.

Table 4 Reporting of pre-specified endpoints in the company submission

Outcome	Assessment method (where relevant)	Endpoint specified in protocol / clinical study report	Reported in CS?
OS	-	Primary	Yes
PFS	BICR	Secondary	Yes
	Investigator	Primary	Yes
ORR	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
DOR	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
PFS rate at 12 months	BICR	Exploratory	Appendix only
	Investigator	Secondary	Yes
EORTC QLQ-C30 global score	-	Secondary	Appendix only
EuroQoL EQ-5D-5L	-	Exploratory	Yes
EORTC QLQ-C30 (scores other than global score)	-	Exploratory	No
EORTC QLQ-CX24	-	Exploratory	No

CONSORT flowchart, discontinuation and treatment switching

Appendix D.2 of the CS reported CONSORT diagrams to illustrate patient flow though the KEYNOTE -826 trial for the CPS≥1 (n=548) and ITT populations (n=617). Discontinuations were broadly similar between treatment arms, except for the noticeably higher rate of discontinuation due to radiographic progression in the placebo arm.

The ERG requested clarifications regarding the 266 participants screened but excluded from the trial (PfC A5). This information is summarised in Table 5. 10.2% of patients were specifically excluded for having an ECOG PS >1, though it is not clear whether further patients with ECOG PS >1 scores were excluded for other reasons. Table 5 Participants screened and excluded prior to randomisation

Table 5 Participants screened and excluded prior to randomisation

Reason for exclusion	Number of participants excluded (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Response to PfC A5

Despite the trial protocol permitting a second course of treatment with pembrolizumab under certain circumstances, the company clarified that no participants in KEYNOTE-826 actually received retreatment (see PfC A4).

No patients switched between the KEYNOTE-826 treatment arms (PfC A13), and a small number switched from cisplatin to carboplatin within the treatment arms (pembrolizumab arm n=11, placebo arm n=6; PfC A14). Consequently, there are no important concerns about trial results being influenced by treatment switching in KEYNOTE-826.

Bevacizumab treatment rules

KEYNOTE-826 did not limit the number of cycles of bevacizumab a patient could receive, and on average patients received more cycles of bevacizumab (median 12) than they did chemotherapy (median 6). This compares with a median of 7 cycles of bevacizumab (range 0-36) in the GOG-240 trial.[4] The BGCS guidelines recommend the addition of bevacizumab to chemotherapy, depending on patient risk factors,[2] and the National Cancer Drugs Fund (CDF) list states that bevacizumab is *only* approved for use in combination with combination chemotherapy and is not approved for use as a single agent maintenance therapy.[21] Therefore patients in KEYNOTE-826 are likely to have been treated with bevacizumab for longer than patients in UK clinical practice.

The company's advisory board (PfC C1) noted [redacted].[22]

The company's base case cost effectiveness analysis includes a six cycle stopping rule for bevacizumab, with a scenario analysis to reflect the longer treatment duration observed in the trial (see 4.2.4).

3.2.1.4 Risk of bias

See section 3.1.4

3.2.2 Population

Section B.2.3.1.1 of the CS (p.34) summarises the population of the KEYNOTE-826 trial.

3.2.2.1 Points for critique

Applicability of the trial population to UK practice

The KEYNOTE-826 excluded patients with an ECOG performance status greater than 1 (i.e. those with lower fitness). However, the anticipated licence for pembrolizumab does not restrict patient eligibility on the basis of performance status, and the ERG's clinical advisors suggest that 20-30% of patients currently receiving systemic therapy have an ECOG performance status of 2 (Table 6). This value may be slightly higher among patients with metastatic disease (30-35%). In addition, the proportion of patients in KEYNOTE-826 with a ECOG performance status of 0 (56.2%) is greater than would be expected in practice (10-15%). Therefore, on average, patients in KEYNOTE-826 are likely to have been fitter than those in the UK treatment population.

Table 6 Proportion of participants by ECOG performance status: KEYNOTE-826 vs UK practice

ECOG performance status	KEYNOTE-826 (CPS≥1 population)	Current recipients of systemic therapy in UK clinical practice (ERG clinical advisor estimates)
0	56.2%	10-15%
1	43.4%	50-60%
2	[redacted]*	20-30%

*Patients with ECOG 2 PS were ineligible for KEYNOTE-826

Despite being an international multicentre trial, KEYNOTE-826 did not include any UK sites. The ERG's clinical advisors noted that the proportion of patients of white ethnicity in the trial (59.3%; Table 6 of the CS) was notably lower than would be seen in UK practice (approximately 85%), but that this is unlikely to cause major generalisability concerns.

Baseline comparability of treatment arms

Table 6 of the CS (p.35) summarises key baseline participant characteristics from KEYNOTE-826. Most characteristics were balanced between arms, except for a greater proportion of patients with adenocarcinoma in the placebo arm (24% placebo vs 17% pembrolizumab). As prognosis for

adenocarcinoma is poorer than for squamous cell disease, this could have affected results to slightly favour pembrolizumab (see risk of bias section 3.1.4)

The ERG requested the proportion of patients receiving cisplatin and paclitaxel and the proportion of patients receiving carboplatin and paclitaxel in each trial arm (PfC A3). These data are reported in Table 7 below and values appear balanced between the trial arms. [redacted] reflects UK practice, where carboplatin/paclitaxel is often preferred due to clinician familiarity with this combination, and toxicity concerns (particularly nephrotoxicity) relating to cisplatin in this population.

Table 7: Distribution of participants by administered treatment from cycle 1 to cycle 6. Participants with CPS ≥1 (APaT)

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

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

Source: Response to PfC A3, Table 1

3.2.3 Effectiveness

Section B.2.6. of the CS presents the clinical effectiveness results of KEYNOTE-826, with further outcome data reported in Appendix O.

3.2.3.1 Points for critique

Progression-free survival per RECIST 1.1 by investigator assessment (CPS≥1 population)

Table 9 and Figure 4 of the CS (p.42-3) present the results for PFS per RECIST 1.1 by investigator assessment, which show a statistically significant reduction in the risk of disease progression or death in patients treated with pembrolizumab compared with placebo. In response to a request from the ERG (PfCs A7, A10), the company provided the PFS Kaplan-Meier plots with added 95% confidence intervals for the CPS≥1 population, both including and excluding the 'metastatic at initial diagnosis' subgroup (see Figure 1 and Figure 2 below). There is a [redacted] between the curves in Figure 2, [redacted]. This is consistent with the data from the subgroup analysis that showed [redacted] (see section 3.2.3.1).

Figure 1: Progression-free survival per RECIST 1.1 by investigator assessment (CPS≥1 population) with 95% confidence intervals added to the curves

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A7)

Figure 2 Progression-free survival as assessed per RECIST 1.1 by investigator assessment (CPS ≥ 1 population, without 'metastatic at initial diagnosis')

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A10)

Overall survival (CPS≥1 population)

Table 10 and Figure 5 of the CS (p.44-5) present the results for OS, which suggests significantly longer survival in the pembrolizumab group compared with the placebo group. As acknowledged in the CS, the OS data are immature, with median OS yet to have been reached for the pembrolizumab arm in the presented interim analysis. This has implications for the cost-effectiveness modelling, which relied on progression data to inform longer-term mortality extrapolations (see Section 4.2.6.1).

The OS Kaplan-Meier plot with added 95% confidence intervals requested by the ERG is presented in Figure 3 below.

Figure 3: Overall survival (CPS≥1 population) with 95% confidence intervals added to the curves

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: Response to PfC A7)

Objective response rate (ORR) per RECIST 1.1 by investigator assessment (CPS≥1 population)

Section B.2.6.1.3 of the CS (p.45) reports ORR from KEYNOTE-826. This significantly favours pembrolizumab over placebo, due to the greater percentage of patients achieving complete response (22.7% vs 13.1%) or partial response (45.4% vs 37.1%).

As shown in section B.2.6.1.5 of the CS, a patient's response status is highly prognostic of both OS (figure 7, p.49) and PFS (figure 8, p.50), with poorer outcomes observed for each decrease in response category. It appears from these figures that pembrolizumab-related gains in PFS and OS observed in KEYNOTE-826 are largely driven by responders. For patients with stable disease status, there appears to be little or no difference between pembrolizumab and placebo arms in terms of PFS (median ~26 weeks in each arm) or OS (median ~52 weeks in each arm). However, the ERG's clinical advisors noted that even achieving stable disease could be considered a good result in this population, particularly among younger patients with young children.

Duration of response per RECIST 1.1 by investigator assessment (CPS≥1 population)

Section B.2.6.1.4 of the CS (p.46) briefly summarises the duration of response data from KEYNOTE-826. The Kaplan-Meier plot with added 95% confidence intervals requested by the ERG is presented in Figure 4 below. Despite the numerically longer median duration of response among pembrolizumab-treated patients, the confidence intervals for the two treatment arms substantially overlap for much of the available follow-up period.

Figure 4: Duration of response (CPS≥1 population) with 95% confidence intervals added to the curves

[redacted]

Key: TRT01PN=1: Pembrolizumab + Chemotherapy, TRT01PN=2: Placebo + Chemotherapy (Source: response to PfC A7)

Health related quality of life

Section B.2.6.2 of the CS reported health related quality of life (HRQoL) outcomes from KEYNOTE-826. The main body of the document presented results of the EuroQol EQ-5D-5L VAS score for the CPS≥1 population. While the proportion of patients with an improved or stable score over a 30-week follow-up slightly favoured pembrolizumab over placebo [redacted]), the between group differences in least-squares mean change from baseline over the same period did not ([redacted]). Time to deterioration on this score was longer among pembrolizumab- than placebo-treated patients, [redacted]).

The principal pre-specified HRQoL measure for the trial was the EORTC QLQ-C30 global score (results reported in CS Appendix O.1.1.2). Briefly, [redacted] difference between treatment arms was observed for this measure, either in terms of difference in least-squares mean change from baseline to week 30 ([redacted]) or time to deterioration ([redacted]).

Based on these results, the observed delays in progression among pembrolizumab-treated CPS≥1 patients in KEYNOTE-826 does not appear to translate into substantial HRQoL benefits.

Subgroup analyses

The company estimated treatment effects, as HRs and corresponding 95% CIs for PFS and OS for the following subgroups in order to determine whether treatment effects were consistent across the subgroups:

1) Metastatic at initial diagnosis (yes/no)
2) Bevacizumab use (yes/no)
3) PD-L1 status (CPS < 1/ 1≤ CPS <10/ CPS ≥ 10)
4) Age (< 65 years/ ≥ 65 years)
5) Race (white/ non-white)
6) ECOG performance status (0/1)

The estimated HRs and 95% CIs were presented graphically as forest plots for the CPS ≥ 1 population (Figures 13 and 14 in CS Document B), and for the ITT population (Figures 5 and 6 in CS Appendix E). The company was confident that the benefit of pembrolizumab compared to placebo was demonstrated for all subgroups for primary and secondary endpoints, as the HRs comparing pembrolizumab to placebo were less than 1 in all subgroups, and were consistent with the overall HR. However, the 95% CI for patients who were metastatic at initial diagnosis, aged ≥65 years, or were not white intersected the line of "null effect" for both PFS and OS, indicating that the HRs for these subgroups were not statistically significant. In their initial submission document, the company did not test for interactions for any of the subgroups.

Although the HRs estimated for patient subgroups are consistent with HRs for the CPS ≥ 1 population from KEYNOTE-826, the results presented in Figures 13 and 14 in CS Document B cannot be considered formal comparisons.

Age

The forest plots in Figures 13 and 14 show that while the benefit of pembrolizumab for patients under 65 years was statistically significant for both OS and PFS, this benefit was not statistically significant in patients aged 65 years or older. The patient age subgroup could become more important over time

especially with the continued uptake of the HPV vaccine; with more vaccinated younger women, over time the population of patients with cervical cancer would be older.

Metastatic at initial diagnosis

Patients who were metastatic at initial diagnosis had statistically significant worse outcomes for PFS and OS compared to patients who were not. The apparent lack of effect was similar in terms of HRs to those seen in the subgroup of patients who had a PD-L1 status of CPS <1, which was excluded from the EMA's marketing authorisation.

In their response to PfCs, the company provided results for a test of interaction for the 'metastatic at initial diagnosis' subgroup (PfC A8). The analysis of deviance for the interaction of patients being metastatic at initial diagnosis and treatment group was shown to be statistically significant [redacted]. However, the company cautioned against over-interpreting results of post-hoc analyses as KEYNOTE-826 was not designed or powered to allow for formal testing of the heterogeneity in subgroups.

Patients diagnosed with Stage IV (or metastatic) cervical cancer have a much lower survival rate comparatively. According to Table 3 in CS Document B, only 17.9% of patients who were diagnosed as stage IV survived beyond 4 years compared to 90.6% of patients who were diagnosed with stage I cervical cancer. In their response to PfC A9, the company reiterated that patients who are metastatic have a poorer prognosis compared to patients who are not. The ERG's clinical advisors considered it plausible that patients who were metastatic at initial diagnosis could respond differently to treatment compared to patients who were not.

PD-L1 Status

The company stratified PD-L1 status into three categories according to the patient's CPS. Patients who had a CPS < 1 were excluded from any clinical- and cost-effectiveness analyses as they were not relevant to the marketing authorisation. The remaining patients were separated into 1 ≤ CPS <10 and CPS ≥ 10. PD-L1 status has been regarded as an important biomarker for predicting treatment effect in previous appraisals (TA 737), and by the company's clinical advisors.[22] Figures 5 and 6 (CS Appendix E.1.2) show that the higher-CPS subgroups have larger point-estimates for PFS and OS, though for the licenced subgroups of interest (i.e. 1≤CPS<10 and CPS≥ 10), the difference is small and both subgroup estimates fall within each other's CI.

In response to a query from the ERG, the company provided mean PD-L1 CPS data by best response category from KEYNOTE-826 (see Table 8). This indicates some evidence of a relationship between CPS and response among pembrolizumab treated patients that is not apparent in placebo treated patients.

Table 8 Mean (SD) PD-L1-CPS by best response category observed in KEYNOTE-826

	Mean (SD) PD-L1 CPS	
Response	**Pembrolizumab + Chemotherapy**	**Placebo + Chemotherapy**
CR as per investigator assessment	[redacted]	[redacted]
CR as per IRC assessment	[redacted]	[redacted]
PR as per investigator assessment	[redacted]	[redacted]
PR as per IRC assessment	[redacted]	[redacted]
SD as per investigator assessment	[redacted]	[redacted]
SD as per IRC assessment	[redacted]	[redacted]
PD as per investigator assessment	[redacted]	[redacted]
PD as per IRC assessment	[redacted]	[redacted]

Source: Response to PfC A6

Bevacizumab use

The ERG considers the subgroup of patients who are eligible for and receive bevacizumab to be a distinct population from patients who are contraindicated and cannot receive it. According to the ERG's clinical advisors a patient's eligibility for bevacizumab depends on their fitness and whether they have comorbidities. Patients who have cardiac symptoms, risks of hypertension and risks for fistulas are generally not eligible for bevacizumab.

In their response to PfC B5, the company disagrees with the ERG as they believe bevacizumab eligibility is not an objective quantity in the way a biomarker, histology or cancer stage would be. The decision to receive bevacizumab is made after discussion between a patient and their clinician following a benefit/risk assessment. The ERG appreciates that it might be difficult to differentiate between the two subpopulations as receiving bevacizumab greatly depends on clinician judgement. However, the ERG considers the two subgroups to differ in terms of prognosis and treatment effect such that they could be considered distinct populations.

As the trial was not powered to formally assess the difference in efficacy in the bevacizumab and non-bevacizumab population, it is difficult to determine whether there was a difference in the two subpopulations in terms of treatment effect. In their response to PfC B5, the company point out that splitting the population into these subgroups would reduce the number of events that would be used to produce robust cost-effectiveness analyses, which the ERG also appreciates.

The company also detailed what they considered negative implications of differentiating between patients based on bevacizumab eligibility. The company believed that different recommendations based on whether patients received bevacizumab could lead to equality concerns, could incentivise clinicians to prescribe bevacizumab in order to allow patients to receive pembrolizumab, or could restrict treatment options for patients.

The ERG does not think patient eligibility for bevacizumab raises any concerns about equality as treatment eligibility is not influenced by any protected characteristics.

3.2.4 Adverse events

Adverse event (AE) data were reported on pages 60-67 of the CS. AEs were assessed in the safety analysis population which comprised 616 patients who had received at least one dose of trial treatment in KEYNOTE-826. Results were presented as tables of frequencies and percentages. Table 13 of the CS presents a summary of AEs. Although [redacted] no tests of statistical significance were presented.

The activation of the immune system by immune checkpoint inhibitors, such as pembrolizumab, can enhance the immune response against cancer cells. However, this activation can also induce the development of immune-related AEs, which may affect multiple organ systems. In the CS, a section on 'Adverse events of special interest' (AESIs, CS p65) collectively included immune-mediated events (associated with pembrolizumab's mechanism of action) and infusion-related reactions. In KEYNOTE-826, rates of the following AESIs were all higher in the pembrolizumab group than in the placebo group: hypothyroidism, hyperthyroidism, thyroiditis, colitis, severe skin reactions, pneumonitis and hepatitis (see CS, Table 17). There was no meaningful difference between groups in the incidence of infusion reactions. The published paper for KEYNOTE-826 also reported that 34% of pembrolizumab patients had potentially immune-mediated AEs compared with 15% in the placebo group, including in 11% and 3%, respectively, who had grade 3 to 5 events.[23] No statistical comparisons for these outcomes were made, partly because immune- or potentially immune-mediated adverse events "*have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation*."[24]

The *Special warnings and precautions for use* section of the SmPC for pembrolizumab lists numerous immune-related adverse reactions and advises that patients should be monitored for such events.[5] This section of the SmPC also advises that pembrolizumab in combination with chemotherapy should be used with caution in patients ≥75 years after careful consideration of the potential benefit/risk on an individual basis. Considering that pembrolizumab has been approved for use in many other types of cancer for several years, the ERG sought to identify broader evidence on the incidence of AESIs. An Information Specialist (HF) designed a search strategy to identify systematic reviews of immune-mediated AEs of pembrolizumab and PD-1 inhibitors. Ovid Embase was the only database used, due to time constraints and because of its extensive coverage of drugs and pharmacology. The strategy used relevant subject headings and search syntax for the database and was limited to English language

papers from 2015 to the present. Eligible reviews had to report a meta-analysis of RCT data comparing immune-mediated AE rates in the pembrolizumab and/or PD-1 inhibitors arms with the placebo/standard care arms. Results had to be reported as odds ratios or relative risks with 95% confidence (or credible) intervals. To maximise sample sizes, eligible reviews had to evaluate more than one type of cancer population.

Fourteen eligible reviews with meta-analyses were identified, which were published between 2017 and 2022 (Table 9). As a class, PD-1 inhibitors significantly increase the risk of patients developing pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders. In the colitis meta-analysis, reported in Wang et al 2020,[25] six of the seven trials of PD-1 inhibitors were of pembrolizumab, whereas in Wang et al's 2020 pruritus meta-analysis only one study was of pembrolizumab. Some of the reviews also reported meta-analyses for only pembrolizumab trials (for some outcomes); these showed pembrolizumab to be significantly associated with increases in the risk of developing pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders.

The evidence of the incidence of rashes was somewhat uncertain. There was no evidence of associations between PD-1 inhibitors and pneumonia and no evidence of associations with cardiovascular AEs.

ERG summary

The main CS document does not clearly state that pembrolizumab is significantly associated with numerous immune-related AEs, which patients need monitoring for (although this is stated in the SmPC). The RCT evidence for pembrolizumab studied in a broad range of cancer populations shows significant associations with pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders. For PD-1 inhibitors as a class, the RCT evidence shows significant associations with pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders.

Table 9 Published recent meta-analyses of PD-1 inhibitor immune-related adverse events

Study, funding	No. of studies, No. of patients	Intervention	AESI outcomes	Results (95% CI), Heterogeneity (I^2 value)
Fujiwara et al 2021,[26] None	8, 5190	PD-1 inhibitors	Pneumonitis grades 1-5 Pneumonitis grades 3-5	OR 2.43 (1.54 to 3.85), I^2=4% OR 2.15 (1.05 to 4.43), I^2=0%
Hu et al 2021,[27] Government (China)	7, NR on forest plot	PD-1 inhibitors	Arrhythmology grades 1–5 Cardiac failure grades 1–5 Coronary artery disease grades 1–5 Pericardial disease grades 1–5 Cardiac arrest grades 1–5	OR 0.77 (0.23 to 2.63), I^2=50% OR 0.96 (0.36 to 2.58), I^2=0% OR 1.17 (0.34 to 4.00), I^2=26% OR 0.88 (0.27 to 2.93), I^2=0% OR 0.79 (0.25 to 2.92), I^2=0%
Huang et al 2019,[28] Government (China)	7, NR on forest plot	Pembrolizumab	Pneumonitis	OR 5.40 (2.39-12.17), NR
Huang et al 2019,[29] NR (no conflict of interests declared)	3, 1286	PD-1 inhibitors	Immune-related AEs grades 3-5	OR 2.27 (1.61 to 4.58), I^2=0%
Rahouma et al 2019,[30] NR (no conflict of interests declared)	13, 6118 (AG) 11, 6118 (HG)	PD-1 inhibitors	All grade pneumonitis (AG) High grade pneumonitis (HG)	OR 4.11 (1.50 to 11.22) I^2=80% OR 2.32 (1.19 to 4.51) I^2=15%
Su et al 2018,[*31] None	9, 4289 (PD1) 4, 2346 (P)	PD-1 inhibitors (PD1) Pembrolizumab PD-1 inhibitors Pembrolizumab (P) PD-1 inhibitors Pembrolizumab	Endocrine disorders grades 1-5 Endocrine disorders grades 1-5 Hyperthyroidism grades 1-5 Hyperthyroidism grades 1-5 Hypothyroidism grades 1-5 Hypothyroidism grades 1-5	OR 10.75 (6.62 to 17.45), I^2=0% OR 9.85 (5.65 to 17.17) I^2=0% OR 4.87 (2.50 to 9.49) I^2=0% OR 5.09 (2.36 to 10.97) I^2=0% OR 8.34 (4.64 to 15.00) I^2=0% OR 7.73 (3.86 to 15.49) I^2=0%
Su et al 2019,[32] NR (no conflict of interests declared)	9, 4767 (PD1) 4, 2824 (P)	PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors (PD1) Pembrolizumab (P)	Pneumonitis grades 1-5 Pneumonitis grades 1-5 Pneumonitis grades 3-5 Pneumonitis grades 3-5 Pneumonia grades 1-5 Pneumonia grades 1-5 Pneumonia grades 3-5 Pneumonia grades 3-5	OR 5.17 (2.82 to 9.47) I^2=0% OR 5.35 (2.61 to 10.96) I^2=0% OR 4.14 (1.82 to 9.42) I^2=0% OR 5.64 (1.94 to 16.38) I^2=0% OR 0.88 (0.34 to 2.30) I^2=28% OR 0.90 (0.37 to 2.19) I^2=0% OR 0.70 (0.42 to 1.17) I^2=6% OR 0.62 (0.36 to 1.05) I^2=0%
Tian et al 2021,[33] Government (China)	15, 8371 11, 6285	PD-1 inhibitors	Hypothyroidism Hyperthyroidism	OR 8.34 (5.24 to 13.28) I^2=37% OR 5.59 (3.46 to 9.04) I^2=0%

Study, funding	No. of studies, No. of patients	Intervention	AESI outcomes	Results (95% CI), Heterogeneity (I^2 value)
Wang et al 2017,[34] Government (China)	5, 2745	PD-1 inhibitors	All-type all-grade hepatotoxicity All-type high-grade hepatotoxicity	OR 1.94 (1.28 to 2.94) I^2=0% OR 1.58 (0.66 to 3.78) I^2=0%
Wang et al 2020,[25] None	18, 9318 (PD1) 6, 4223 (P) 10, 5840 (PD1) 6, 4223 (P) 7, 4714 (PD1) 5, 3223 (PD1) 8, 5125 (PD1) 6, 4223 (P) 7, 4714 (PD1) 3, 2139 (PD1) 8, 4193 (PD1) 12, 10193 (PD1) 3, 2791 (P)	PD-1 inhibitors (PD1) Pembrolizumab (P) PD-1 inhibitors Pembrolizumab PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors Pembrolizumab PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors PD-1 inhibitors Pembrolizumab	Any immune-related AE Any immune-related AE Pneumonitis Pneumonitis Colitis Hypophysitis Hypothyroidism Hypothyroidism Hyperthyroidism Hepatitis Pruritus Rash Rash	RR 2.65 (1.84 to 3.83) I^2=90% RR 3.56 (2.49 to 5.10) I^2=81% RR 2.10 (0.85 to 5.18), I^2=82% RR 2.92 (1.92 to 4.44), I^2=0% RR 2.96 (1.62 to 5.38) I^2=0% RR 4.79 (1.54 to 14.89) I^2=0% RR 7.78 (5.36 to 11.57) I^2=0% RR 8.15 (5.44 to 12.20) I^2=30% RR 7.03 (4.35 to 11.34) I^2=0% RR 9.31 (2.18 to 39.85) I^2=0% RR 2.28 (1.38 to 3.76) I^2=77% RR 1.58 (0.98 to 2.54) I^2=86% RR 1.42 (0.76 to 2.68 I^2=85%
Wei et al 2020,[35] NR (no conflict of interests declared)	9, NR on forest plot 7 NR on forest plot	PD-1 inhibitors PD-1 inhibitors	Grade 1-5 Colitis Grade 3-5 Colitis	OR 3.64 (1.87 to 7.06) I^2=0% OR 4.56 (1.68 to 12.36) I^2=0%
Xavier et al 2022,[36] Hospital (Brazil)	5, 2575	PD-1 inhibitors	All grade cardiovascular AEs Grade 3–5 cardiovascular AEs	RR 0.96 (0.77 to 1.20) I^2=0% RR 1.28 (0.77 to 2.12) I^2=0%
Yang et al 2019,[37] NR	11, 6001	PD-1 inhibitors	Rash Pruritus	RR 2.11 (1.63 to 2.74) I^2=41% RR 4.49 (3.04 to 6.65) I^2=53%
Yang et al 2021,[38] None	17, NR on forest plot 16, NR on forest plot 8, NR on forest plot	PD-1 inhibitors	Hypothyroidism Hyperthyroidsim Thyroiditis	RR 8.78 (5.07 to 15.22) I^2=52% RR 7.94 (5.17 to 12.19) I^2=0% RR 5.93 (2.30 to 15.31) I^2=0%

*Reports using risk ratios in the methods section and odds ratios in the forest plots. Key: AEs Adverse events, AESI Adverse events of special interest, AG All grade, CI Confidence interval, HG High grade, NR Not reported, OR Odds ratio, P Pembrolizumab,PD1 PD-1 inhibitors, RR Relative risk

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an SLR to identify relevant clinical evidence on pharmacological treatments for recurrent, persistent, or metastatic cervical cancer. Of the 56 publications (41 trials) that were identified, only 7 trials (3 single-arm and 4 RCTs) investigated comparators that were considered clinically relevant to UK practice by the company Table 10.The ERG's clinical advisors agreed that the comparators chosen were reasonable, although topotecan is used in clinical practice in a minority of patients (circa 10%).

All trials evaluated the use of cisplatin and paclitaxel; one trial[39] compared carboplatin and paclitaxel to cisplatin and paclitaxel. Two trials[4, 40] compared treatment with cisplatin and paclitaxel to other treatments such as topotecan, vinorelbine, and gemcitabine, but these treatment arms were ignored by the company as they were not relevant comparators. GOG-240[4] was the only trial that provided evidence on the use of bevacizumab and was used by the company to validate the economic model (see Section 4.2.6.1)

Table 10. Summary of relevant comparators identified in the SLR

Study	Trial Type/ Phase	Location	ECOG Performance Status	Cancer Stage	Treatment	Age, Median (Range)	Cycles, Median (Range)	N	Median Follow-up (months)	Median OS, months (95% CI)	Median PFS, months (95% CI)	ORR, n(%)
Coronel 2018[41]	Single arm/ Phase II	Mexico	1-3	Recurrent or persistent to primary treatment, or untreated Stage IVB	Cisplatin + Paclitaxel	54 (26-91)	5 (1-6)	30	12.5 (Range:1-37)	7.7	14.3	CR: 3 (10) PR: 9 (30)
Papadimitriou 1994[42]	Single arm/ Phase II	Greece	0-3	Primary stage IV, or recurrent	Cisplatin + Paclitaxel	51 (24-77)	6 (1-6)	34	NR	9 (Range: 0.5-22.5+)	NR	CR: 5 (14.7) PR: 11 (32.4)
Rose 1999[43]	Single arm/ Phase II	US	0-2	NR	Cisplatin + Paclitaxel	47 (24-67)	6 (1-10)	41	NR	10.0+ (Range: 0.9-22.2)	5.4+ (Range: 0.3-22.0+)	CR: 5 (12.2) PR: 14 (34.1)
Monk 2008 (GOG-204)[40]	RCT/ Phase III	NR	0-1	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	50 (29-81)	6	103	NR	12.87 (10.02, 16.76)	5.82 (4.53, 7.59)	CR: 3 (2.9) PR: 27 (26.2)
					Cisplatin + Vinorelbine	49 (24-76)	5	108			3.98 (3.19, 5.16)	CR: 8 (7.4) PR: 20 (18.5)
					Cisplatin + Gemcitabine	45 (20-89)	4	112			4.70 (3.58, 5.59)	CR: 1 (0.9) PR: 24 (21.4)
					Cisplatin + Topotecan	48 (25-75)	5	111			4.57 (3.71, 5.75)	CR: 2 (0.9) PR: 24 (21.6)

Tewari 2017 (GOG-240)[4]	RCT/ Phase III	US, Canada, and Spain	0-1	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	46.5 (SD:12.1)	6 (1-6)	114	NR	15.0	6.7 (5.7, 8.1)†	CR: 11 (9.6) PR: 41 (36.0)
					Cisplatin + Paclitaxel + Bevacizumab			115		17.5	9.6 (7.2, 12.7)†	CR: 18 (15.7) PR: 40 (34.8)
					Topotecan + Paclitaxel	48.9 (SD:11.7)		111		16.2	NR	CR: 13 (11.7) PR: 41 (36.9)
					Topotecan + Paclitaxel + Bevacizumab			112		12.0	NR	CR: 13 (12) PR: 41 (37)
Kitagawa 2015 (JCOG0505)[39]	RCT/ Phase III	Japan	0-2	IVB, recurrent, or persistent	Cisplatin + Paclitaxel	53 (29-74)	NR	123	17.6	18.3 (16.1, 22.9)	6.9 (5.7, 7.9)	NR
					Carboplatin + Paclitaxel	53 (22-72)		121		17.5 (14.2, 20.3)	6.2 (5.5, 7.2)	NR
Moore 2004[44]	RCT/ Phase III	NR	0-2	IVB, recurrent, or persistent	Cisplatin	46.0 (22-84)	Unclear, in absence of disease, toxicity patients supposed to receive 6 cycles	134	NR	8.8	2.8	CR: 8 (6.0) PR: 18 (13.4)
					Cisplatin + Paclitaxel	48.5 (21-77)		130		9.7	4.8	CR: 20 (15.4) PR: 27 (20.8)

Unless specified differently for a particular study, the uncertainty for each estimate is indicated in brackets after the estimate.

† While these values do not appear in the peer-reviewed publications, they are available from the ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/results/NCT00803062) and Table 5 in Appendix D of the CS.

Abbreviations: CI: confidence interval, CR: complete responders, NR: not reported, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PR: partial responders, SD: standard deviation.

The company did not conduct an ITC, as they did not believe that it would add to the evidence provided in KEYNOTE-826. The ERG agrees with the company that the evidence available would not provide useful comparisons between treatments. However, evidence from the other studies should probably not be disregarded completely as these studies may provide longer-term survival data for comparator treatments, which were not available for KEYNOTE-826 using the current data cut-off. While most studies[40-44] identified in the SLR did not present KM plots for OS and PFS for longer than 3 years, two studies Tewari 2017[4] and Kitagawa[39] reported KM plots for 4 and 5 years, respectively.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect treatment comparison; the reasons are discussed in Section 3.3.

3.5 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence for pembrolizumab plus chemotherapy versus placebo plus chemotherapy is based on single trial (KEYNOTE-826). The study appears to be at low risk of bias for most domains, although some aspects of the trial design and the availability of only an interim analysis create areas of uncertainty.

KEYNOTE-826 shows that pembrolizumab is associated with improved PFS in the CPS≥1 population, a difference that appears to be driven largely by PFS gains among patients who achieve complete response. A similar pattern of improvement can be seen for OS, although the available data are immature and the effect is uncertain.

The company model uses PFS as surrogate for unavailable longer-term OS, though the ERG's clinical advisors were not confident that this was appropriate in the population under consideration. Extrapolation estimates of OS beyond the available trial data and into the longer-term are therefore highly uncertain.

Where reported, HRQoL differences between the treatment arms of KEYNOTE-826 are relatively small and mostly statistically non-significant.

The safety and adverse event evidence from KEYNOTE-826 is broadly in line with wider RCT evidence for pembrolizumab used in a range of cancer populations which shows significant associations with pneumonitis, hypothyroidism, hyperthyroidism and endocrine disorders. For PD-1 inhibitors as a class, the RCT evidence shows significant associations with pneumonitis, colitis, pruritis, hepatitis/hepatotoxicity, hypothyroidism, hyperthyroidism, thyroiditis and endocrine disorders.

The subgroup of patients in KEYNOTE-826 with metastases at initial diagnosis had statistically significantly worse PFS outcomes than patients without metastases at initial diagnosis. OS results were also notably different. This apparent lack of effect for PFS (in particular) and for OS was similar (in terms of hazard ratios) to that seen in the PD-L1 CPS <1 subgroup, which was excluded from the EMA's marketing authorisation.

Three issues suggest that pembrolizumab may be less efficacious when used in an NHS setting than was observed in KEYNOTE-826:

Firstly, KEYNOTE-826 excluded patients with an ECOG 2 performance status. However, the ERG's advisors estimated that 20-30% of ECOG 2 patients would be eligible for systemic treatments in the NHS. Conversely, patients with an ECOG 0 status were over-represented in KEYNOTE-826 (56% of patients) compared with the ERG advisors' estimate for the relevant NHS population (10-15%).

Secondly, in the NHS, bevacizumab would not be continued for as many cycles as was used in KEYNOTE-826 (where the number of permitted cycles was unlimited).

Finally, in KEYNOTE-826, a small chance baseline imbalance in histology (17% had adenocarcinoma in the pembrolizumab group versus 24% in the placebo group) could potentially have affected results to slightly favour pembrolizumab.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company undertook two systematic literature reviews (SLRs) to identify relevant economic evaluations and studies reporting on the health-related quality of life (HRQoL) of patients with high risk, locally advanced, and persistent, recurrent, or metastatic cervical cancer in the first-line setting.

4.1.1 Searches

The original company submission included searches to identify cost-effectiveness evidence, cost and healthcare resource use measurement and valuation, and health-related quality of life studies for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies was included in CS Appendix G (Pages 43-50) and Pages 9-21 of an embedded economic SLR report on Page 50 of Appendix G.

In response to the ERG's PFCs, a further document was provided by the company, which included clarifications on issues raised by the ERG. The ERG was largely satisfied that the conduct of the cost-effectiveness searches was methodologically sound. The ERG raised a couple of minor reservations with regards to ambiguous reporting of several aspects of the cost-effectiveness and resource use searches. A detailed appraisal of evidence identification methods is provided in Appendix 9.1.1 to 9.1.4 to the ERG Report.

4.1.2 Eligibility criteria used for study selection

Study eligibility criteria applied by the company were described in CS Appendix G for the review of economic evaluations, and CS Appendix H for the quality-of-life studies. There was no date or language limit applied. The population of interest in both cases was to include patients of broadly similar characteristics to those in KEYNOTE-826. Two reviewers independently assessed studies based on title and abstracts, with discrepancies reconciled by a third reviewer. Full text screening and data extraction was again performed by two reviewers, with any discrepancies resolved by a third reviewer.

The ERG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate.

4.1.3 Studies included in the cost-effectiveness review

A total of 30 unique studies met the inclusion criteria, of which 18 were cost-effectiveness analyses, with one budget impact model, and one NICE health technology appraisal (TA183). The company considered only the NICE appraisal relevant to the UK setting, which was published in 2009. Due to

the age of the study, the company considered it of limited relevance for the present appraisal, but did provide a comparison of their *de novo* economic analysis with TA183 in Table 20 of the CS.

The second review of HRQoL studies identified no studies relevant to the UK setting in the population under consideration. A total of 29 studies were identified which reported HRQoL data.

The ERG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses conducted in a relevant population and setting. The ERG is therefore satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 11 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 11 NICE reference case checklist

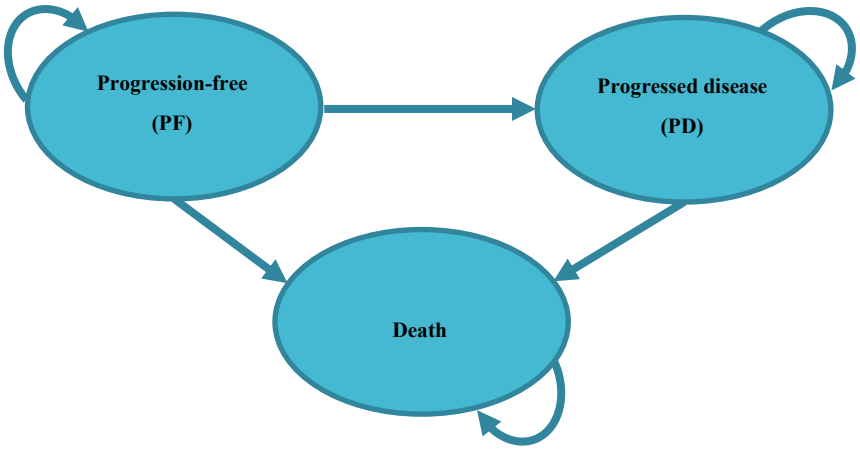
Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits to treated individuals were considered.
Perspective on costs	NHS and PSS	NHS and PSS costs have been considered.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model uses a 50-year time horizon. This is sufficient given the disease area.
Synthesis of evidence on health effects	Based on systematic review	The company initiated a systematic review to identify relevant sources of data.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	EQ-5D-5L data was collected in the KEYNOTE 826 trial. These values were cross-walked to EQ-5D-3L values using the van Hout *et al.*[46] mapping function.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Derived from EQ-5D data directly obtained from patients in the KEYNOTE 826 trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were based on UK sources including the BNF and NHS reference costs. Resource use rates were based on clinical advice.

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits have been discounted at 3.5% per annum. Scenario analysis was performed applying an annual discount rate of 1.5%.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a state transition model (STM) in Microsoft Excel to simulate the lifetime cost-effectiveness outcomes of patients with recurrent, persistent or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥ 1, who are on treatment with the standard of care (platinum-based chemotherapy +/- bevacizumab) compared to standard of care in combination with pembrolizumab. The model uses a one-week cycle length with no half-cycle correction applied. The model structure consists of three health states of 'progression-free', 'progressed disease' and 'death', See Figure 5.

Figure 5 Illustration of state transition model structure (CS Figure 16, Page 79)



In this model, the following transitions are permitted in each cycle, patients in the:

- 'Progression-free' health state could remain in the progression free state, transition into 'progressed-disease' health state or transition to the 'death' state,
- 'Progressed disease' health state could remain in the progressed disease state or transition into the 'death' state.
- 'Death' state will always remain in that state. This is an absorbing state.

At each model cycle, transition probabilities and health state occupancy were determined based on patient-level data from the KEYNOTE-826 trial for time to progression (TTP), progression-free

survival (PFS) and post-progression survival (PPS) extrapolated over the model time horizon using parametric survival models (see Section 4.2.6 for further details).

A key feature of the company's modelling approach is that it uses a STM rather than a partitioned survival model (PSM), which is typically adopted in advanced cancer evaluations. There are several key differences between a STM and a PSM in this context. Foremost among these is that a STM explicitly models the transitions between each health state, whereas a PSM model does not. This has consequences for how state occupancy is estimated. In a state transition model, state occupancy is a function of the transition probabilities applied to each health state. In a PSM, transitions between health states are not explicitly modelled. State occupancy is instead directly determined by the (observed and extrapolated) survival data (typically PFS and OS).

The company's justification for a state transition approach is described on page 37 of the CS and claims several advantages of adopting a state transition approach. A key part of this justification is founded upon the company's preferred extrapolations of TTP and PFS, which use a piece-wise approach (Kaplan-Meier (KM) data followed by parametric survival models fit from 37-weeks onwards). These preferred extrapolations lead to long tails in PFS with the consequence that extrapolated PFS and OS [redacted] for the pembrolizumab arm and standard of care (SoC) arm respectively (see Figure 6 and Figure 7 below). In a PSM (where state occupancy is determined directly from the survival curves), this would lead to inconsistencies in model predictions because the proportion of patients alive would be less than those in the progression-free state. The company's STM avoids this issue by imposing a structural surrogate relationship between PFS and OS. This surrogate relationship implies that PFS is the main determinate of predicted OS. Note this contrasts with a PSM model where OS is estimated directly using the OS curve.[47]

Figure 6 Illustration of PFS and OS KM data and parametric extrapolations; Pembrolizumab arm CPS≥1 population of KEYNOTE-826 (CS Figure 17, Page 81)

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

Figure 7 Illustration of PFS and OS KM data and parametric extrapolations; SoC arm CPS≥1 population of KEYNOTE-826 (CS Figure 18, Page 82)

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

4.2.2.1 Points for critique

In principle, the ERG considers that the STM structure can have several advantages over a PSM when mature PFS and OS data are available. Specifically, the structural links imposed in STMs imply an explicit disease model that allows both the natural history of the disease and the effect of treatment to be reflected when extrapolating beyond the trial data. The assumptions underpinning these extrapolations are also made explicit and therefore subject to scrutiny and sensitivity analyses.[47] Importantly, PSMs and STMs are also expected to produce similar results for within-trial data because relationships between endpoints are reflected within the data.

An STM is, however, a substantially more complicated approach and has several drawbacks when data are immature. One important consequence of the STM approach is the structural link between PFS and OS which implies a surrogate relationship between PFS and OS. The CS does not fully justify this assumption. The CS states that elicited clinical opinion supported the concept of a positive relationship between the duration of progression and PPS survival. Appendix Q of the CS also provides evidence from a within trial analysis of KEYNOTE-826 examining the relationship between TTP/PFS and PPS, and reports a positive correlation between TTP and PPS. While the ERG considers this evidence broadly supportive of this assumption, no evidence is provided to suggest that TTP/PFS is a validated surrogate for OS, and notes that the observed correlation between PFS and PPS does not necessarily indicate a causal relationship. . The ERG considers the lack of supporting evidence for a surrogate relationship between PFS and OS to be an important omission. A failure to validate may lead to misleading cost-effectiveness estimates.[48, 49] Moreover, the NICE methods guide states: *"When the use of 'final' clinical endpoints is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling."* The ERG also highlights precedent from previous technology appraisals, which have raised concerns regarding the validity of PFS as a surrogate for OS (TA658).[50]

In the context of the current model, the ERG notes that the model predictions do not align well with the observed OS data from KEYNOTE-826. As illustrated in Table 12, the base-case model systematically overpredicts the proportion of patients alive at early time points and then underpredicts at later time points. The ERG is particular concerned about the underprediction at 24 months which is more pronounced in the SoC arm suggesting a bias in favour of pembrolizumab. The ERG notes this issue is persistent and is not sensitive to the parametric models used to extrapolate TTP, PFS, and PPS, suggesting it is a consequence of the modelling approach. The ERG considers that this is likely to be a consequence of how PPS transitions are modelled, as PFS predictions align relatively well

with the observed data. Specifically, this may result from the assumption that transitions in the PPS health state are unrelated to the timing of progression events. The duration of PPS is therefore the same regardless of whether a progression occurs in cycle one or cycle 1001. It is not clear if this is appropriate, and this assumption is not assumed in a PSM where PFS curves and OS curves are estimated independently.

Table 12 Comparison of model predictions and observed OS data

	Pembrolizumab		SoC	
	KEYNOTE 826	Economic model	KEYNOTE 826	Economic model
6 Months	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	[redacted]	[redacted]	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]	[redacted]
24 Months	[redacted]	[redacted]	[redacted]	[redacted]

In addition to the above, the ERG also has substantive concerns regarding the company's justification for the STM approach. As stated above, the company's justification is founded on the extrapolations of PFS data and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations. However, it is not clear that the PFS extrapolations preferred by the company are clinically plausible, and the ERG notes that the crossing of PFS and OS is solely because a piecewise approach is adopted to the extrapolation of PFS. Crossing does not occur when a single-parametric curve is fitted to the whole KM data.

The ERG further notes that the company's base-case analysis predicts that a non-negligible proportion of patients will achieve long-term survival of 5 or more years with a smaller proportion effectively cured and achieving survival near that of the general population. Importantly, the proportion of long-term survivors is substantially greater in the pembrolizumab arm of the model (22.7% in the pembrolizumab arm survive for 5 or more years compared with 8.9% of patients receiving SoC) and this drives a significant proportion of the benefits associated with pembrolizumab. The plausibility of these predictions is discussed in later sections but in terms of the model structure the ERG highlights that the long-term benefits of pembrolizumab predicted by the model are heavily dependent on the approach to extrapolating PFS, and are a direct consequence of the structural link between PFS and OS imposed by the STM.

4.2.3 Population

The modelled population is adults with untreated recurrent, persistent or metastatic cervical cancer whose tumours express PD-L1 (CPS≥1). This population aligns fully with the anticipated marketing authorisation for pembrolizumab but is a narrower population than that defined by the NICE scope which included all adult patients with untreated recurrent, persistent or metastatic cervical cancer.

In line with the narrower focus of the marketing authorisation, the modelled population is based upon CPS≥1 subgroup of KEYNOTE-826 which accounted for approximately 89% of the ITT population (n=548). The baseline characteristics of the modelled population are presented in Table 13 and include age, sex, weight, and body surface area. Age and sex were used to parameterise a general population mortality cap imposed in the model. Age also drives age-related utility adjustments to HRQoL. Weight and body surface area were used to inform the dose associated with several interventions and comparators, see Section 4.2.8.1 for details.

Table 13 Baseline patient characteristics of modelled population

Age	[redacted]
Sex	100% female
Weight	[redacted]
Body surface area	[redacted]

The NICE scope listed several subgroups of relevance, histology, pelvic disease status, PD-L1 expression (CPS<10, CPS ≥10) and tumour mutational burden. At the clarification stage the ERG also requested subgroup analysis according to whether patients received bevacizumab. The company did not consider any patient subgroups in the model, in the base-case or otherwise.

4.2.3.1 Points for critique

ECOG Performance Status

Inclusion criteria applied in KEYNOTE-826 restricted eligibility to patients with an ECOG performance status of either 0 or 1. Consequently, with the exception of one patient in the pembrolizumab arm, there were no patients in the trial with an ECOG status of 2. Discussions with the ERG's clinical advisors, however, suggested that some patients (circa 20-30%) with an ECOG status of 2 would receive systemic treatment in NHS practice. The ERG notes that the anticipated marketing authorisation for pembrolizumab does not restrict eligibility by ECOG status and therefore patients with an ECOG status of 2 could be eligible to receive pembrolizumab in practice (see Section 3.2.2.1). The ERG's clinical advisors considered this clinically plausible.

The lack of clinical evidence to support effectiveness in this sub-population represents a significant uncertainty. ECOG status is an established prognostic factor and may also impact on relative treatment effects, though the direction of this effect is unknown. The cost-effectiveness of pembrolizumab in an ECOG 2 population is therefore highly uncertain and the ERG considers that it would be inappropriate to extrapolate cost-effectiveness estimates from an ECOG <2 population to an ECOG 2 population given these uncertainties.

Eligibility for Bevacizumab

In base case cost-effectiveness analyses the company did not differentiate between patient subpopulations based on their eligibility for bevacizumab and did not provide relevant subgroup analysis following a request by the ERG at the clarification stage; their reasons for not differentiating the subpopulations are detailed in Section 3.2.3.1. The ERG considers that eligibility to receive bevacizumab defines two distinct decision problems as these represent distinct populations that may differ with respect to prognosis, relative treatment effects and costs. Pooling these populations, as has been done in the company's base-case analysis, therefore fails to recognise the potential for heterogeneity in cost-effectiveness estimates across these two populations. The ERG considers that further efforts to explore this uncertainty are necessary to establish the cost-effectiveness of pembrolizumab in both groups of patients.

Metastatic Patients

As discussed in Section 3.2.3.1, subgroup analysis presented in Figures 13 and 14 of CS Document B, demonstrates a substantial difference in the point estimates according to whether or not they were diagnosed with metastatic disease at their initial diagnosis (OS: HR 0.88, 95% CI (0.58, 1.35) vs HR 0.56, 95% CI (0.41, 0.75) respectively). Importantly, these analyses show no statistically significant treatment effect in the metastatic population, and additional analysis requested at clarification indicates a statistically significant interaction between treatment and metastatic status.

The ERG is conscious that the trial was not powered to formally investigate treatment effectiveness in subgroups but considers the results strongly suggestive of a difference in the relative treatment effects across these two groups. The company acknowledges that patients who are metastatic have a poorer prognosis, and according to the ERG's clinical advisors it is biologically plausible that treatment effect may differ in patients relative to baseline metastatic status. Therefore, the ERG considers that it would have been appropriate to explore this subgroup within the economic analysis and notes that the failure to do so means that heterogeneity in cost-effectiveness estimates is not fully reflected in the company's economic analysis.

4.2.4 Interventions and comparators

As described in Section 2.2, pembrolizumab is a humanised monoclonal anti-PD-L1 antibody, which binds to the PD-1 receptor expressed by tumour cells and thus allows the patient's immune system to target and destroy these cells. The anticipated marketing authorisation permits use of pembrolizumab only in combination with chemotherapy, with bevacizumab as an optional additional therapy.

The recommended dose of pembrolizumab in adults is either 200mg Q3W or 400mg Q6W, administered as an intravenous infusion over 30 minutes. Patients in KEYNOTE-826 received 200mg Q3W until discontinuation, or for up to a maximum of 24 months, or up to a maximum of 35 cycles. Pembrolizumab treatment is implemented in the economic model as per its use in KEYNOTE-826, i.e., 200mg Q3W up to a maximum of 35 cycles in combination with SoC.

The NICE scope identified several relevant comparators; platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel, topotecan, or etoposide. In addition, for those who would receive bevacizumab: paclitaxel and carboplatin or cisplatin with bevacizumab (15mg/kg Q3W). The company's submission did not address etoposide or topotecan, reasoning that cervical cancer is not included as an indication in the etoposide SmPC, and is used only in small cell cervical cancer, which was not covered in the KEYNOTE-826 trial. Topotecan was recommended in this population in TA183, but the company stated that their clinical experts agreed that topotecan was not currently in use in the NHS for this indication. Platinum-based monotherapy was also excluded from the list of comparators to align with options recommended by the BGCS guidelines[2] and clinician feedback.

The comparators as modelled by the company were platinum chemotherapy in combination with paclitaxel, with or without bevacizumab, up to a maximum of 6 treatment cycles. Carboplatin is modelled at a flat dose of 750 mg Q3W. Cisplatin is modelled at a dose of 50 mg/m^2 Q3W. Paclitaxel is modelled at a dose of 175 mg/m^2 Q3W. Bevacizumab is implemented in the model at a dose of 15 mg/kg Q3W.

The company submission noted that bevacizumab was available as an option through the Cancer Drugs Fund (CDF), but the ERG has clarified with NICE that bevacizumab is now in routine commissioning in this indication.

The composition of SoC was modelled according to the proportions on each treatment arm in KEYNOTE-826 and are reproduced in Table 14 below.

Table 14 Modelled comparator therapies (CS Table 21, Page 91)

Treatment	Pembrolizumab + SoC n (%), n total = 272	SoC only n (%), n total = 275
Pembrolizumab	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin + Carboplatin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]

Points for critique

Exclusion of etoposide and topotecan

The ERG considers the interventions and comparators included in the economic model to be broadly appropriate and consistent with the decision problem. The ERG's clinical advisor agreed with the exclusion of etoposide as a comparator but stated that topotecan was still used in some patients (circa 10%). The efficacy of topotecan is unlikely to differ significantly from SoC, and as the proportion of patients receiving this treatment on the NHS is unclear, the ERG does not consider this uncertainty to have meaningful implications for estimates of the cost-effectiveness of pembrolizumab.

Inclusion of bevacizumab as a comparator

The ERG accepts that bevacizumab combination therapy is used routinely in NHS practice for the treatment of recurrent, persistent or metastatic cervical cancer. However, the ERG considers a comparison with bevacizumab combination therapy to be problematic due to the unique circumstances in which it entered commissioning on the NHS. The ERG understands that bevacizumab underwent no formal public assessment of cost-effectiveness prior to its entry into the CDF and was not reviewed by NICE when it entered routine commissioning. The cost-effectiveness of bevacizumab is therefore unknown and it is plausible that bevacizumab is not a cost-effective technology.

Further, while the ERG recognises that consideration of the cost-effectiveness of bevacizumab is beyond the scope of this appraisal, its cost-effectiveness has implications for the cost-effectiveness of pembrolizumab and therefore the ERG considers it relevant to the current decision problem. The impact of this issue on cost-effectiveness estimates is difficult to untangle due to pembrolizumab being an adjunctive therapy, and ideally would be addressed by fully incremental analysis considering each of the four alternatives (doublet chemotherapy, doublet chemotherapy plus bevacizumab, doublet chemotherapy plus pembrolizumab, doublet chemotherapy plus bevacizumab and pembrolizumab) in

a bevacizumab eligible population. Lack of appropriate comparative evidence, however, makes any such comparison difficult. Resolution of this uncertainty may be partially addressed by considering subgroup analysis of KEYNOTE-826 stratifying by eligibility to receive bevacizumab. Subgroup analysis was requested by the ERG at the clarification stage but was not provided by the company in their response. The ERG considers that this issue should be further explored as part of the Technical Engagement process.

Bevacizumab monotherapy

Bevacizumab monotherapy was permitted to continue in KEYNOTE-826 beyond completion of the allowed cycles of platinum-based chemotherapy, with a median of [redacted] cycles in the pembrolizumab arm, and [redacted] cycles in the SoC arm. As noted in the CS, bevacizumab may only be used in conjunction with chemotherapy on the NHS. The company therefore adjusted the administration and acquisition associated with bevacizumab assuming a maximum treatment duration of 6 cycles. Clinical advice to the ERG suggests that, while official guidance restricts bevacizumab use to 6 cycles, it is sometimes used as a maintenance therapy. This appears to be confirmed by the company's clinical advisors, as reported in the advisory group meeting report.[22] The frequency with which bevacizumab maintenance therapy is used in the NHS is unclear, though it appears to be in a minority of patients. The ERG, notes that scenario analysis exploring this uncertainty results in a reduction in the ICER. The company's base case is therefore conservative with respect to this assumption.

Retreatment with pembrolizumab

The ERG noted that re-treatment with pembrolizumab was permitted in the KEYNOTE-826 protocol and requested that the company provide information on the proportion of patients receiving re-treatment and the duration of any such re-treatment. The company stated that while no patients received re-treatment as defined in the protocol, a small number of patients were treated with pembrolizumab following progression, amounting to [redacted] of progressed patients in the pembrolizumab arm, and [redacted] of progressed patients in the SoC arm. The company therefore provided a scenario analysis accounting for these costs. The ERG considers it unlikely that NHS England would approve retreatment with pembrolizumab. However, the effect of retreatment in terms of costs and predicted benefits is unlikely to have a significant impact upon the estimates of cost-effectiveness as illustrated by the scenario analysis.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[51] the company's analysis adopted a NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. The impact of alternative discount rates for costs and QALYs (1.5%) were explored in scenario analysis.

A lifetime horizon of 50 years was chosen to capture all relevant differences in costs and benefits between comparators. The impact of a shorter 40-year time horizon was also explored in scenario analysis. The use of a lifetime horizon is considered appropriate by the ERG and necessary to account for the claimed long-term survival gains associated with pembrolizumab.

4.2.6 Treatment effectiveness and extrapolation

As discussed in detail in Section 4.2.2, the company used a STM consisting of three health states: Pre-progression, Post-progression, and Death. Consistent with this model structure TTP, PFS and PPS were estimated. Each of these were informed by data from the KEYNOTE-826 trial which was the primary data source for the economic analysis. All model inputs from the KEYNOTE-826 trial are based on the interim May 2021 data cut. The ERG notes that a further and final data cut is expected to be available in [redacted] of [redacted].

4.2.6.1 Progression free health state

In line with the STM approach, transition probabilities were estimated to determine state occupancy. In the progression-free health state, patients could remain in the progression free health state, or transition to either the progressed disease or death health states. Transition probabilities were estimated using TTP and PFS data from the KEYNOTE-826 trial. Transition probabilities associated with remaining in the progression free health state or transitioning to the progressed disease state were informed by TTP, while transitions to the death state were modelled using the difference between TTP and PFS.

To inform the transition probabilities used in the progression free health state it was necessary to extrapolate the available TTP and PFS survival data. This was done using standard parametric models, with the same model type used for both TTP and PFS to ensure model results remained clinically plausible.

The company's base case model adopts a two-piece approach to modelling TTP and PFS. This two-piece approach directly applied observed TTP and PFS KM data from the KEYNOTE-826 trial to inform transition probabilities up to 37 weeks, followed by the use of parametric survival models fitted to the remaining observed data. This approach was adopted to inform the long-term extrapolations of the data after the company concluded that a single piece model (a parametric distribution fitted to the whole KM curve) had poor visual fit to the observed data and was unable to appropriately capture what they considered an emerging plateau in the observed survival data and the associated changes in the hazard function. In their justification for a two-piece approach, the company noted an 'inflection point' in the KM data between weeks 40 and 60, after which there is plateau in observed progression events. The company considered this plateau to exist in both the pembrolizumab and SoC arms, but that it was more pronounced in the pembrolizumab arm leading to divergence in

the KM curves. Cumulative hazard plots were reported as supportive evidence for this decline in the hazard rate. These are reported in in Figures 26 and 27 of the CS and show that the hazard rate begins to decline from approximately 37 weeks. Statistical assessment of a structural break was also assessed using a Chow test which supported a cut-off at 65 weeks for pembrolizumab and at 63 weeks for SoC.

In exploring alternative cut points, the company considered it preferable to align time points with the completion of tumour imaging assessment schedules. This suggested 37 weeks, 46 weeks or 55 weeks as potential cut-off points. Based on the number of patients at risk after each of these points a 55-week cut off was dismissed as inappropriate. A 37-week cut- off was selected for the base case analysis, with scenario analysis considering a 46-week cut-off.

The company's process for fitting survival models was by testing the proportional hazards assumptions (using log-cumulative hazards plots and Grambsch-Therneau correlation tests between Schoenfeld residuals); these indicated that the proportional hazards assumption was violated and independent models were fitted to each treatment arm. Model selection was based on: Akaike information criterion (AIC) and Bayesian information criterion (BIC); visual fit; the desire for common functional form of models to both arms; the plausibility of hazard assumptions and clinical plausibility of the survival predictions. The AIC and BIC for the models fitted to both arms of KEYNOTE 826 can be seen in Table 23 of the CS (p104); visual inspection of the models overlying the Kaplan-Meier data can be seen in Figure 25 of the CS (p103).

Based on the criteria outlined above, the log-logistic model was selected as the most appropriate and used in the base case analysis, see Figure 8 and Figure 9 for visual fit to KM data. The company also supplied a pessimistic analysis for both the SoC and pembrolizumab arms, which was an average of the Weibull and log-logistic piecewise models for TTP and PFS.

Figure 8 Modelled TTP (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 28, Page 109)

Figure 9: Modelled PFS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 29, Page 108)

Points for critique

Extrapolation of PFS

The ERG has substantive concerns regarding the company's approach to extrapolating PFS and the two-piece approach adopted by the company. The ERG considers the company's justification for adopting a two-piece approach to be inadequate and that it emphasises fit to the pembrolizumab PFS data without appropriate consideration of the clinical plausibility of the corresponding predictions in the SoC arm.

Considering the SoC arm, the ERG disputes the company's claim that a one-piece model does not adequately fit the data. The ERG considers that several one-piece extrapolations have good visual and statistical fit to this data and generate predictions that align reasonably well with the observed data, see Figure 11 for visual fit based on ERG's preference single piece extrapolation (log-logistic model). Moreover, the ERG sees no evidence of a plateau in PFS outcomes for SoC, and considers that the inflection point followed by a rapid decline in hazards as predicted by the two-piece approach to be unrealistic, and to result in clinically implausible predictions. Specifically, the ERG highlights that the model predicts that a non-negligible proportion of patients will remain progression-free beyond 5 years ([redacted]) leading to 5-year OS of [redacted]. Clinical advice provided to the ERG suggests that it is rare for patients to achieve such long-term freedom from progression and survival on SoC, with only a minority of patients surviving beyond 5 years. In this regard, the ERG also notes that company's own clinical advisors considered the long-term (20-year) predictions for SoC overly optimistic.

Figure 10 ERG preferred Single piece extrapolation to TTP (log-logistic model)

Figure 11 ERG preferred Single piece extrapolation to PFS (log-logistic model)

With regards to the company's parametric model selection process, the ERG also questions the company's use of GOG 240[4] to validate the long-term predictions of the model, and notes several weaknesses with this approach. Firstly, while GOG 240[4] reports data at 4 years, the numbers at risk are very small and thus the landmark PFS and OS used to validate the model predictions are based on very few patients and are thus subject to substantial uncertainty. Secondly, GOG 240[4] also has important external validity issues and may not be representative of patients treated in NHS practice. The ERG especially highlights a retrospective study carried out in the US which found that only 14.5% of patients treated with bevacizumab in clinical practice would be eligible for the GOG 240 trial.[52] The GOG 240[4] population therefore represents a highly restricted population and may not be an appropriate reference for validation.

With respect to the SoC arm, the ERG therefore considers the application of a two-piece model to be inappropriate and has a strong preference for a one-piece approach. Moreover, the ERG considers issues associated with a two-piece model in the SoC arm to be relevant to establishing the credibility of predictions in the pembrolizumab arm. NICE DSU TSD 19[47] recommends that the same model type should be adopted in both the treatment and comparator arms unless strong evidence to justify a differential approach is presented.

Considering the evidence for a two-piece approach, the ERG agrees with the company that KEYNOTE-826 shows some evidence of a reduction in hazards, with some evidence suggestive of a

plateau emerging in the relevant TTD and PFS KM curves. However, the company's approach to model selection and validation using visual fit and the hazard trends places too much emphasis on the tail of the KM curve, the shape of which is driven by very few events and small numbers at risk, and is subject to a high degree of censoring. Importantly, the rapidly declining hazards result in very substantial PFS and OS gains for pembrolizumab compared to SoC. These benefits are accrued almost entirely in the extrapolated region of the curves, and are not yet in evidence in the observed data. This is exemplified by the observed median gains from KEYNOTE-826 versus the mean PFS gains predicted by the model. In the trial, median PFS was 10.4 months on pembrolizumab compared to 8.2 months in the SoC group (i.e. 2.2-month improvement), whereas the model predicted a mean improvement of 2.7 years (32 months) for pembrolizumab compared to SoC.

Moreover, the long tails predicted by the two-piece approach lead to a very substantial proportion of patients achieving long-term survival. In the base case analysis, [redacted] of patients on pembrolizumab remain in the progression-free health state at 5 years and [redacted] at 10 years. These projections are highly optimistic and imply that a proportion of patients achieve cure-like benefits. When requested to comment on the plausibility of such benefits and the significant number of long-term survivors, the company emphasised the lack of clinical experience in using both bevacizumab and pembrolizumab in this indication, but noted that long tails are commonly associated with immunotherapies in other indications. The company further highlighted the small numbers of patients eligible for systemic treatment in the UK creates challenges to eliciting accurate expectations about long-survival, particularly for patients in the pembrolizumab arm of the model.

While the ERG acknowledges that immunotherapies have historically been associated with durable response rates in other indications, there is insufficient evidence in cervical cancer to suggest that short term treatment with an immunotherapy translates into such long survival gains, nor has a possible mechanism for cure been established. The ERG consequently does not consider existing evidence to be sufficient to demonstrate the paradigm shift in outcomes modelled by the company. Of the parametric models fitted by the company, there was a clear choice made to discount the single piece models which predicted more conservative PFS (and OS) gains, and instead it is assumed that a significant proportion of patients would instead survive for many years or even decades. See Table 15 for a comparison of landmarks associated with each approach. The final data cut from KEYNOTE-826, [redacted], will likely be helpful in resolving this uncertainty and may help substantiate the purported inflection point in hazards.

Table 15 Comparison of model predictions and observed OS data

	Pembrolizumab	SoC

	Two-piece (log-logistic)	Single-piece (log-logistic)	Two-piece (log-logistic)	Single-piece (log-logistic)
1 year	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]

Duration of treatment benefit

The company assumed a lifetime treatment effect of pembrolizumab in their base case analysis. Following a request at the clarification stage, the company also presented scenario analysis to explore the impact of a gradual loss of treatment effect between three and five years. In this scenario, the rate of progression on pembrolizumab is adjusted gradually to essentially switch the curve to be equal to that of the SoC arm after five years. It therefore assumes a complete loss of treatment effect five years after patients have discontinued treatment.

In defence of the base case assumption, the company highlights that treatment waning assumptions have been applied inconsistently in previous appraisals of immunotherapies, noting specific evidence for both nivolumab and pembrolizumab. The company also outline that they consider there to be no evidence of treatment waning in this indication and that longer-term follow-up on pembrolizumab in other indications shows only limited evidence of a waning effect (see response to PfC Question B3 part c).

While the ERG accepts that it may be biologically plausible for the maintenance of a treatment effect after stopping pembrolizumab, the duration of this effect is uncertain. Moreover, the ERG considers the company's characterisation of previous NICE decisions inaccurate, as the case for waning is not necessarily applicable to all immunotherapy appraisals and will depend on the length of trial follow-up and presence of a stopping rule. In the context of the current appraisal, the ERG highlights there is no indication-specific evidence to support a sustained treatment effect, and that the overall immaturity of the survival evidence means any such claimed benefit is highly uncertain. Importantly, the application of a stopping rule in the present appraisal implies the effect of pembrolizumab on PFS (and OS) persists long after patients have stopped receiving treatment (i.e. a patient who is alive 10 years after discontinuing pembrolizumab has a lower probability of PFS event and will have a better survival prognosis compared with an identical surviving patient who received SoC). Contrary to the company's response, the ERG notes that committees have routinely assumed a waning of the

treatment effect 3 to 5 years after discontinuation of treatment where a stopping rule has been applied.[7-12, 53-56]

In summary, given the short follow-up from KEYNOTE-826, the ERG believes that it is unknown whether, or for how long, the effects of pembrolizumab on PFS (and OS) are maintained after treatment discontinuation. This uncertainty may be resolved in part through more mature data from KEYNOTE-826.

4.2.6.2 Post-progression survival

State occupancy in the progressed disease health state was determined by PPS survival data from KEYNOTE-826. Transition probabilities were applied such that time in state was independent of when a patient entered the progressed disease health state, see Section 4.2.2 for further discussion of this point.

Single parametric models were fitted independently to both treatment arms of KEYNOTE-826, as the proportional hazards assumption was judged to have been violated. In line with the approach to modelling TTP and PFS, visual fit to the KM data together with cumulative and log-cumulative hazard plots were assessed for evidence of an inflection point. The company concluded standard parametric survival models were appropriate, and it was not necessary to explore other model types.

Model selection was undertaken using the same process as for TTP and PFS and has been outlined previously. On the basis of these criteria, the generalised gamma distribution was selected for the base case analysis, see Figure 36 of the CS for visual fit to KM data. Scenario analyses were also presented considering the log-normal and log-logistic functions, which demonstrated similar visual and statistical fit to the data while also generating predictions that the company considered clinically plausible.

Figure 12: Modelled PPS (base case analysis) for PEM+SoC and SoC in the CPS≥1 population (CS Figure 36, Page 116)

Points for critique

Model Selection

The ERG has several concerns regarding the company's approach to model selection for PPS and the use of GOG 240[4] to validate model predictions. As noted previously, the GOG 240[4] population is highly restricted, and there are notable differences in predicted PPS between GOG 240[4] and KEYNOTE-826, particularly at later time points. The use of GOG 240[4] as a source of data to validate model selection consequently results in preferences for curves that significantly over-predict the proportion of patients alive, as observed in KEYNOTE-826. This is evident in the company's preferred generalised gamma curve, as well as the secondary preferences (log-logistic and log-normal). Indeed, the best match to the observed data is the Weibull curve. Moreover, the ERG is concerned by the company's preference for models that exhibit decreasing hazards. The ERG accepts the description of the hazard trend as reported in the CS but is concerned that the long-tails predicted by these models lack clinical plausibility. Patients who have progressed in this population have very few treatment options with no established standard of care. Consequently, the prognosis for this population is very poor, with few if any patients achieving a durable response. The ERG therefore considers there to be uncertainty in the modelling of post-progression survival and that further clinical validation of model predictions would be useful.

Assumption of differential post-progression survival benefit

As modelled in the company's base case, it is assumed that patients progressing on pembrolizumab will have a sustained and persistent post-progression survival benefit. However, available KM data shows limited evidence to support this, with curves actually crossing at around week 63. The company do note in the CS that patients with longer pre-progression survival tend to have a longer post-progression and consider this supportive of the base case assumptions. However, the company do not present a formal statistical comparison of post-progression survival provided to justify the differential assumptions. The clinical plausibility of differential post-progression survival is also not clear. Treatment options following progression will be similar, if not identical between arms, and it is unknown whether any benefits of pembrolizumab will persist beyond progression. Given this absence of evidence, the ERG considers that a more conservative assumption where no treatment effect is assumed to persist beyond progression is preferable.

4.2.6.3 Adverse events

AEs included in the economic model were Grade 3+ and with ≥ 5% incidence in either treatment arm. The impact of AEs was modelled to account for both the incidence and duration of events, which were used to estimate per cycle disutilities and costs associated with each event. To inform the disutilities and costs associated with each AE, cycle-specific event rates were estimated independently for the pembrolizumab and SoC arms of the model. Event rates were estimated as function of incidence and time on treatment. The incidence of each AE and the rate per model cycle (week) are summarised in Table 16.

Table 16 Incidence and rate of AE by treatment arm (adapted from Table 30 of the CS)

	PEM+SoC		SoC	
Adverse event (grade 3+)	**Incidence**	**Rate per cycle**	**Incidence**	**Rate per cycle**
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

At the clarification stage the ERG noted that the company's approach accounts only for Grade 3 and 4 AEs and does not account for notable differences in some Grade 1 and 2 AEs of special interest. The company justified their approach noting the expectation that these AEs would not impact materially on the results of the economic analysis. The company did however provide scenario analysis in which

QALY losses and costs associated with Grade 1 and Grade 2 AEs of special interest occurring in >5% of patients are accounted for. These scenarios are presented in Section 5 and show that including these lower grade events has a minimal impact on the ICER.

Points for critique

The ERG considers the company's approach to modelling AEs to be broadly appropriate and to accurately reflect the burden of AEs associated with each treatment regimen. The ERG, however, notes the omission of Grade 3 and 4 adverse events occurring in less than 5% of people, which included leukopenia, fatigue and diarrhoea amongst many others. The overall impact of this omission is likely to be modest given the low incidence of these individual AEs, but will favour the pembrolizumab arm given the pattern of low frequency AEs observed in the trial.

The ERG notes AEs may manifest in patients on subsequent therapies; however, these events are not considered within the company's model. The impact of these AEs is also likely to be modest. It is unclear whether this omission would favour the pembrolizumab or SoC arm of the model given the limited information available on subsequent therapies received.

4.2.7 Health related quality of life

4.2.7.1 Health state utilities

Health state utilities in the economic analysis were estimated from health-related quality of life (HRQoL) data collected in KEYNOTE-826 and analysed using linear mixed regression to account for repeat observations. Data were collected using the EQ-5D-5L questionnaire, and mapped to the EQ-5D-3L using the van Hout *et al*. algorithm.[46] In the trial, EQ-5D assessments were taken every 3 weeks (on the first day of each treatment) for the first 14 cycles, and then every 6 weeks (every 2 treatment cycles) thereafter. After patients discontinued primary treatment or after disease progression, assessments were administered at the end of treatment, and 30 days after the last treatment or before the initiation of a new anti-cancer treatment, whichever came first.

The company base case analysis considered an approach for deriving health state utilities based on time to death (TTD) (Table 17), with scenario analysis also considering a progression-based approach (Table 18). The TTD utilities were derived based on the following time before death categories:

- Group 1: less than 30 days before death,
- Group 2: between 30 and 90 days before death,
- Group 3: between 90 days and 180 days before death,
- Group 4: between 180 and 360 days before death,
- Group 5: more than 360 days before death.

Table 17 Summary of health state utilities TTD approach (CS Table 32, Page 123)

Health state	Mean (SE)
Time to Death <30 days (intercept)	[redacted]
Time to Death 30-90 days (vs intercept)	[redacted]
Time to Death 90-180 days (vs intercept)	[redacted]
Time to Death 180-360 days (vs intercept)	[redacted]
Time to Death ≥ 360 days (vs intercept)	[redacted]
Grade3+ AEs	[redacted]

Key: SE, standard error; AEs, adverse events; TTD, time to death

Table 18 Summary of health state utilities progression status approach (CS Table 33, Page 124)

Health state	Mean (SE)
Progression free	[redacted]
Progression Status (PF vs PD)	[redacted]
Grade3+ AEs	[redacted]

Key: SE, standard error; AEs, adverse event; PF, progression-free; PD, progressed disease

The company justified the use of the TTD approach noting that progression-based methods typically used in oncology may be less appropriate when assessing immunotherapies due to patients experiencing "pseudo-progression" where the action of treatment is mistaken for disease. The company further notes that delays between progression and experiencing symptoms, as well as different types of progression, may blur the impact of progression on quality of life.

Points for critique

Appropriateness of TTD approach

The ERG has concerns regarding the TTD approach. Time to death is not a causal determinant of HRQoL, as it can only be measured retrospectively and an event that occurs in the future cannot determine something which has occurred in the past. The observed correlations between HRQoL and TTD are most likely due to confounding, with time to death acting as a proxy for severity of disease, which is likely to be highly correlated with both OS and HRQoL. This reversal of causality is inherently problematic and leads to predictions that either lack clinical plausibility or which are not substantiated by the current evidence base.

Firstly, the use of TTD death utilities severs the link between progression status and HRQoL and violates the accepted norm that progression status is major driver of HRQoL. The clinical plausibility of this is unclear, and the company offers no evidence to suggest that the underling mechanism of utility generation is based on TTD rather than progression. Moreover, the method used by the company to apply TTD utilities means that it is difficult to estimate how the predicted utility values evolve over time and as such how the utility values applied using the TTD approach align with a progression-based approach.

Secondly, the applications of TTD utilities imply a treatment related differential in the average utilities applied, which are higher for pembrolizumab. This is driven by the fact that TTD is longer on average in both health states. The justification for such a benefit is not clear and it notable that treatment specific utilities are not applied when considering a progression-based approach. This suggests that the company do not consider there to be specific HRQoL benefits associated with receiving pembrolizumab.

Given these conceptual issues with the TTD approach, the ERG favours a progression-based approach and notes that precedent from previous appraisals supports this position with the majority of previous appraisals of immunotherapies rejecting a TTD-based approach.

Mapping algorithm

As noted above the company used the van Hout *et al.* algorithm.[46] to map values from EQ-5D-5L to EQ-5D-3L. The ERG notes that the latest methods guide recommends that the Hernández-Alava algorithm should be used, and that this had been highlighted to the company at the decision problem stage. At the clarification stage the ERG asked the company to justify the use of the van Hout *et al.* algorithm.[46] In their response the company noted the recommendations in the latest NICE methods guide and advice provided by the ERG. The company, however, justified the use of the van Hout *et al.* algorithm[46] noting that the latest methods do not apply to this appraisal and that the choice of algorithm did not have a significant impact on the values generated.

Points for critique

The ERG considers that it would have been preferable for the company to use the Hernández-Alava algorithm as recommended in the latest methods guide (this updates previous guidance which recommended the van Hout *et al.* algorithm[46]). The ERG, however, notes analysis by the Policy Research Unit in Economic Evaluation of Health and Care Interventions suggesting that both algorithms produce similar predictions with differences only apparent in very poor health states. The ERG is therefore satisfied that the company's approach is acceptable in the context of the current appraisal, if not methodologically ideal.

4.2.7.2 Age adjustment

The model applies age adjustments to all utility values used in the model. These account for the impact of ageing on HRQoL. These are applied using a multiplicative approach in which a utility decrement is estimated relative to the utility of a 51-year-old (starting age) in the general population using data from Ara and Brazier.[57] This decrement is then subtracted from each health state utility value to generate an age-specific value.

Points for critique

The ERG considers the application of an age-related decrement appropriate, given the long-time horizon considered in the economic analysis and the long OS benefits predicted by the base case analysis.

4.2.7.3 Impact of AEs

To account for the impact of AEs on quality of life, utility decrements were applied in the model. The AE-specific utility decrement was based on regression analysis of HRQoL data captured in the KEYNOTE-826 trial, which was used to estimate an average decrement associated with experiencing a Grade 3/4 AE, See Table 17 and Table 18. This was then combined with evidence on the frequency and duration of Grade 3/4 AEs to estimate a treatment specific disutility that was applied on a per cycle basis while patients were on treatment.

Points for critique

The ERG considers that it was appropriate to capture the HRQoL impact of AEs and that the general approach taken by the company is reasonable though somewhat convoluted.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs, costs associated with management of adverse events, monitoring costs, costs of testing, cost of subsequent treatments, and the costs of end-of-life care.

The company's submission did not describe their approach to identifying resource use and cost data in this indication, stating only that the cost inputs used in TA183 were outdated and unsuitable for use in this submission. Resource use data appears to be at least in part based on the company's advisory board meeting.[22]

4.2.8.1 Treatment acquisition costs

Acquisition costs for pembrolizumab in the model were based on the anticipated licence and the dosing of pembrolizumab in KEYNOTE-826, i.e. a 200mg Q3W fixed dose. The cost per administration of pembrolizumab at list price is £5,260, comprising two 100mg vials at a unit cost of £2,630 each. A patient access scheme is available for pembrolizumab consisting of a simple discount of [redacted]. This reduces the acquisition costs associated with pembrolizumab to [redacted] per 100mg vial.

Dosing schedules and costs modelled for the comparators cisplatin, carboplatin, paclitaxel, and bevacizumab are summarised in Table 19. Cost of treatments with weight or body surface area-based dosing were based on the characteristics of the KEYNOTE-826 population, in which mean body weight was [redacted] kg, and mean body surface area was [redacted] m^2. The number of vials required for each

administration was estimated from the licensed dose. It was assumed that no vial sharing between patients would occur for weight or body surface area-based dosing, i.e. drug wastage was taken into account for paclitaxel, cisplatin, and bevacizumab.

Cisplatin, carboplatin, and paclitaxel are available in generic formulation, with costs sourced from the electronic market information tool (eMIT) where available. List prices for pembrolizumab and bevacizumab were based on the Monthly Index of Medical Specialities (MIMS) database. Bevacizumab is available as a number of biosimilar formulations, the company applied the list price for Alymsys (biosimilar) in a scenario analysis but used the list price of Avastin (originator) in the base case analysis. The ERG notes that there is a Commercial Medicines Unit discount available for Avastin. The prices of bevacizumab biosimilars are negotiated regionally and were also supplied to the ERG. Analyses inclusive of all confidential pricing arrangements are included in a confidential appendix to the ERG Report.

The distribution of patients across the modelled treatments was based on the KEYNOTE-826 trial and is presented in Table 19.

Table 19 Dosing schedule and costs applied in the company model (adapted from CS Tables 34 and 35)

Drug	Dosing per administration	Dosing frequency	Cost per administration	Source
Pembrolizumab	200 mg	Q3W	£5,260 (exclusive of PAS)	MIMS 2020
Paclitaxel	175 mg/m^2	Q3W	£37.44	eMIT 2020
Cisplatin	50 mg/m^2	Q3W	£5.66	eMIT 2020
Carboplatin	750 mg	Q3W	£35.27	eMIT 2020
Bevacizumab (Avastin)	15 mg/kg	Q3W	£2,375.11	MIMS 2020
Bevacizumab (Alymsys)	15 mg/kg	Q3W	£2,070.88	MIMS 2020

The company's base case analysis also accounted for missed doses using the proportion of administered vs expected doses observed in KEYNOTE-826. The proportion of actual vs expected doses for each modelled treatment arm are presented in Table 20. In all cases, patients treated with SoC alone received more of each drug on average than on PEM+SoC. Patients received more than the number of cycles permitted on the NHS for paclitaxel, cisplatin, and carboplatin in both treatment arms.

Table 20 Modelled treatment cycles derived from KEYNOTE-826 (CS Table 36, Page 128)

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

Points for critique

The ERG considers the acquisition costs applied in the model to be largely appropriate. The ERG, however notes several uncertainties.

Firstly, the ERG considers it realistic that a significant proportion of patients initiated on bevacizumab will be given a biosimilar product. A scenario is therefore presented in Section 6 in which all patients receive biosimilar bevacizumab to explore the cost-effectiveness implications for pembrolizumab. Secondly, the ERG considers it potentially inappropriate to base the number of administered doses of paclitaxel, cisplatin, and carboplatin on KEYNOTE-826, as patients on average received over 100% of the permitted number of cycles. This is unlikely to represent NHS practice, and treatment costs should at the very least be capped to 100% of the number of cycles permitted on the NHS. However, the ERG notes that this has a very small impact on the ICER due to the low price of platinum-based chemotherapies. The ERG therefore does not consider this to represent an important uncertainty.

4.2.8.2 Treatment duration

The duration of treatment applied in the model was based directly on time on treatment (ToT) data from KEYNOTE-826. As there are stopping rules in place for pembrolizumab and bevacizumab, KM data were used to calculate the proportion of patients remaining on treatment until these respective cycle-based stopping rules were reached – 24 months for pembrolizumab, and 18 weeks for platinum-based chemotherapy, paclitaxel, and bevacizumab. The ToT curves and stopping rules applied in the model are reproduced in Figure 13.

Figure 13 Time on treatment KM data applied in the company model (CS Figure 38, Page 130)

Points for critique

The application of a stopping rule at 24 months may underestimate the real-world cost of treatment, and severs the link between treatment costs and health effects. In KEYNOTE-826, patients were strictly limited to 35 cycles of pembrolizumab treatment but in many cases [redacted] continued to receive treatment beyond 24 months. This reflects patients experiencing short breaks in treatment (perhaps due to AEs) before receiving further cycles. The application of a strict 24-month stopping rule in the model assumes that all these patients will discontinue therapy before reaching their full allocation of pembrolizumab doses. The ERG does not consider this reflective of practice and notes previous NHS England policy permits patients to receive a full allocation of doses under these circumstances. The exclusion of these costs also serves to break the link between benefits and costs in the model because patients receive the benefits associated with continued pembrolizumab treatment in the trial, but the accompanying costs are not accounted for. A scenario is therefore presented in Section 6 in which the effect of removing the modelled cap on pembrolizumab treatment is explored.

4.2.8.3 Treatment administration costs

All included treatments were administered intravenously. When multiple treatments are administered on the same day, modelled patients incur a unit cost of £329.75 (NHS Reference Cost SB13Z: deliver complex parenteral chemotherapy). When only one treatment is administered in one day, a unit cost of £295.92 was applied (NHS Reference Cost SB12Z: deliver simple parenteral chemotherapy).

Points for critique

The ERG considers the company's approach to modelling administration costs using the simple and complex parenteral chemotherapy costs appropriate, and in line with previous appraisals.

4.2.8.4 Subsequent treatments

The company applied a one-off cost associated with subsequent treatments at the point of disease progression, with the average duration of treatment based on data from KEYNOTE-826. The model assumed that [redacted] of patients would receive second-line treatment, which was based on advice from the company's advisory board. The company modelled paclitaxel monotherapy, doxorubicin, fluorouracil (5FU), and cisplatin + gemcitabine as second-line treatment options. This was based on the advice of the company's clinicians rather than on the KEYNOTE-826 trial, as there was little overlap in second-line therapies between the trial and NHS practice. The modelled proportion of patients on each, and the mean duration of treatment is detailed in Table 21. Acquisition costs are listed in Table 44 of the CS (Page 135).

Table 21 Subsequent treatments in company model (CS Table 43, Page 135)

Subsequent treatment	PEM + SoC		SoC	
	Proportion of patients	Mean treatment duration (days)	Proportion of patients	Mean treatment duration (days)
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]

The ERG requested further information on the subsequent treatments received in the KEYNOTE-826 trial, and that a scenario be constructed in which patients receive subsequent treatment per the distribution observed in the trial. The company included only subsequent therapies received by >3% of patients in the analysis submitted. In the data provided only [redacted] of patients who progressed received a second line treatment in the pembrolizumab arm, whilst this was [redacted] for the SoC arm – significantly lower than the [redacted] estimated by the company's clinicians.

Points for critique

The company stated that there was little overlap between the subsequent treatments in KEYNOTE-826 and NHS practice, but no details of the subsequent therapies used were provided in the submission or accompanying documents. Moreover, the company's response to clarification does little to resolve this uncertainty as the company's scenario only accounts for therapies received by >3% of patients. It is therefore unclear how many patients received subsequent therapy, or how this differed across treatment arms. The company state that this approach was adopted in the interests of time and the model is not sensitive to subsequent treatment costs. The ERG, however, cannot validate this claim given the partial answer provided by the company.

Given the limited information provided it is unclear if the company's base case assumptions are appropriate. The company's response while incomplete, indicates that far fewer patients went on to

receive subsequent therapy than modelled in the base case analysis. It also suggests that that more patients went on to receive subsequent therapies in the pembrolizumab trial arm than on SoC.

Moreover, advice from the ERG's clinical advisor raised concerns about the clinical plausibility of the modelled assumptions, stating that fewer than 50% of patients would proceed to subsequent treatment in NHS practice. Additional concerns were also raised regarding the composition of subsequent treatments modelled. Doxorubicin was highlighted as a treatment seeing very little use in cervical cancer, and it was suggested that topotecan may be used at this line of therapy. The assumption that 50% of patients would receive paclitaxel was also considered unrealistic and unreflective of UK practice.

The ERG considers both the proportion of patients receiving subsequent therapies, and the types of subsequent therapies received a potential source of uncertainty. The ERG's preference would be to base the proportions of subsequent therapies received on the full data for each treatment arm from the KEYNOTE-826 trial. Further information may also need to be elicited from UK clinicians on the composition of subsequent treatment in NHS practice.

4.2.8.5 Monitoring and health state costs

Healthcare resource use in the model was specific to each health state, and it was assumed that monitoring costs were the same regardless of treatment received. Health state resource use was based on clinician input, values applied in the model are summarised in Table 22 below. Pre-progression costs were applied on a per-cycle basis, while monitoring costs in the progressed disease health state were applied as a one-off cost upon progression for the [redacted] of patients who received a subsequent treatment.

The company assumed that monitoring costs for the remainder of patients who did not receive subsequent treatment would be captured in the one-off cost associated with end-of-life care. This one-off terminal care cost was applied at the time of death, and amounted to £4,611.54 based on Round *et al.*, which was inflated from 2015 to the 2019/20 cost year.

Table 22 Health state resource use applied in company model (Adapted from CS Table 40, Page 132)

	Unit cost	Progression-free			Progressed disease	
Resource		**Year 1**	**Year 2**	**Year 3+**	**On Tx**	**Off Tx**
Consultant outpatient appointment	£131.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	£107.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

GP visits	£33.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse/Nurse specialist visits	£81.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood-count	£2.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thyroid function test	£2.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In response to the ERG's clarification request, the company provided a scenario in which a number of cost-elements typically included in advanced cancer models were added to the model. These costs comprised GP visits, nurse/nurse specialist visits, a blood count, and thyroid function count, and were assumed to occur at the same frequency as the health-state resources included in the original model.

Points for critique

In the original model submitted by the company, only two cost elements were considered in the pre- and post-progression health states (consultant outpatient appointment, CT scan). At the clarification stage the ERG requested that the company add cost items typically included in advanced cancer models, namely, GP visits, nurse/nurse specialist visits, and blood counts. The company provided a scenario analysis in which these cost items were considered, which is replicated in Section 5. This change had a minimal impact upon the apparent cost-effectiveness of pembrolizumab.

4.2.8.6 Adverse reaction unit costs and resource use

Costs associated with the management of adverse events were based on Grade 3 or higher events occurring in more than 5% of patients in KEYNOTE-826. Unit costs were derived from NHS Reference Costs 2019/20 and other recent appraisals of pembrolizumab, and were inflated to the current price year using the HCHS index. The AE costs and the sources cited by the company in their submission are summarised in Table 23.

Table 23 Adverse event costs applied in the company model (CS Table 39)

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
Anaemia	£2,700.00	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Neutrophil count decreased	£672.40	Assumed same as neutropenia	N/A
Neutropenia	£672.40	Weighted average of mean costs for HRG code WJ11Z: Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	NHS reference costs 2019/20[58]
Hypertension	£639.00	EB04Z, Hypertension, HRG	NHS reference costs 2019/20[58]
Thrombocytopenia	£782.31	TA600: Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small cell lung cancer (2018)	TA600: Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer

Adverse event (grade 3+)	Unit Cost	Description (Assumption)	Reference
Febrile neutropenia	£7,200.69	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2019-20 prices using the Hospital & community health services (HCHS) index	TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma
Platelet count decreased	£672.40	Assumed same as neutropenia.	N/A
White blood cell count decreased	£1,515.42	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay	NHS reference costs 2019/20[58]
Key: HRG, Healthcare Resource Groups; SE, standard error.			

Points for critique

The methods used to derive the costs of AEs and implementing them into the model appear reasonable and are broadly comparable to other appraisals of pembrolizumab.

At clarification, the ERG requested that the cost associated with treatment of febrile neutropenia be inflated to the 2019-20 cost year, rather than 2017-18 as in the original submission. This was corrected and included as a scenario in the updated version of the company model.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections are inclusive of the PAS discounts for pembrolizumab unless otherwise stated. Results including commercial arrangements available for the comparator treatments are provided in a confidential appendix to the ERG report.

5.1.1 *Deterministic Results*

The company presents a series of ICERs for pembrolizumab versus a pooled SoC group of patients receiving platinum-based chemotherapy in combination with paclitaxel with or without bevacizumab. The use of a pooled analysis in the estimation of costs and effects of the SoC group of patients receiving/not receiving bevacizumab implies that the company views these populations as a homogenous group and not as distinct patient groups. As discussed in Section 2.2.1 and 4.2.3, the ERG does not consider this characterisation appropriate. The ERG considers there to be two relevant populations: i) those in whom bevacizumab is clinically indicated as they have better ECOG performance status, no significant comorbidities (e.g. hypertension), and low risk of bowel fistula formation and, ii) patients where bevacizumab is not clinically indicated.

The results of the company's cost-effectiveness analysis are summarised in Table 24. The company's base case exclusive of the PAS discount for pembrolizumab, is associated with increased costs (cost difference of [redacted]) but also greater benefits (QALY difference of [redacted]) yielding an ICER of [redacted] per QALY gained. After applying the PAS discount for pembrolizumab (only), the results suggest pembrolizumab is associated with increased costs (cost difference of [redacted]) with greater benefits (QALY difference of [redacted]) yielding an ICER of £34,017 per QALY gained. In all the scenarios, higher costs are primarily a result of the higher acquisition costs associated with pembrolizumab, while the QALY benefits are driven primarily by longer OS in the pembrolizumab arm compared to SoC arm.

Table 24 Company base case and scenario results: deterministic analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Company base case (Without PAS)							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case (With CAA for pembrolizumab)							
SoC	[redacted]	2.51	[redacted]				

Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,017
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.1.2 *Probabilistic Results*

The ERG performed probabilistic analyses on the company's base case model, running 5,000 iterations for each comparison. The results are presented in Table 25. The mean probabilistic ICER for pembrolizumab compared to SoC was £1,242 lower than the deterministic ICER. The ERG noted that because ToT for pembrolizumab is calculated directly from the KEYNOTE-826 data, acquisition cost calculations are independent of the number of patients remaining progression free at any time in a given model iteration. As pembrolizumab costs are essentially fixed and independent of QALY gain, the incremental costs across the PSA vary very little. Whilst there should generally be a positive relationship between acquisition costs and increasing QALYs, the scatter plot in the company's PSA shows no such trend. The PSA cannot therefore claim to represent the cost uncertainty associated with pembrolizumab.

Figure 14 presents the cost-effectiveness acceptability curve for the comparison of pembrolizumab versus SoC in the company's model. In this analysis, pembrolizumab had a 38% probability of being cost-effective versus SoC at a threshold of £30,000 per QALY gained, and 86% probability at a willingness-to-pay threshold of £50,000 per QALY gained.

Table 25 Company base case and scenario results: probabilistic analysis (including pembrolizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
SoC	[redacted]	2.60	[redacted]				
Pembrolizumab	[redacted]	5.46	[redacted]	[redacted]	[redacted]	[redacted]	£32,775
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

Figure 14 Cost-effectiveness acceptability curve for PEM+SoC versus SoC (generated from company's model, inclusive of PAS discount)

5.2 Company's additional analyses

At the clarification stage, the ERG requested that the company present a number of scenarios which explored alternative assumptions and parameter inputs. The results of this analysis are presented in Table 26. The scenarios explored were as follows:

i. Treatment waning effect applied for pembrolizumab for three and 5 years (2 to 5 or 7 year onset);
ii. Correction of general population mortality cap;
iii. The inclusion of any adverse event of special interest occurring in more than 5% of patients;
iv. Inclusion of subsequent treatment distribution from KEYNOTE-826;
v. Stopping rule removed for bevacizumab to match number of cycles in KEYNOTE-826;
vi. Inclusion of GP and nurse visits, blood counts, and thyroid function test costs;
vii. Correction to febrile neutropenia costs;
viii. Hernàndez-Alava algorithm used to map from EQ-5D-5L to EQ-5D-3L.

Table 26 Company's additional scenario analysis: deterministic analysis (inclusive of pembrolizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs company base case (£/QALY)
i) a) Inclusion of a treatment waning effect for pembrolizumab for three years							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	4.46	[redacted]	[redacted]	[redacted]	[redacted]	£43,647
ii) **b) Inclusion of a treatment waning effect for pembrolizumab for five years**							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	4.74	[redacted]	[redacted]	[redacted]	[redacted]	£39,209
iii) Correction of general population mortality cap							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,021
iv) The inclusion of any adverse event of special interest occurring in more than 5% of patients							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,215
v) Inclusion of subsequent treatment distribution from KEYNOTE-826							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£33,467
v) Stopping rule removed for bevacizumab to match number of cycles in KEYNOTE-826							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£32,881
vi) Inclusion of GP and nurse visits, blood counts, and thyroid function test costs							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£35,073
vii) Correction of inflation of febrile neutropenia cost to 2019/20							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£34,023
viii) Use of Hernàndez-Alava EQ-5D-3L mapping algorithm							
SoC	[redacted]	2.51	[redacted]				
Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	[redacted]	£33,923

Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

5.3 Company's deterministic sensitivity analyses

The company performed a series of one-way sensitivity analyses, setting the lower and upper bounds of each parameter to ±1.96*SE of the mean or base-case value, when the standard error (SE) was

derived from the data source. When this information was unavailable, SE was assumed to be within ±10% of the base-case value.

The input parameter with the greatest effect upon the ICER were dose intensity (actual vs. expected treatment cycles), followed by resource use estimators, and the mean treatment duration of paclitaxel in second line. The tornado diagram (Figure 15) showed that other parameters have a notably smaller effect on the ICER.

Figure 15 Tornado diagram showing DSA results of company model, PEM+SoC versus SoC, inclusive PAS discount.

5.4 Model validation and face validity check

5.4.1 *Validation undertaken by the company*

The CS stated that the outcomes of the model were clinically validated to ensure the face validity of predictions. This was undertaken by comparing PFS, OS and PPS data from the model to data from GOG 240[4] and KEYNOTE-826 trials, and was further supported by expert UK clinical opinion.

5.4.2 *Internal validation undertaken by ERG*

As part of the ERG assessment of the economic analysis, the ERG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Several minor model errors were identified as part of the ERG's validation checks. These related to the application of a general mortality cap for PFS and PPS curves to ensure that they are higher than the general population as they age. This meant that patients resided in the progression-free and progressed disease states longer than expected. This specifically impacted the cost and QALY outcomes per patient at the end of the model. The impact of this issue was relatively minor in the state transition model. All identified errors

were corrected by the company and verified by the ERG. Revised results correcting for this error are reported in Section 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. A number of alternative scenarios are presented in areas where the ERG felt that an alternative approach was more appropriate, or where it was considered important to explore the impact of uncertainty.

Descriptions of the exploratory analyses are described in Section 6.1and the impact of these analyses on the company's base case are presented in Sections 6.2 and 6.3 along with the ERG's preferred base case. Several scenarios were implemented by the company in response to the ERG's clarification questions, a number of which are reproduced in the present analysis.

Several further scenarios are included in the following section to illustrate the impact of alternative assumptions on the ERG base-case.

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted the following exploratory analyses after applying the corrections to the calculation of mortality, and using the correctly inflated cost for febrile neutropenia as described in Sections 4 and 5. Each of the following analyses are based upon this 'corrected' version of the company's model.

1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model

As described in Section 4.2.6.1, the ERG considers the use of a two-piece extrapolation approach to be potentially inappropriate given the immaturity of the data supporting the purported 'inflection point' in the TTP curve for pembrolizumab, and what this implies for long-term outcomes. The significant modelled QALY gain associated with pembrolizumab derives mostly from this long tail and results in predictions that the ERG considers highly optimistic. Moreover, the use of a simple parametric log-logistic model resulted in predictions in a pattern more reflective of long-term data available for the standard of care. Model fit statistics also supported the use of the log-logistic model to extrapolate PFS and TTP KM data. The final data cut from KEYNOTE-826 [redacted] may go some way to resolving the uncertainty associated with the apparent inflection point in hazards.

2. Pooled extrapolation of PPS

As described in Section 4.2.6.1, the ERG considers the use of a separate survival function to model PPS to be potentially inappropriate given the limited evidence to justify to support this assumption.

The clinical plausibility of the modelled parametric extrapolation is also uncertain and the ERG is concerned that the company's preferred generalised gamma distribution leads to an overly long tail with a small proportion of patients predicted to remain alive more than 3 years following progression. The ERG therefore considers two scenarios to explore this uncertainty. Scenario 2 (a) assumes a pooled PPS curve using a generalised gamma curve preferred by the company. Scenario 2 (b) assumes a pooled PPS curve using a Weibull curve. The Weibull curve is more pessimistic than the generalised gamma curve providing potentially more plausible predictions of PPS. The Weibull curve, however, does not offer as good a visual or statistical fit to the observed data as the generalised gamma.

3. Including treatment waning effect for pembrolizumab

As discussed in Section 4.2.6.1, the company have assumed a lifetime duration of the treatment effect associated with pembrolizumab on the basis of an observed effect for up to 2 years, in which patients were yet to discontinue treatment. The ERG considers, a lifetime treatment effect requires substantial supporting clinical evidence, which has not been presented by the company. The ERG notes that previous appraisals of immunotherapies have applied a waning effect, in which mortality rates gradually return to those of the comparator therapy over a number of years following the discontinuation of treatment.

To explore uncertainty associated with the longevity of the treatment effect, and to explore the potential impact of waning efficacy upon cost-effectiveness, the ERG presents scenarios in which the mortality rate experienced by patients previously treated with pembrolizumab returns to that of patients on SoC. In line with previous TA's waning over 3 and 5 years is considered.

4. Progression based utilities

The company's base case analysis uses a time to death approach to model HRQoL. As discussed in Section 4.2.7.1, the ERG considers this approach to have conceptual limitations and results in predictions that do not align well with accepted norms regarding the impact of progression on HRQoL. This scenario therefore replicates analysis implemented by the company in which progression-based utilities are used.

5. Subsequent therapy distribution from KEYNOTE-826

As discussed in Section 4.2.8.4, the ERG requested that the company use the treatment arm-specific distributions of subsequent therapies received by patients in the KEYNOTE-826 trial. As this analysis included only those treatments received by >3% of patients, the ERG does not consider it sufficiently representative of the distribution of treatments received in the trial. However, the ERG prefers this approach to modelling subsequent therapies to that based on estimates from the company's clinical

advisers. The ERG's preference is for this scenario to be implemented in full in future iterations of the model.

6. Full pembrolizumab ToT KM curve used to calculate costs

As discussed in Section 4.2.8.2, the ERG disagreed with the imposition of a 24 month stopping rule to pembrolizumab treatment in KEYNOTE-826, as a 35-cycle stopping rule was already in place in the trial. By removing the cost of pembrolizumab treatment beyond 24 months, the company still receive the QALY benefits of this treatment but not model all treatment costs. The ERG therefore considers it appropriate to apply the ToT KM curve from KEYNOTE-826 in full to calculate pembrolizumab acquisition costs.

7. All patients receive a biosimilar bevacizumab

The ERG explored a scenario where all patients received biosimilar bevacizumab (Alymsys). This was to assess the cost implications of all patients using cheaper alternatives to proprietary bevacizumab (Avastin). This does not include the available commercial arrangements for biosimilar bevacizumab – analysis inclusive of all discounts will be provided in a confidential appendix.

8. Bevacizumab maintenance therapy allowed

As described in Section 4.2.4, the ERG considers it plausible that patients may continue to be administered bevacizumab beyond the recommended 6 cycles. This more closely matches the use of bevacizumab in the KEYNOTE-826 trial.

9. GP visits, nurse/nurse specialist visits, blood-counts, and thyroid function tests costs

As described in Section 4.2.8.5, the ERG requested that the company include a number of health state costs typically applied in cancer appraisals, including GP and nurse visits, blood counts, and thyroid function tests. This scenario replicates that analysis.

10. All AEs of special interest occurring in more than 5% of patients modelled

The ERG replicated the scenario offered by the company in their clarification response which accounted for all adverse events of special interest regardless of their grading.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the scenario analyses are presented in Table 27. The results include the pembrolizumab PAS only.

Table 27 ERG Exploratory Scenario Analyses (Including Pembrolizumab PAS)

Scenario	Technology	Total			Incremental			ΔICER vs corrected BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
ERG-corrected company base-case	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,021	-
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	SoC	[redacted]	2.06	[redacted]				
	Pembrolizumab	[redacted]	3.09	[redacted]	[redacted]	[redacted]	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	SoC	[redacted]	2.53	[redacted]				
	Pembrolizumab	[redacted]	5.21	[redacted]	[redacted]	[redacted]	£36,231	£2,209
2. b) Pooled survival curve for PPS using Weibull curve.	SoC	[redacted]	2.41	[redacted]				
	Pembrolizumab	[redacted]	5.16	[redacted]	[redacted]	[redacted]	£34,832	£811
3. a) Treatment waning for pembrolizumab between 2 and 5 years	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	4.48	[redacted]	[redacted]	[redacted]	£42,919	£8,897
3. b) Treatment waning for pembrolizumab between 2 and 7 years	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	4.76	[redacted]	[redacted]	[redacted]	£38,823	£4,802
4. Progression based utilities	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£36,591	£2,569
5. Subsequent therapy distribution from KEYNOTE-826	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£33,472	-£549
6. Full Pembro ToT KM curve used to calculate costs	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,952	£930
7. All patients receive biosimilar bevacizumab	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,056	£34
8. Bevacizumab maintenance treatment allowed	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£32,885	-£1,136
9. GP/nurse visits, blood-counts, and thyroid function tests costs	SoC	[redacted]	2.51	[redacted]				
	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£35,072	£1,051
	SoC	[redacted]	2.51	[redacted]				

10. All AEs of special interest occurring in more than 5% of patients modelled	Pembrolizumab	[redacted]	5.31	[redacted]	[redacted]	[redacted]	£34,220	£198

6.3 ERG's preferred assumptions

The cumulative impact of the ERG's preferred assumptions are presented in Table 28. The ERG base-case adopts the following scenarios described in Section 6.1:

Scenario 1: One-piece log-logistic extrapolation of the PFS and TTP curve;
Scenario 2 (a): Pooled PPS using the generalised gamma curve;
Scenario 3 (a): Treatment waning for pembrolizumab (3-year treatment);
Scenario 4: Progression based utilities;
Scenario 6: Full pembroliumab ToT KM curve used to calculate costs;
Scenario 9: GP/nurse visits, blood-counts, and thyroid function tests costs;
Scenario 10: All AEs of special interest occurring in more than 5% of patients.

The choice of extrapolation had by far the largest incremental impact on the ICER in the ERG's alternative preferred base-case, accounting for an increase of £37,886 per QALY. In the ERG preferred base-case, pembrolizumab was predicted to generate [redacted] incremental QALYs, at an additional cost of [redacted] versus SoC to get an ICER for pembrolizumab of £95,529 per QALY gained.

Table 28 ERG's preferred model assumptions (Deterministic)

Scenario	**Section of ERG Report**	**Cumulative ICER**	**ΔICER vs corrected BC**
ERG-corrected company base-case	4 & 5	£34,021	
1. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	6.1.1	£71,907	£37,886
2. a) Pooled survival curve for PPS using generalised gamma curve.	6.1.3	£83,725	£49,704
3(a) Treatment waning for pembrolizumab (3 year treatment effect)	6.1.4	£88,795	£54,774
4. Progression based utilities	6.1.6	£89,909	£55,888
6. Full Pembro ToT KM curve used to calculate costs	6.1.7	£92,442	£58,421
9. GP visits, nurse/nurse specialist visits, blood-counts, and thyroid function tests costs	6.1.9	£93,709	£59,687
7. All AEs of special interest occurring in more than 5% of patients	6.1.11	£95,529	£61,508
ERG base case			
ERG preferred base-case (Scenarios 1, 2 (a), 3 (a), 4, 6, 9 & 10)	**Inc. costs**	**Inc. QALYs**	**ICER**
	[redacted]	[redacted]	£95,529

Probabilistic results for the ERG's alternative base-case are presented in Table 29. The model was set to the ERG's preferred assumptions and run with 5,000 iterations. As discussed in Section 5.1.2, the ERG did not consider the PSA to have been constructed appropriately, which was an issue the ERG was unable to resolve given the model structure and limitations in the data available. The probabilistic ICER was £93,159 – somewhat lower than the deterministic ICER. This difference was driven both by lower average incremental costs and higher average incremental QALYs than in the deterministic analysis.

Table 29 ERG's alternative base-case analysis results (probabilistic)

Scenario	Technology	Total			Incremental		
		Costs	LYs	QALYs	Costs	QALYs	ICER
ERG-corrected company base-case (probabilistic)	SoC	[redacted]	2.11	[redacted]			
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£93,159

6.3.1 Additional scenario analysis on the ERG's base case

In addition to the ERG base case, the ERG presents the results of several scenario analyses on the ERG base-case. Table 30 presents the results of this analysis.

Table 30 ERG Exploratory Scenario Analyses on the ERG base case

Scenario	Technology	Total			Incremental			ΔICER vs corrected BC
		Costs	LYs	QALYs	Costs	QALYs	ICER	
ERG-base case	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£95,529	-
2. b) Pooled survival curve for PPS using Weibull curve.	SoC	[redacted]	1.99	[redacted]				
	Pembrolizumab	[redacted]	2.82	[redacted]	[redacted]	[redacted]	£95,550	£21
3. b) Treatment waning (5 year treatment effect)	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.93	[redacted]	[redacted]	[redacted]	£92,595	-£2,934
5. Subsequent therapy distribution from KEYNOTE-826	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£94,021	-£1,508
7. All patients receive biosimilar bevacizumab	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£95,622	£93
8. Bevacizumab maintenance treatment allowed	SoC	[redacted]	2.08	[redacted]				
	Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	[redacted]	£90,604	-£4,925

6.4 Conclusions of the cost effectiveness section

The company submitted a de novo economic analysis to assess the cost-effectiveness of pembrolizumab versus SoC in the treatment recurrent, persistent or metastatic cervical cancer. The company's analysis was based on STM consisting of three health states (pre-progression, post-progression, and death). The company's base-case economic analysis suggested that pembrolizumab is more costly but is also more effective than both SoC. The company's deterministic base case ICER was £34,017 per QALY. The company's probabilistic base case ICER was £32,775 per QALY. At a £30,000 per QALY threshold, the probabilistic analysis suggests a [redacted] probability that pembrolizumab is cost-effective. At a £50,000 per QALY this increase to [redacted] probability. Note that these results are based on the net price of pembrolizumab but are exclusive of confidential discounts for bevacizumab and other treatments.

6.4.1 Conclusions of ERG's Critique

The ERG considers the submitted evidence to broadly reflect the decision problem defined in the final scope, and that the submitted analyses meet the requirements of the NICE reference case. The ERG's review of the company submission identified several key uncertainties, which the ERG has sought to address in the revised base case and scenario analyses.

A key area of uncertainty relates to the model structure adopted by the company. The STM approach used in the company's base case implies a structural link between PFS and OS which assumes a surrogate relationship between PFS and OS. The CS does not fully justify this assumption, providing only limited evidence based on clinical opinion and statistical analysis of KEYNOTE-826. The ERG considers the lack of supporting evidence to be an important omission. Moreover, the ERG is concerned that the model's predictions do not align well with the observed OS data from KEYNOTE-826 and it systematically under-predicts the proportion of patients alive in both treatment arms at 24 months. Importantly, this issue is more pronounced in the SoC arm suggesting a bias in favour of pembrolizumab.

The ERG also has substantive concerns regarding the company's justification for the STM approach. The company's justification is founded on the extrapolations of PFS data and the conclusion that resulting PFS extrapolations are inconsistent with OS extrapolations. However, as discussed below, it is not clear that the PFS extrapolations preferred by the company are clinically plausible and the ERG notes that the crossing of PFS and OS is solely because a piecewise approach is adopted to the extrapolation of PFS. Crossing does not occur when a single-parametric curve is fitted to the whole KM data.

A key uncertainty relates to the approach taken to extrapolation of TTP and PFS in the model, as these are drivers of cost-effectiveness. The company's base-case analysis approach adopts a two-piece approach to modelling TTP and PFS curves to capture a purported point of inflection around 40 to 60 weeks in the KM curve from KEYNOTE-826. This approach leads to very long tails in TTP (& PFS) and results in the model predicting that a substantial proportion of patients will remain alive for five or more years, with a non-negligible proportion of patients achieving survival that could be considered akin to cure. While the ERG acknowledges that immunotherapies have historically been associated with durable response rates in other indications, there is insufficient evidence in cervical cancer to suggest that short term treatment with immunotherapy translates into such long survival gain, nor has a possible mechanism for cure been established. The ERG also notes that the two-piece approach appears to produce optimistic estimates of survival in the SoC arm, while these broadly align with data from GOG 240 they do not align with clinical expectations regarding long-term survival in this patient population. The final data cut from KEYNOTE-826 expected [redacted] may go some way to resolving the uncertainty associated with the apparent inflection point in hazards.

Related to the above, the economic analysis also makes strong assumptions about the durability of the treatment effect, assuming that the benefits to mortality gained while on treatment are maintained beyond treatment discontinuation. Although it is biologically plausible for the treatment effect to continue after pembrolizumab, its duration is uncertain. Given the short follow-up from KEYNOTE-826, the ERG believes that it is unknown whether, or for how long, the effects of pembrolizumab are maintained after treatment discontinuation. As a result, survival benefits predicted by the company's base-case analysis may be overly optimistic.

The ERG also has concerns regarding the company's approach to modelled HRQoL. In the company's base case, a TTD approach is used in which utility values are determined by proximity to death. The ERG has conceptual issues with this approach as it relies on future death events to predict current HRQoL status. The ERG is also concerned that the TTD approach severs the link between progression and HRQoL, and violates the accepted norm that progression status is major driver of HRQoL. Moreover, the predictions of the TTD approach are difficult to reconcile with a progression-based approach.

Additionally, the ERG identified several resource use issues, which have a smaller impact on the results. These include the use of the full pembrolizumab ToT curve; inclusion of GP visits, nurse/nurse specialist visits, blood-counts and thyroid function tests costs; and bevacizumab use. These issues were explored in scenario analysis presented by either the company or the ERG and were all demonstrated to have a modest impact on the cost-effectiveness of pembrolizumab.

The impact of these uncertainties was considered in a series of exploratory analyses. The results of which demonstrate that the extrapolation modelling approach adopted for TTP and PFS is a key driver of overall benefits and cost-effectiveness. Taking the ERG base-case, which uses a single piece log-logistic model, the comparison of pembrolizumab against SoC resulted in an ICER of £95,529 per QALY, which is £61,508 higher than the company base case ICER. Results are exclusive of confidential price discounts for the other drugs.

7 END OF LIFE

The CS (Table 19, p73 CS) presents evidence to support pembrolizumab as an end-of-life therapy.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The reported median OS for SoC patients was 16.3 months (95% CI 14.5 to 19.4) based on data from KEYNOTE-826. Similar estimates were also obtained from GOG 240[4] which reports median survival ranging between 13.3 and 16.8 months. Based on parametric extrapolations used in the company base case analysis economic analysis, mean life expectancy for patients receiving SoC was 2.51 years (30.12 months). Based on the ERG preferred assumptions, mean life expectancy was estimated to be 2.08 years (24.96 months). These data suggest that there is uncertainty over whether the first criterion is met. The ERG notes that the EoL criteria are typically interpreted with respect to mean or average life expectancy. This is in line with decision making for cost-effectiveness which is based on mean costs and QALY gains. Such an interpretation would suggest that the first criterion for end of life is not met. The ERG, however, notes several mitigating factors that may imply that mean OS is overestimated in the KEYNOTE-286 trial informing the economic analysis. As noted in Section 2.2.1, some patients in NHS practice may receive a monotherapy chemotherapy regimen which may be less effective than the doublet and triplet chemotherapy considered in the KEYNOTE-826 trial. Further, the KEYNOTE-826 population excluded patients with performance status of >1; clinical advice suggests that a proportion of ECOG status 2 patients receive systemic treatment and that in principal ECOG 2 patients may be eligible for pembrolizumab combination therapy. It is widely accepted that performance status is a prognostic indicator.

Criterion 2: There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

Median OS for pembrolizumab has not been reached in the KEYNOTE 826 study and therefore a comparison of median OS gains based on observed data is currently not possible. Based on extrapolated evidence used in the economic analysis, median survival gains are predicted to be 7.13 months. Further, based on the company's base-case economic analysis, mean extension to life is estimated to be 2.80 years (33.64 months). In the ERG's base-case analysis, which makes more conservative assumptions about the benefits of pembrolizumab, this is reduced to a mean extension of 0.82 years (9.84 months). Despite stated uncertainties regarding the extrapolations of OS, the ERG considers that there is strong evidence to indicate that the second criterion is met.

The ERG concludes that there is substantial uncertainty regarding whether pembrolizumab meets the end of life criteria given current life-expectancy on SoC. It is highly likely that Criterion 2 is met.

Uncertainties regarding life expectancy on current SoC, however, mean it is uncertain whether Criterion 1 is met.

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9 APPENDICES

9.1 Appraisal of company search strategies

9.1.1 Clinical Evidence Searches

The original company submission included searches to identify clinical evidence for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix D (pp. 4-15). The embedded systematic literature review (SLR) report on page 4 of Appendix D was included in the original company submission but was not reviewed as it would not open.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG

Table 31 ERG appraisal of clinical evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Inaccessible Data** The embedded systematic literature review (SLR) report on page 4 of Appendix D was included in the original company submission but was not reviewed initially as it would not open: this was raised as a PfC. In response to PfCs, the company sent through the full SLR which provided some of the missing search strategies. **Missing Search Strategies:** In the original submission, there was insufficient information on the searches of the clinical trials registries and conference proceedings (listed in Appendix D, D.1.1, pp. 4-5). Additional data was provided in the response to PfCs with fully documented searches of conference proceedings through the Northern Light Life Sciences Conference Abstracts database (mistakenly referred to as the Northern Nights database in parts of the SLR). However, the clinical trials registries that were searched were not documented. **Error in Description of Date Limits for Conference Proceedings:** The search strategy for ASCO 2019 was not contained in the document 'ID3798 MER36645 Cervical cancer UK SLR report UK' but has since been provided. The ERG can now confirm that searches of conference proceedings were carried out as detailed on page 18 of the document 'ID3798 MER36645 Cervical cancer UK SLR report UK'. **Error in Search Results:** Appendix D, D.1.3. lists the total figures from the databases as 4,417. However, the number of results listed for Medline, Embase, and CENTRAL combined comes to 4,416. The figure 4,416 is also reported in the PRISMA diagram. **EUCTR not in PRISMA diagram:** The PRISMA diagram does not list the number of records from 'European Union Clinical Trials Registry' (EU CTR) even though this source is listed as one of the sources searched on Appendix D, D.1.1, page 4. In the response to PfCs the company indicated that this is because the database retrieved 0 relevant records. **Errors with explode function (exp) on databases**

		In several instances, exp was used in front of a subject heading when the subject heading could not be exploded. This will not affect the number of hits, but gives the false impression that all these subject headings have narrower subject headings: Appendix D, pages 5-6 (Embase strategy): exp pembrolizumab/, exp cisplatin/, exp paclitaxel/, exp bevacizumab/, exp topotecan/, exp carboplatin/, exp gemcitabine/, exp etoposide/, exp vinorelbine/ [the correct Emtree term is vinorelbine tartrate/], exp ifosfamide/, exp docetaxel/, exp fluorouracil/ Appendix D, pages 7-8 (Medline strategy), and pages 9-10 (Cochrane CENTRAL strategy): uterine cervical neoplasms/, exp cisplatin/, exp bevacizumab/, exp topotecan/, exp carboplatin/, exp etoposide/, exp vinorelbine/, exp ifosfamide/, exp docetaxel/
Were appropriate sources searched?	YES	A range of relevant databases, conference proceedings, and trials registry databases were searched. The searches could have benefitted from searching a larger number of databases though.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the intervention and the study type.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** Although the truncation and adjacency on line 2 of each of the database searches will successfully capture several terms for the condition, the following terms would be missed: • carcinoma colli uteri • endocervical carcinoma • endocervix carcinoma • uterine cervix adenocarcinoma Notably, adenocarcinoma is even listed as an eligible subtype in Appendix D, Table 2, page 11. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant. **Missed Field Codes:** There are field codes that could have been used for the free-text term lines for the interventions, in addition to the title and abstract. On Medline these are rn (registry name / name of substance), or nm (name of substance word). On Embase these are: tn (drug trade name), or du (drug index terms). The same comment may apply to Cochrane but we do not have access to the Cochrane CENTRAL via Ovid. Exclusion of these field codes could have missed relevant papers. **Emtree Subject Headings used outside of Embase** On Medline and Cochrane CENTRAL, the following Emtree Terms were used: exp pembrolizumab/, exp gemcitabine/ but these are not MeSH terms and not appropriate for these databases. However, as there are no equivalent MeSH terms that represent these intervention terms, it is unlikely any relevant papers would have been missed as a result.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	For Ovid Medline and Embase, study design filters by the Scottish Intercollegiate Guidelines Network were used for clinical trials. The filter was referenced, though it is not a validated filter.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.2 Cost-Effectiveness Searches

The original company submission included searches to identify cost-effectiveness for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 32 ERG appraisal of cost-effectiveness evidence identification

TOPIC	ERG RESPONSE	NOTE:
Is the report of the search clear and comprehensive?	PARTLY	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Missing Search Strategy** There is mention of searches on the NICE website on page 19 of the embedded document on page 50 of Appendix G, but the searches are not documented.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with economics study filters.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com and the search of PubMed (in the economic review searches: pages 9-11 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant.

		The search strategy for the economic review searches using the CRD databases NHS EED, HTA, and DARE (page 11 of the document embedded on page 50 of Appendix G) is very basic and no MeSH terms were used. A search for just the MeSH term Uterine Cervical Neoplasms on its own will bring back 541 hits (which is more than the strategy in the company submission retrieved). Therefore, relevant papers may have been missed. Moreover, a search just for 'cervical cancer' is also quite limited. This was raised as a PfC and the company response was that this was unlikely to miss relevant papers due to the databases being out-of-date and indexed in other sources that were searched.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.3 Health-Related Quality of Life Searches

The original company submission included searches to identify health-related quality of life studies for adult patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and all of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included clarifications on issues raised by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 33 ERG appraisal of HRQoL evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Errors with explode function on databases**

		In the searches of Cochrane CENTRAL a MeSH subject heading (uterine cervical neoplasms) was exploded when the subject heading does not have narrower terms (on page 13 of the document embedded on page 50 of Appendix G). This will not affect the number of hits but gives the false impression that the subject heading has narrower subject headings.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with a health-related quality of life study filter.
Were appropriate search terms used?	YES	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com, the search of PubMed, and the searches of Cochrane CENTRAL and CDSR (in the humanistic review searches: pages 11-13 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

9.1.4 Cost and Healthcare Resource Identification, Measurement, and Valuation Searches

The original company submission included searches for cost and healthcare resource identification, measurement, and valuation for patients with persistent, recurrent, or metastatic cervical cancer. A detailed description of the searches and most of the search strategies were included in Appendix G (pp. 43-50) and pages 9-21 of an embedded economic systematic literature review (SLR) report on page 50 of Appendix G.

In response to the ERG's PfCs, a further document was provided by the company, which included missing or additional search strategies and corrections to errors identified by the ERG.

NB: We cannot access some of the databases to fully assess the suitability of the strategies (this applies to Medline or Embase via embase.com). The strategy and documentation have been assessed as far as is possible without access to these databases.

Table 34 ERG appraisal of cost and healthcare resource evidence identification

TOPIC	ERG RESPONSE	NOTE:
Is the report of the search clear and comprehensive?	PARTLY	**Ambiguous Representation of Databases Used** Table 11 on page 44 of Appendix G indicates that Cochrane CENTRAL and CDSR are only searched for the humanistic searches rather than the economic searches – this was not at all clear for the write up under G.1.1 on page 43 of Appendix G. **Ambiguous Table** Table 11 on page 44 of Appendix G is also misleading because there was one multifile search of Embase and Medline via embase.com for the economic review and one multifile search of Embase and Medline via embase.com for the humanistic review but the way it is represented could suggest that a single strategy was used to find either economic papers OR humanistic papers. **Missing Search Strategy** There is mention of searches on the NICE website on page 19 of the embedded document on page 50 of Appendix G, but the searches are not documented.
Were appropriate sources searched?	YES	A range of relevant databases, grey literature sources, and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with economics study filters.
Were appropriate search terms used?	PARTLY	**Missed Condition Terms:** The following terms would be missed on the searches of Medline and Embase via embase.com and the search of PubMed (in the economic review searches: pages 9-11 of the document embedded on page 50 of Appendix G): carcinoma colli uteri, endocervical carcinoma, endocervix carcinoma. This was raised as a PfC and the company re-ran the searches with these terms included. Although additional studies were retrieved, these were not relevant. The search strategy for the economic review searches using the CRD databases NHS EED, HTA, and DARE (page 11 of the document embedded on page 50 of Appendix G) is very basic and no MeSH terms were used. A search for just the MeSH term Uterine Cervical Neoplasms on its own will bring back 541 hits (which is more than the strategy in the company submission retrieved). Therefore, relevant papers may have been missed. Moreover, a search just for 'cervical cancer' is also quite limited. This was raised as a PfC and the company response was that this was unlikely to miss relevant papers due to the databases being out-of-date and indexed in other sources that were searched.
Were any search restrictions applied appropriate?	N/A	
Were any search filters used validated and referenced?	YES	Used and adapted, though were not validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE