

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

**Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901)
[ID6610]**

Contents:

The following documents are made available to stakeholders:

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

- 1. Company submission** from Regeneron:
 - a. Company main submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Expert personal perspectives** from:
 - a. Dr Alexandra Taylor – clinical expert nominated by Regeneron
 - b. Dr Gemma Eminowicz – clinical expert nominated by Regeneron
 - c. Katrina Cowley – patient expert
- 4. External Assessment Report** prepared by ScHARR
- 5. External Assessment Group response to factual accuracy check of EAR**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Company evidence submission

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Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

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List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
5FU	Fluorouracil
AC	Adenocarcinoma/adenosquamous cell carcinoma
ACD	Appraisal Consultation Document
AE	Adverse event
APBI	The Association for British Pharmaceutical Industry
BAS	Biomarker analysis set
BGCS	British Gynaecological Cancer Society
BSC	Best supportive care
C	Cycle
CC	Cervical cancer
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CIC	Commercial-in-Confidence
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
CTCAE	Common terminology Criteria for Adverse Events
CUA	Cost-utility analysis
D	Day
DOR	Duration of response
DSA	Deterministic sensitivity analysis
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
FAD	Final Appraisal Document
FAS	Full analysis set
FoI	Freedom of Information
F-U	Follow-up
GB	Great Britain

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GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
IC	Investigator's choice
ICER	Incremental cost-effectiveness ratio
ILAP	Innovative Licensing and Access Pathway
irAE	Immune-related adverse event
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LS	Least-squares
LY	Life-year
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PACE	Patient and Clinician Engagement
PartSA	Partition survival analysis
PAS	Patient Access Scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
Q3W	Every three weeks
QALY	Quality-adjusted life year
QoL	Quality of life
r/m	Recurrent or metastatic
RCT	Randomised controlled trial

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RECIST	Response Evaluation Criteria in Solid Tumours
ROS1	Proto-oncogene tyrosine-protein kinase ROS
ROW	Rest of world
S	Survival
SAF	Safety analysis set
SCC	Squamous cell carcinoma
SE	Standard error
SG-TAG	Scottish Genomic Test Advisory Group
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPaN	Scottish Pathology Network
SPC	Summary of Products Characteristics
t	Time
TBC	To be confirmed
TEAE	Treatment-emergent adverse event
TOT	Time on treatment
UK	United Kingdom
US	United States
WTP	Willingness-to-pay
Y/N	Yes/no

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

Key points

Recurrent or metastatic cervical cancer after platinum-based chemotherapy

- Recurrent or metastatic cervical cancer (r/m CC) is usually incurable and carries a high and complex symptom burden,^{1,2} including pain, fatigue, gastro-intestinal problems, and mental health issues.^{2,3} Patients are often young, of working age, and have carer responsibilities.¹ Those with r/m CC that has progressed on or after platinum-based chemotherapy have a dismal prognosis, with reported median overall survival of 5.0-12.7 months.⁴
- The main aim of treatment in this second-line, end-of-life setting is to relieve symptoms, maintain quality of life, and to extend life if possible.^{4,5} However, for the vast majority of patients, the only current second-line treatment option after platinum-based chemotherapy is further chemotherapy (usually single-agent), which has poor response rates^{1,4} and is associated with a high toxicity burden.⁶⁻⁸
- Clinical experts confirm there is a high unmet need for an immunotherapy option in this second-line setting with an acceptable toxicity profile and good response rate that prolongs survival, regardless of PD-L1 status, whilst maintaining or improving quality of life.⁶⁻⁸

Cemiplimab (LIBTAYO®)

- Cemiplimab as monotherapy is indicated for the treatment of adult patients with r/m CC and disease progression on or after platinum-based chemotherapy.⁹ It is the only immunotherapy that is licensed for use as monotherapy in this disease area.

- It is an immune checkpoint inhibitor that has shown an important survival benefit over chemotherapy in this second-line setting, together with better tolerability and quality of life scores (see Section 2).¹⁰⁻¹²
- In line with its recommendation in the most up-to-date, evidence-based European clinical guidelines,¹³ it is anticipated cemiplimab will be used in practice in this second-line setting in patients who have not received prior immunotherapy, where it will address a high unmet need in a small population of patients who currently have no access to immunotherapy in their treatment pathway.

1.1 Decision problem

Cemiplimab (LIBTAYO®) as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.⁹ The submission covers the technology's full marketing authorisation for this indication. A summary of the decision-problem addressed in this submission is provided in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with recurrent or metastatic cervical cancer that has progressed on or after having platinum-based chemotherapy.	As NICE scope. Adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy (in line with the licensed indication for cemiplimab). ⁹	N/A
Intervention	Cemiplimab	As NICE scope. Cemiplimab	N/A
Comparator(s)	Single-agent chemotherapy Best supportive care Tisotumab vedotin monotherapy (subject to NICE evaluation)	Basket of single agent chemotherapy regimens. As noted in the NICE scope, there is no standard of care therapy in this setting, therefore the basket of investigator-chosen single agent chemotherapies observed in the EMPOWER Cervical-1 trial is used in the base case. An alternative distribution of 2L chemotherapies based on regimens stated by clinical experts as being most commonly used in NHS practice is explored in a scenario analysis.	Best supportive care is not considered a relevant comparator, as the minority of patients who are not suitable for active 2L treatment with existing chemotherapy options are also not anticipated to be eligible for cemiplimab. Although their licensed indications theoretically overlap, tisotumab vedotin is not considered a relevant comparator for cemiplimab in this appraisal. According to the NICE Reference case, ¹⁴ tisotumab vedotin would not constitute a relevant comparator, as its use cannot be considered to be established clinical practice for the following reasons:

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			• It is not currently in routine use in NHS clinical practice, • It does not currently have a positive recommendation for use by NICE, • NICE guidance for tisotumab vedotin is not scheduled to be published until 25th June 2026,¹⁵ which is >6 months after the scheduled submission date for cemiplimab, and >1 month after the scheduled appraisal committee meeting for cemiplimab, and • Even if NICE makes a positive recommendation for tisotumab vedotin, it cannot reasonably be considered to have become established clinical practice within the planned timescale of the appraisal of cemiplimab. Furthermore, we anticipate that, in practice, cemiplimab and tisotumab vedotin may be used in different populations. Cemiplimab provides a chemotherapy-free immunotherapy option for those patients who have not received first-line immunotherapy. In contrast, tisotumab vedotin is a type of chemotherapy, rather than an immunotherapy, and as such could be offered to patients who have received

			prior immunotherapy. Given that cemiplimab will only be used following platinum-based chemotherapy, the alternative use of further chemotherapy with tisotumab vedotin following platinum-based chemotherapy may not be clinically desirable.
Outcomes	• Progression-free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	As NICE scope. Response rates are not modelled but are presented narratively.	N/A
Subgroups to be considered	N/A, the final scope does not specify any subgroups	As NICE scope. The submission relates to the whole licensed population.	N/A
Special considerations including issues related to equity or equality	None specified.	Cervical cancer disproportionately affects people in more deprived socioeconomic groups (see Section 1.5). These groups are therefore disproportionately affected by the current lack of effective and well tolerated treatments after platinum-based chemotherapy, and by decision-making on new treatments.	

Abbreviations: 2L, second line; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service.

1.2 Description of the technology being evaluated

The Summary of Product Characteristics is supplied as Appendix A1 and the European Public Assessment Report (EPAR) as Appendix A2.

Table 2. Technology being evaluated.

UK approved name and brand name	Cemiplimab (LIBTAYO®)
Mechanism of action	Cemiplimab is an immunotherapy (an immune checkpoint inhibitor). It is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2, which may be expressed by tumour cells and/or other cells in the tumour microenvironment. Engagement of PD-1 with its ligands results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. ⁹
Marketing authorisation/CE mark status	Cemiplimab was approved in November 2022 by the EMA as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy. ¹⁶ Cemiplimab has a UK marketing authorisation in this indication. MHRA approval was granted on 27/04/2023, through the Reliance procedure based on EMA approval.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Cemiplimab (LIBTAYO®) as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy. ⁹ No further restrictions are described in the SmPC.
Method of administration and dosage	The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes. Treatment may be continued until disease progression or unacceptable toxicity. ⁹ No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in the SmPC. ⁹
Additional tests or investigations	No additional tests or investigations are needed beyond those conducted in routine clinical practice. Of note, PD-L1 testing is not required for cemiplimab in cervical cancer. ⁹
List price and average cost of a course of treatment	The formulation licensed for the treatment of recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy is LIBTAYO® 350 mg

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	concentrate for solution for infusion. ⁹ The list price is £4,650.00 per vial. ¹⁷ The average cost of a course of treatment (at list price) is £[REDACTED]. The average cost at the confidential discounted price is £[REDACTED] (costs are as calculated by the Budget Impact model; see Budget Impact document for derivation).
Patient access scheme (if applicable)	An application for extension of the existing patient access scheme (simple discount of [REDACTED]%) to the indication covered in this submission has been made to NHS England.

Abbreviations: CE, Conformité Européene; EMA, European Medicines Agency; IgG4, immunoglobulin G4; NHS, National Health Service; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; Q3W, every 3 weeks; SmPC, summary of product characteristics.

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

1.3.1 Disease overview

The cervix is the neck of the womb that opens into the vagina. While early-stage disease is confined to the cervix and surrounding tissues, late-stage cervical cancer involves spread to organs such as the bladder, ureters, rectum and distant organs such as the lung and liver (metastatic disease).³ There are two main histologic subtypes: squamous cell carcinoma (SCC; 80-90% of cases) and adenocarcinoma (10-20% of cases); 3-10% of CC cases have mixed histology (adenosquamous carcinoma).³

People with recurrent or metastatic CC (r/m CC) have a high and complex symptom burden,^{1,2} with pain, fatigue, gastro-intestinal symptoms (including bowel obstruction), anorexia, poor wellbeing and mental health issues (anxiety or depression) all common.^{2,3} This morbidity can be severely debilitating.¹ Many are also living with the complications of previous surgical and/or systemic treatment, which can include (but are not limited to) menopausal symptoms, altered body image, sexual/vaginal dysfunction, diarrhoea, lymphoedema, peripheral neuropathy, fatigue, and social difficulties.¹³ In particular, platinum-based chemotherapy results in persistent sensory peripheral neuropathy for some patients.¹⁸

Patients are often young, of working age, and may have small children and/or elderly relatives to care for.¹ R/m CC is described by the European Society of Medical Oncology (ESMO) guidelines as “usually symptomatic and devastating for the patient”.⁴

An insight into the impact of r/mCC on patients and their families and caregivers is provided by Patient And Clinician Engagement (PACE) meeting from the appraisal of cemiplimab by the SMC.¹⁹ As well as confirming the high and debilitating symptom burden, the PACE statement notes that patients are generally left unable to work, unable to care for their children and will require hospital care and symptom control

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after diagnosis due to severity of symptoms. They worry about the return of the cancer and the future more generally for themselves and for their loved ones.¹⁹

Metastatic CC is not normally curable,¹ and patients with r/m CC that has progressed on or after platinum-based chemotherapy have a dismal prognosis. Median overall survival with investigator's choice of chemotherapy in the EMPOWER Cervical-1 trial (final analysis) was 8.5 (95% CI 7.5-9.6) months.¹⁰ This aligns with a summary of second-line therapy outcomes in metastatic CC presented by ESMO in their clinical practice guideline (prior to the availability of cemiplimab), in which OS is reported to range from 5.0 to 12.7 months.⁴

The combination of impaired quality of life and such a dismal prognosis in this patient group leads to a significant quality-adjusted life year (QALY) shortfall compared with population norms. With an absolute severity shortfall of 14.61 QALYs and a proportional shortfall of 0.96 QALY, cemiplimab meets the criteria for a severity weight of 1.7. There is a clear, high unmet need for new, more effective and well-tolerated treatment options for these patients (see Section 1.3.3 below for further details).

1.3.2 Epidemiology

In 2022, 2641 cases of cervical cancer were diagnosed in England (not including cervical carcinoma in situ).²⁰ The age-standardised incidence rate/100,000 females (2017-2019) is 9.9 (95% CI 9.7, 10.1), and there were an average of 685 cervical cancer deaths per year in England over this period (and 159 cases and 52 deaths per year in Wales).²¹ The main cause of cervical cancer is infection with human papillomavirus (HPV). Risk is increased by smoking and other lifestyle factors.³ Cervical cancer affects a younger age group than many other cancers, with incidence rates peaking at age 30-34 years.²¹

Approximately 850 to 880 patients will be diagnosed with r/m CC in England each year over the next five years (see Budget Impact document for details of calculation).

Cervical cancer disproportionately affects people in more deprived socioeconomic groups (see Section 1.5 for details).

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1.3.3 Current treatment and clinical guidelines

1.3.3.1 Current treatment

The main aim of treatment in r/mCC is to relieve symptoms and improve quality of life, and to extend life if possible.^{4,5} The current treatment pathway in NHS practice in England is summarised in Figure 1. Of note, people in Scotland can now receive cemiplimab as second line treatment in line with its full licensed indication, as it was accepted by the SMC in February 2025.¹⁹ In addition, tisotumab vedotin was approved by the EMA on 31 March 2025 for adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy.²² However, tisotumab vedotin is not currently used in routine NHS clinical practice and is therefore not considered a relevant comparator in the submission.

First line (1L): In 2023, NICE recommended pembrolizumab plus chemotherapy with or without bevacizumab as an option for treating persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a combined positive score ≥ 1 (TA939).⁵ NHS gynaecologic consultant oncologist experts practicing in England, consulted for this submission, indicated that $\geq 95\%$ of PD-L1-positive patients are now offered pembrolizumab + chemotherapy +/- bevacizumab in 1L.⁶⁻⁸ Possible reasons for not using pembrolizumab in these patients were cited as contraindications to immunotherapies (e.g. uncontrolled autoimmune disease); delay in receiving PD-L1 results or failure of the test sample; patient declining immunotherapy; or patient considered not fit enough to tolerate the combination therapy. Additionally, pembrolizumab is currently under appraisal by NICE for use in combination with chemoradiation in untreated high-risk locally advanced cervical cancer (ID6138),²³ which may result in additional patients receiving pembrolizumab earlier in the treatment pathway. As a result of routine 1L usage, and also due to the relative lack of evidence on PD-L1 rechallenge, pembrolizumab is not likely to be used in the 2L setting, and is therefore not a relevant comparator to cemiplimab.

Patients with PD-L1 < 1 , together with the small percentage of PD-L1 positive patients who do not receive pembrolizumab ($\leq 5\%$ according to NHS gynaecologic

consultant oncologist experts practising in England),⁶⁻⁸ are offered platinum-based chemotherapy (usually carboplatin + paclitaxel) +/- bevacizumab.

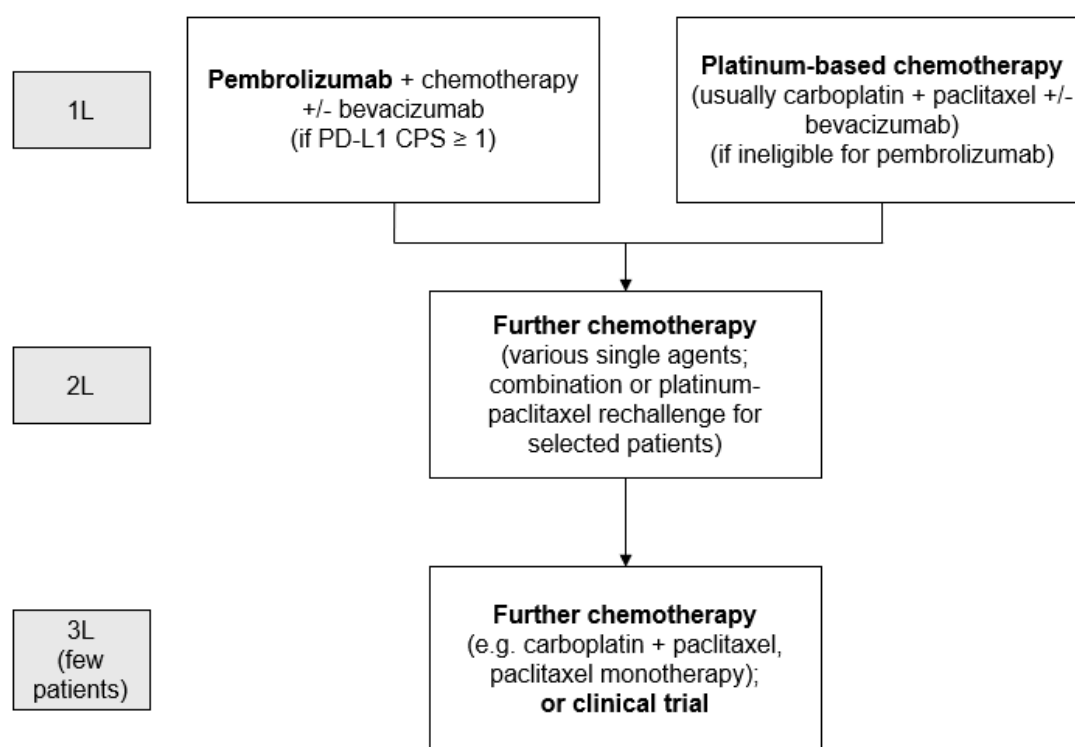
Second line (2L): Clinical guidelines show that there is no clear standard of care after progression on 1L platinum-based chemotherapy^{1,4} (see Section 1.3.3.3), and this was confirmed by NHS gynaecologic consultant oncologist experts practising in England.⁶⁻⁸ Pembrolizumab is theoretically available for r/m CC patients with PD-L1 CPS $\geq$ 1 as 2L treatment, because the licensed indication²⁴ and the NICE recommendation⁵ do not specify whether or not patients must have received previous treatment for r/m CC. However, as noted above, clinical experts confirm that almost all patients who are eligible for pembrolizumab receive it in the 1L setting.

Further chemotherapy is, therefore, currently the only option available in routine NHS practice (see treatment guidelines below) after failure of platinum-based chemotherapy, with options including monotherapies (e.g. mitomycin/5FU, vinorelbine, irinotecan, docetaxel, gemcitabine, weekly paclitaxel and topotecan), or combination therapies such as cisplatin + topotecan and platinum/paclitaxel rechallenge (selected patients only); however, response to all these treatments is poor,^{1,4} and chemotherapy is generally associated with a high toxicity burden, as confirmed by clinical experts (see Section 1.3.3.2 below).

NHS gynaecologic consultant oncologist experts practicing in England⁶⁻⁸ indicated that there is no standard of care for 2L chemotherapy in the NHS, and clinical practice varies. Weekly paclitaxel monotherapy is a commonly used 2L treatment and single-agent chemotherapy with topotecan, gemcitabine, irinotecan or vinorelbine is also used in some cases. Patients who have had a long interval since the last treatment (> 6-12 months) may be rechallenged with carboplatin + paclitaxel. Clinical trials are also an option in 2L if available.

Third line (3L): NHS gynaecologic consultant oncologist experts practicing in England confirm that few patients are fit enough to receive 3L treatment, but in those

who do receive 3L treatment this could consist of carboplatin + paclitaxel, paclitaxel monotherapy, or a clinical trial.⁶⁻⁸



Abbreviations: 1L, first-line; 2L, second line; 3L, third line; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Figure 1. Current treatment pathway in r/mCC.

1.3.3.2 Unmet need in 2L treatment

Cemiplimab addresses an important unmet need in the 2L setting. Patients in England who have progressed after platinum-based chemotherapy currently have no option for 2L treatment other than further chemotherapy, which has limited efficacy and a high toxicity burden. In addition, many patients will already have received chemotherapy in the neoadjuvant or adjuvant as well as the r/m setting, which may limit their ability to tolerate further chemotherapy cycles. An effective and well-tolerated alternative to further chemotherapy is urgently needed.

The specific toxicities of chemotherapy vary by regimen. Paclitaxel (commonly used as 2L chemotherapy) is particularly associated with sensory peripheral neuropathy,

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characterised by a burning, tingling or numb sensation in the hands and lower legs which can progress to motor weakness with continued use.¹⁸ Most patients have already received paclitaxel in 1L in combination with carboplatin or cisplatin, and previous exposure predisposes people treated with paclitaxel to neuropathy.¹⁸ A 2022 Cochrane review of taxane monotherapy in recurrent ovarian cancer found that weekly paclitaxel may reduce the risk of neutropenia compared with three-weekly administration, but may make no difference to the risk of neuropathy. The review also found that the risk of alopecia (hair loss) remains high with weekly paclitaxel (46% in the study identified).²⁵ Other toxicities commonly associated with paclitaxel (>10% incidence) include neutropenia and associated infections, bruising and bleeding, diarrhoea, nausea and vomiting, mouth sores, muscle and joint pain and urinary tract infections.²⁶

NHS gynaecologic consultant oncologist experts practicing in England confirm that chemotherapy-related toxicity typically has a negative impact on quality of life.⁶⁻⁸

Comments made in the consultation included:

- *“Most certainly, chemotherapy has important side effects. Immunotherapies are very well tolerated, and patients on immunotherapies tend to have good quality of life, that you don’t see on chemotherapy.”*
- *“Chemotherapy does have a lot of quality-of-life impact. It is going to be much less for immunotherapy or just targeted therapy.”*
- *“After first line the residual side effects of chemo also has a huge impact on quality of life.”*

Notably, patients with PD-L1<1 or who did not receive pembrolizumab for other reasons currently have no access to immunotherapy at any point in the current treatment pathway. Clinical experts confirm there is a high unmet need for an immunotherapy option in 2L with an acceptable toxicity profile and good response rate that prolongs survival regardless of PD-L1 status, whilst maintaining or improving quality of life.⁶⁻⁸ Quality of life is of utmost importance in this end-of-life setting, particularly for (but not limited to) young patients caring for children.

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Further comments made in the consultation with clinical experts included:

- *“There is definitely an unmet need for second line immunotherapies as those [who were not eligible for pembrolizumab] currently have no access to immunotherapies.”*
- *“It’s a small number of patients but these are generally young women with no options and desperate for anything that will give them a bit longer.”*

Further detail of how cemiplimab addresses this unmet need is provided in Section 2.14.5.

1.3.3.3 Clinical guidelines

There is no NICE guideline on the treatment of cervical cancer. Relevant guidelines are summarised below, and these confirm the potential of cemiplimab to address the high unmet need in the 2L treatment setting.

ESGO/ESTRO/ESP guidelines

The most recent applicable guidelines are the 2023 joint guidelines from the European Society of Gynecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP).¹³ These recommend pembrolizumab in combination with chemotherapy, with or without bevacizumab, for the 1L treatment of distant recurrent and metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS $\geq$ 1. The guideline gives a clear recommendation for cemiplimab in the 2L setting:

- *“Patients who progressed after first-line platinum-based chemotherapy should be offered treatment with the anti PD-1 agent, cemiplimab, regardless of PDL-1 tumor status as long as they had not previously received immunotherapy [I, A].”¹³ [I indicates evidence from at least one large RCT of good methodological quality, A indicates strong evidence for efficacy with a substantial clinical benefit, strongly recommended.]*

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- Chemotherapy is recommended for patients who are not eligible for cemiplimab because they have had previous immunotherapy, but no specific regimens are detailed.

British Gynaecological Cancer Society (BGCS) guidelines

British Gynaecological Cancer Society (BGCS) cervical cancer guidelines (2021) do not mention pembrolizumab or cemiplimab, as they predate their approval for the treatment of cervical cancer. They indicate that standard of care in the UK for relapsed or metastatic CC (r/m CC) (before the advent of pembrolizumab-based treatment) was platinum-based chemotherapy, typically platinum paclitaxel doublet +/- bevacizumab. The guidelines also recognised the potential for immunotherapy to improve outcomes in the 2L setting given the poor response rates with chemotherapy:¹

- The guideline states that there is no standard of care for 2L treatment. It states that mitomycin/5FU, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity. Rechallenge with platinum/paclitaxel could be considered in those patients with a good partial response to 1L treatment and are who more than 6 months out.
- It states that “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”.

European Society of Medical oncology (ESMO) guidelines

The ESMO guidelines on metastatic CC were last updated in 2017 (before pembrolizumab or cemiplimab were approved for use in cervical cancer).

- They state that: “In patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates are low and duration of responses is short. Therefore, no recommendation can be given about the most effective second-line treatment.”

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- A summary table of second-line therapy outcomes in metastatic CC presented in the guideline shows OS ranging from 5.0 to 12.7 months.⁴

1.3.4 Position of cemiplimab in the treatment pathway

NHS consultant gynaecologic oncologists consulted for the submission have confirmed that, since the NICE recommendation for pembrolizumab in December 2023 (TA939), pembrolizumab + chemotherapy +/- bevacizumab has become routinely used as 1L treatment for r/m CC in patients whose tumours express PD-L1 with a CPS $\geq$ 1. The exact proportion of patients whose tumours are PD-L1 positive is uncertain but it was estimated at 88.8% in the NICE appraisal of pembrolizumab in r/m CC (TA939: resource impact analysis; estimate based on NHS England expert input).²⁷ Patients with PD-L1 <1 receive platinum-based chemotherapy.

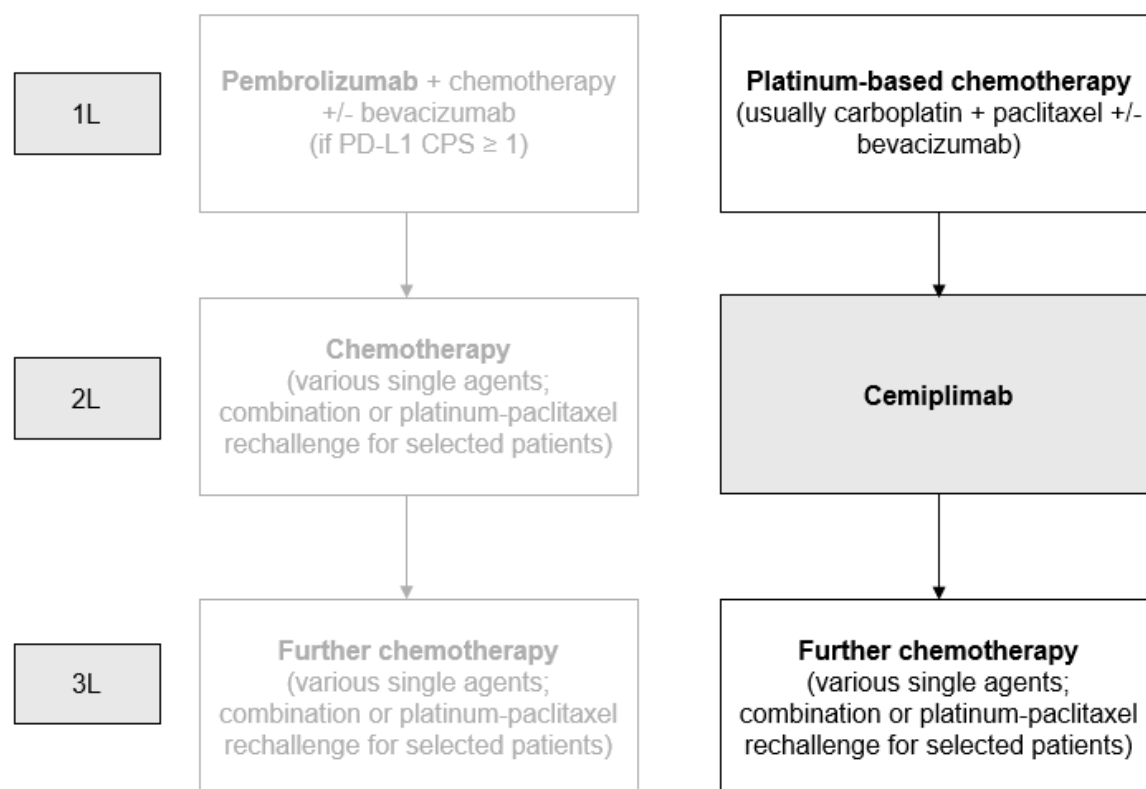
Cemiplimab as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.⁹

In line with the most up-to-date, evidence-based European clinical guidelines from ESGO/ESTRO/ESP,¹³ and the population of its pivotal phase 3 trial (EMPOWER Cervical-1):

- Cemiplimab is only expected to be used in patients who have not previously received immunotherapy (i.e. with pembrolizumab), regardless of their PD-L1 status.
- This positioning was confirmed by the NHS gynaecologic consultant oncologist experts practising in England who were consulted.⁶⁻⁸
- Cemiplimab is approved in this position by the SMC.¹⁹
- Approximately 128-132 patients are expected to fall into this category each year over the next 5 years (see Budget Impact Document for details). This represents only a small proportion of the overall population of 2L r/mCC patients.
- Cemiplimab thus addresses an important unmet need in a small population of patients who currently have no access to immunotherapy during their

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treatment pathway. It provides a much-needed, more efficacious and tolerable, chemotherapy-free alternative to the poorly efficacious and highly toxic chemotherapy that is currently the only routinely available option in these patients (see Section 2.14.5 for further discussion).



Abbreviations: 1L, first-line; 2L, second line; 3L, third line; CPS, combined positive score; PD-L1, programmed death-ligand 1

Figure 2. Positioning of cemiplimab in the treatment pathway.

1.4 Equality considerations

Cervical cancer disproportionately affects people in more deprived socioeconomic groups. For the period 2013-2017, the incidence rate was 65% higher in the most deprived socioeconomic (Index of Multiple Deprivation) quintile than in the least deprived. Cancer Research UK estimates that there are around 520 more cases of cervical cancer each year in England than there would be if all quintiles had the same age-specific crude incidence rates as the least deprived quintile (2013-2017

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period).²¹ People living with deprivation are also more likely to be diagnosed later and therefore more likely to experience advanced cervical cancer.²⁸

Thus, decision-making on treatments for cervical cancer disproportionately affects people in more deprived socioeconomic groups. These groups are also disproportionately affected by the current lack of an effective and well-tolerated 2L treatment for r/m CC. Reducing health inequalities for people in the most deprived IMD quintile is a key focus of Core20PLUS5, the national NHS England approach to reducing healthcare inequalities.²⁹ Making cemiplimab available would represent a positive step towards addressing this inequality in r/m CC.

2 Clinical effectiveness

Key points

- Cemiplimab is an immunotherapy indicated as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer (r/m CC) and disease progression on or after platinum-based chemotherapy.⁹ As such, it provides the only alternative to chemotherapy in the 2L setting.
- Its efficacy and safety were assessed in the EMPOWER Cervical-1 phase 3 randomised controlled trial,^{10,12,30} which is the largest clinical trial to date in this population and was assessed as being high quality with low risk of bias in the systematic literature review (Appendix B) and in ESGO/ESTRO/ESP guidelines.¹³ The final analysis provides mature survival data, with median follow-up of almost 4 years.¹⁰
- Cemiplimab resulted in a statistically and clinically significant improvement in OS compared with chemotherapy in patients with r/m CC that had progressed on or after platinum-based chemotherapy.^{10,12,30}
 - In the final analysis (median follow-up 47.3 months), the gain in median OS for cemiplimab vs chemotherapy in the overall population was 3.2 months (11.7 vs 8.5 months), with a 33% reduction in the hazard for death (HR 0.67 [95% CI 0.56, 0.80]).¹⁰
 - The OS benefit was consistent across pre-specified subgroups.
 - The OS benefit was observed early and was maintained throughout follow-up, as demonstrated by the early and sustained separation of OS Kaplan-Meier curves.
 - At 24 months, an estimated 28.2% (95% CI 23.0, 33.5) of patients in the cemiplimab arm were still alive, compared with 11.9% (8.4, 16.1)

in the chemotherapy arm. This is noteworthy in this 2L population, who have a dismal prognosis under current treatment.¹⁰

- Approximately one-fifth of patients in the cemiplimab arm were still alive after 36 months (estimated probability of survival 22.0% [95% CI 17.3, 27.0] compared with 8.3% [5.3, 12.0] in the chemotherapy arm).¹⁰
- Cemiplimab was also associated with a statistically and clinically significant PFS benefit over chemotherapy (HR 0.741 [95% CI 0.62–0.88]; one-sided $P=0.00031$).¹²
- Objective response rate was markedly higher with cemiplimab than with chemotherapy (17.1% [95% CI: 13.0%, 21.8%]) vs. 6.3% [95% CI: 3.8% to 9.6%]; odds ratio 3.1 [95% CI: 1.8, 5.5]).¹⁰
- Median duration of response was over twice as long in the cemiplimab arm than in the chemotherapy arm, at 18.7 months (95% CI: 16.4 to NE) and 7.2 months (95% CI: 5.1 to 9.9), respectively.¹²
- Cemiplimab-treated patients had quality of life benefits versus chemotherapy across a range of EORTC QLQ-C30 measures. Changes from baseline in Global Health Status, Physical Functioning and most symptom scales favoured cemiplimab, with clinically meaningful favourable differences compared with chemotherapy in role functioning, appetite loss and pain.¹¹

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify interventional studies of treatment of adult patients with recurrent, persistent and/or metastatic cervical cancer that had progressed after platinum-containing chemotherapy given to treat recurrent or metastatic cervical cancer. The report describing the methods and

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results is provided as Appendix B. The SLR was carried out in accordance with best practice guidelines outlined by Cochrane, the Centre for Reviews and Dissemination (CRD), the PRISMA statement and the National Institute for Health and Care Excellence (NICE).³¹⁻³⁴ .

2.2 List of relevant clinical effectiveness evidence

EMPOWER Cervical-1^{10,30} (NCT03257267) was identified as the only fully published RCT providing evidence on cemiplimab in this setting (i.e. adult patients with recurrent, persistent and/or metastatic cervical cancer that had progressed after platinum-containing chemotherapy). This large, pivotal, phase 3 trial compared cemiplimab with investigator's choice of chemotherapy, and is used to inform the economic model (see Table 3).

A 2024 conference abstract of a small RCT from Uzbekistan comparing cemiplimab with investigator's choice of chemotherapy was also identified (N=180 patients). Owing to the limited amount of information available on this study (no full publication was identified), it is not used to inform the economic model. The results are presented in Section 2.9.1 for completeness. The results of this study were very similar to those seen in EMPOWER Cervical-1. This study was not sponsored or funded by Regeneron.

Real-world evidence on use of cemiplimab in r/m CC is available from two published studies, including one from a UK centre, described in Section 2.9.2.

Table 3. Clinical effectiveness evidence: EMPOWER Cervical-1

Study	EMPOWER Cervical-1 ^{10,30}
Study design	Open label, randomised, phase 3 trial
Population	Patients with recurrent or metastatic cervical carcinoma (r/m CC) that had progressed after platinum-containing chemotherapy
Intervention(s)	Cemiplimab 350 mg intravenously (IV) every 21 days for up to 96 weeks
Comparator(s)	Investigator's choice of chemotherapy, determined for each patient before randomisation
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A – the economic model is based on the EMPOWER Cervical-1 RCT
Reported outcomes specified in the decision problem	Overall survival (Primary endpoint)* Progression-free survival* Objective response rate Health-related quality of life* Adverse events*
All other reported outcomes	The following outcomes are also reported by the trial (only duration of response is reported in the submission): Duration of response Association between efficacy and biomarker status (exploratory) Pharmacokinetic variables Anti-drug antibody variables

Abbreviations: IV, intravenous; r/m CC, recurrent/metastatic cervical cancer; RCT, randomised controlled trial

*Bold indicates outcomes that are incorporated in the economic model.

Clinical experts practising in England (NHS consultant gynaecologic oncologists) were consulted to inform the submission with regard to NHS clinical practice, patient characteristics and burden, patient experience with standard of care, and validation of various model inputs and assumptions. Their input is noted at relevant points in the submission document, and the interviews are supplied as references. An overview of the expert elicitation process is given in Appendix R.

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2.3 Summary of methodology of the relevant clinical effectiveness evidence

The relevant clinical effectiveness evidence is provided by the EMPOWER Cervical-1 trial. Methods are taken from the primary study publication (Tewari et al. 2022,³⁰ data cut-off 4 January 2021) and its supplementary materials. Survival, response and safety data are taken from the final study analysis publication (Oaknin et al. 2025¹⁰) and clinical study report,¹² data cut-off 3 October 2023, as this provides the most mature and complete data. (NB the Oaknin 2025 publication erroneously states April 20 2023 as the data cut-off, but the April date was in fact the Last Patient Last Visit date; database lock was 3 October 2023 as stated in the submission and the CSR.) Patient-reported outcomes are described based on a separate publication by Oaknin et al. 2022 (data cut-off 4 January 2021, final PRO analysis).¹¹ The available data sources, length of follow-up and their use in the submission are summarised in Table 4.

Table 4 Summary of data cut-off dates and median follow-up, and their use in the submission

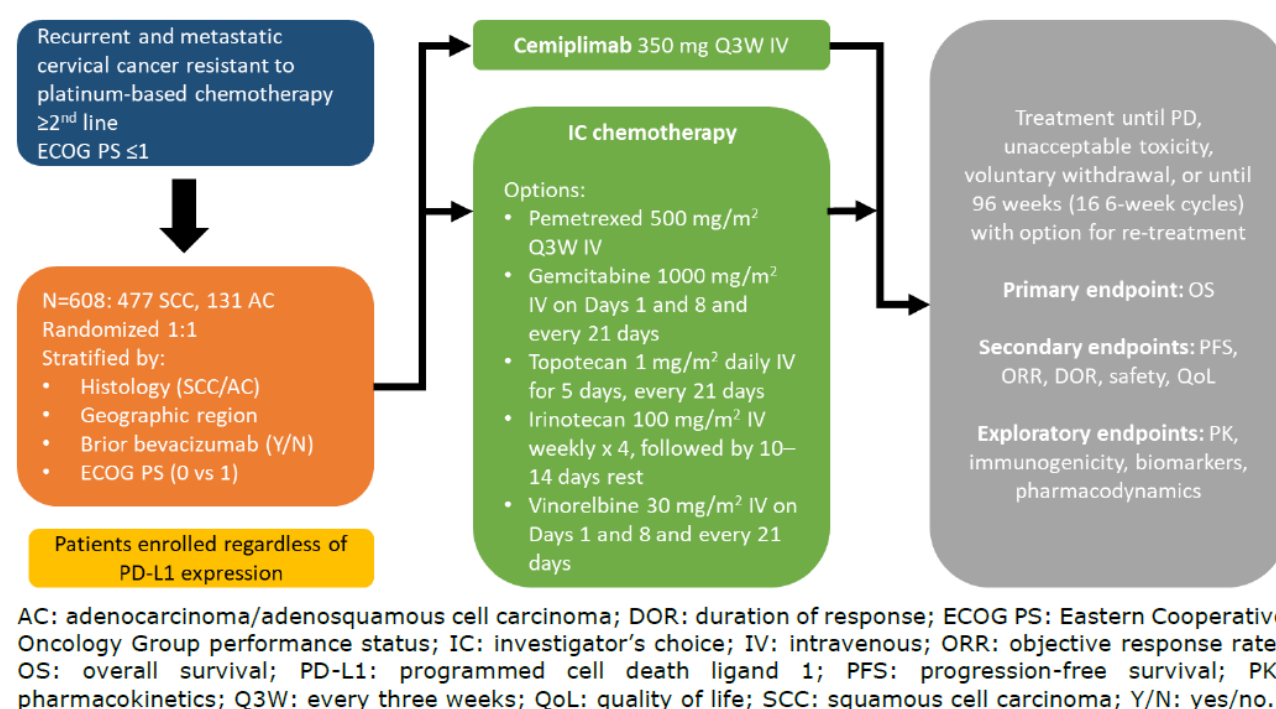
Analysis and source	Source	Data cut-off & median follow-up (overall population)	Use in submission
Primary analysis (2nd interim analysis)	Tewari 2022 ³⁰ Primary CSR	4 Jan 2021 18.2 months	Methods and baseline characteristics only.
Updated exploratory OS analysis	European Public Assessment Report (EPAR) ¹⁶	4 Jan 2022	Used for the exploratory analysis of OS discussed in the EPAR. Superseded by final analysis. Not used in the submission.
Final study analysis	Oaknin 2025 ¹⁰ Final CSR	3 October 2023 (NB the published paper erroneously states April 20 2023 as the data cut-off, but the April date was in fact the Last Patient Last Visit date; database lock was 3 October 2023 as stated in the submission and the CSR) 47.3 months	Results presented in Section 2.6 and 2.12. Used to inform AEs in the model
Survival analysis	Patient level data of the final data-cut used for the final CSR	3 October 2023 47.3 months	Results presented in section 3.3.2, and Appendix L and M. Used to derive efficacy inputs for OS, PFS and time on treatment for the model
Final PRO analysis	Oaknin 2022 ¹¹	4 Jan 2021 18.2 months	The published PRO results are presented in Section 2.6.6. For the economic modelling, EORTC QLQ-C30 scores at each visit were mapped on to the EQ-5D-3L using individual patient-level data (see Section 3.4.2 and Appendix N)

Abbreviations: AE, adverse event; CSR, clinical study report; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EPAR, European Public Assessment Report; EQ-5D-3L, EuroQol-5 Dimension 3-Level; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcome.

2.3.1 Methods

EMPOWER Cervical-1 is the largest OS-powered phase 3 RCT in 2L r/m CC conducted to date, and enrolled both squamous and adenocarcinoma histologies regardless of PD-L1 status. The trial population is the same as the population covered by cemiplimab's licensed indication in cervical cancer (and the population covered by this submission): patients had to have recurrent or metastatic cervical carcinoma where the tumour had progressed after platinum-containing therapy used to treat recurrence or metastases. Previous treatment with agents targeting PD-1/PD-L1 pathway was not permitted.³⁰

Study design is shown in Figure 3 and methodology is described in Table 5.



Source: Adapted from Tewari et al. 2022³⁰

Figure 3. EMPOWER Cervical-1 study design.

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Table 5. EMPOWER Cervical-1 methodology.

Trial name	EMPOWER Cervical-1 (NCT03257267)³⁰
Trial design	Prospective, multicenter, multinational, randomised (1:1), open-label, parallel-group, 2-arm phase 3 study.
Study locations	97 sites in 14 countries (Australia, Belgium, Brazil, Canada, Greece, Italy, Japan, Poland, Republic of Korea, Russian Federation, Spain, Taiwan, UK, US); 2 sites in the UK (England).
Randomisation and blinding	Patients were randomised 1:1 to cemiplimab or investigator choice (IC) of chemotherapy. Randomisation was stratified by histology (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]), geographic region (North America, Asia, or rest of the world), previous bevacizumab exposure (yes or no)*, and ECOG performance-status score (0 or 1)*. Investigators determined IC chemotherapy regimen before randomisation from protocol-specified options reflecting local treatment availability. *Not included in the statistical model for analysis of primary endpoint Randomisation was done using an interactive web response system.³⁵ Blinding: trial was open label.
Key eligibility criteria	Inclusion criteria • Age 18 years or older • Recurrent or metastatic cervical carcinoma where tumour had progressed after platinum-containing therapy used to treat recurrence or metastases; required to have measurable disease. • Previously treated with bevacizumab and paclitaxel (unless treatment declined, deemed unsuitable, or bevacizumab not available). • Previous bevacizumab treatment must have been discontinued due progression or toxicity before enrolment. • Adequate renal, hepatic, and bone marrow function • ECOG performance status 0 or 1 • Anticipated life expectancy >12 weeks Exclusion criteria • Candidates for pelvic exenteration • Evidence of significant autoimmune disease within last 5 years that required systemic immunosuppressive treatment • Prior treatment with agents targeting PD-1/PD-L1 pathway • Treatment with other systemic immune-modulating agents within 4 weeks before trial enrolment • Known history of brain metastases that may be considered active A full list of inclusion and exclusion criteria is available in Tewari 2022 Suppl.³⁰

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	Enrolment of patients with adenocarcinoma or adenosquamous carcinoma was capped with the intent to enroll a trial population matching the real-world distribution of histological types.
Study medicines	Cemiplimab: flat dose of 350 mg intravenously (IV) every 21 days for up to 96 weeks, with option of repeat treatment for patients completing 16 treatment cycles who then had progressive disease in the post-treatment follow-up period. (Note: only ■ [■]%) patients in the cemiplimab arm received any post-treatment anti-PD-L1 therapy.¹²⁾ Patients with an unconventional response consistent with pseudo-progression could be treated beyond progression provided the following conditions were met: no increase in ECOG PS score, no rapid disease progression and, no severe adverse events warranting cemiplimab discontinuation. Investigator's choice (IC) chemotherapy: the following options were available, all for up to 96 weeks; option was determined for each patient prior to randomisation: • Pemetrexed (500 mg/m² body-surface area IV every 21 days), with vitamin B12 and folate support as needed; or • Topotecan (1 mg/m² IV daily for 5 days); or • Irinotecan (100 mg/m² IV weekly for 4 weeks); or • Gemcitabine (1000 mg m² IV on days 1 and 8 every 21 days); or • Vinorelbine (30 mg/m² IV on days 1 and 8 every 21 days) IC chemotherapy was discontinued at disease progression or development of unacceptable toxic effects (stopping rules for adverse events were outlined in the protocol). Crossover was not permitted.
Permitted and disallowed concomitant medication	A summary is given below, full details are available in the study protocol.³⁶⁾ Disallowed: anti-cancer treatments other than study medication; live vaccines; bisphosphonates; denosumab. Systemic corticosteroids not recommended except in emergency or to treat immune-related AEs. Permitted: Physiologic replacement of systemic corticosteroids; brief course of corticosteroids for prophylaxis or treatment of non-autoimmune conditions; palliative radiation therapy to non-target lesions in certain circumstances.
Primary endpoint	Overall survival (OS; time from randomisation to date of death).
Secondary endpoints	Key secondary endpoints • Progression-free survival (PFS; time from randomisation to the date of the first documented tumour progression using RECIST 1.1, or death due to any cause). Assessed on day 42 (+/- 7 days) of the 6-week cycle, in cycles 1-4, 6, 8, 10, 12, 14 and 16 and follow-up visits 1 and 2 and survival follow-up assessments). • Objective response rate (ORR; number of patients with a best overall response of confirmed CR or PR divided by the number

	of patients in the efficacy analysis set). Assessed by the investigator by RECIST 1.1. Assessment schedule as for PFS. Other secondary endpoints • Duration of response (DOR; time between the date of first response (CR or PR) to the date of the first documented tumour progression (per RECIST 1.1) or death due to any cause. • Quality of life measured by the EORTC QLQ-C30 instrument (administered at screening visit and on Day 1 of each 6-week cycle, and follow-up visits 1 and 2) • Safety and tolerability
Exploratory variables (PD-L1 biomarker)	Exploratory analyses were performed on archival tumour samples to evaluate associations between efficacy endpoints and biomarkers, including PD-L1 expression in tumour cells (detected using the SP263 monoclonal antibody [Ventana]). PD-L1 expression status was categorized as either $\geq 1\%$ or $< 1\%$ in tumour cells.
Pre-planned subgroups	Pre-specified subgroup analyses of the primary and key secondary endpoints were performed on the following factors. As subgroup analyses do not have enough power for hypothesis tests, the analysis was descriptive only.³⁵ • age group (<65, ≥ 65) • race (White, Non-white) • geographic region (North America, Asia and ROW) • geographic region (Japan, outside of Japan) • histology (Squamous, Adenocarcinoma/adenosquamous) • prior bevacizumab use (Yes, No) • baseline ECOG status (0, 1) • choice of IC chemotherapy • number of prior lines of systemic therapy for recurrent or metastatic disease (1 line, >1 line)

Abbreviations: AE, adverse event; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IC, investigator choice; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-1, programmed cell-death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response evaluation criteria in solid tumors; ROW, rest of world

Source: Tewari 2022;³⁰ study protocol³⁶

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

Statistical analyses in the EMPOWER Cervical-1 trial are summarised in Table 6. Further details are available in the Statistical Analysis Plan published as a supplement to Tewari et al. 2022.³⁵ Patient disposition is shown in Section 2.6.1.

Table 6. EMPOWER Cervical-1 statistical methods.

Sample size calculation	Approximately 460 patients with squamous cell carcinoma (SCC) would need to be enrolled, with approximately 340 deaths expected, to provide 90% power to detect at least a 30% lower risk of death in the cemiplimab group than in the chemotherapy group with an overall one-sided type I error of 2.5% in the population with squamous-cell carcinoma. Approximately 590 patients in the overall population (i.e., patients with either histologic subtype) were projected to be needed to complete enrolment of 460 patients with SCC.
Analysis sets	• All efficacy endpoints were analysed in the full analysis set (FAS), which includes all randomised patients based on the treatment allocated at randomisation (ITT population). • The safety analysis set (SAF) includes all randomized patients who received any study drug and is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables were analysed using the SAF. • Biomarker analysis set (BAS) was to include all treated patients with at least one sample assayed. Only samples stained within 6 months after slide sectioning were analysed in the primary analysis, in accordance with the assay manufacturer's instructions for use.
Hierarchical testing plan	A hierarchical testing plan that started with an analysis of overall survival in the population with SCC was used to control Type I error; if these results were significant, overall survival was analysed in the overall population. The hierarchical testing order is shown in Tewari 2022, Table S2.³⁰
Interim analyses	Two interim analyses were planned after approximately 70% and 85% of deaths had occurred among the patients with SCC. These were conducted by an independent statistics group and reviewed by the independent data and safety monitoring committee.
Analysis of primary endpoint	The primary endpoint of OS was analysed in SCC patients by stratified log-rank test using geographic region (North America versus Asia-Pacific versus ROW) as a stratification factor. The hazard ratio (HR) and its 95% confidence interval (CI) were estimated by a stratified Cox regression model with Efron's method for tie handling and using the treatment as covariate. The distribution of OS was estimated using the Kaplan-Meier method.

Analysis of secondary endpoints	• Analysis of PFS used the same methods as for OS. • ORR was analysed using the Cochran-Mantel-Haenszel test with the same stratification factors as described for OS with regard to the SCC and overall population. ORR and the corresponding 95% exact CI were calculated by Clopper-Pearson method for each treatment arm. • Patient-reported outcomes: Mixed models for repeated measures (MMRM) were used to estimate least-squares (LS) mean changes from baseline. The following covariates were included as fixed effects: treatment arm, timepoint, baseline patient-reported outcome (PRO) score, geographic region, histology (for the overall population only), interaction of baseline PRO score and timepoint, and interaction of treatment arm and timepoint. In each population (SCC, AC and overall). MMRM analyses did not include cycles when the sample size dropped below 10 patients in either treatment group.¹¹ • Responder analyses for PROs calculated the proportion of patients with clinically meaningful improvement (increase of ≥ 10 points), maintenance (between -10 and $+10$ points), or clinically meaningful worsening (reduction of ≥ 10 points) from baseline using a missing-at-random assumption, with a missing-not-at-random assumption as a sensitivity analysis. Time to definitive deterioration was defined as the time from randomisation to clinically meaningful worsening (i.e., a ≥ 10-point change) from baseline that was sustained at all subsequent timepoints or followed by patient withdrawal after worsening, resulting in missing data. The nonparametric Kaplan–Meier method was used to estimate survival curves and median values (with 95% CI) for each PRO scale. The treatment difference was assessed by stratified log-rank test using geographic region and histology as strata for the overall population and geographic region only for the SCC population. A stratified Cox proportional hazard model was used to assess the HR, using the same strata as above.¹¹ • All other secondary variables were analysed descriptively.

Abbreviations: AC, adenocarcinoma; BAS, biomarker analysis set; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; LS, least-squares; MMRM, mixed models for repeated measures; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; ROW, rest of world; SAF, safety analysis set; SCC, squamous cell carcinoma

Source: Tewari 2022;³⁰ Statistical analysis plan³⁵; Oaknin 2022¹¹

2.5 Critical appraisal of the relevant clinical effectiveness evidence

EMPOWER Cervical-1 was assessed as having a low risk of bias in all domains using the Cochrane risk of bias assessment tool (see Appendix B, Section 8.3), and

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the ESGO/ESTR/ESP guidelines report the trial provides level I, A evidence (where I indicates evidence from at least one large RCT of good methodological quality, and A indicates strong evidence for efficacy with a substantial clinical benefit, strongly recommended).¹³ Overall, the study provides robust evidence supporting the efficacy of cemiplimab versus investigator's choice of chemotherapy in this end-of-life population, for whom no clear standard of care is available and current treatment options (i.e. further chemotherapy) result in poor response rates and reduced quality of life.^{1,4} Strengths and limitations of the evidence base are discussed further in Section 2.14.

2.6 Results

EMPOWER Cervical-1 was stratified by histology and results were reported for the overall, squamous cell and adenocarcinoma populations.¹⁰ In the submission, results are presented for the overall study (ITT) population, which is the population of interest per the licensed indication and is reflected in the economic modelling. Prespecified subgroup analyses, including by histology, are reported in Section 2.8.

2.6.1 Patient disposition and baseline characteristics

Patient disposition in the EMPOWER Cervical-1 trial at the final analysis is shown in Figure 4. A total of 608 patients were randomised (304 to cemiplimab and 304 to chemotherapy). At the final analysis (data cut-off 3 Oct 2023), all patients were off-study and none had ongoing treatment. Final data on treatment discontinuation are summarised in Table 7. A total of 12.5% of patients in the cemiplimab arm and 0% of patients in chemotherapy arm completed the study per protocol. In both treatment groups, the most common reason for study discontinuation was disease progression. Of note, the rates of discontinuation due to adverse events reported in Table 7 are not exposure adjusted. The exposure-adjusted rate of permanent discontinuation

due to TEAEs was lower for cemiplimab than for chemotherapy, at 15.68 and 18.53 per 100 patient-years treated, respectively.¹²

The median duration of treatment exposure at the final analysis was 15.2 weeks (range, 1.4 to 107.7) for cemiplimab and 10.1 weeks (range, 1.0 to 91.1) for chemotherapy.¹²

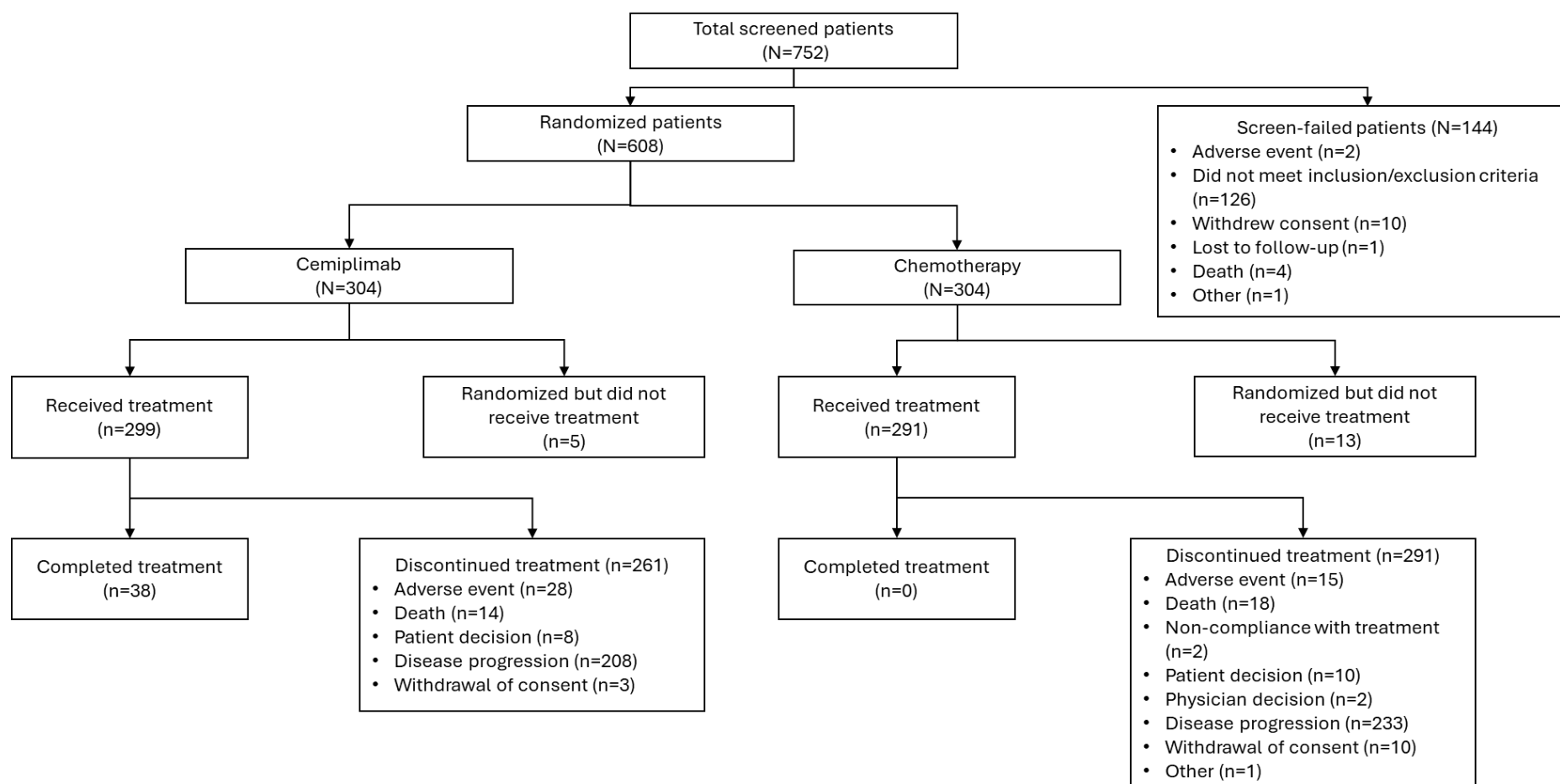


Figure 4. Patient disposition of the EMPOWER Cervical-1 trial (final analysis).

Source: Oaknin et al. 2025 (Suppl)¹⁰

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Table 7. Treatment discontinuation (final analysis).

	Cemiplimab (N=304)	Chemotherapy (N=304)
Randomized but Never Treated, n (%)	5 (1.6%)	13 (4.3%)
Treatment ongoing, n (%)	0	0
Off treatment, n (%)	299 (98.4%)	291 (95.7%)
Treatment completed (per study protocol)	38 (12.5%)	0
Treatment discontinued	261 (85.9%)	291 (95.7%)
Primary reason for treatment discontinuation		
Adverse event*	28 (9.2%)	15 (4.9%)
Death	14 (4.6%)	18 (5.9%)
Non-compliance with study drug(s)	0	2 (0.7%)
Subject decision	8 (2.6%)	10 (3.3%)
Physician decision	0	2 (0.7%)
Disease progression	208 (68.4%)	233 (76.6%)
Withdrawal of consent	3 (1.0%)	10 (3.3%)
Other	0	1 (0.3%)

Source: Oaknin et al. 2025 (Suppl)¹⁰

Note: * discontinuations due to adverse events not adjusted for treatment exposure.

Baseline demographics and disease characteristics were well-balanced between treatment arms, and are summarized in Table 8. Median age for the overall population was 51 years (range, 22 to 87), and the great majority (87.7%) were aged <65 years. Just over half (53.5%) had ECOG performance status (PS)1, indicating some performance status impairment. In total, 473 (77.8%) had squamous-cell carcinoma and 135 (22.2%) had adenocarcinoma or adenosquamous carcinoma.³⁰

All patients had previously experienced disease progression after platinum-containing therapy used to treat recurrence or metastasis. Approximately 40% of patients in each group had received more than one previous line of systemic therapy for recurrence or metastasis, and approximately 50% in each group had previously received bevacizumab. In 87.8% of patients, disease progression had occurred ≤ 6 months after prior platinum chemotherapy, emphasising the poor prognosis in this group.

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Table 8. Patient characteristics of the EMPOWER Cervical-1 trial at baseline.

Characteristic	Cemiplimab (N = 304)	Chemotherapy (N = 304)	Overall (N = 608)
Age			
Median, yr (range)	51 (22-81)	50 (24-87)	51 (22-87)
<65 years, n (%)	269 (88.5)	264 (86.8)	533 (87.7)
Race or ethnic group, n (%) [*]			
White	193 (63.5)	192 (63.2)	385 (63.3)
Black	9 (3.0)	12 (3.9)	21 (3.5)
Asian	88 (28.9)	88 (28.9)	176 (28.9)
American Indian or Alaska Native	2 (0.7)	1 (0.3)	3 (0.5)
Other	8 (2.6)	4 (1.3)	12 (2.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Not reported	3 (1.0)	6 (2.0)	9 (1.5)
Hispanic or Latino			
Yes	251 (82.6)	250 (82.2)	501 (82.4)
No	47 (15.5)	44 (14.5)	91 (15.0)
Not reported	6 (2.0)	10 (3.3)	16 (2.6)
Region of enrollment, n (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of the world	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance status score, n (%) ^{*†}			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)
Histologic type, n (%) ^{*‡}			
Squamous-cell carcinoma	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma or adenosquamous carcinoma	64 (21.1)	71 (23.4)	135 (22.2)
Extent of disease, n (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent or persistent	20 (6.60)	14 (4.6)	34 (5.6)
Previous lines of therapy for recurrent or metastatic disease, n (%)			
One	177 (58.2)	169 (55.6)	346 (56.9)
More than one	124 (40.8)	135 (44.4)	259 (42.6)
Previous bevacizumab use, n (%) [§]			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)
Previous paclitaxel use, n (%) [§]			
Yes	273 (89.8)	287 (94.4)	560 (92.1)
No	31 (10.2)	17 (5.6)	48 (7.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

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* Information is from the electronic data-capture system; † Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability; ‡ At the time of randomization, discrepancies between the electronic data-capture system and interactive Web response system in the distribution of histologic types were introduced. According to the electronic data-capture system, 77.8% of the patients had squamous-cell carcinoma and 22.2% had adenocarcinoma or adenosquamous carcinoma. According to the interactive Web response system, 78.5% of the patients had squamous-cell carcinoma and 21.5% had adenocarcinoma or adenosquamous carcinoma; § Information is from the interactive Web response system.

Source: Tewari 2022³⁰

2.6.2 Overall survival (primary endpoint)

Cemiplimab resulted in a statistically and clinically significant improvement in OS compared with chemotherapy (Table 9). In the final analysis, with a median follow-up of 47.3 months:¹⁰

- The gain in median OS for cemiplimab vs chemotherapy in the overall population was 3.2 months (11.7 vs 8.5 months), with a 33% reduction in the hazard for death (HR 0.67 [95% CI 0.56, 0.80]).
 - The OS benefit was observed early and was maintained throughout follow-up, as demonstrated by the early and sustained separation of OS Kaplan-Meier curves (Figure 5).
 - The long tail on the survival curve suggests long-term response to cemiplimab in a substantial proportion of patients, which is a well-documented phenomenon with immunotherapy treatments.³⁷
- The estimated probability of survival at 12 months was 49.0% (95% CI: 43.2-54.6) vs. 34.2% (95% CI: 28.6-39.8) for the cemiplimab and chemotherapy arms, respectively.
- At 24 months, an estimated 28.2% (95% CI 23.0, 33.5) of patients in the cemiplimab arm were still alive, compared with 11.9% (8.4, 16.1) in the chemotherapy arm. This is noteworthy in this 2L+ population, who have a poor prognosis under current treatment.

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- Approximately one-fifth of patients in the cemiplimab arm were still alive after 36 months (estimated probability of survival 22.0% (95% CI 17.3, 27.0), compared with 8.3% (5.3, 12.0) in the chemotherapy arm.

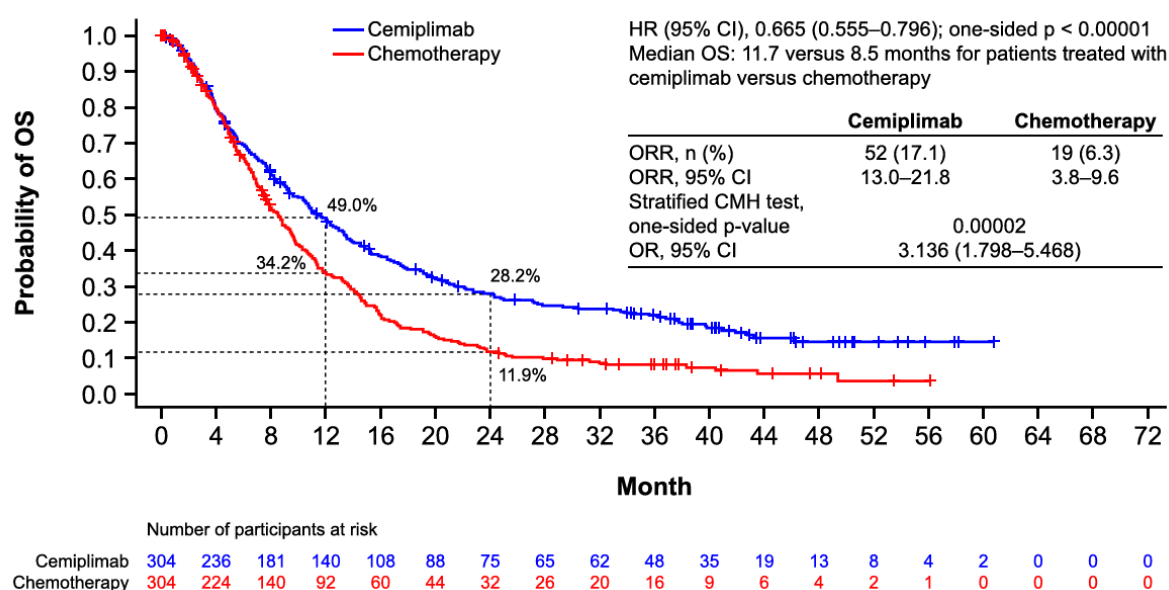
Table 9 Overall survival in final analysis (overall population)

	Cemiplimab (n = 304)	Chemotherapy (n = 304)
Deaths, n (%)	237 (78.0)	256 (84.2)
Censored patients, n (%)	67 (22.0)	48 (15.8)
Median OS (95% CI), months ^a	11.7 (9.6–13.4)	8.5 (7.5–9.6)
Stratified log-rank test one-sided p-value ^{b,c}	<0.00001	
HR (95% CI)^{b,d}	0.67 (0.56–0.80)	
Estimated survival probability, months, % (95% CI) ^a		
6	69.6 (64.0–74.5)	66.1 (60.3–71.3)
12	49.0 (43.2–54.6)	34.2 (28.6–39.8)
24	28.2 (23.0–33.5)	11.9 (8.4–16.1)
36	22.0 (17.3–27.0)	8.3 (5.3–12.0)
48	14.7 (10.3–19.9)	5.7 (3.0–9.7)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

^aBased on the Kaplan–Meier method; ^bStratified by geographic region (North America vs Asia vs rest of world) and histology (squamous cell carcinoma vs adenocarcinoma); ^cOne-sided p-value converted from a stratified log-rank test two-sided p-value; ^dBased on a stratified proportional hazards model (cemiplimab vs chemotherapy).

Source: Oaknin et al. 2025¹⁰



Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival

Note: One-sided nominal P value was converted from stratified log-rank test 2-sided nominal P value.

Source: Oaknin et al. 2025¹⁰

Figure 5. Kaplan-Meier curve of overall survival in the EMPOWER Cervical-1 trial (overall population), final analysis.

The survival benefit was consistent across the prespecified subgroups (forest plots are shown in Section 2.8). Some subgroups had small patient numbers, resulting in wide confidence intervals. The direction and magnitude of the treatment effect in the subgroup analyses supported the licensing of cemiplimab in the ITT population enrolled in the trial.¹⁶

2.6.3 Progression-free survival

Cemiplimab was associated with a statistically significant PFS benefit over chemotherapy (Table 10). This was shown by the HRs for progression or death, despite median PFS values being similar between arms. The Kaplan-Meier curve for the final PFS analysis (Figure 6) shows that the curves separate after median PFS is reached, and the overall HR is driven by the differences between the tails of the curves.¹²

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- As with OS, the long tail on the survival curve suggests long-term response to cemiplimab in a substantial proportion of patients, which is a well-documented phenomenon with immunotherapy treatments.³⁷

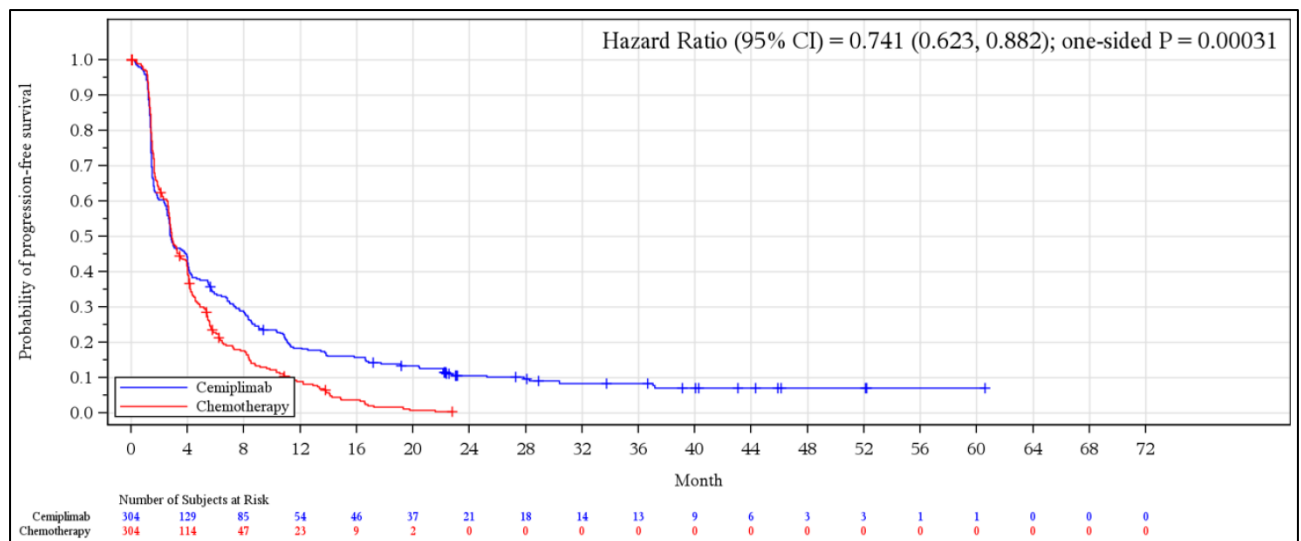
The estimated probability of being event-free for PFS at 12 months was 18.4% (95% CI 14.3, 23.0) in the cemiplimab arm and 8.9% (5.9, 12.7) in the chemotherapy arm. In the cemiplimab arm, patients had an estimated 10.6% (7.4, 14.5) probability of still being event-free at 24 months (probability not estimable in the chemotherapy arm; the probability of being event-free with chemotherapy at 18 months was only 1.6% (0.6, 3.9).¹² There was a consistent PFS benefit across the prespecified subgroups.¹²

Table 10. Progression-free survival in final analysis, overall population.

	Cemiplimab (N=304)	Chemotherapy (N=304)	HR for progression or death (95% CI)
Number of events, n(%)	272 (89.5%)	278 (91.4%)	-
Median PFS (95% CI); months	2.8 (2.6–3.9)	2.9 (2.7–3.5)	0.741 (0.62–0.88); one-sided P=0.00031

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Source: EMPOWER Cervical-1 Trial Final Clinical Study Report¹²



Abbreviations: CI, confidence interval

Note: One-sided nominal P value was converted from stratified log-rank test 2-sided nominal P value

Source: EMPOWER Cervical-1 Trial Final Clinical Study Report¹²

Figure 6. Kaplan-Meier curve of progression-free survival in the EMPOWER Cervical-1 trial (overall population), final analysis.

2.6.4 Objective response rate (ORR)

Treatment with cemiplimab resulted in a significantly higher objective response rate (ORR, defined as rate of best overall response of complete response or partial response) than with chemotherapy (Table 11).¹⁰ In the final analysis, the increase in ORR in the overall population for cemiplimab vs. chemotherapy was 10.8 percentage points (ORR 17.1% vs. 6.3%). The odds ratio for comparison of cemiplimab to chemotherapy was 3.1 (95% CI: 1.8, 5.5).¹⁰

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Table 11. Objective response rate in final analysis (overall population).

	Cemiplimab (N=304)	Chemotherapy (N=304)	Odds ratio (95% CI)
Complete response			-
Partial response			
Stable disease			
ORR % (95% CI)	17.1 (13.0–21.8)	6.3 (3.8–9.6)	3.1 (1.8–5.5)

Abbreviations: CI, confidence interval; ORR, objective response rate (based on patients with confirmed CR or PR)

Source: Oaknin et al 2025¹⁰ (Suppl) and clinical study report¹²

2.6.5 Duration of response (DOR)

Median DOR in the overall population was over twice as long in the cemiplimab arm than in the chemotherapy arm, at 18.7 months (95% CI: 16.4 to NE) and 7.2 months (95% CI: 5.1 to 9.9), respectively (Table 12).¹²

Table 12. Duration of response in final analysis (overall population).

	DOR (95% CI); months	
	Cemiplimab	Chemotherapy
	N=52	N=19
Final analysis*	18.7 (16.4–NE)	7.2 (5.1–9.9)

Abbreviations: CI, confidence interval; DOR, duration of response; NE, not evaluable

*Based on patients with confirmed CR or PR.

Source: EMPOWER Cervical-1 Trial Final Clinical Study Report¹²

2.6.6 Patient-reported outcomes

Notes for interpretation of patient reported outcomes (PROs):

PROs were assessed in the trial using European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30), which includes five function scales, eight symptom scales (plus a further scale of financial difficulty, which is not reported here), and a global health status and quality-of-life scale (GHS/QoL). Scores on each EORTC QLQ-C30 scale range from 0 to 100; higher scores for GHS/QoL and functioning scales indicate better health status and function, and higher scores for symptom scales indicate more symptoms.

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A 10-point threshold for clinically meaningful differences was used to assess changes from baseline (within patient or within group) and differences between treatment groups, as recommended by EORTC.³⁸ The recall period for each question was 'during the past week'.¹¹ Completion rates for EORTC QLQ-C30 were ~90% over the duration of follow-up.¹¹

The statistical hierarchy of EMPOWER Cervical-1 included MMRM analysis of GHS/QoL and physical functioning, in the SCC and overall populations, for overall change from baseline and change from baseline to cycle 2 (week 6).¹¹ Secondary end-points in the statistical hierarchy were assessed for statistically significant differences at a one-sided P value of 0.025, with multiplicity adjustment. After the first end-point in the hierarchy failed this test, subsequent comparisons were not tested formally. End-points not in the statistical hierarchy were tested at a two-sided P value of 0.05, without multiplicity adjustment. P values after the break of hierarchy were nominal.

PRO results were published by Oaknin et al. 2022 (data cut-off 4 January 2021, final PRO analysis).¹¹

Key points

Patient-reported outcome scores in EMPOWER Cervical-1 consistently favoured cemiplimab over chemotherapy on a wide range of measures in the overall study population:

- Least-squares (LS) mean Global health status/Quality of life (GHS/QoL) scores and physical functioning scores were generally maintained or improved with cemiplimab at each visit compared with baseline, whereas those for chemotherapy generally worsened at cycles 2-4 (Figure 7).¹¹
- LS mean overall changes from baseline in GHS/QoL and physical functioning favoured cemiplimab compared with chemotherapy (Figure 7)

(GHS/QoL: 7.81; 95% CI: 3.30-12.33, P = 0.0004; physical functioning: 8.26; 95% CI: 4.29-12.22, P < 0.0001).¹¹

- Overall changes from baseline in most functioning and symptom scales favoured cemiplimab, and treatment differences met the clinically meaningful threshold in role functioning, appetite loss and pain.¹¹
- Sensitivity analyses, responder analyses and time to definitive deterioration all favoured cemiplimab.¹¹

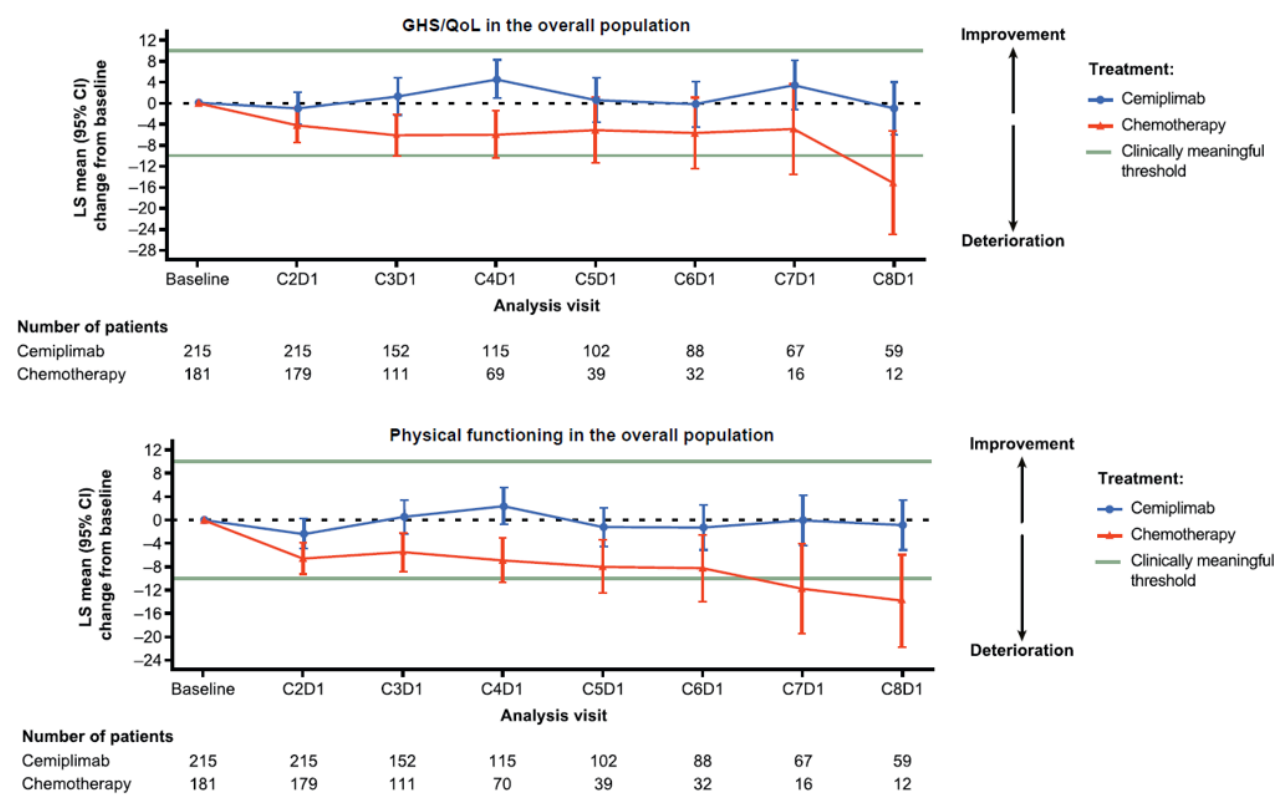
These results are in line with clinical opinion stated during the expert consultation process, that chemotherapy has important side effects whereas immunotherapies are better tolerated, with the result that patients on immunotherapies tend to have better quality of life than those on chemotherapy (see Section 2.14.5).⁶⁻⁸

2.6.6.1 *Global health status/Quality of life (GHS/QoL) and physical functioning*

- LS mean overall changes from baseline in Global health status/Quality of life (GHS/QoL) and physical functioning favoured cemiplimab compared with chemotherapy in the overall population (Figure 7 and Figure 8); (difference for GHS/QoL: 7.81; 95% CI: 3.30-12.33, P = 0.0004; difference for physical functioning: 8.26; 95% CI: 4.29-12.22, P < 0.0001).
 - Early differences favouring cemiplimab over chemotherapy were observed in GHS/QoL at cycle 2 and separation of scores was seen by cycle 3 or 4.
 - Mixed models repeated measures (MMRM) results for GHS/QoL and physical functioning showed that at each cycle, scores were generally maintained or improved with cemiplimab, while those for chemotherapy generally worsened (95% CIs did not include null).
 - The proportion of patients who reported a ≥10-point GHS/QoL or physical functioning improvement (a clinically meaningful within-patient

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change on the EORTC QLQ-C30 scale) was higher, and the proportion with ≥ 10 -point worsening was lower, with cemiplimab compared with chemotherapy.¹¹



Abbreviations: C, cycle; CI, confidence interval; D, day; GHS, global health status; LS, least squares; QoL, quality of life

Note: Scheduled visits with <10 patients in either arm, unscheduled visits, and off-treatment visits were not included in the analysis.

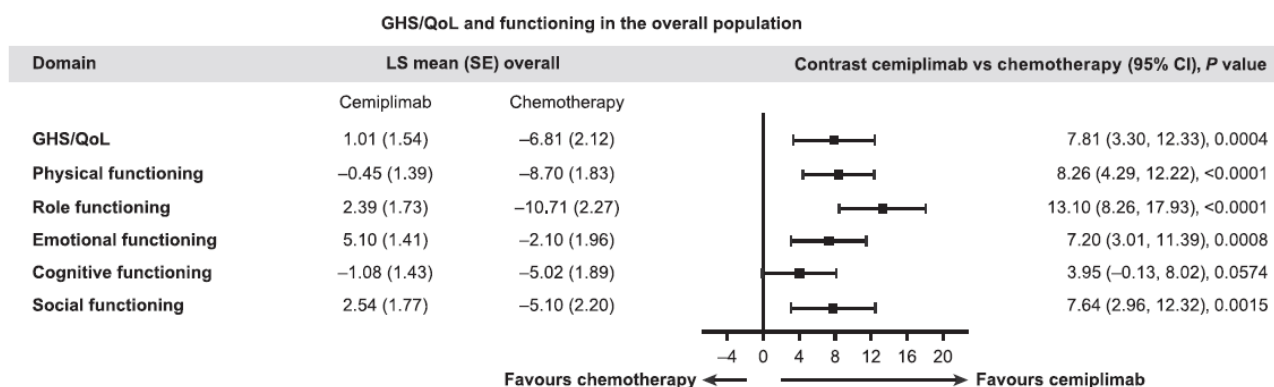
Source: Oaknin 2022¹¹

Figure 7. Change from baseline to each visit for pre-specified secondary endpoints (GHS/QoL and physical functioning) in the overall population (mixed models for repeated measures [MMRM]).

2.6.6.2 Other EORTC QLQ-C30 functioning scales

Differences between treatment groups in overall LS mean changes from baseline favoured cemiplimab for role functioning, emotional functioning and social functioning in the overall population (Figure 8). Treatment differences for role functioning exceeded the clinically meaningful threshold of 10 points.¹¹

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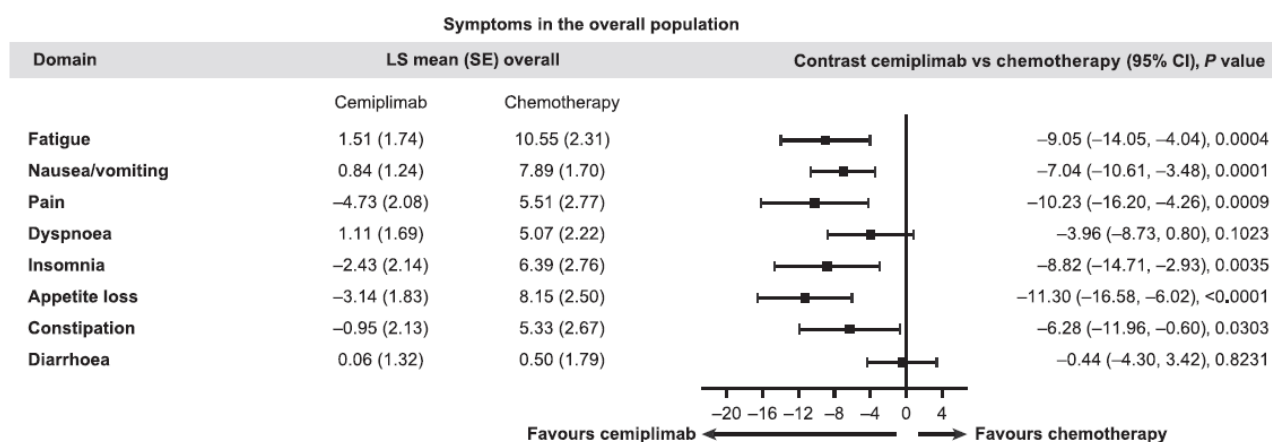
Abbreviations: CI, confidence interval; LS, least-squares; GHS, global health status; QoL, quality of life; SCC, squamous cell carcinoma; SE, standard error.

Source: Oaknin 2022¹¹

Figure 8. Overall changes from baseline and differences between treatment groups in GHS/QoL and functioning scales in the overall population.

2.6.6.3 EORTC QLQ-C30 Symptom scores

- Treatment differences for fatigue, nausea/vomiting, pain, insomnia, appetite loss and constipation all favoured cemiplimab (Figure 9).¹¹ Differences in appetite loss and pain exceeded the clinically meaningful threshold.¹¹
- Median time to definitive deterioration (sustained worsening of 10 points or more) was longer with cemiplimab than with chemotherapy for pain, fatigue and nausea/vomiting, dyspnoea, insomnia, appetite loss and constipation.¹¹



Abbreviations: CI, confidence interval; GHS, global health status; LS, least-squares; QoL, quality of life; SCC, squamous cell carcinoma; SE, standard error.

Source: Oaknin 2022¹¹

Figure 9. Overall changes from baseline and differences between treatment groups in symptoms scores in the overall population.

2.7 Subsequent treatments used in EMPOWER Cervical-1

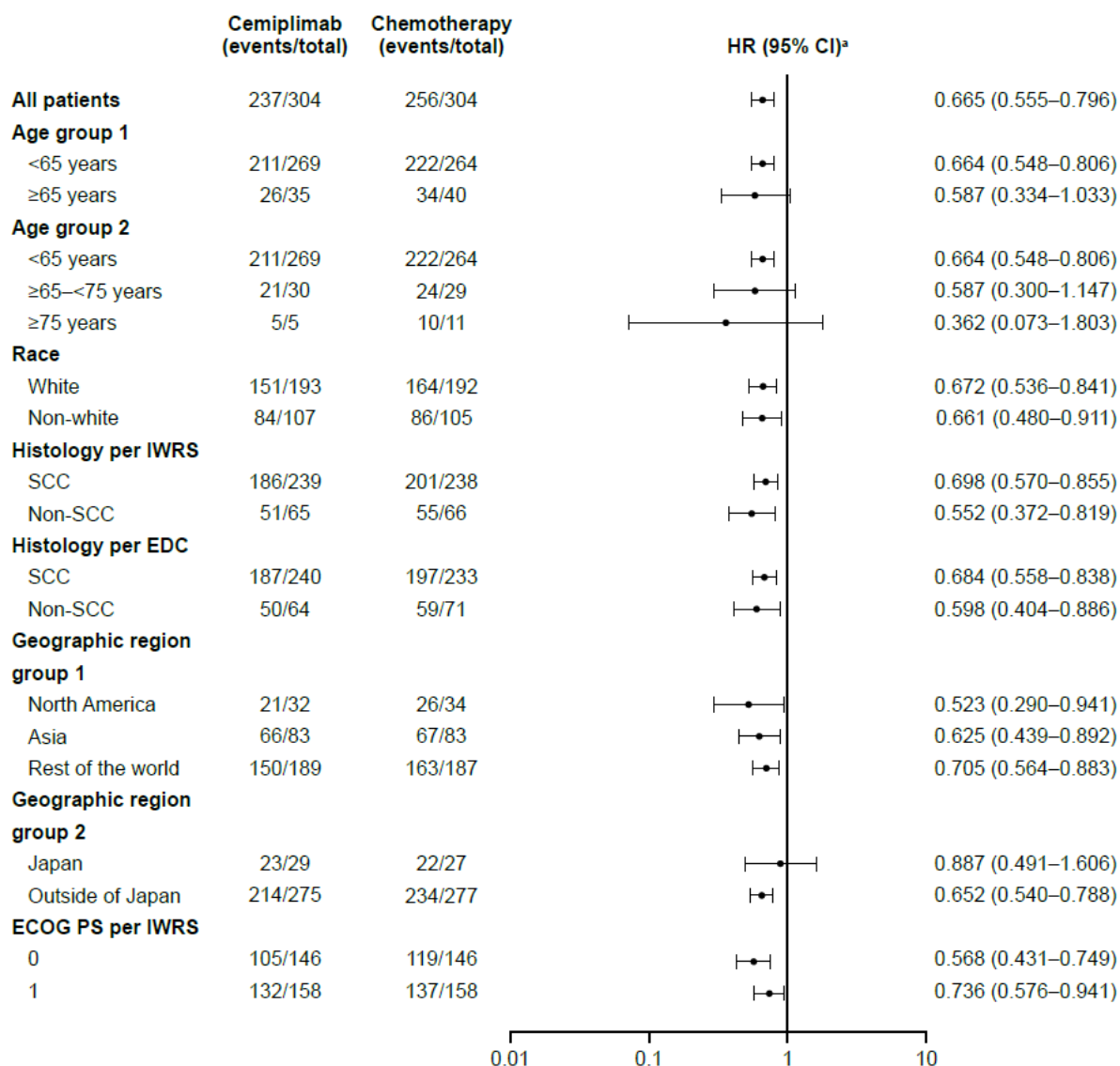
Slightly fewer participants in the cemiplimab arm received any post-trial treatment anti-cancer therapy (████%) than in the chemotherapy arm (████%). In the chemotherapy arm, ███ patients (████%) went on to receive subsequent treatment with an immune checkpoint inhibitor, compared with 7 patients (████%) in the cemiplimab arm.¹²

2.8 Subgroup analysis

2.8.1 Pre-specified subgroup analyses of overall survival: Final analysis

Cemiplimab showed a consistent OS benefit over chemotherapy across the prespecified subgroups. The 95% confidence interval for the hazard ratio spans 1 in a small number of groups (age >65 years and patients enrolled in Japan); however, this is likely due to the very small patient numbers in those subgroups. Forest plots for OS by subgroup for the final analysis (data cut-off 3 October 2023) are shown in Figure 10.¹⁰

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Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EDC, Electronic Data Capture; HR, hazard ratio; IWRS, Interactive Web Response System; SCC, squamous cell carcinoma

Source: Oaknin et al. 2025¹⁰

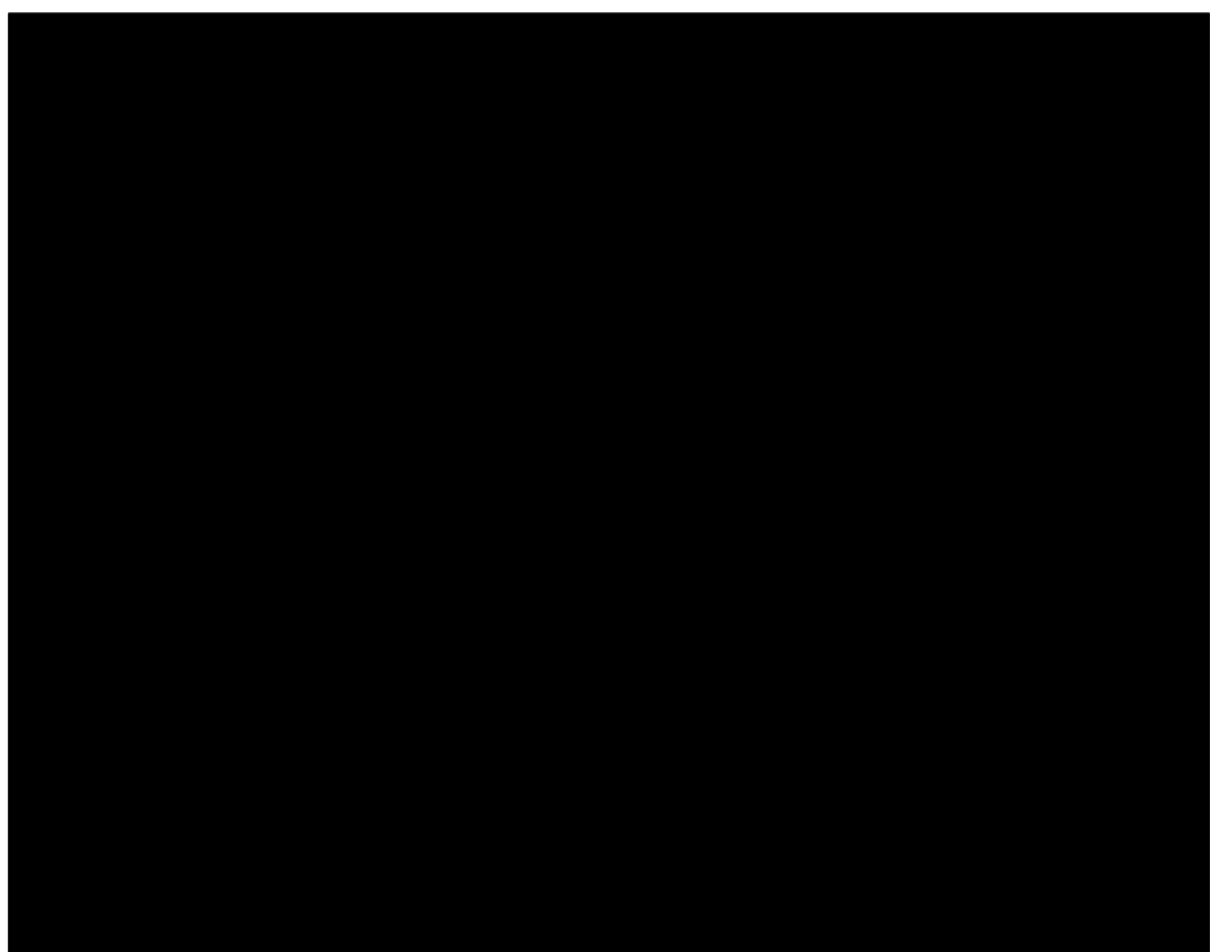
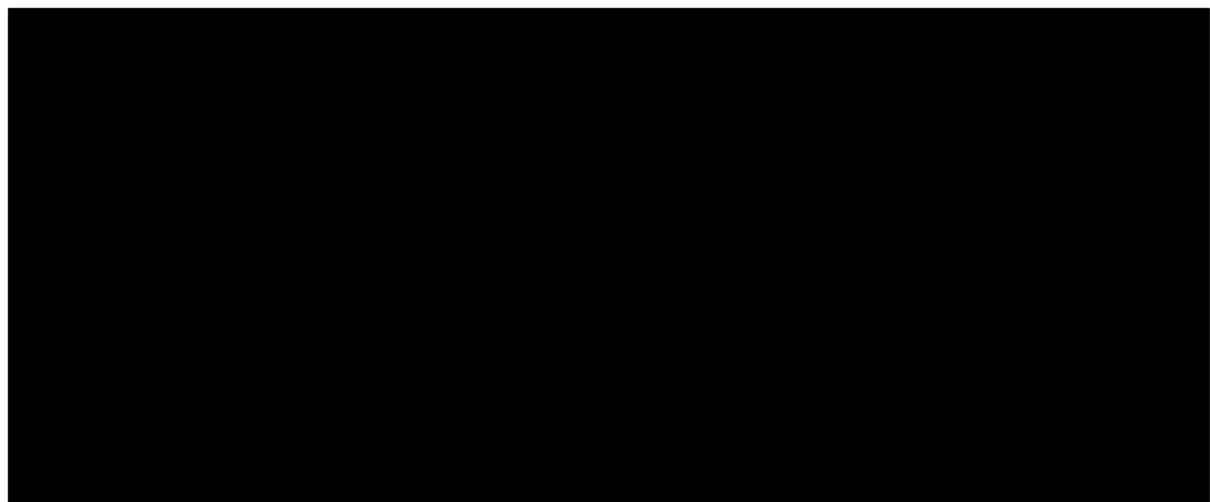
Figure 10. Forest plot for overall survival by subgroup (full analysis set), final analysis.

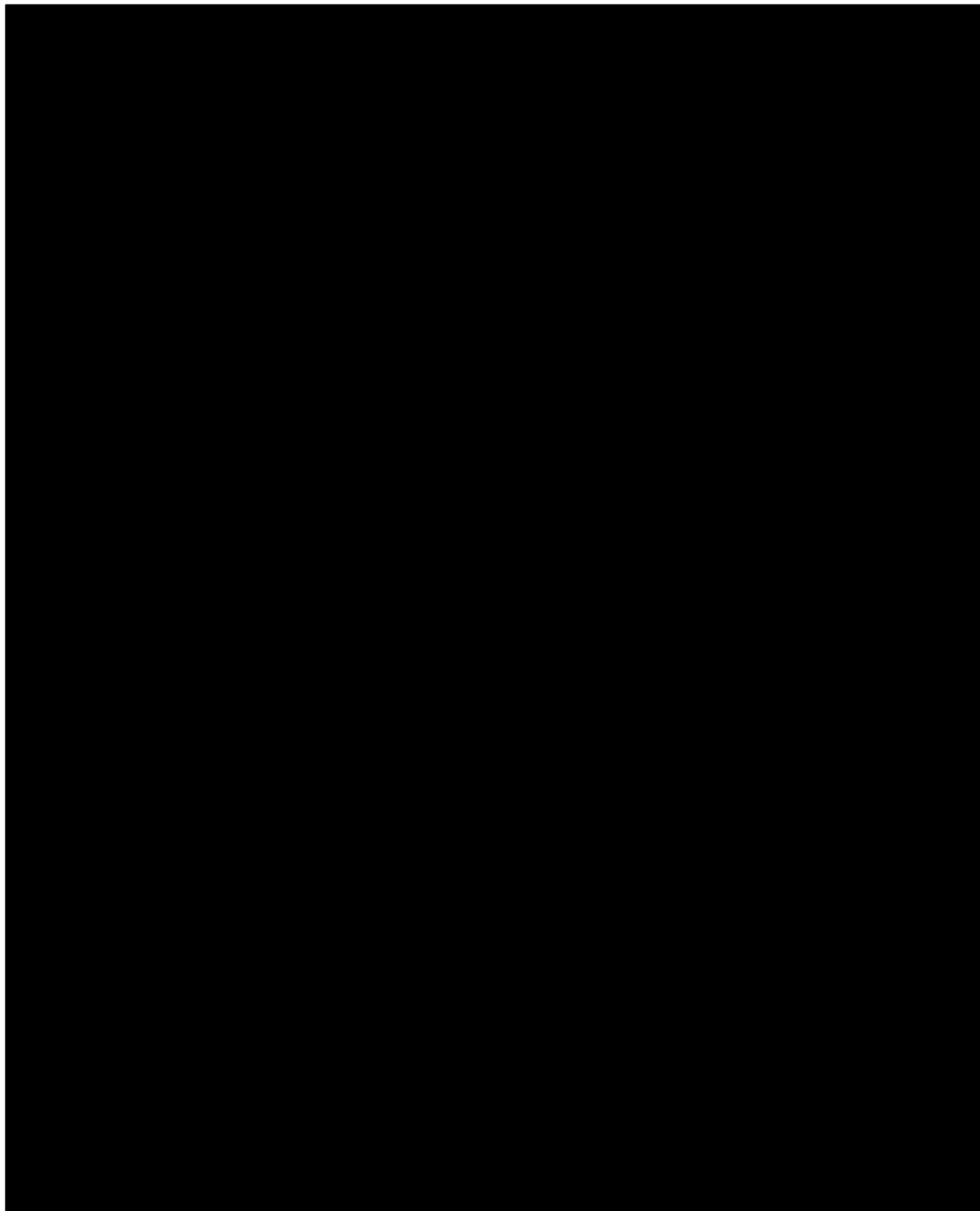
2.8.2 Pre-specified subgroup analyses of progression-free survival: Final analysis

There was also a consistent PFS benefit in prespecified subgroups, as shown in Figure 11 below. Although the 95% interval of the hazard ratio spanned 1 in a few

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subgroups, these generally had a very small sample size and thus a higher degree of uncertainty.





Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EDC, Electronic Data Capture; Inv, investigator; IWRS, Interactive Web Response System; SCC, squamous cell carcinoma

Source: Clinical study report¹²

Figure 11. Forest plot for progression-free survival by subgroup (full analysis set), final analysis.

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2.9 Real-world and additional RCT evidence

2.9.1 Additional identified RCT

The systematic literature review identified a 2024 conference abstract of a small RCT from Uzbekistan comparing cemiplimab with physician's choice of single-agent chemotherapy in r/m CC patients who had disease progression after first-line platinum-containing chemotherapy.³⁹ Treatment arm was randomly assigned, and there were 90 patients in each arm; however, as no full publication was identified, and as the study was not sponsored by Regeneron, full details are lacking.

The results of this study were very consistent with those seen in EMPOWER Cervical-1:

- Median overall survival was 12.4 months in the cemiplimab arm and 7.5 months in the chemotherapy arm (HR for death, 0.69; 95%CI 0.56 to 0.84; two-sided $P < 0.001$). Median follow-up was not reported.
- Progression-free survival was also longer in the cemiplimab group than in the chemotherapy group (HR for disease progression or death, 0.75; 95% CI, 0.63 to 0.89; two-sided $P < 0.001$).
- Objective response occurred in 16.1% (95% CI, 12.5 to 21.1) of patients in the cemiplimab group and 6.3% (95% CI, 3.8 to 9.6) in the chemotherapy group.
- Grade 3 or higher adverse events occurred in 45.0% of patients who received cemiplimab and 53.4% of those who received chemotherapy.

2.9.2 Real-world evidence

Reports of outcomes with cemiplimab in r/m CC in real-world practice are available from the UK and Italy.

UK: a series of 28 cemiplimab-treated patients from a single UK centre published in 2025 reported that the response rate in clinical practice (objective response rate 25%) was consistent with the clinical trial data (other outcomes were not reported).⁴⁰

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Italy: The MITO 44 study reported on 135 patients enrolled in the Italian nominal use program at 12 Multicenter Italian Trials in Ovarian cancer and Gynecologic Malignancies (MITO) Centers, of whom 128 started treatment.⁴¹ Median PFS was 4.0 months (range 3.0–6.0) and median OS was 12.0 months (12.0- NR; median follow-up not reported). These results are consistent with those in the EMPOWER CERVICAL-1 trial. Of note, 18.8% of patients had ECOG PS 2 at baseline (ECOG PS 2 was an exclusion criteria in EMPOWER CERVICAL-1); OS and PFS in this group were similar to those with ECOG PS 0 or 1, which the authors noted confirms the efficacy of cemiplimab in frail patients. In this cohort, 43.9% of patients had already received $\geq$ two systemic treatments and 14.9% had undergone two or more surgeries before starting cemiplimab. Complete response (CR) or no evidence of disease (NED) were observed in 8.6%, partial response (PR) in 21.1%.

2.10 Meta-analysis

Not applicable. Only one fully reported RCT (EMPOWER Cervical-1, described in full above) was identified. A conference abstract of a small additional RCT from Uzbekistan was identified,³⁹ but a meta-analysis was not appropriate as insufficient detail of this study was available.

2.11 Indirect and mixed treatment comparisons

Not applicable. No indirect treatment comparison versus chemotherapy is required, as direct evidence versus the only relevant comparator (i.e. chemotherapy) is available from the pivotal RCT.

2.12 Adverse reactions

Key points

- Cemiplimab is a monotherapy and represents a chemotherapy-sparing option for patients with a high disease burden and unmet need
- The safety profile of cemiplimab was favourable compared to chemotherapy in several ways that are clinically important for patients, including fewer exposure-adjusted treatment-emergent adverse events (TEAE)s, grade ≥ 3 TEAEs, serious adverse events (SAEs; particularly less haematological toxicity), and a reduced exposure-adjusted requirement for dose delays/infusion interruptions, dose reductions and permanent treatment discontinuations.^{10,12}
- Fewer patients experienced TEAEs of grade ≥ 3 with cemiplimab vs chemotherapy (47.0% vs 53.8% in the final analysis), despite a longer duration of exposure to cemiplimab.¹⁰
 - The exposure-adjusted rate of serious TEAEs was [REDACTED] and [REDACTED] per 100 patient-years in participants treated with cemiplimab and chemotherapy, respectively (final analysis).¹²
 - The exposure-adjusted rate of permanent discontinuation due to TEAEs was [REDACTED] and [REDACTED] per 100 patient-years in patients treated with cemiplimab and chemotherapy, respectively.¹²
- Patients treated with cemiplimab had a lower incidence of treatment-related TEAEs than with chemotherapy (occurring in 57.3% vs 81.7% of patients, respectively), and a lower incidence of treatment-related TEAEs of $\geq$ grade 3 (occurring in [REDACTED]% vs [REDACTED]%, respectively).^{10,12}
- No new safety signals were identified compared to the safety profile of other PD-1/PD-L1 immunotherapy agents.³⁰

2.12.1 Safety in EMPOWER Cervical-1

Summary of treatment-emergent and treatment-related AEs

Table 13 shows treatment-emergent AEs (TEAEs) occurring at any time and AEs reported until 90 days after the last dose of treatment or 1 day before the start of post-treatment therapy, whichever commenced earlier, regardless of the relationship to the trial treatment.¹² Table 14 summarises AEs judged by the investigator to be treatment-related.

- Although patients had a longer median duration of exposure to cemiplimab (15.2 weeks) than to chemotherapy (10.1 weeks), cemiplimab-treated patients experienced similar rates of AEs of any grade to those who received chemotherapy (89.7% vs 91.7%), and lower rates of grade 3 or higher AEs (47.0% vs 53.8%), treatment-related AEs (57.3% vs 81.7%) or AEs leading to dose delay or infusion interruption (█████% vs █████%) (Table 13 and Table 14).^{10,12}
- Immune-related AEs (regardless of attribution; not tabulated) occurred in █████% of patients in the cemiplimab group and in █████% of those in the chemotherapy group. The majority of these events in the cemiplimab group were grades 1 or 2: █████ patients (█████%) experienced immune-related AEs of ≥ grade 3 (compared with █████ patients [█████%] in the chemotherapy group).¹²

Given the differences in treatment duration (median 15.2 weeks (range 1.4–107.7) for cemiplimab and median 10.1 weeks (range 1.0–91.1) for chemotherapy, exposure-adjusted analyses were conducted to provide a more like-for-like comparison between treatment arms.

- The exposure-adjusted rate of TEAEs was markedly lower with cemiplimab than with chemotherapy (█████ and █████/100 patient-years, respectively).¹²

- The exposure-adjusted rate of serious TEAEs was also markedly lower with cemiplimab than with chemotherapy (██████████ and ██████████/100 patient-years, respectively).¹²

Table 13. Summary of treatment-emergent adverse events (safety analysis set).

	Cemiplimab (N=300)	Chemotherapy (N=290)
Number of patients with any TEAE, n (%)	269 (89.7%)	266 (91.7%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	141 (47.0%)	156 (53.8%)
Number of patients with any serious TEAE, n (%)	██████████	██████████
Number of patients who discontinued study treatment due to TEAEs, n (%)	27 (9.0%)	15 (5.2%)
Number of patients with any TEAE leading to dose interruption/delay, n (%)	██████████	██████████
Number of patients with any TEAE leading to a dose reduction, n (%)	█	██████████
Number of patients with any TEAE resulting in death, n (%)	5 (1.7%)*	2 (0.7%)

Abbreviations: NCI, National Cancer Institute; TEAE, treatment-emergent adverse event

* None of the AEs leading to death were considered by the treating investigator to be related to cemiplimab.

NCI grades were coded using CTCAE Version 4.03. A patient is counted only once for all multiple occurrences within a category. The data are not exposure-adjusted.

Source: EMPOWER Cervical-1 Final clinical study report;¹² Oaknin et al. 2025¹⁰

Table 14. Summary of treatment-related adverse events (safety analysis set).

	Cemiplimab (N=300)	Chemotherapy (N=290)
Number of patients with any TR-TEAE, n (%)	172 (57.3%)	237 (81.7%)
Number of patients with any NCI grade 3/4/5 TR-TEAE, n (%)	██████████	██████████
Number of patients with any serious TR-TEAE, n (%)	██████████	██████████
Number of patients who discontinued study treatment due to TR-TEAEs, n (%)	17 (5.7%)	10 (3.4%)
Number of patients with any TR-TEAE leading to dose interruption/delay, n (%)	██████████	██████████
Number of patients with any TR-TEAE leading to a dose reduction, n (%)	█	██████████
Number of patients with any TR-TEAE resulting in death, n (%)	0	2 (0.7%)

Abbreviations: ANCI, National Cancer Institute; TR-TEAE, treatment-related treatment-emergent adverse event

NCI grades were coded using CTCAE Version 4.03. A patient is counted only once for all multiple occurrences within a category. The data are not exposure-adjusted.

Source: EMPOWER Cervical-1 Final clinical study report;¹² Oaknin et al. 2025¹⁰

Summary of most common adverse events

The majority of common TEAEs were reported for a lower or similar proportion of patients in the cemiplimab arm than in the chemotherapy arm. The most common TEAEs in the cemiplimab arm included (cemiplimab arm vs. chemotherapy arm): anaemia (25.7% vs. 44.1%), nausea (19.0% vs. 34.1%), fatigue (17.0% vs. 15.5%), vomiting (16.7% vs. 23.4%), constipation (15.0% vs. 20.0%), and decreased appetite (15.3% vs. 15.9%); see Table 15.^{10,12}

Table 15. Treatment-emergent adverse events regardless of attribution (safety analysis set).

Adverse event	Cemiplimab (N=300)		Chemotherapy (N=290)	
	Any grade	Grade 3, 4, or 5	Any grade	Grade 3, 4, or 5
Number of patients (%)				
<i>Occurred in ≥10% in either group†</i>				
Anaemia	77 (25.7%)	██████████	128 (44.1%)	██████████
Nausea	57 (19.0%)	██████████	99 (34.1%)	██████████
Fatigue	51 (17.0%)	██████████	45 (15.5%)	██████████
Vomiting	50 (16.7%)	██████████	68 (23.4%)	██████████
Decreased appetite	46 (15.3%)	██████████	46 (15.9%)	██████████
Constipation	45 (15.0%)	██████████	58 (20.0%)	██████████
Pyrexia	39 (13.0%)	██████████	62 (21.4%)	██████████
Urinary tract infection	██████████	██████████	██████████	██████████
Asthenia	35 (11.7%)	██████████	44 (15.2%)	██████████
Diarrhoea	34 (11.3%)	██████████	39 (13.4%)	██████████
Arthralgia	33 (11.0%)	██████████	8 (2.8%)	██████████
Back pain	32 (10.7%)	██████████	28 (9.7%)	██████████
Abdominal pain	30 (10.0%)	██████████	33 (11.4%)	██████████
Neutropenia	6 (2.0%)	██████████	45 (15.5%)	██████████

†The events are listed in descending order of frequency in the cemiplimab group. The data are not exposure-adjusted.

Source: Tewari et al. 2022;³⁰ Final Clinical Study Report to reflect final analysis;¹² Oaknin et al. 2025¹⁰

As with TEAEs overall, the majority of treatment-related TEAEs were reported at a lower or similar frequency in the cemiplimab arm compared with the chemotherapy arm. The most common treatment-related TEAEs of any grade by, experienced by ≥5% of patients in the cemiplimab arm were (cemiplimab arm vs. chemotherapy arm): fatigue (10.7% vs. 13.4%), nausea (9.3% vs. 30.3%), anaemia (7.7% vs. 36.9%), asthenia (7.7% vs. 11.4%), decreased appetite (████% vs. █████%), diarrhoea (████% vs. █████%), hypothyroidism (████% vs. █████%), arthralgia (████% vs. █████%), vomiting (5.7% vs. 18.3%), pruritus (████% vs. █████%), and rash (████% vs. █████%) (Table 16).

None of the AEs leading to death were considered by the treating investigator to be related to cemiplimab. Chemotherapy was reported to be related to the deaths of 2 (0.7%) of patients in the chemotherapy group.

Table 16. Treatment-related adverse events (safety analysis set).

Treatment-related adverse event	Cemiplimab (N=300)		Chemotherapy (N=290)	
	Any grade	Grade 3, 4, or 5	Any grade	Grade 3, 4, or 5
Number of patients (%)				
Occurred in ≥5% in either group†				
Fatigue	32 (10.7%)		39 (13.4%)	
Nausea	28 (9.3%)		88 (30.3%)	
Anaemia	23 (7.7%)		107 (36.9%)	
Asthenia	23 (7.7%)		33 (11.4%)	
Decreased appetite				
Diarrhoea				
Hypothyroidism				
Arthralgia				
Vomiting	17 (5.7%)		53 (18.3%)	
Pruritus				
Rash				
Increased alanine aminotransferase				
Pyrexia	10 (3.3%)		29 (10.0%)	
Stomatitis				
Neutropenia	6 (2.0%)		44 (15.2%)	
Constipation				
Thrombocytopenia				

†The events are listed in descending order of frequency in the cemiplimab group. The data are not exposure-adjusted.

Source: Tewari et al. 2022;³⁰ Final Clinical Study Report to reflect final analysis;¹² Oaknin et al. 2025¹⁰

2.12.2 Safety summary in patients with advanced solid malignancies

The safety of cemiplimab as monotherapy has been evaluated in 1,281 patients with advanced solid malignancies who received cemiplimab monotherapy in 5 clinical studies.⁹ The median duration of exposure to cemiplimab was 28 weeks (range: 2 days to 144 weeks). The summary from the Summary of Product Characteristics is given in Appendix D.

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2.12.3 Post-marketing safety

Cumulatively up to 27 Mar 2024, 7021 patients have been treated with investigational cemiplimab monotherapy, combination therapy or comparator in multiple clinical trials. In the reporting interval (28 September 2023 to 27 March 2024) for the latest cemiplimab periodic risk benefit evaluation report (PBRER), the cumulative exposure from marketing experience to date was estimated to be 52,273 patient-years.⁴² Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of cemiplimab in all approved indications, including cervical cancer, remains positive.

2.13 Ongoing studies

There are no ongoing RCTs of cemiplimab in r/m CC.

2.14 Interpretation of clinical effectiveness and safety evidence

2.14.1 Summary of findings

Cemiplimab provided statistically and clinically significant improvements in overall survival compared with investigator's choice of chemotherapy. In the final analysis, median OS was 11.7 months with cemiplimab vs 8.5 months with chemotherapy (HR 0.67 [0.56, 0.80], $P < 0.00001$).^{10,12}

An estimated 28.2% (95%CI 23.0, 33.5) of patients in the cemiplimab arm were still alive at 24 months, compared with 11.9% (8.4, 16.1) in the chemotherapy arm. This is noteworthy in this 2L population, who have a poor prognosis under current treatment, particularly as 87.8% of patients had experienced disease progression ≤ 6 months after prior platinum chemotherapy. Approximately one-fifth of patients in the cemiplimab arm were still alive after 36 months (estimated probability of survival 22.0% (95% CI 17.3, 27.0), compared with an estimated 8.3% (5.3, 12.0) in the chemotherapy arm.¹²

The safety profile of cemiplimab was favourable compared to chemotherapy in several ways that are important for patients, including fewer exposure-adjusted treatment-emergent adverse events (TEAEs), grade ≥ 3 TEAEs, serious adverse

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events (SAEs; particularly less haematological toxicity), and a reduced exposure-adjusted requirement for dose delays/infusion interruptions, dose reductions and permanent treatment discontinuations.¹²

Global health status/Quality of life (GHS/QoL) scores and physical functioning scores were generally maintained or improved with cemiplimab at each visit compared with baseline, whereas those for chemotherapy generally worsened at cycles 2-4. Overall changes from baseline in most functioning and symptom scales favoured cemiplimab.¹¹ These are key considerations for patients with r/m CC.

2.14.2 Strengths and limitations of the evidence base

EMPOWER Cervical-1 is the largest OS-powered phase 3 RCT in 2L r/mCC conducted to date, enrolling 608 patients, with both squamous and adenocarcinoma histologies and regardless of PD-L1 status. It was also the first such study to examine patient-reported outcomes. The trial provides direct comparative data for cemiplimab versus investigator's choice of chemotherapy, which is the only relevant comparator for this appraisal, and was assessed as having a low risk of bias in all domains using the Cochrane risk of bias assessment tool (see Appendix B). The ESGO/ESTR/ESP guidelines concur with this assessment, reporting the trial provides level I, A evidence (where I indicates evidence from at least one large RCT of good methodological quality, and A indicates strong evidence for efficacy with a substantial clinical benefit, strongly recommended).¹³ Overall, the study provides robust evidence supporting the efficacy of cemiplimab versus the relevant comparator in this end-of-life orphan population, for whom no clear standard of care is available and current treatment options (i.e. further chemotherapy) result in poor response rates and reduced quality of life.^{1,4}

The maturity of the data is a key strength of the evidence base. At the time of the final analysis (median follow-up 47.3 months), 78% and 84% of patients in the cemiplimab and chemotherapy arms, respectively, had died.¹⁰ Consequently, the level of uncertainty around survival is lower than in most oncology appraisals. Another strength is the availability of patient-reported outcomes, enabling patients' health-related quality of life to be assessed alongside efficacy and safety.

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A potential limitation is the open-label study design. This design was necessary because of the differences in administration schedule and AE profiles between cemiplimab and the chemotherapy options (i.e., immune-related adverse events [irAEs] with cemiplimab and white blood cell count suppression with chemotherapy).³⁶ This did not introduce bias for assessment of the primary endpoint, as overall survival is not a subjective endpoint that is susceptible to bias. For context, the pivotal trial of bevacizumab in this setting was open label,⁴³ and the trial of pembrolizumab was single-arm.⁴⁴

Whilst the open-label design has the potential to introduce bias into subjective, patient-reported outcome results, several studies have shown that the potential for such bias may be lower than is commonly assumed.^{45,46} In addition, PRO completion rates in this study were high and similar in both treatment arms, suggesting low risk of bias.¹¹

The EMPOWER Cervical-1 study protocol allowed repeat treatment with cemiplimab for patients who completed 16 treatment cycles and then had progressive disease in the post-treatment follow-up period, whereas this option is not given in the SmPC. However, only █ patients (██%) in the cemiplimab arm received any subsequent anti-PD-L1 treatment.¹² Therefore, any retreatment is unlikely to have meaningfully impacted the OS results.

2.14.3 Relevance of outcomes to patients

The outcomes assessed in EMPOWER Cervical-1 are highly relevant to patients, address their unmet needs, and reflect the clinical benefits expected to be experienced with cemiplimab treatment in clinical practice.

OS is a final outcome, is considered the gold standard in oncology trials, and is of fundamental importance to patients and their families. It provides essential and objective information on the efficacy of treatments, especially in a disease where the life expectancy is so low (see Section 1.3.1). The final study analysis, as presented in the submission and used in the economic model, provides mature direct

comparative OS data, which gives a clear picture of the survival benefit of cemiplimab.

The OS data is supported by measures assessing response to treatment (ORR and DOR) and PFS. Adverse event data confirm that the benefits with cemiplimab are achieved with a more favourable safety and tolerability profile compared with chemotherapy. As confirmed by NHS gynaecologic consultant oncologist experts practising in England, disease progression and treatment toxicities are the most important determinants of quality of life for patients in this setting, in which maintaining quality of life is of prime importance.⁶⁻⁸ They also determine disease management and resource use.

Additionally, the EMPOWER Cervical-1 trial is the first RCT in 2L treatment for r/m CC to assess patient reported outcomes (PROs) using EORTC-QLQ-30. PROs not only describe the wellbeing of patients, which is significantly associated with OS in advanced cancer,⁴⁷ but are also used by clinicians to assess treatment choices.

2.14.4 Generalisability of the trial to clinical practice

The NHS gynaecologic consultant oncologist experts practicing in England, who were interviewed for the submission, indicated that the patients enrolled in the EMPOWER Cervical-1 trial were generally reflective of patients anticipated to receive cemiplimab in clinical practice, although it excluded patients with ECOG PS >1. Importantly, these clinicians also confirmed the outcomes observed with the chemotherapy comparator in the EMPOWER Cervical-1 trial were reflective of outcomes observed with chemotherapy regimens used in current UK clinical practice.⁶⁻⁸

Real world evidence has also confirmed that the outcomes observed with cemiplimab in the EMPOWER Cervical-1 trial are achieved with its use in clinical practice settings. A case series of 28 cemiplimab-treated patients from a UK centre, published in 2025, reported an ORR (complete response plus partial response) of 25%,⁴⁰ which is consistent with the ORR of 17.1% observed with cemiplimab in EMPOWER Cervical-1.¹⁰ Furthermore, a nominal use program in Italy (MITO 44

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study) reported outcomes with cemiplimab treatment in 128 patients across 12 centres that were also highly consistent with those seen in the EMPOWER Cervical-1 trial: median PFS was 4.0 months (c.f. 2.8 months in the EMPOWER Cervical-1 trial), median OS was 12.0 months (c.f. 11.7 months) and ORR was 29.7% (c.f. 17.1%).⁴¹ Of note, these consistent results were achieved in MITO 44 even though 18% of the population had ECOG PS 2, indicating that the exclusion of patients with ECOG PS >1 from the EMPOWER Cervical-1 trial is unlikely to have biased results or reduced their generalisability.

Therefore, based on clinical expert opinion and real-world evidence, the results of the EMPOWER Cervical-1 trial are generalisable to clinical practice. It is also of note that, although details are limited, the results of the EMPOWER Cervical-1 trial were closely replicated in a smaller RCT (n=180) of cemiplimab in r/m CC after platinum-based chemotherapy, conducted in Uzbekistan³⁹ (see Section 2.9.1). This study was not sponsored or funded by Regeneron, but the similarity of results suggests that EMPOWER Cervical-1 is likely to be generalisable to patients across a range of healthcare systems.

2.14.5 Addressing unmet need and quality of life

The NHS gynaecologic consultant oncologist experts practising in England interviewed for this submission attested to the important unmet need for an effective and well tolerated immunotherapy alternative to further chemotherapy that would allow patients with r/mCC and disease progression to maintain their quality of life for longer.⁶⁻⁸ Quotes from clinical experts on unmet need and how it can be addressed with immunotherapies such as cemiplimab include:

- *“There is definitely an unmet need for second line immunotherapies as those previously on first line chemotherapies and bevacizumab currently have no access to immunotherapies in the second line”.*
- *“Most certainly, chemotherapy has important side effects. Immunotherapies are very well tolerated, and patients on immunotherapies tend to have good quality of life, that you don’t see on chemotherapy.”*

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- *“Chemotherapy does have a lot of quality-of-life impact. It is going to be much less for immunotherapy or just targeted therapy.”*
- *“After first line the residual side effects of chemo also has a huge impact on quality of life. Patients will become very tired, the neuropathies, and low magnesium levels and other side effects will have a huge impact on quality of life.”*
- *“Due to the improvement of response rates with cemiplimab, quality of life is better with cemiplimab. The patients are often more symptomatic from the disease, so if you control the disease, you get more improvement in quality of life, because they are fit and young and recover quickly if disease burden is reduced.”*

Cemiplimab provided prolonged survival compared with investigator’s choice of chemotherapy coupled with statistically significant improvements in PROs, many of which (averaged over the study population) reached the threshold designated ‘clinically meaningful’. Additionally, as highlighted in the positive SMC advice for cemiplimab:

- *“clinical experts consulted by SMC concluded that cemiplimab fills an unmet need and is a therapeutic advancement since there is no current standard of care and currently used treatments have very poor responses”.¹⁹*

Given that weekly paclitaxel is currently a commonly used treatment in English centres following progression on platinum-based chemotherapy, the three-weekly dosing of cemiplimab is anticipated to confer a particular advantage to patients. Weekly hospital visits are likely to be inconvenient, tiring and expensive for patients, and will often involve a burden for family members, for example the need for childcare or to accompany the patient. In addition, cemiplimab is given by a 30-minute infusion with no requirement in the SmPC for premedication,⁹ whereas paclitaxel requires IV premedication with corticosteroids, antihistamines, and H₂ antagonists and is infused over a period of 3 hours.²⁴ Thus, treatment visits for cemiplimab will be significantly shorter than those required for paclitaxel.

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The Patient and Clinician Engagement (PACE) statement from the SMC appraisal of cemiplimab in this indication¹⁹ notes:

- *“the ability to continue caring for their families [both children and older relatives] is of the utmost importance to this patient group, and minimising time in hospital whilst providing meaningful clinical benefit cannot be underestimated.”*
- *“given the anticipated clinical benefits of cemiplimab, patients can expect to spend less time in hospital compared with conventional chemotherapy treatment. PACE participants highlighted how difficult family members, particularly children, find having the patient away from home for extended periods. Cemiplimab has the potential to help patients return to normal day-to-day life quickly, which is highly valued by families.”*

Service-related benefits: the less frequent (3-weekly vs weekly) and shorter (30 minutes without premedication vs 3 hours + IV premedication) administration time for cemiplimab compared with weekly paclitaxel^{9,24} will reduce the demand for chair-time in chemotherapy infusion suites, freeing up staff time and chair capacity and helping to reduce waiting times for IV therapies. This is an important consideration at many centres, where pressure on infusion suite capacity can result in delays for patients requiring IV treatment.

2.14.6 Summary

In summary, cemiplimab provides an effective and well tolerated immunotherapy option for this group of end-of-life patients who would otherwise have only further chemotherapy available as a treatment option. Furthermore, patients only need attend hospital for treatment every 3 weeks, rather than weekly as required with paclitaxel. The median survival gain of 3.2 months with cemiplimab is highly clinically significant in this setting and a substantial proportion of patients experience a much longer survival benefit: approximately one-fifth of patients in the cemiplimab arm were still alive after 36 months (estimated probability of survival 22.0% [95% CI 17.3, 27.0], compared with only 8.3% [5.3, 12.0] in the chemotherapy arm. Furthermore,

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patient-reported outcome scores in EMPOWER Cervical-1 consistently favoured cemiplimab over chemotherapy on a wide range of measures. Having access to a more effective treatment with a better tolerability profile than chemotherapy will offer additional hope to patients and their families in this clinically severe orphan condition with a currently dismal prognosis.

3 Cost effectiveness

Key points

- A de novo cost-utility analysis was conducted with the commonly used partitioned survival analysis approach, which is appropriate given the nearly complete PFS curves and highly mature OS curves (with 237 events [78.0%] reported in the cemiplimab arm, and 256 events [84.2%] reported in the chemotherapy arm).^{10,12} This approach is in line with previously published cost-effectiveness analyses in this patient population⁴⁸⁻⁵⁰ and the NICE Committee's suggestion in TA939 / TA885.⁵
- The model compared cemiplimab to chemotherapy in its proposed positioning for the treatment of adults with recurrent, persistent or metastatic cervical cancer (r/m CC) who have progressed on or after platinum-based therapy, and who have not previously received immunotherapy.
- OS, PFS and time-on-treatment (ToT) survival curves obtained from the EMPOWER Cervical-1 trial determined the proportion of patients in the modelled health states (pre-progression on treatment/off treatment, post-progression and death) over time. These mature time-to-event data were extrapolated according to NICE guidelines and the results were validated by five clinical experts practicing in the UK.^{6-8,51,52}
- A confidential simple upfront PAS discount of [REDACTED] is currently in place for cemiplimab. The results in this submission reflect the current NHS net price, which includes this discount.
- Utility values were derived from quality-of-life data collected directly from patients enrolled in the EMPOWER-Cervical 1 trial and mapped on to the EQ-5D-3L. The resulting utility values were validated by five clinical experts

practising in the UK.^{6-8,51,52} As the trial analysis showed statistically significantly better utilities for cemiplimab compared to chemotherapy, and the clinical experts stressed the higher quality of life expected with cemiplimab compared to chemotherapy, treatment-specific utility values were used for the two treatment arms.

- Resource use and unit costs for drug acquisition and administration costs, subsequent treatment costs, disease management costs and treatment-emergent adverse event costs were obtained from publicly available UK databases, the pivotal EMPOWER-Cervical 1 trial, clinical protocols and input from four clinical experts practicing in England.^{6-8,51}
- To ensure plausibility, model structure, major assumptions, survival extrapolations and resource use were all validated by five clinical experts practicing in the UK. They were also tested in extensive sensitivity and scenario analyses.
- Compared to chemotherapy, without severity weighting, cemiplimab resulted in a 0.79 discounted QALY gain, mainly driven by the increased time in the pre-progression period. Cemiplimab increased total costs due to the higher acquisition cost of cemiplimab compared to the mostly generic chemotherapy comparator costs and also its longer duration of treatment arising from its greater efficacy in preventing disease progression and prolonging survival. These resulted in a discounted incremental cost effectiveness ratio (ICER) of £[REDACTED]/QALY gained.
- With an absolute severity shortfall of 14.61 QALYs and a proportional shortfall of 0.96 QALY, cemiplimab meets the criteria for a severity weight of 1.7. With application of the x1.7 severity weighting estimated in Section 3.6, the ICER is £[REDACTED]/QALY gained, which is below the lower estimate of the threshold used by NICE to indicate the cost-effective use of NHS resources.

- A large number of sensitivity analyses confirmed the robustness of results. With application of the x1.7 severity weighting in all scenarios tested, cemiplimab had an ICER below £23,000/QALY. In probabilistic sensitivity analyses, the probability of cemiplimab being cost-effective at £30,000/QALY willingness-to-pay thresholds was found to be 99%.
- In its proposed positioning, cemiplimab provides a clinically and cost-effective immunotherapy option for a small group of end-of-life patients who would otherwise have only further chemotherapy available as a treatment option.

3.1 Published cost-effectiveness studies

An SLR was conducted on 2nd September 2020 and updated 12th June 2025 to identify the evidence base available and the economic impact on patients who have progressed on or after prior platinum treatment for metastatic or recurrent cervical cancer. The report is supplied in Appendix E.

In the latest iteration of the SLR a search of HTA websites indicated that NICE has published an appraisal for pembrolizumab in the first line cervical cancer treatment setting (TA939).⁵ An appraisal of tisotumab vedotin⁵³ is ongoing with publication not expected until June 2026.

The SLR identified a further 32 published cost effectiveness studies of treatments for cervical cancer, of which 13 were cost-utility analyses (CUA), 13 were economic burden/cost studies and six were healthcare resource utilization (HCRU) studies. Of the 13 CUAs identified, only 4 were conducted in the population of interest. These are summarised below in Table 17. All four of these studies were conducted from a third-party payer perspective in the USA.

In addition to the 4 studies described below, Barrington 2022⁵⁴ published a model based on the Shi 2022⁵⁰ analysis of pembrolizumab, but comparing platinum-based

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chemotherapy + pembrolizumab ± bevacizumab with platinum based chemotherapy + bevacizumab. There were several conference proceedings utilising the data from KEYNOTE-826 and adapting either the Shi 2022 or Barrington 2022 models (see Appendix E for details of the conference proceedings and Barrington 2022).

Table 17. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Comments / relevance to decision problem
Liu 2023 ⁷	2023	Cost-utility analysis Authors described it as Markov model, but based on efficacy inputs is a PartSA	Patients with recurrent cervical cancer previously treated with platinum-based chemotherapy (average age not reported)	Cemiplimab: 1.704	Cemiplimab: \$141,700	\$111,212/QALY	Same indication, same model structure US-based model with efficacy inputs based on aggregate published efficacy data, and non-cervical cancer utilities
				Chemotherapy: 1.107	Chemotherapy: \$75,296		
Huo 2024 ⁴⁹	2023	Cost-utility analysis Authors described it as Markov model, but based on description is a PartSA	Patients with previously treated recurrent or metastatic cervical cancer (50 years)	Tisotumab vedotin: 1.15	Tisotumab vedotin: \$293,641	\$839,108/QALY	Same indication, same model structure US-based model with efficacy inputs based on aggregate published efficacy data, and non-cervical cancer utilities
				Chemotherapy: 0.90	Chemotherapy: \$86,862		
Phippen 2013 ⁴	2012	Cost-utility analysis Decision tree	Patients with inoperable recurrent cancer of the uterine cervix who have received prior chemoradiation	Not reported (Due to the lack of utility studies published at the time of model development the authors estimated that the QALY was 1	Home hospice for all: \$10,890	0	Population and comparators not relevant to decision problem US-based model with utilities based on assumptions
					Single-agent chemotherapy with home hospice for all: \$15,818	\$44,392/QALY	
					Selective chemotherapy: \$29,112	\$78,404/QALY	

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Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Comments / relevance to decision problem
				for all treatment options)	Standard doublet chemotherapy for all: \$33,368	\$275,630/QALY	
Shi 2022 ⁶	2020	Cost-utility analysis PartSA	Adults (≥18 years of age) with persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix who had not received systemic chemotherapy and weren't amenable to curative treatment	Pembrolizumab: 2.23	Pembrolizumab: \$432,196		Population and comparators not relevant to decision problem US-based model with non-cervical cancer utilities
				Placebo: 1.50	Placebo: \$249,925	\$247,663/QALY	

Abbreviations: ICER, incremental cost-effectiveness ratio; PartSA, partitioned survival analysis; QALYs, quality-adjusted life years

3.2 Economic analysis

At the time of the development of the model structure (2022), only Phippen 2013⁴ was available, which used a simple decision-tree structure with median survivals assigned for each treatment strategy. This model was not appropriate for the scope of the current model (Table 17), and therefore, was not used for the development of the model structure. Instead, a de novo model was developed.

The two more recent 2L models, and the Shi 2022 1L model, all used progression and death to determine health states, via PartSA, which is the approach adopted for the de novo model developed for this submission. These structures are based on the implicit assumption that progression and mortality drive costs and health outcomes. The US-based cost inputs from these models were not relevant for decision making. The efficacy and safety data were either for comparators or trials not relevant to the decision problem or were based on aggregate data, while the model developed by Regeneron was based on patient level data, specifically collected in the population of interest. The utility inputs were evaluated for relevance to the decision problem (please see Section 3.4.3).

Two previously completed NICE TAs of therapies for advanced cervical cancer were identified:

- TA183 published in 2009: Topotecan for the treatment of recurrent and stage IVB cervical cancer⁵⁵
- TA939/TA885 published in 2023: Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer.⁵

In the most recent NICE TA in CC (TA939/TA885 for pembrolizumab plus chemotherapy with or without bevacizumab), the Committee agreed that, as the OS data were immature, a state transition model was more appropriate as it can use an assumed structural link between PFS and OS, rather than directly extrapolating immature OS data.⁵ However, the Committee also noted that with more mature data, a PartSA approach might be more appropriate.

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The OS data from the cemiplimab pivotal trial (EMPOWER Cervical-1) are highly mature.¹² At the time of the final analysis the median follow-up was 47.3 months in 2L+ in the EMPOWER Cervical-1 trial vs 28.6 months in KEYNOTE-826 in 1L+.^{5,10} In the EMPOWER Cervical-1 trial final analysis, 78% and 84% of patients in the cemiplimab and chemotherapy arms, respectively, had died.¹⁰ Consequently, the level of uncertainty around survival is much lower with cemiplimab than with pembrolizumab in the updated TA (TA939), and a PartSA model is more appropriate. For cemiplimab, a PartSA was therefore implemented in line with the Committee's suggestion in TA939 / TA885.⁵

A comparison of the current model with the prior TAs is given in Section 3.2.7.

3.2.1 Patient population

The patient group covered by the economic evaluation is patients with recurrent, persistent and/or metastatic cervical cancer who have progressed on or after platinum-based chemotherapy, and who have not received prior immunotherapy. This aligns with the patient population of the cemiplimab pivotal trial (the EMPOWER Cervical-1 trial),³⁰ clinical expert opinion on the anticipated use of cemiplimab in clinical practice in England and Wales,^{6-8,51} and the strong recommendations (category I,A) on the use of cemiplimab included in the most up-to-date ESGO/ESTRO/ESP clinical guideline on the management of CC (see Section 1.3.3.3).¹³ This population also aligns with the population defined in the scope for this appraisal (see Table 1).⁵⁶

3.2.2 Perspective

In line with the Reference case and the scope,^{14,56} the analysis takes the perspective of all health effects for patients and NHS and Personal Social Services (PSS) for costs.

3.2.3 Type of economic evaluation

In line with the NICE reference case,¹⁴ a cost-utility analysis (CUA) with fully incremental analysis was undertaken, since both, patients' life expectancy (mortality) and quality of life (QoL; morbidity) are affected by cervical cancer.^{57,58} Thus, health

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effects are expressed in terms of life-years (LYs) and quality-adjusted life-years (QALYs) gained. The analysis calculates incremental cost-effectiveness ratios (ICERs) as incremental costs per QALY gained.

3.2.4 Time horizon

In line with the NICE Reference case¹⁴ and the scope,⁵⁶ the time horizon is lifetime, to reflect all differences in costs or outcomes between the technologies being compared. The lifetime horizon was defined as 33 years, based on the life expectancy in the general female population in England and Wales at the mean baseline age of females enrolled in the EMPOWER Cervical-1 trial (51 years).^{12,59} At the end of this lifetime horizon, 0%-0.3% of patients remained alive in the model, depending on the treatment arm.

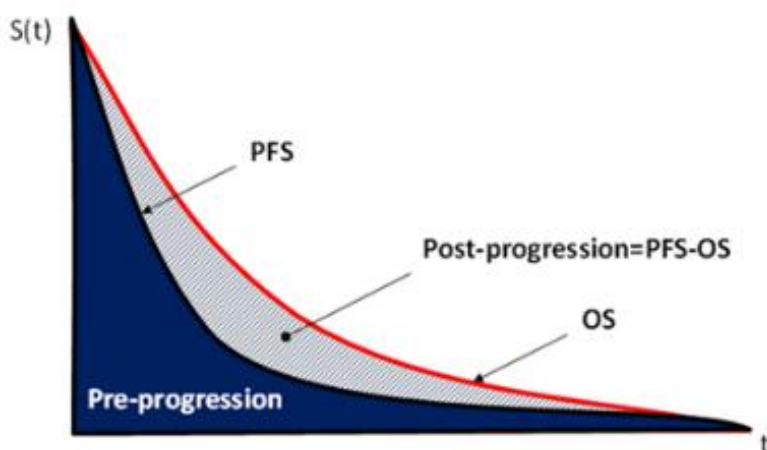
Scenario analyses were conducted to assess the impact on the results of assuming a much shorter time horizon of 20 or 10 years.

3.2.5 Model structure

To account for the progressive nature of recurrent, persistent and/or metastatic cervical cancer (r/m CC), a partitioned survival analysis (PartSA)^{60,61} approach has been implemented. The PartSA approach has been used extensively in oncology since it is particularly suited to conditions where the survival curves are essential in describing the clinical outcomes, and in which ongoing risks exist, although the size of these risks may vary over time. This approach allows a closer fit to the actual PFS and OS data (i.e. Kaplan-Meier [KM] curves) observed in the clinical trial for the intervention and the relevant comparator, making the model intuitive and straightforward.

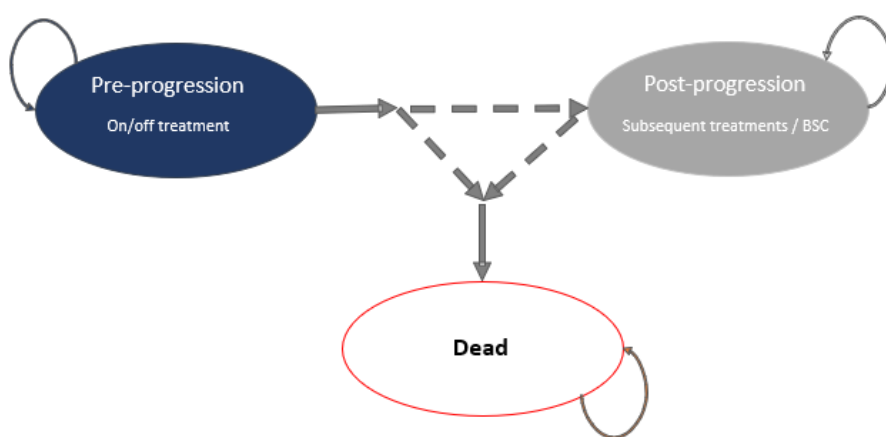
The distribution of the patient cohort between the different health states defined by these curves can be estimated in each cycle, as demonstrated in Figure 12. To follow patient flow, the PartSA model includes three health states: pre-progression, post-progression, and death, which are defined by OS and PFS (Figure 12, Figure 13). To account for the proportion of patients in each health state, the area under the survival curves is used instead of transition probabilities.

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Abbreviations: OS, overall survival; PFS, progression-free survival; S, survival; t, time

Figure 12. Model structure: Partitioned survival analysis approach



Abbreviations: BSC, best supportive of care

Figure 13. Model structure: Cohort model with the three main health states

All patients are assumed to start in the 'pre-progression' state; in each following model cycle they can either:

- have stable disease or respond to therapy (as defined in the EMPOWER Cervical-1 trial^{12,30}) and stay in this health state
- progress (as defined in the EMPOWER Cervical-1 trial^{12,30}) and move to the 'Post-progression' health state
- die and move to the absorbing 'Dead' health state.

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Patients in the 'Pre-progression' health state can either be 'on treatment' or 'off treatment' as defined by the time-on-treatment (ToT) survival curve from the trial. Patients who are in the 'Post-progression' health state can receive subsequent treatment(s) or best support of care (BSC) or can enrol in clinical trials according to the clinical experts from England and Wales,^{6-8,51} the choice of which impacts the costs. Patients stay in the 'Post-progression' health state until death, in which case they move to the 'Dead' health state. Patients can die at any time point in any health state.

The proportion of patients in the pre-progression health state decreases over time according to the PFS curve. The proportion of patients who are dead increases over time according to OS curve. The difference between the proportion of patients alive and proportion of patients in the pre-progression health state represents the proportion of patients who transition to the post-progression health state in each cycle.

Based on clinical expert opinion, progression is one of the most important drivers of cost and utility changes.^{6-8,51} An additional important driver of costs is 'being on treatment', which is included using the ToT survival curve. Quality of life is also affected by the type of treatment (chemotherapy vs. immunotherapy) due to their different toxicity profiles. This is taken into account in the treatment-specific health state utilities (please see Appendix N for more information).

In the analysis, the proportion of patients in the pre- and post-progression health states in each cycle is multiplied with the corresponding utility value (discounted over time). In the last 30 days prior to death, a specific end-of-life utility is used instead of the health state utilities, to reflect the further decrease in patients' quality of life as they approach death. Similarly to utilities, expected routine care costs by treatment are calculated and multiplied by the proportion of patients in the pre- and post-progression health states (again discounted over time). End-of-life costs are added to the last 30 days of life to reflect the different components of health care resource use and costs as patients approach death. The acquisition and administration costs of the intervention and comparators are multiplied by the proportion of patients on

treatment in each cycle. One-off AE costs are applied in the first cycle, while subsequent treatment costs are applied at the time of progression.

As the model progresses cycle by cycle within the selected time horizon, treatment-specific cost and utility-adjusted life year (LY) data are summed, which allows the calculation of total and incremental costs and QALYs between comparators at model completion.

A seven-day cycle length was used in the economic model to account for the different administration schedules of the comparators and to provide the granularity required. Half-cycle corrections were not needed due to this very short cycle length.

3.2.6 Discounting

In accordance with the NICE Reference case, an annual discount rate of 3.5% was applied to both costs and health benefits.¹⁴

As the model uses weekly cycles, the following calculation method was used for the discounting:

$$D(x) = \frac{x}{(1 + r)^{\frac{t}{\frac{365.25}{7}}}}$$

Where x is the value to be discounted, r is the discount rate, and t is the current cycle number. The number of cycles per year was estimated to be 365.25/7 taking into account the four-yearly leap year.

Discounting starts for the modelled outcomes and costs accrued beyond the first 12 months.

3.2.7 Comparison to previous TAs

Table 18 compares the main features of two previously completed NICE TAs of therapies for advanced cervical cancer. As noted in Section 3.2 above, the survival data for cemiplimab are very mature and a PartSA was therefore implemented in line with the Committee's suggestion in TA939 / TA885.⁵

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The lifetime time horizon is shorter for cemiplimab than in TA939, as TA939 included patients from first line, while cemiplimab is licenced from second line onwards (Table 18). Treatment waning is not relevant for cemiplimab, as the highly mature survival curves already include any treatment waning effect in the observed survival curves and no additional assumptions are required. In TA939, survival curves were immature, and due to the high uncertainty, treatment waning effect was assumed. The source of costs and utilities is similar to those in previous TAs (Table 18).

Table 18 Features of the economic analysis

Factor	Previous evaluation, TA183⁵⁵	Previous evaluation, TA939⁵	Current evaluation, chosen values	Current evaluation, justification
Population	Carcinoma of the cervix recurrent after radiotherapy and patients newly presenting with stage IVB disease	Adults with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS $\geq$ 1)	Patients with recurrent, persistent and/or metastatic cervical cancer who have progressed on, or after platinum-based therapy, and who have not received prior immunotherapy	In line with the scope ⁵⁶ Aligns with population in the pivotal EMPOWER Cervical-1 trial, ³⁰ clinical expert input on anticipated use in npractice ^{6-8,51} and the European clinical guideline on the management of CC ¹³ (see Section 3.2.1)
Time horizon	36 months for the within trial analysis and 24 months for the indirect comparison	50 years	33 years	In line with the scope and NICE Reference case, a lifetime horizon to reflect all important differences in costs and/or outcomes between the technologies being compared. ^{57,58} Lifetime horizon was defined as 33 years, the life expectancy in the general female population in England and Wales at the mean baseline age in the EMPOWER Cervical-1 trial ^{12,59} (see Section 3.2.4)
Treatment waning effect?	NA	Treatment effect waning assumed from 3 years to 5 years after stopping pembrolizumab (immature data)	NA	Due to the highly mature survival curves any treatment waning effect is already included in the observed survival curves and so no additional assumptions are required The PFS curves are nearly complete and only required a very short extrapolation The OS curves are also highly mature (with 237 events (78.0%) reported in the cemiplimab arm, and 256 events (84.2%) reported in the chemotherapy arm ¹²

Factor	Previous evaluation, TA183 ⁵⁵	Previous evaluation, TA939 ⁵	Current evaluation, chosen values	Current evaluation, justification
Source of utilities	FACT-G data were mapped to utilities using an algorithm developed by researchers at the School of Public Health, University of Illinois at Chicago	KN-826 EQ-5D-5L data were mapped to EQ-5D-3L and the UK tariff was used to obtain utilities	EORTC QLQ-C30 scores collected in the pivotal EMPOWER Cervical-1 trial were mapped to the EQ-5D-3L using the Longworth mapping algorithm ⁶²	Utilities obtained in the cemiplimab pivotal EMPOWER Cervical-1 trial have been used in the base case to reflect the values for cemiplimab and for the target population Utilities identified in literature and previous TAs have been tested in scenario analyses
Source of costs	NHS reference costs and PSSRU	Resource use: Feedback from UK clinical experts Unit costs: MIMS, eMIT, NHS reference costs, PSSRU	Resource use: Feedback from UK clinical experts Unit costs: eMIT, BNF, NHS reference costs, PSSRU	In line with NICE Reference case ¹⁴ and the prior TAs ^{27,55} using the most up-to-date data

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; EQ-5D-3L, EuroQol-5 dimensions 3-level; EQ-5D-5L, EuroQol-5 dimensions 5-level; MIMS, Monthly Index of Medical Specialties; NA, not applicable; NICE, National Institute for Care and Health Excellence; OS, overall survival; PFS, progression-free survival; PSSRU, Personal and Social Services Research Unit; TA, technology appraisal

3.2.8 Intervention technology and comparators

In CC in England and Wales, as described in the NICE scope⁵⁶ and the British Gynaecological Cancer Society (BGCS) cervical cancer guidelines (2021)¹, there is no standard 2L treatment for people with disease progression on or after systemic treatment.

The final NICE scope for the appraisal of cemiplimab listed single agent-chemotherapy, best supportive care, and tisotumab vedotin (subject to NICE evaluation) as comparators.⁵⁶ Of these, only single agent-chemotherapy is a relevant comparator, as detailed in Table 1, in Section 1.1.

In the base case, to align with the efficacy and safety inputs, the basket of single-agent chemotherapies is adopted based on the observed distribution of single-agent chemotherapies used in the EMPOWER Cervical-1 trial (Table 19). Additionally, the clinical experts validated the efficacy results of the EMPOWER Cervical-1 trial single-agent chemotherapy arm as representative of expected outcomes with chemotherapy regimens used in UK clinical practice.^{6-8,51} The impact of adopting the alternative costs of the basket of chemotherapies stated by clinical experts as being most commonly used in NHS practice is assessed in a scenario analysis.

All treatments are administered in secondary care setting. Neither cemiplimab nor the comparator requires any biomarker testing.

Table 19. Distribution of chemotherapies used in the EMPOWER Cervical-1 comparator arm

Chemotherapies included	Percentage of patients receiving
Pemetrexed	36.5%
Gemcitabine	39.8%
Topotecan	6.9%
Irinotecan	6.3%
Vinorelbine	10.5%

Source: EMPOWER Cervical-1 trial CSR¹² (Data available in Tewari et al.)³⁰

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3.3 Clinical parameters and variables

Clinical parameters and variables incorporated in the model and described in the next sections include:

- Patient characteristics
- Treatment efficacy, including OS, PFS and ToT
- Safety.

3.3.1 Patient characteristics

The model uses the mean baseline age (51.1 years) from the EMPOWER Cervical-1 trial as the starting age in cycle zero.³⁰ Drug cost calculations, when not based on flat dosing, use the mean body surface area (BSA) and the mean body weight of the total ITT population from the EMPOWER Cervical-1 trial (Table 20).

Table 20. Baseline patient characteristics

Patient characteristics	Mean	Standard error
Age	51.14 years	0.47 years
Body surface area	██████	██████
Weight	██████	██████

Source: EMPOWER Cervical-1 trial¹²

3.3.2 Treatment efficacy

The cost-effectiveness model is based on time-to-event (TTE) outcomes, including OS, PFS, and ToT. The TTE outcomes are estimated from the EMPOWER Cervical-1 trial patient level data from the final analysis (data cut-off 3 Oct 2023) (see section 2.6 for more information).

The trial-based TTE curves were highly mature but extrapolation to the lifetime horizon using parametric survival analysis was required. In the parametric survival analysis, in line with guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14,⁶³ the six commonly used parametric model structures were used to capture and extrapolate data for each TTE outcome of interest: exponential, generalized gamma, Gompertz, Weibull, log-logistic, log-normal. More

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complex methods, such as piecewise fits or polynomial distributions, were not required as single distributions provided an appropriate fit without increasing uncertainty.

For each TTE outcome, it was assessed whether treatment effect was best captured using a treatment arm covariate in a single parametric model (a 'joint' model), or by separate ('independent') models fitted to each treatment arm. Visual inspection of KM data, and diagnostic plots were used to choose between the jointly or independently fitted parametric survival models, with consideration of the different implicit assumptions of modelling treatment effect as a covariate across different parametric models.

Selection of the base case parametric model for each TTE outcome was based on the following standard criteria, following TSD 14:⁶³

- Proportional hazards (PH) assumption was checked using Schoenfeld residuals, Schoenfeld tests and visual inspection of log-log survival plots
- Objective statistical measures of goodness of fit to observed KM data: Akaike information criterion (AIC)⁶⁴ and Bayesian information criterion (BIC) statistics⁶⁵
- Visual inspection of goodness of fit to observed KM data
- The clinical/biological plausibility of extrapolations beyond the observed KM data, using the predicted landmark OS and PFS values were validated by five UK clinical experts^{6-8,51,52} (see Appendix R for an overview of the clinical validation process).

All analyses were conducted using R® version 3.6.19. The package "flexsurv" was used for parametric survival analysis.

Given the lifetime horizon of the model, PFS, OS and ToT extrapolations were sustained over the full time horizon. For more information, please see the Survival analysis report in Appendix L.

The base case parametric models are presented in Table 21. More detail for each TTE outcome can be found in the following sections.

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Table 21. Base case parametric models

Treatment	Base case distributions used for cemiplimab	Base case distributions used for chemotherapy
Overall survival	Generalised gamma	Generalised gamma
Progression-free survival	Generalised gamma	Generalised gamma
Time-on-treatment	Log-normal	Log-normal

To avoid accidental crossing of the OS, PFS and ToT curves, ToT was constrained not to exceed PFS. The same approach was applied to PFS to ensure it could not exceed OS.

A treatment waning effect was not incorporated in the model as the PFS curves, being nearly complete, only required a short extrapolation. In addition, the trial OS curves are very mature (with 237 events (78.0%) reported in the cemiplimab arm, and 256 events (84.2%) reported in the chemotherapy arm).¹² The extrapolated curves provide a good fit to these mature data and were validated by clinical experts as plausible representations of expected outcomes over time.^{6-8,51,52}

3.3.2.1 Overall survival

Based on the Schoenfeld residuals, Schoenfeld tests and visual inspection of log-log cumulative hazards plots, the PH assumption did not appear to hold, therefore the comparators were extrapolated using independently fitted curves. Further details can be found in the Survival analysis report (Appendix L).

For chemotherapy, the smallest AIC/BIC values for OS are associated with the log-logistic model, followed by log-normal and generalised gamma models (Table 22, Table 23). All three models provide a good visual fit to the KM curve (Figure 14). However, UK clinical experts, who were consulted independently, stated that predictions with the log-logistic and Gompertz models (which only provided the fourth best fit in terms of statistical criteria) are too optimistic for chemotherapies, and the predictions with the generalised gamma model reflect best the survival with chemotherapies in current clinical practice for this patient population.^{6-8,51,52} Some of the experts also recommended predictions with the log-normal distribution as

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representative of current UK clinical practice.^{6-8,51} As a result, the generalised gamma model was selected in the base case, and the log-normal and log-logistic models were tested in scenario analyses (which, given the high maturity of the data, had little impact on the base case ICERs).

For cemiplimab, the smallest AIC/BIC values for OS are associated with the log-normal model, with generalised gamma and the log-logistic models providing the second best fit depending on which statistical criterion is looked at (Table 22, Table 23). These three models visually fit the KM curve better than other curves (Figure 14). UK clinical experts felt that the predictions with the Gompertz model (which provided the worse fit in terms of statistical criteria) were too optimistic.^{6-8,51} The 10-year prediction of 3%-4% of patients alive was deemed realistic, which is achieved with the lognormal, log-logistic and generalised gamma models.⁷ To be consistent with the chemotherapy arm, in the base case, the generalised gamma model was selected. In scenario analysis, allowing for different parametric models for the two treatment arms, due to the different mechanism of action of the immunotherapy (cemiplimab) and the chemotherapies, the log-normal model was tested for cemiplimab. (Further details can be found in the Survival analysis report in Appendix L).

Table 22. Selection of the parametric survival models for overall survival

Decision criteria	Cemiplimab arm	Chemotherapy arm
Testing for proportional hazard assumption*	Proportional hazard assumption did not appear to hold	
Statistical criteria	Best fit: log-normal model, closely followed by generalised gamma and the log-logistic models	Best fit: log-logistic model, closely followed by log-normal and generalised gamma models
Fit of predicted survival curve to observed Kaplan-Meier curve	Best fit: log-normal, generalised gamma and the log-logistic models	Best fit: log-logistic, log-normal and generalised gamma models
Clinically/biologically plausible predictions	Best fit: generalised gamma, log-normal and the log-logistic models	Best fit: Generalized gamma model
Conclusion	Independently fitted generalised gamma model	Independently fitted generalised gamma model

*Tests used included Schoenfeld residuals, Schoenfeld tests, log-log cumulative hazards plots

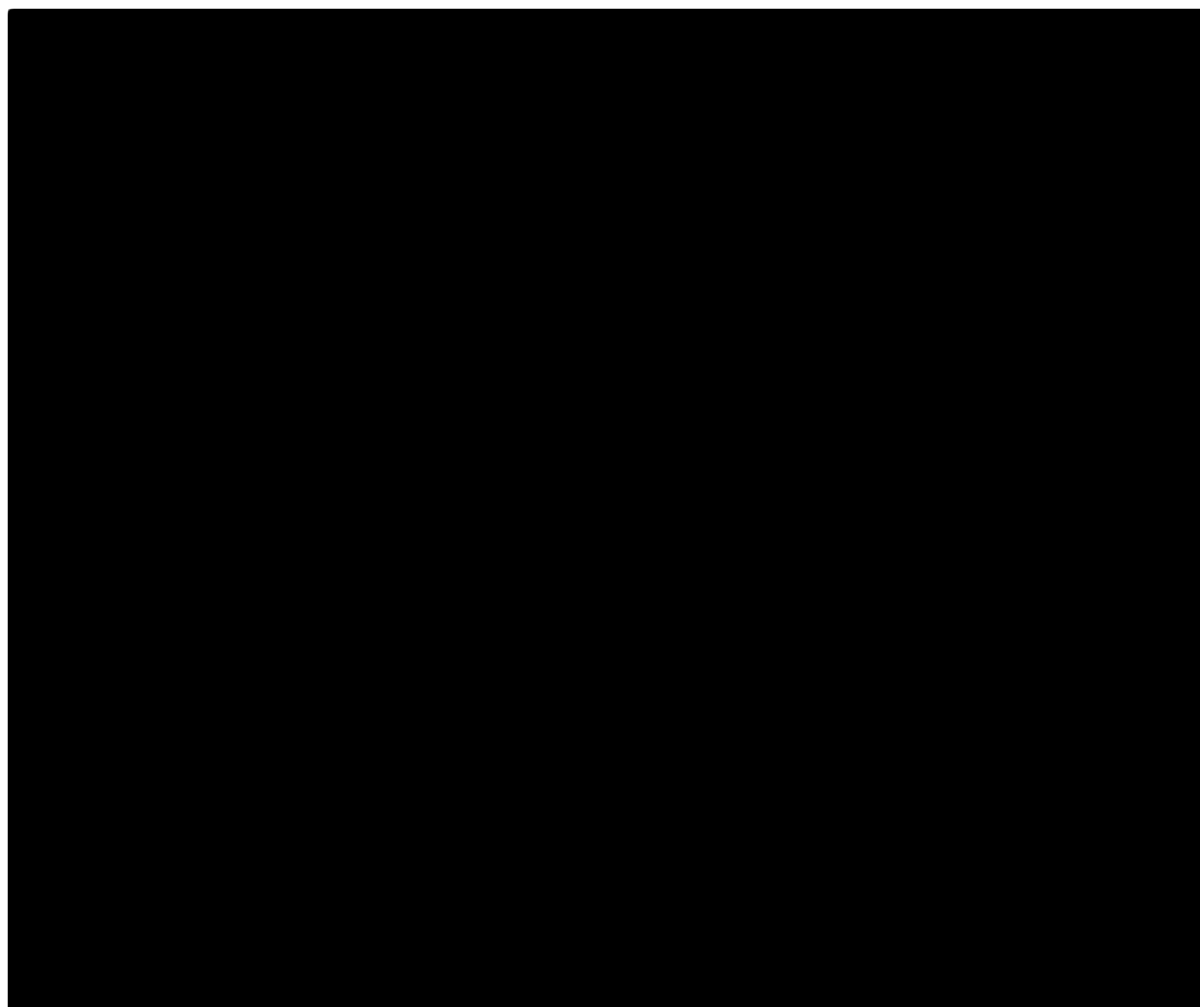
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Table 23. Statistical criteria for cemiplimab and chemotherapy OS parametric curve fit from the EMPOWER Cervical-1 trial

Functional form	AIC: Chemotherapy	AIC: Cemiplimab 350 mg	BIC: Chemotherapy	BIC: Cemiplimab 350 mg
Exponential	1823.0 (5)	1916.4 (6)	1826.7 (4)	1920.1 (5)
Weibull	1819.4 (4)	1915.6 (5)	1826.8 (5)	1923 (6)
Log-normal	1786.3 (2)	1881.7 (1)	1793.7 (2)	1889.1 (1)
Generalised gamma	1788.1 (3)	1882.4 (2)	1799.2 (3)	1893.6 (3)
Gompertz	1823.4 (6)	1898.2 (4)	1830.8 (6)	1905.7 (4)
Log-logistic	1780.8 (1)	1884.4 (3)	1788.2 (1)	1891.9 (2)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

NOTE: Ranking according to fit criteria is given in brackets.



Abbreviations: Ind, independently fitted

Figure 14. Cemiplimab and chemotherapy OS Kaplan Meier curve and parametric models from EMPOWER Cervical-1 trial

For the estimated parameters and the variance-covariance matrices used in sensitivity analyses, please see Appendix M. OS estimates were capped by age-dependent annual probability of general female population mortality in England and Wales.⁵⁹

3.3.2.2 Progression-free survival (PFS)

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Similarly to the OS curves, the PH assumption did not appear to hold based on the Schoenfeld residuals, Schoenfeld tests and visual inspection of log-log cumulative hazards plots; as such the PFS curves for the comparators were extrapolated using independent models. Further details can be found in the Survival analysis report (Appendix L).

For both cemiplimab and chemotherapy, the generalised gamma model provided the best fit, in terms of smallest AIC/BIC value (Table 24, Table 25). The generalised gamma model also provided a good visual fit to the KM curve (see Figure 14).

UK clinical experts stated that with chemotherapy PFS is very unlikely at 10 years, and would be close to zero at 5 years, with some exceptions.^{6-8,51} All models predict <0.1% PFS at 10 years (with Gompertz being the highest at 0.062%), and <0.3% PFS at 5 years. One of the experts found extrapolation with 2% PFS at 2 years the most plausible,⁵² which is predicted by the generalised gamma and log-logistic models.

For cemiplimab, clinical experts found the predictions with the exponential and Weibull too low, as “a tail is expected”.^{6-8,51} The models with the most plausible predictions were felt to be generalised gamma and Gompertz. Predictions with the Gompertz model however were thought implausible by UK clinical experts in the chemotherapy arm.

Therefore, the generalised gamma model was selected for the base case for both treatment arms. The second best-fitting parametric model, log-normal, was tested in scenario analysis. (Further details can be found in the Survival analysis report in Appendix L).

For the estimated parameters and the variance-covariance matrices used in sensitivity analyses, please see Appendix M.

Table 24. Selection of the parametric survival models for progression-free survival

Decision criteria	Cemiplimab arm	Chemotherapy arm
Testing for proportional hazard assumption*	Proportional hazard assumption did not appear to hold	
Statistical criteria	Best fit: generalised gamma model followed by log-normal	Best fit: generalised gamma model followed by log-normal
Fit of predicted survival curve to observed Kaplan-Meier curve	Best fit: generalised gamma	Best fit: all models provided similar fit
Clinically/biologically plausible predictions	Generalised gamma and the log-logistic models with a tail	All models with the Gompertz model the least plausible
Conclusion	Independently fitted generalised gamma model	Independently fitted generalised gamma model

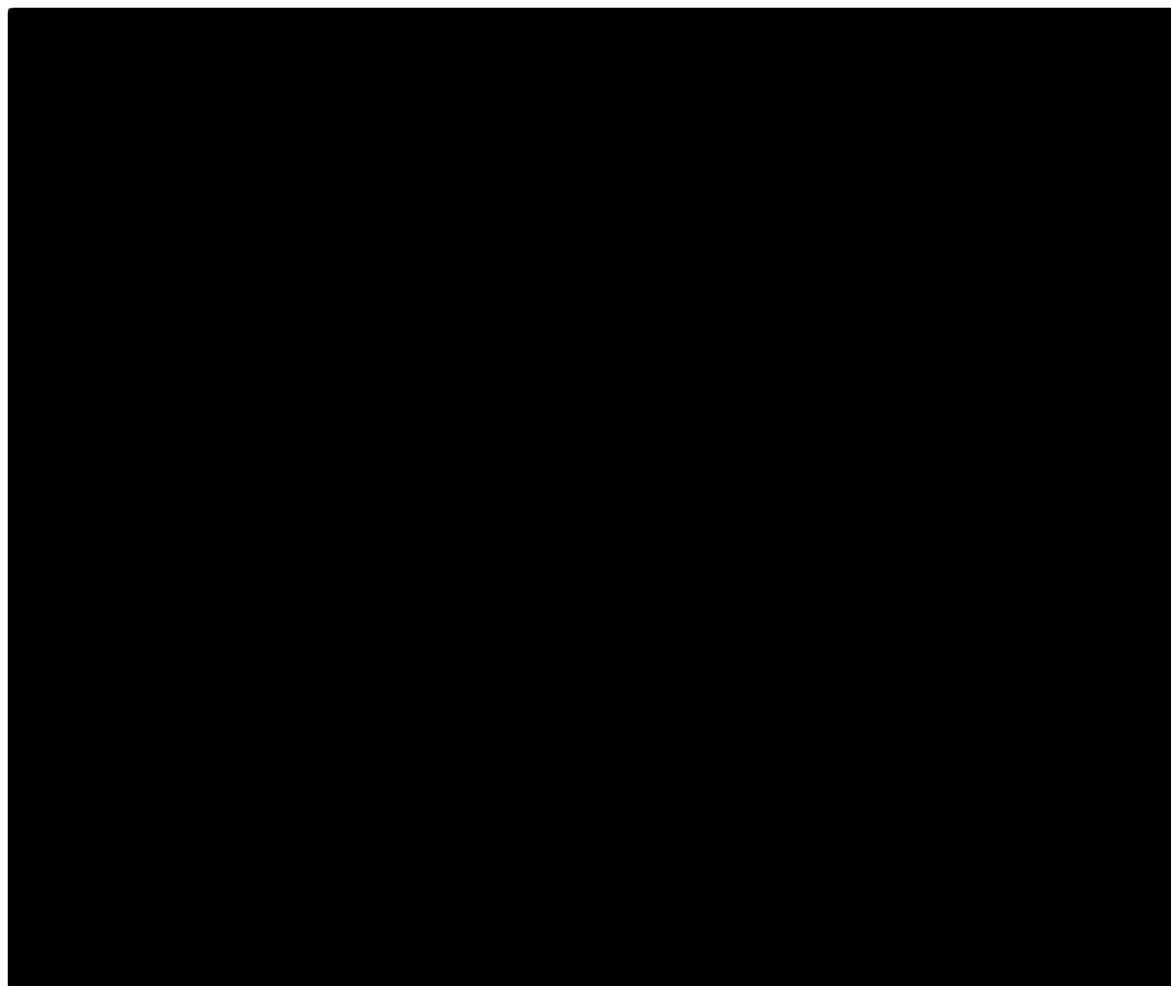
*Tests used included Schoenfeld residuals, Schoenfeld tests, log-log cumulative hazards plots

Table 25. Statistical criteria for cemiplimab and chemotherapy PFS parametric curve fit from the EMPOWER Cervical-1 trial

Functional form	AIC: Chemotherapy	AIC: Cemiplimab 350 mg	BIC: Chemotherapy	BIC: Cemiplimab 350 mg
Exponential	1408.5 (5)	1704.0 (6)	1412.2 (5)	1707.7 (6)
Weibull	1396.0(4)	1670.0 (5)	1403.5 (4)	1677.4 (5)
Log-normal	1340.7 (2)	1581.5 (2)	1348.1 (2)	1588.9 (2)
Generalised gamma	1336.7 (1)	1538.7 (1)	1347.9 (1)	1549.9 (1)
Gompertz	1410.0 (6)	1605.6 (4)	1417.4 (6)	1613.0 (4)
Log-logistic	1353.1 (3)	1583.5 (3)	1360.5 (3)	1590.9 (3)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

NOTE: Ranking according to fit criteria is given in brackets.



Abbreviations: Ind, independently fitted

Figure 15. Cemiplimab and chemotherapy PFS Kaplan Meier curve and parametric models from EMPOWER Cervical-1 trial

3.3.2.3 *Time on Treatment (ToT)*

The PH assumption, based on the above-mentioned criteria, did not appear to hold for this outcome either, therefore the comparators were extrapolated using independent models. Further details can be found in the Survival analysis report (Appendix L).

For both cemiplimab and chemotherapy, the generalised gamma model provided the best fit using AIC followed by the log-normal model, and log-normal model provided the best fit according to BIC followed by the generalised gamma model (Table 26,

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Table 27). As the difference between the two models was slightly larger using BIC, the log-normal model was selected for the base case for both treatment arms. Both models also provided a good visual fit to the KM curve (Figure 16). For cemiplimab, as the duration of the study treatment period for a patient was up to 96 weeks (up to 16 cycles of 6 weeks each),¹² most patients stopped treatment at 96 weeks. Therefore, there is a sudden drop in the curve at that timepoint. However, as [REDACTED]% of patients were on cemiplimab treatment for 96 weeks or longer¹² due to delays and interruptions, censoring patients at that time would have underestimated the cemiplimab costs. The use of the log-normal curve without censoring patients at 96 weeks resulted in very similar mean ToT to that seen in the EMPOWER Cervical-1 trial ([REDACTED] weeks in the trial vs. [REDACTED] weeks in the model). Generalised gamma model was included in scenario analysis. (Further details can be found in the Survival analysis report in Appendix L.)

For the estimated parameters and the variance-covariance matrices used in sensitivity analyses, please see Appendix M.

Table 26. Selection of the parametric survival models for time-on-treatment survival curve

Decision criteria	Cemiplimab arm	Chemotherapy arm
Testing for proportional hazard assumption*	Proportional hazard assumption did not appear to hold	
Statistical criteria	Best fit: generalised gamma and log-normal models depending on the criteria used with slight advantage for log-normal model	Best fit: generalised gamma and log-normal models depending on the criteria used with slight advantage for log-normal model
Fit of predicted survival curve to observed Kaplan-Meier curve	Best fit: generalised gamma and log-normal models	Best fit: generalised gamma and log-normal models
Clinically/biologically plausible predictions	Validation not conducted as based on observed trial data	Validation not conducted as based on observed trial data
Conclusion	Independently fitted log-normal model	Independently fitted log-normal model

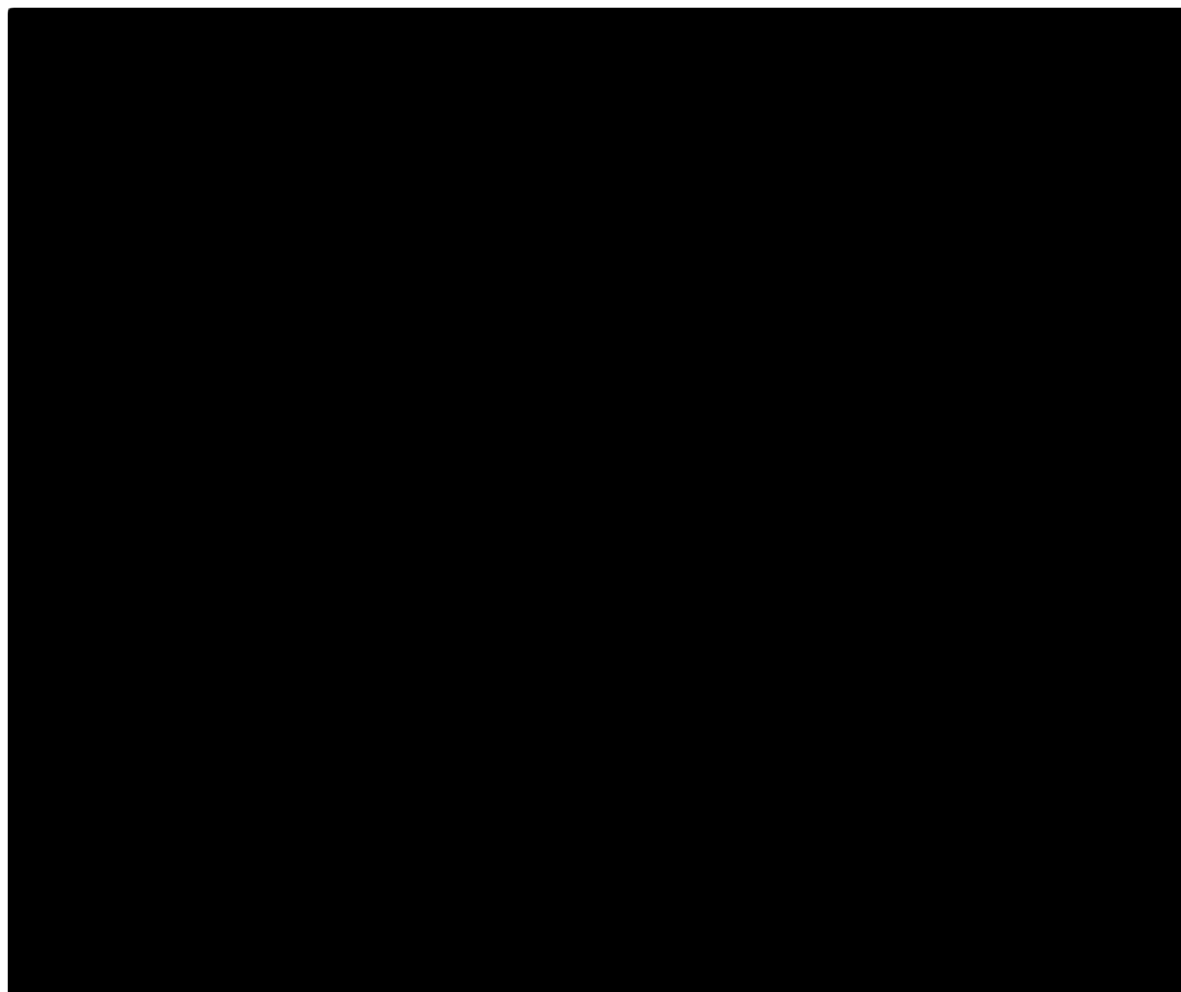
*Tests used included Schoenfeld residuals, Schoenfeld tests, log-log cumulative hazards plots

Table 27. Statistical criteria for cemiplimab and chemotherapy ToT parametric curve fit from the EMPOWER Cervical-1 trial

Functional form	AIC: Chemotherapy	AIC: Cemiplimab 350 mg	BIC: Chemotherapy	BIC: Cemiplimab 350 mg
Exponential	1763.4 (4)	1339.5 (5)	1767.1 (4)	1343.2 (5)
Weibull	1765.4 (6)	1332.7 (4)	1772.8 (6)	1340.1 (4)
Log-normal	1726.3 (2)	1310.9 (2)	1733.7 (1)	1318.3 (1)
Generalised gamma	1724.9 (1)	1310.4 (1)	1736 (2)	1321.5 (2)
Gompertz	1764.8 (5)	1341.2 (6)	1772.2 (5)	1348.6 (6)
Log-logistic	1748.2 (3)	1317.8 (3)	1755.6 (3)	1325.2 (3)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ToT, time-on-treatment

NOTE: Ranking according to fit criteria is given in brackets.



Abbreviations: Ind, independently fitted

Figure 16. Cemiplimab and chemotherapy ToT Kaplan Meier curve and parametric models from EMPOWER Cervical-1 trial

3.3.3 Safety

Only Grade 3 and 4 TEAEs were included in the CEM since only those AEs are considered to have important cost and quality of life consequences at the population level.

TEAEs for cemiplimab and chemotherapy was obtained from the EMPOWER Cervical-1 trial final analysis.¹² The most common grade 3 or higher AEs, experienced by $\geq 2\%$ of patients in either treatment arm, or by $>5\%$ of patients including all grades, were included in the model (Table 28).

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Table 28. Treatment-emergent adverse events rate included in the cost-utility model¹²

Adverse event	Cemiplimab	Chemotherapy
	% of patients experiencing event	
Abdominal pain		
Alanine aminotransferase increased		
Anaemia		
Arthralgia		
Aspartate aminotransferase increase		
Asthenia		
Back pain		
Blood creatinine increased		
Constipation		
Cough		
Decreased appetite		
Diarrhoea		
Dyspnoea		
Fatigue		
Headache		
Hydronephrosis		
Hyperglycaemia		
Hypoalbuminaemia		
Hypokalaemia		
Hypothyroidism		
Insomnia		
Leukopenia		
Nausea		
Neutropenia		
Neutrophil count decreased		
Oedema peripheral		
Pain in extremity		
Pelvic Pain		
Pruritus		
Pyrexia		
Rash		
Stomatitis		
Thrombocytopenia		
Urinary tract infection		
Vomiting		
White blood cell count decreased		

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3.4 Measurement and valuation of health effects

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

The EMPOWER Cervical-1 trial did not collect utility data. To assess health-related quality-of-life in the EMPOWER Cervical-1 trial, the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30)^{11,12} was administered at baseline and at eight visits scheduled for treatment administration planned up to 96 weeks. Patient-reported outcome scores consistently favoured cemiplimab over chemotherapy on a wide range of measures in the overall study population. (Please see Section 2.6.6 for more details.)

3.4.2 Mapping

To estimate utility values for the model, the EORTC QLQ-C30 scores collected at each visit in the trial were mapped on to the EQ-5D-3L using the Longworth mapping algorithm. The Longworth algorithm has been externally validated in datasets of patients with multiple myeloma, breast and lung cancer.⁶² No algorithm specific to cervical cancer was found in the literature; however, this mapping algorithm was implicitly accepted for use in cervical cancer in the recent positive SMC advice for cemiplimab.¹⁹ (Please see Appendix N for more information on the mapping.)

To account for the multiple data points for the same patient, a linear mixed-effect repeated measures model (MMRM) of the post EQ-5D-3L score was used, with the following covariates fitted as fixed effects:

- Treatment arm (cemiplimab /chemotherapy)
- Visit number (two to eight)
- Baseline EQ-5D score
- Geographical region (Asia/North America/Rest of World)
- Histology (squamous cell carcinoma (SCC)/non-SCC)
- Treatment-by-visit interaction
- Baseline EQ-5D score-by-visit interaction.

3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL and utility data related to patients with recurrent or metastatic cervical cancer who have progressed on or after platinum-based chemotherapy. The report is provided in Appendix F.

Three studies were identified that included utility values for Pre-progression and Post-progression health states:

- Liu 2023 conducted a cost-utility analysis utilising data from EMPOWER Cervical-1 and previous literature.⁴⁸ The utility values were taken from an unresectable or metastatic endometrial cancer population and disutility due to AEs values were taken from a lung cancer population.
- Zhu 2025 conducted a cost-utility analysis utilising data from the BEATcc trial.⁶⁶ The utility values were taken from a previous study evaluating HPV vaccines in China, and the values themselves were for 'cured cancer' (pre-progression health state) and for 'distant cancer' (for the post-progression health state) in the Chinese population.^{66,67}
- Shi 2021 assessed the cost-effectiveness of pembrolizumab for treatment of US patients with persistent, recurrent, or metastatic cervical cancer.⁵⁰ The utility values used, similarly to Liu 2023⁴⁸, were from unresectable or metastatic endometrial cancer for US patients.

The SMC appraisal of bevacizumab in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent or metastatic carcinoma of the cervix, also reported utility values.⁶⁸ In that appraisal, the pre-progression value was mapped from a Canadian study in patients with a range of cancers (breast, lung and colorectal) and the post-progression value was based on an assumption of 20% decrement.

As the utility values reported in these studies were either for a different indication^{48,50,68} or for different health states,⁶⁶ they were not considered appropriate for the decision problem and were not included in the base case. The values from

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the SMC appraisal of bevacizumab were included in a scenario analysis, as they were deemed acceptable by the SMC.

Utility values in the NICE appraisal of pembrolizumab in CC (TA939) are redacted as confidential, and therefore not available for exploration in the current model.²⁷

3.4.4 Adverse reactions

As the pre-progression utility values in the base case were taken from the EMPOWER Cervical-1 trial, the HRQoL consequences of TEAEs are expected to be represented in the treatment-specific utility values. However, for completeness, the use of additional TEAE disutilities, applied as total disutilities in the first cycle, were tested in a scenario analysis (Please see disutilities in Appendix K).

In the scenario analysis, the total QALY loss due to TEAEs for each comparator was estimated as a weighted average of the disutility, the duration of TEAE (assumed to be 28 days for all TEAEs) and the probability of having that TEAE.

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

The EQ-5D-3L utility values mapped from the EORTC QLQ-C30 data collected in the pivotal EMPOWER Cervical-1 trial represent the quality of life of the specific patient population of interest when treated with cemiplimab and the relevant comparator. These utility values were therefore adopted appropriately in the base case model.

In the analysis of the mapped values, no clear evidence of a time-dependent treatment effect over the duration of the study period could be found. As a result, single health state utilities were deemed appropriate for the cost-utility model. (Please see Appendix N for further details.) As data from the EMPOWER Cervical -1 trial did not capture the time period close to death, end-of-life utilities were applied for the last 30 days of life.

The overall mean treatment effect, and the mean pre- and post-progression treatment effects, were estimated for the model. In the overall analysis, looking at all visits, without separating them according to health states, cemiplimab resulted in

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significantly higher utilities at each separate visit, with the exception of Visit 6. When the analysis was restricted to patients in the pre-progression health state, the trajectories were similar; however, the difference between treatment arms was slightly larger (mean difference: [REDACTED], 95% CI: [REDACTED]) and statistically significant across all visits.

As a result, treatment-specific utilities were included in the model for the pre-progression health state. The pre-progression mean score in the cemiplimab arm was 0.735 (95% CI: 0.702 to 0.768) compared to 0.622 (95% CI: 0.583 to 0.661) in the chemotherapy arm. The lower quality of life observed with chemotherapy in the trial was validated by clinical experts from the UK.^{6-8,51,52} According to the clinical experts:

- *“Chemotherapy does have a lot of quality-of-life impact. It is going to be much less for immunotherapy or just targeted therapy.”*
- *“ Chemotherapy has important side effects. Immunotherapies are very well tolerated, and patients on immunotherapies tend to have good quality of life, that you don’t see on chemotherapy.”*
- *“Due to the improvement of response rates with cemiplimab, quality of life is better with cemiplimab. The patients are often more symptomatic from the disease, so if you control the disease, you get more improvement in quality of life, because they are fit and young and recover quickly if disease burden is reduced. Additionally, there are more appointments with weekly paclitaxel, and that reduces quality of life.”*
- *“If you have two cohorts, one on immuno and one on chemo, the chemo ones have a worse quality of life, no doubt.”*

Three of the experts agreed that utility values estimated from the EMPOWER Cervical-1 trial represent what they see in clinical practice.⁶⁻⁸ Two of the experts stressed that, while the cemiplimab pre-progression utility value from the EMPOWER Cervical-1 trial reflects what they would expect from a 2L immunotherapy, a lower

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value than the one observed in the trial would be expected for chemotherapy treatment, due to the range, severity and persistence of side effects.^{51,52} Both clinicians independently commented that a utility value of 0.5 would be closer to what is seen in clinical practice with chemotherapies in 2L pre-progression.^{51,52} However, although potentially overestimating the chemotherapy utilities, for the purpose of consistency, the decision was made to use the higher value for chemotherapy derived from the trial in the base case; the effect of the lower value for chemotherapy recommended by clinical experts was tested in a scenario analysis (Table 29, Table 30).

For the post-progression health state, fewer data points were available to model treatment differences in patients (scores were only available for [REDACTED] of the 396 patients included in the analysis), especially in the chemotherapy arm. [REDACTED] out of [REDACTED] ([REDACTED]%) of all post-progression observations were in the cemiplimab arm, and only [REDACTED] out of [REDACTED] ([REDACTED]%) were in the chemotherapy arm. Additionally, data was only available for the first few visits in the chemotherapy arm, with only [REDACTED] patients completing the HRQoL questionnaire for the second visit and fewer than [REDACTED] patients beyond the fourth visit. (See Appendix N for further details). As a result, the treatment effect in terms of utility for cemiplimab vs. chemotherapy could not be estimated for the post-progression state.

The combined post-progression mean score was 0.613 (95% CI: 0.570 to 0.656), which represents almost the same value as the pre-progression utility for chemotherapy (0.622). Using this utility for both treatment arms would assume that patients' HRQoL is not affected by progression if they were taking chemotherapy but is affected by progression if they were taking cemiplimab. This is counterintuitive and contradicts the experience reported by the clinical experts.^{6-8,51}

Additionally, all clinical experts agreed that utilities post-progression would differ between patients who have progressed on 2L cemiplimab vs those who have progressed on 2L chemotherapy, due to persistent AEs with chemotherapy.^{6-8,51,52} According to the clinical experts:

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- *“If using weekly taxol, they can be left with significant peripheral neuropathy that’s ongoing.”*
- *“Some AEs can persist. For example, those who have persistent neuropathy with chemotherapy, their quality of life would be affected after progression also. With chemotherapy there is also slightly more fatigue that is persistent. There is some hangover from fatigue with immunotherapies also, but less. I would expect to see a difference, but not large.”*
- *“Quality of life is expected to be better for those who were on immunotherapy than those who were on chemotherapy. Chemotherapy patients will have more lingering side effects. With immunotherapies, side effects may happen after treatment discontinuation, but they are not lingering side effects.”*
- *“[chemotherapy patients] have the double whammy, the cancer progressing, and the lingering toxicities.”*

The combined post-progression mean value from the EMPOWER Cervical-1 trial was therefore used for the cemiplimab arm, as it is mainly based on cemiplimab patients. This is a conservative assumption, as it also includes patients on chemotherapy (■■■■%), who would likely have lower quality of life. As the clinical experts provided no value for chemotherapy post-progression, the relative disutility from pre- to post-progression observed for cemiplimab was applied for chemotherapy (■■■% reduction in utility from pre- to post-progression), resulting in a post-progression utility of 0.519 for the chemotherapy arm (Table 29). These inputs are conservative as these post-progression values are still higher than the pre-progression utility value suggested by the clinical experts (0.5) for chemotherapy. Same post-progression utilities, and alternative utility values based on the experts’ recommendations and from the literature, are explored in the scenario analyses (Table 30).

For the end-of-life period (last 30 days of life), the utility value for palliative treatment from Chevalier et al. (2016) for the health state ‘progression with palliative treatment’ in CC was assumed to represent end-of-life with a value of 0.092⁶⁹ (Table 29), since

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insufficient data were available from the EMPOWER Cervical-1 trial. Although values from Chevalier et al. (2016) do not meet the reference case (they are time trade-off values directly elicited from the French general population based on vignettes) and the study was only available as a conference abstract,⁶⁹ no alternative values were available. Health state utilities are further adjusted by age-related relative disutilities for the UK population.⁷⁰

Table 29. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Pre-progression - Cemiplimab	0.74 (0.02)	0.702 to 0.768	3.4.5 (page 110) Appendix N	Estimated from the pivotal EMPOWER Cervical-1 trial (significantly higher than for chemotherapy due to different safety profile), validated by clinical experts
Pre-progression - Chemotherapy	0.62 (0.02)	0.583 to 0.661	3.4.5 (page 110) Appendix N	Estimated from the pivotal EMPOWER Cervical-1 trial (significantly lower than for cemiplimab due to different safety profile), validated by clinical experts
Post-progression - Cemiplimab	0.61 (0.02)	0.570 to 0.656	3.4.5 (page 111) Appendix N	Estimated from the pivotal EMPOWER Cervical-1 trial, validated by clinical experts
Post-progression - Chemotherapy	0.52 (0.05)	NA	3.4.5 (page 112) Appendix N	Not available from the pivotal EMPOWER Cervical-1 trial, assumed same relative disutility for progression as for cemiplimab, validated by clinical experts
End-of-life (last 30 days of life)	0.092	NA	3.4.5 (page 112)	Not available from the pivotal EMPOWER Cervical-1 trial, taken from the only

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State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
				available source, Chevalier 2016, for the health state 'progression with palliative treatment' in cervical cancer

Source: EMPOWER Cervical-1 trial (Appendix N), clinical expert input (Appendix xx), Chevalier et al. 2016⁶⁹

Table 30. Alternative health state utilities for scenario analyses

	Cemiplimab		Chemotherapy	
	Mean	Standard error	Mean	Standard error
EMPOWER Cervical-1 trial utilities (assuming same post-progression value for both treatment arms) (Appendix N)				
Pre-progression	0.74	0.02	0.62	0.02
Post-progression	0.61	0.02	0.61	0.02
Utility values mentioned in the SMC bevacizumab assessment in 2016⁶⁸ assuming no treatment effect				
Pre-progression	0.79	0.08	0.79	0.02
Post-progression	0.63	0.06	0.63	0.06
Utility values from clinical expert input based on EMPOWER Cervical-1 trial utilities				
Pre-progression	0.74	0.02	0.50	0.05
Post-progression	0.61	0.02	0.42	0.04

3.5 Cost and healthcare resource use identification, measurement and valuation

Direct medical costs incorporated in the model included:

- Drug acquisition and administration costs
- Subsequent treatment costs

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- Disease management costs
- Adverse event costs.

3.5.1 Resource identification, measurement and valuation studies

To understand the current evidence base and the economic impact on patients who have failed prior platinum treatment for metastatic or recurrent cervical cancer, a systematic literature review of health care resource use and costs was conducted. No studies assessing UK resource use or costs for patients with recurrent, persistent and/or metastatic cervical cancer who have progressed on, or after platinum-based therapy was identified. See the SLR report for further details, supplied as Appendix G.

3.5.2 Intervention and comparators' costs and resource use

The list price of cemiplimab is £4,650, as obtained from the British National Formulary (BNF). Within the NHS, cemiplimab has a ■■■% simple PAS discount. To reflect true costs for the NHS, the current net price of £■■■■, which includes the existing PAS discount, is used in the base case analysis and sensitivity and scenario analyses. Results using the list price are also reported in Appendix O.

Cemiplimab is administered once every 21-day cycle at a flat dose of 350mg.

The chemotherapy drug costs were obtained from the Drugs and pharmaceutical electronic market information tool (eMIT)⁷¹ according to the NICE Reference case¹⁴ (Table 31). As multiple strengths and vial sizes are available for the drugs contained in the comparator chemotherapy basket, the lowest per mg costs of these drugs were used. In scenario analyses, the use of the average and the use of the highest chemotherapy drug costs were also tested. (Please see Appendix P for more details.)

For treatments included in the EMPOWER Cervical-1 trial, the trial dosing regimen was used (Table 32).¹² For treatments not included in the trial, clinical expert recommendation^{6-8,51} and NHS treatment protocols were used.

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Table 31. Unit costs associated with the technology and comparator chemotherapies in the economic model (£)

Items	Intervention (cemiplimab 350mg)	Pemetrexed	Gemcitabine	Topotecan	Irinotecan	Reference in submission
Technology cost	██████*	0.05**	0.01**	10.41**	0.03**	Section 3.5.2 Appendix I
Mean cost of technology treatment per administration^	██████*	40.9	18.0	17.3	5.5	Section 3.5.2 Appendix J
Administration cost per administration	152.13	152.13	152.13	152.13	152.13	Section 3.5.2
Monitoring cost	0	0	0	0	0	NA
Tests	0	0	0	0	0	NA
Total	██████	193.03	170.13	169.43	157.63	-
	Vinorelbine	Paclitaxel	Carboplatin + pegylated liposomal doxorubicin	Carboplatin + gemcitabine	Carboplatin	Reference in submission
Technology cost	0.35**	0.06**	0.03 and 5.68**	0.03 and 0.01**	0.03**	Section 3.5.2 Appendix I
Mean cost of technology treatment per administration^	17.5	8.3	24.7 and 282.4	19.8 and 18.0	24.7	Section 3.5.2 Appendix J
Administration cost per administration	152.13	152.13	201.66	201.66	152.13	Section 3.5.2
Monitoring cost	0	0	0	0	0	NA

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Tests	0	0	0	0	0	NA
Total	169.63	160.43	508.76	Total per administration cost cannot be estimated, as each drug has a different dosing schedule	176.83	-

*Includes simple PAS discount

**Lowest costs per mg.

^Relative dose intensity in Table 33 is not included in these numbers

Source for chemotherapy costs: eMIT 2025⁷¹, source for administration costs: NHS Reference costs 2023/24⁷²

Table 32. Dosing regimens for comparator chemotherapies (including regimens included in scenario analysis)

Regimen	Dose			Source
	Mg/administration	Per	Dosing schedule	
Pemetrexed	500.00	mg/m2	Once every cycle	Tewari et al 2022 ³⁰
Gemcitabine	1,000.00	mg/m2	Day 1 & 8	Tewari et al 2022 ³⁰
Topotecan	1.00	mg/m2	Day 1-5	Tewari et al 2022 ³⁰
Irinotecan	100.00	mg/m2	Days 1, 8, 15, 22, then 10-14-day rest	Tewari et al 2022 ³⁰
Vinorelbine	30.00	mg/m2	Day 1 & 8	Tewari et al 2022 ³⁰
Paclitaxel	80.00	mg/m2	Day 1,8,15	NHS Chemotherapy protocol ⁷³
Carboplatin in combination with pegylated liposomal doxorubicin				
Carboplatin	750.00*	Flat dose	Day 1	NHS Chemotherapy protocol ⁷⁴
Pegylated liposomal doxorubicin	30.00	mg/m2	Day 1	
Carboplatin in combination with gemcitabine				
Carboplatin	600.00^	Flat dose	Day 1	NHS Chemotherapy protocol ⁷⁵
Gemcitabine	1,000.00	mg/m2	Day 1 & 8	
Carboplatin monotherapy	750.00*	Flat dose	Day 1	NHS Chemotherapy protocol ⁷⁶

NOTE: Calvert equation used for calculating carboplatin dose (mg) = AUC (CrCl +25), with CrCl assumed to be 125 based on the clinical expert's estimation.

In the base case, wastage was not taken into consideration in the model for any of the treatments examined. As cemiplimab is administered as a flat dose, no wastage is assumed. For chemotherapy, because all the drugs are commonly used in multiple indications, vials are assumed to be shared between patients suffering from other cancer types. As vial sharing might not be practiced in every situation, assuming no wastage for chemotherapy is likely to underestimate the comparator costs, resulting

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in conservative cost-effectiveness estimates for cemiplimab. Wastage for chemotherapy has been included in scenario analysis.

Relative dose intensity (RDI) is included to reflect the drug usage associated with the efficacy and safety outcomes in the EMPOWER Cervical-1 trial¹² (Table 33). For chemotherapies not included in the trial, the average chemotherapy RDI (■%) from the trial was assumed in the model.

The unit costs of administering each drug in the model were taken from the National schedule of NHS costs (2023/24).⁷² For monotherapies (including cemiplimab), a unit cost of delivering simple parenteral chemotherapy (Outpatient code SB12Z) of £152.13 was used in line with TA939⁵. For combination therapies, the unit cost of delivering complex parenteral chemotherapy (Outpatient code SB13Z) of £201.66 was implemented.

No additional biomarker testing or monitoring are required. Regular monitoring costs are included in the health state costs in Section 3.5.3. The cost of enrolling in clinical trials and the costs of receiving best supportive care are assumed to be £0.

Table 33. Relative dose intensity (% achieving) in the EMPOWER Cervical-1 trial¹²

Level of RDI	Point estimate used*	Cemiplimab	Pemetrexed	Topotecan	Irinotecan	Gemcitabine	Vinorelbine
<60%	60%	■	■	■	■	■	■
60-80%	70%	■	■	■	■	■	■
80-100%	90%	■	■	■	■	■	■
>100%	100%	■	■	■	■	■	■
Average		■	■	■	■	■	■

Abbreviations: RDI, relative dose intensity

*For the bottom and top category, conservative point estimates were used.

3.5.3 Health-state unit costs and resource use

Routine care costs were estimated for four time periods in the model:

- Pre-progression on treatment per cycle (per week)
- Pre-progression off-treatment per cycle (per week)
- Post-progression per cycle (per week)
- End-of-life (defined as the last 30 days of life).

Due to lack of published data, resource use associated with each of the health states was obtained from the clinical experts from England and Wales (Table 34, Table 35)⁷⁷⁻⁸⁰, and unit costs taken from the Personal and Social Services Research Unit (PSSRU)⁸¹ and the National schedule of NHS costs (2023/24).⁷² Where more than one HRG code was relevant, a weighted average cost was estimated using the number of activities within each code. Detailed information on the interviews with clinical experts is available in the questionnaire documents as cited in the references, and unit costs and cost calculations are available in Appendix J. The summary of disease management costs by health states is presented in Table 36.

Table 34. Resource use based on UK clinical expert input – cemiplimab

Activity	Pre-progression On treatment		Pre-progression Off treatment		Post-progression		End-of life (last 30 days of life)	
	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year
Hospital based visits								
Gynaecologist	0%	0.00	0%	0.00	1%	1.00	0%	0.00
Oncologist (face-to-face)	100%	16.77	100%	13.42	50%	17.02	0%	0.00
Oncologist (non-face-to-face)	0%	0.00	0%	0.00	1%	1.00	0%	0.00
Specialist nurse	45%	8.20	45%	8.20	25%	1.50	5%	1.00
Community based care								
GP	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Nurse	24%	26.09	24%	26.09	25%	0.00	33%	0.00
Pain specialist	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Specialist nurse	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Palliative care team	41%	33.03	41%	33.03	95%	86.25	97%	365.25
Imaging								
CT scan	100%	4.66	75%	4.55	55%	3.95	0%	0.00
ECG	25%	1.00	25%	1.00	0%	0.00	0%	0.00
Lab tests								
Complete blood count	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Hepatic function	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Renal function	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Cortisol	75%	15.46	50%	14.49	45%	12.93	0%	0.00
Glucose, HBA1C	25%	17.39	0%	0.00	0%	0.00	0%	0.00
Thyroid	100%	17.39	75%	17.39	45%	12.93	0%	0.00
Magnesium	25%	17.39	25%	17.39	10%	17.39	0%	0.00

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, general practitioner

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Table 35. Resource use based on UK clinical expert input – Chemotherapy

Activity	Pre-progression On treatment		Pre-progression Off treatment		Post-progression		End-of life (last 30 days of life)	
	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year	Proportion of patients	Frequency per year
Hospital based visits								
Gynaecologist	0%	0.00	0%	0.00	1%	1.00	0%	0.00
Oncologist (face-to-face)	100%	16.77	100%	13.42	50%	17.02	0%	0.00
Oncologist (non-face-to-face)	0%	0.00	0%	0.00	1%	1.00	0%	0.00
Specialist nurse	70%	17.06	70%	17.06	35%	18.14	5%	1.00
Community based care								
GP	0%	0.00	0%	0.00	25%	0.00	33%	0.00
Nurse	24%	26.09	24%	26.09	0%	0.00	0%	0.00
Pain specialist	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Specialist nurse	0%	0.00	0%	0.00	25%	0.00	33%	0.00
Palliative care team	41%	33.03	41%	33.03	95%	86.25	97%	365.25
Imaging								
CT scan	100%	4.66	75%	4.55	55%	3.95	0%	0.00
ECG	25%	1.00	25%	1.00	0%	0.00	0%	0.00
Lab tests								
Complete blood count	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Hepatic function	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Renal function	100%	17.39	75%	17.39	30%	17.39	0%	0.00
Cortisol	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Glucose, HBA1C	25%	17.39	0%	0.00	0%	0.00	0%	0.00
Thyroid	0%	0.00	0%	0.00	0%	0.00	0%	0.00
Magnesium	25%	17.39	25%	17.39	10%	17.39	0%	0.00

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, general practitioner

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Table 36. Disease management costs

Intervention	Per cycle cost (£ per week)						One-off cost	
	Pre-progression on treatment		Pre-progression off treatment		Post-progression		End-of-Life (30 days)	
	Mean	Standard error	Mean	Standard error	Mean	Standard error	Mean	Standard error
Cemiplimab	118.17	11.82	100.82	10.08	185.50	18.55	627.83	62.78
Chemotherapy	131.85	13.19	115.54	11.55	196.63	19.66	627.83	62.78

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, general practitioner

3.5.4 Adverse reaction unit costs and resource use

In the model, all patients with grade 3 and higher TEAEs were assumed to be treated in hospital. Hospitalisation costs were taken from the National schedule of NHS costs 2023/24⁷² using total HRGs (Table 37). Where multiple HRG codes are relevant, weighted average costs were estimated using unit costs and the frequency of activity. Details of the calculations can be found in Appendix J.

Table 37. Adverse event costs⁷²

Adverse event	Unit cost (£)	Reference
Abdominal pain	728.07	Weighted average of costs for HRG code FD05A and FD05B : Abdominal Pain w/wo Interventions
Alanine aminotransferase increased	2,318.25	Weighted average of costs for HRG code GC17: Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions
Anaemia	858.34	Weighted average of costs for HRG code SA04G, SA04H, SA04J, SA04K & SA04L : Iron Deficiency Anaemia
Arthralgia	1,399.81	Weighted average of costs for HRG code HD26: Musculoskeletal Signs or Symptoms
Aspartate aminotransferase increase	2,318.25	Assumed same as alanine aminotransferase increased
Asthenia	1,345.20	Assumed same as pyrexia
Back pain	1,334.39	Weighted average of costs for HRG code HC32G, HC32H, HC32J and HC32K : Low back pain w/wo Interventions
Blood creatinine increased	2,318.25	Assumed same as alanine aminotransferase increased
Constipation	2,012.65	Weighted average of HRG code FD10A:FD10M : Non-Malignant Gastrointestinal Tract Disorders w/wo Interventions
Cough	856.81	Weighted average of costs for HRG code DZ19H:DZ19N : Other Respiratory Disorders w/wo Interventions
Decreased appetite	2,012.65	Assumed same as constipation
Diarrhoea	2,012.65	Assumed same as constipation
Dyspnoea	856.81	Assumed same as cough
Fatigue	1,345.20	Assumed same as pyrexia
Headache	848.08	Weighted average of costs for HRG code AA31C-AA31E: Headache, Migraine or Cerebrospinal Fluid Leak
Hydronephrosis	5,858.57	Weighted average of costs for HRG code LA09J-LA09L: General Renal Disorders with Interventions

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Adverse event	Unit cost (£)	Reference
Hyperglycaemia	633.91	Weighted average of costs for HRG code WH13A:WH13C : Abnormal Findings without Diagnosis, w/wo interventions
Hypoalbuminemia	1,534.73	Assumed same as leukopenia
Hypokalaemia	1,534.73	Assumed same as leukopenia
Hypothyroidism	1,121.30	Weighted average of costs for HRG code KA07 : Non-Surgical Thyroid Disorders
Insomnia	969.73	Weighted average of costs for HRG code AA43: Sleep Disorders, excluding Sleep Apnoea
Leukopenia	1,534.73	Weighted average of costs for HRG code SA08: Other Haematological or Splenic Disorders
Nausea	2,012.65	Assumed same as constipation
Neutropenia	2,398.15	Weighted average of costs for HRG code SA35A:SA35E : Agranulocytosis
Neutrophil count decreased	2,398.15	Assumed same as neutropenia
Oedema peripheral	732.60	Weighted average of costs for HRG code WH10: Unspecified Oedema
Pain in extremity	1,399.81	Assumed same as back pain
Pelvic Pain	1,491.27	Weighted average of costs for HRG code MB09A : Non-Malignant Gynaecological Disorders w/wo Interventions
Pruritus	600.40	Assumed same as rash
Pyrexia	1,345.20	Weighted average of costs for HRG code WJ07A:WJ07D : Fever of Unknown Origin w/wo Interventions
Rash	600.40	HRG code JD07K: Skin Disorders without Interventions
Stomatitis	1,346.14	HRG code CB02A-CB02F : Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, w/wo Interventions
Thrombocytopenia	1,033.62	Weighted average of costs for HRG code SA012: Thrombocytopenia
Urinary tract infection	2,290.61	Weighted average of costs for HRG code LA04 : Kidney or Urinary Tract Infections, w/wo Interventions
Vomiting	2,012.65	Weighted average of costs for HRG code FD10A:FD10M : Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions
White blood cell count decreased	1,534.73	Assumed same as leukopenia

Abbreviations: HRG, healthcare resource group

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3.5.5 Miscellaneous unit costs and resource use

3.5.5.1 Subsequent treatment costs

As with 2L treatments, there is no routine standard of care in 3rd or subsequent line treatment. According to the clinical experts interviewed from England and Wales, treatment options in the 3L setting and beyond in the UK consist of (Table 38):^{6-8,51}

- Single-agent chemotherapies such as weekly paclitaxel, topotecan and carboplatin
- Potential rechallenge with platinum-based chemotherapy including carboplatin monotherapy or combination therapies for selected patients (carboplatin in combination with gemcitabine or with paclitaxel).
- Best supportive care
- Clinical trials.

The choice of chemotherapy varies by clinician.^{6-8,51}

Table 38. Subsequent treatments following 2L therapy^{6-8,51}

Regimen	% of patients receiving treatment	
	Cemiplimab	Chemotherapy
Carboplatin in combination with paclitaxel	13.8%	12.5%
Carboplatin in combination with gemcitabine	7.5%	6.3%
Carboplatin	1.9%	1.9%
Paclitaxel	21.3%	6.3%
Topotecan	5.0%	5.0%
Clinical trial or BSC	50.6%	68.1%

Abbreviations: BSC, best supportive care

Similarly to comparator chemotherapies, the drug costs for subsequent treatments were obtained from the eMIT database,⁷¹ using mean cost per mg (Table 31), and the dosing was based on the EMPOWER Cervical-1 trial (for topotecan)³⁰ and NHS chemotherapy protocols^{73,75,76,82} (Table 39). The cost of enrolling in clinical trials and the costs of receiving best supportive care is assumed to be £0.

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The cost of subsequent treatments has been included as a lump sum cost occurring at the time of progression, corresponding to the time at which patients would initiate subsequent treatments. The lump sum cost was estimated for each comparator as the weighted average of the cost of each therapy per cycle, the length of the treatment and the proportion of patients receiving it after progression on each comparator. The subsequent costs estimated by this approach were £133.75 for cemiplimab and £103.97 for the comparator chemotherapy arm.

Table 39. Dosing regimens for subsequent chemotherapies

	Dose (mg)		Administration	Treatment	Cycle
	mg	per	per cycle	duration	length
				(cycle)	(days)
Carboplatin in combination with paclitaxel					
Carboplatin	750.00	Flat dose	1	6.00	21
Paclitaxel	175.00	mg/m2	1	6.00	21
Carboplatin in combination with gemcitabine					
Carboplatin	600.00	Flat dose	1	6.00	21
Paclitaxel	1,000.00	mg/m2	2	6.00	21
Carboplatin	750.00	Flat dose	1	6.00	21
Paclitaxel	80.00	mg/m2	3	6.00	21
Topotecan	1.50	mg/m2	5	6.00	21

NOTE: Calvert equation used for calculating carboplatin dose (mg) = AUC (CrCl +25), with CrCl assumed to be 125 based on the clinical expert's estimation.

Sources: EMPOWER Cervical-1 trial (for topotecan)³⁰ and NHS chemotherapy protocols^{73,75,76,82}

3.6 Severity

With an absolute severity shortfall of 14.61 QALYs and a proportional shortfall of 0.96 QALY, cemiplimab meets the criteria for a severity weight of 1.7.

The severity shortfall calculations were conducted in line with the NICE TSD23⁸³ and the accompanying DSU severity shortfall calculator.⁸⁴ Patient characteristics and discount rate used in the analysis were consistent with those informing the base-case economic analysis (Table 40). Utility values and LYs for current clinical practice for patients with recurrent, persistent and/or metastatic CC who have progressed on or after platinum-based therapy, and who have not received prior immunotherapy,

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were from the base case cost-effectiveness analysis (Table 41). For the general population, life tables were from the ONS National Life Tables for England and Wales (for the years 2021-2023),⁵⁹ and utility data were from Ara & Brazier 2011.⁷⁰ No QALY shortfall calculation is available from previous evaluations in this disease area.

Table 40. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution (female)	100%	2.6.1
Starting age	51 (Table 20)	3.3.1

Table 41. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Pre-progression	0.62 (0.02)	0.41
Post-progression	0.52 (0.05)	0.71
End-of-life	0.09 (0.01)	

Table 42. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
15.18	0.57	Absolute: 14.61 Proportional: 0.96

For the list of assumptions, please see Section 3.7.2.

3.7 Summary of base-case analysis inputs and assumptions

3.7.1 Summary of base-case analysis inputs

Table 43 describes the variables applied in the economic model.

Table 43. Summary of variables applied in the base case economic model

Variable	Value	Standard error	Distribution	Reference to section in submission
Discount Rate costs	0.035	NA	NA	3.2.5
Discount Rate health outcomes	0.035	NA	NA	3.2.5
Mean age	51.14	0.47	Normal	3.3.1
Mean body surface area (BSA)	1.66	0.01	Normal	
Mean body weight	63.87	0.66	Normal	
Cemiplimab cost per vial		NA	NA	3.5.2
Pemetrexed cost per administration	40.94	4.09	Gamma	3.5.2
Gemcitabine cost per administration	18.02	1.80	Gamma	3.5.2
Topotecan cost per administration	17.26	1.73	Gamma	3.5.2
Irinotecan cost per administration	5.50	0.55	Gamma	3.5.2
Vinorelbine cost per administration	17.46	1.75	Gamma	3.5.2
Paclitaxel cost per administration	8.29	0.83	Gamma	3.5.2
Carboplatin + doxorubicin pegylated liposomal cost per administration	0.00	0.00	Gamma	3.5.2
Carboplatin cost per administration	24.69	2.47	Gamma	3.5.2
Doxorubicin pegylated liposomal cost per administration	282.40	28.24	Gamma	3.5.2
Carboplatin + gemcitabine cost per administration	0.00	0.00	Gamma	3.5.2
Carboplatin cost per administration	19.75	1.98	Gamma	3.5.2
Gemcitabine cost per administration	18.02	1.80	Gamma	3.5.2
Carboplatin cost per administration	24.69	2.47	Gamma	3.5.2
Clinical trials cost per administration	0.00	0.00	Gamma	3.5.2

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Variable	Value	Standard error	Distribution	Reference to section in submission
Cemiplimab routine care costs pre-progression on treatment	118.17	11.82	Gamma	3.5.3
Chemotherapy routine care costs pre-progression on treatment	131.85	13.19	Gamma	3.5.3
Cemiplimab routine care costs pre-progression off treatment	100.82	10.08	Gamma	3.5.3
Chemotherapy routine care costs pre-progression off treatment	115.54	11.55	Gamma	3.5.3
Cemiplimab routine care costs post-progression off treatment	185.50	18.55	Gamma	3.5.3
Chemotherapy routine care costs post-progression off treatment	196.63	19.66	Gamma	3.5.3
Cemiplimab End of life costs	627.83	62.78	Gamma	3.5.3
Chemotherapy End of life costs	627.83	62.78	Gamma	3.5.3
Cemiplimab AE costs	722.15	72.21	Gamma	3.5.4
Chemotherapy AE costs	1,100.27	110.03	Gamma	3.5.4
Distribution of chemotherapy comparators: Pemetrexed percentage	36.51%	0.04	Beta	3.2.6
Distribution of chemotherapy comparators: Gemcitabine percentage	39.80%	0.04	Beta	3.2.6
Distribution of chemotherapy comparators: Topotecan percentage	6.91%	0.01	Beta	3.2.6
Distribution of chemotherapy comparators: Irinotecan percentage	6.25%	0.01	Beta	3.2.6
Distribution of chemotherapy comparators: Vinorelbine percentage	10.53%	0.01	Beta	3.2.6

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Variable	Value	Standard error	Distribution	Reference to section in submission
Utility pre -progression: Cemiplimab	0.74	0.02	Beta	3.4.5
Utility pre -progression: Chemotherapy	0.62	0.02	Beta	3.4.5
Utility post -progression: Cemiplimab	0.61	0.02	Beta	3.4.5
Utility post -progression: Chemotherapy	0.52	0.05	Beta	3.4.5
Utility end of life	0.09	0.01	Beta	3.4.5
Cemiplimab PFS Generalised Gamma	See Appendix M for details		Multivariate Normal	3.3.2
Cemiplimab OS Generalised Gamma			Multivariate Normal	3.3.2
Cemiplimab TOT Log-normal			Multivariate Normal	3.3.2
Chemotherapy PFS Generalised Gamma			Multivariate Normal	3.3.2
Chemotherapy OS Generalised Gamma			Multivariate Normal	3.3.2
Chemotherapy TOT Log-normal			Multivariate Normal	3.3.2

Abbreviations: AE, adverse event; BSA, body surface area; NA, not applicable; OS, overall survival; PFS, progression-free survival; TOT, time on treatment

3.7.2 Assumptions

Table 44 provides a summary of the main assumptions and their rationale.

Table 44. Main assumptions

Description	Justification
Costs and utilities are driven by progression status	In line with previous CEM in similar patient population. ⁵ Utilities in the EMPOWER Cervical-1 trial reduce after progression (see Appendix N). Assumption was validated by clinical experts from the UK. ^{6-8,51}
The patient population of the EMPOWER Cervical-1 trial can be generalized to the clinical practice in England and Wales	Assumption validated by clinical experts from England and Wales. ^{6-8,51} The EMPOWER Cervical-1 study also included two UK sites ¹² .
The efficacy and safety of the chemotherapy arm of the EMPOWER Cervical-1 trial can be generalized to that of chemotherapies used in England and Wales	According to clinical experts from England and Wales. ^{6-8,51} survival and progression-free survival predictions for chemotherapy from the EMPOWER Cervical-1 trial are representative of outcomes with chemotherapy regimens used in clinical practice in England and Wales.
Progression-free survival from the pivotal EMPOWER Cervical-1 trial can be extrapolated to a lifetime horizon using separately fitted generalised gamma distribution for all comparators	The proportional hazard assumption did not appear to hold, so independently fitted survival curves were most appropriate. The generalized gamma model presented the best statistical and visual fit and its predictions were aligned with the clinical expert expectations (Appendix L). Alternative distribution was tested in scenario analyses.
Overall survival from the pivotal EMPOWER Cervical-1 trial can be extrapolated to a lifetime horizon using separately fitted generalised gamma distribution for all comparators	The proportional hazard assumption did not appear to hold, so independently fitted survival curves were most appropriate. The generalised gamma model had a good statistical and visual fit, and its predictions were aligned with the clinical expert expectations (see Appendix L). Alternative distribution was tested in scenario analyses.
Time-on-treatment curves from the pivotal EMPOWER Cervical-1 trial can be extrapolated to a lifetime horizon using separately fitted log-normal distribution for all comparators	The proportional hazard assumption did not appear to hold, so independently fitted survival curves were most appropriate. The log-normal model had the best statistical and visual fit for cemiplimab and chemotherapy (see Appendix L).

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Description	Justification
Utilities are higher for cemiplimab than for chemotherapy in both pre- and post-progression.	Pre-progression: Mapped utilities from the EMPOWER Cervical-1 trial in the pre-progression health state showed statistically significant difference between treatment arms across all visits (mean difference: [REDACTED], 95% CI: [REDACTED]), with cemiplimab associated with higher utilities. Post-progression: [REDACTED]% of all post-progression observations were in the cemiplimab arm; in the chemotherapy arm only [REDACTED] patients had data for the second visit and <[REDACTED] patients beyond the fourth visit (see Appendix N). Pooled utility value had face validity issues for chemotherapy. Clinical experts confirmed that utilities would be higher for patients treated with immunotherapies compared to those treated with chemotherapies, due to the difference in lingering toxicities in both pre- and post-progression.^{6-8,51}

Abbreviations: CEM, cost-effectiveness model; CI, confidence interval

3.8 Base-case results

Results are presented discounted and using the currently available [REDACTED]% PAS discount price for cemiplimab (Table 45). Compared to chemotherapy, cemiplimab resulted in 1.02 discounted additional LYs. The additional LYs are mainly driven by the increased pre-progression period due to the better PFS results with cemiplimab (Appendix M). This is reflected in the QALY results, where cemiplimab resulted in 0.79 discounted QALY gained.

Compared with chemotherapy, the total incremental cost associated with cemiplimab treatment is £[REDACTED]. The total incremental costs are driven by the drug acquisition costs ([REDACTED]); cemiplimab has a higher drug acquisition cost than the comparator chemotherapies, which are mostly generic, and a longer duration of treatment due to its greater efficacy (mean modelled ToT [REDACTED] months vs. [REDACTED] months with cemiplimab and chemotherapy, respectively). Additionally, the increased life expectancy came with increased routine care costs due to the greater efficacy in

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preventing disease progression and prolonging survival with cemiplimab. These are partially offset by savings in TEAE costs (Appendix H).

These incremental costs and QALYs resulted in an ICER (without application of the severity weighting) of £[REDACTED]/QALY gained at the [REDACTED]% PAS discount price of cemiplimab, with a NHB of [REDACTED] QALYs at the £30,000/QALY threshold (Table 45).

With application of the 1.7 severity weighting estimated in Section 3.6, the ICER is £[REDACTED]/QALY gained using the available [REDACTED]% PAS price discount, with a NHB of [REDACTED] QALYs at the £30,000/QALY threshold (Table 46).

Net health benefit (without and with severity weighting) is presented in Table 47 and Table 48, respectively.

Disaggregated results are presented in Appendix H. Summary results based on the list price are presented Appendix O.

Table 45. Discounted base-case results with the existing [REDACTED] PAS price discount (without severity weighting).

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Cemiplimab	[REDACTED]	2.09	1.36				
Chemotherapy	12,247	1.08	0.57	[REDACTED]	1.02	0.79	[REDACTED]

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

Table 46. Discounted base-case results with the existing [REDACTED] PAS price discount and severity weighting.

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Cemiplimab	[REDACTED]	2.09	2.31				
Chemotherapy	12,247	1.08	0.96	[REDACTED]	1.02	1.34	[REDACTED]

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

Table 47. Net health benefit (without severity weighting).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Cemiplimab	[REDACTED]	1.36				
Chemotherapy	12,247	0.57	[REDACTED]	0.79	[REDACTED]	[REDACTED]

Abbreviations: NHB, net health benefit; QALYs, quality-adjusted life years

Table 48. Net health benefit (with severity weighting).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Cemiplimab		2.31				
Chemotherapy	12,247	0.96		1.34		

Abbreviations: NHB, net health benefit; QALYs, quality-adjusted life years

3.9 Exploring uncertainty

In line with the ISPOR-SMDM and the NICE Reference case,^{14,85} various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including:

- Parameter uncertainty
- Structural uncertainty
- Methodological uncertainty.

Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess parameter uncertainty; scenario analyses were performed to explore both structural and methodological uncertainty.

3.9.1 Probabilistic sensitivity analysis

PSA was performed to account for joint parameter uncertainty. The probabilistic analyses were run for 1,500 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs, LYs and QALYs. Inputs with parameter uncertainty were varied simultaneously and independently of one another.

Beta distributions were selected for utilities and percentages due to the bounds of the distribution (i.e., 0 to 1 and 0% to 100%). Standard errors were used as the source of variation to calculate alpha and beta parameters of the distribution. Gamma distribution was chosen for subsequent treatment costs, administration costs, routine care costs, and AEs costs. Parametric distributions were varied using the means and variance-covariance matrices of the parameters applying the Cholesky decomposition method⁶¹ to help account for the correlation between parameters. Normal distribution was chosen for all other parameters. Parameters and distributions used are described in Table 43.

Since time horizon and discount rates are not subject to parameter uncertainty, they were excluded from PSA.

PSA enables the generation of cost-effectiveness acceptability curves (CEACs) which show the proportion of simulations for which the drug is found cost-effective over a range of willingness-to-pay thresholds for a QALY gain. Scatter plots were also generated, in

which the incremental health outcome gains were plotted against the incremental costs of cemiplimab versus chemotherapy on the cost-effectiveness plane.

3.9.1.1 Results

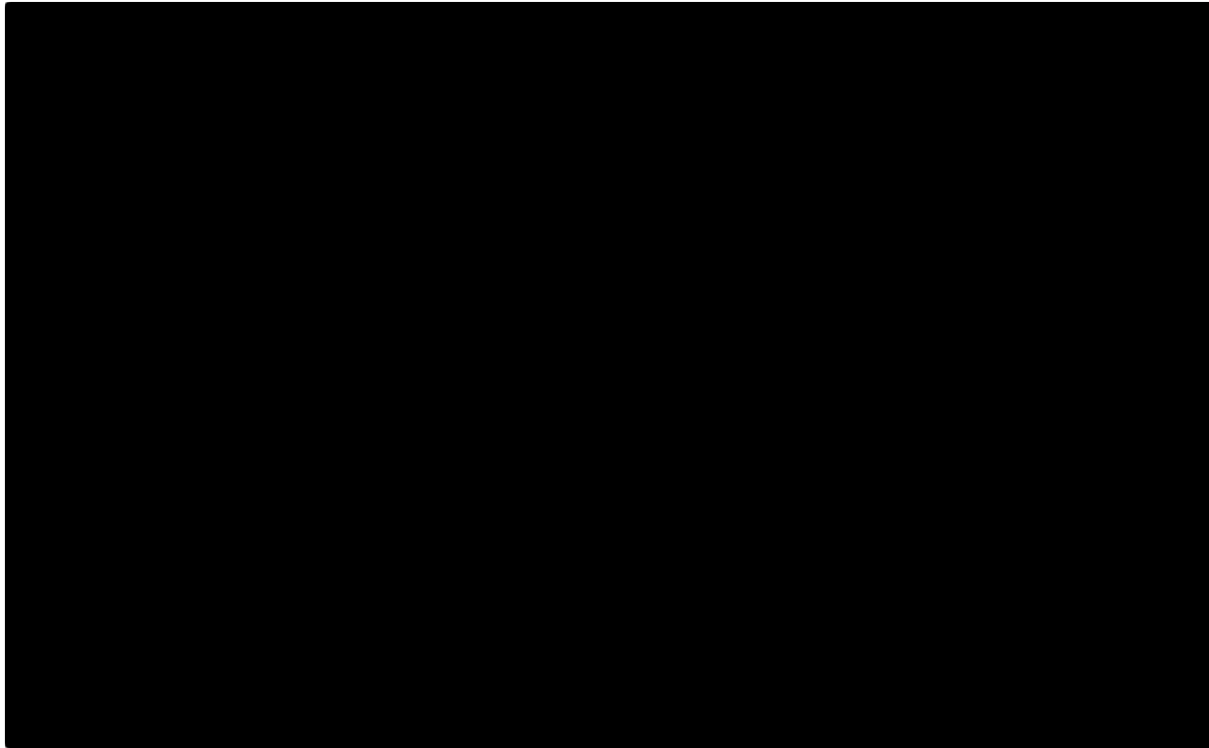
The mean probabilistic results are presented in Table 49 and are highly consistent with the deterministic results.

Table 49. Comparison of the probabilistic and deterministic results with the existing 3% PAS discount (without severity weighting).

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results	10,000	1.02	0.79	12,658
Probabilistic results	10,000	1.03	0.80	12,500

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

All simulations were in the upper right-hand quadrant of the cost-effectiveness plane, where cemiplimab is more effective and more costly than the comparator (Figure 17 and Figure 19). The probability of cemiplimab being cost-effective compared to chemotherapy at the threshold of £30,000 is 95% without application of the severity weighting (Figure 18) and 95% with the application of the severity weighting (Figure 20).



Abbreviations: QALY, quality-adjusted life year

Figure 17. Cost-effectiveness plane with the existing ■% PAS discount (without severity weighting).

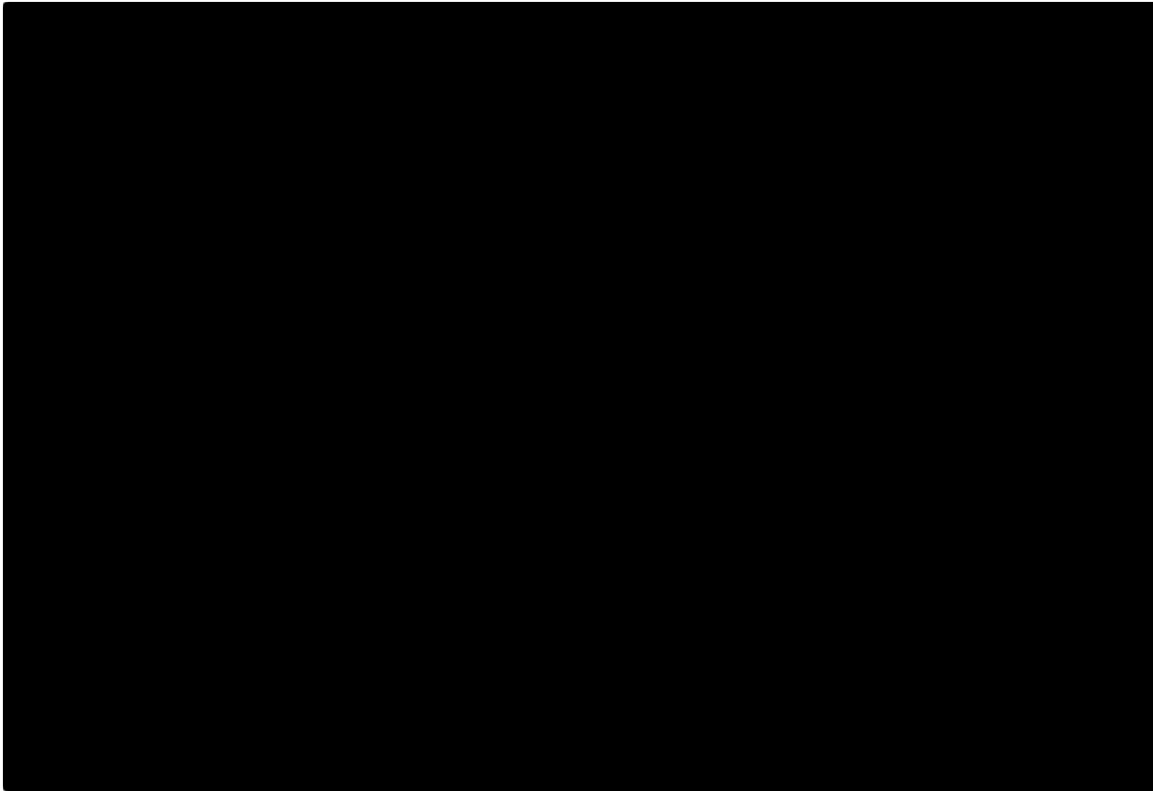


Figure 18. Cost-effectiveness acceptability curve (CEAC) with the existing 10% PAS discount (without severity weighting).

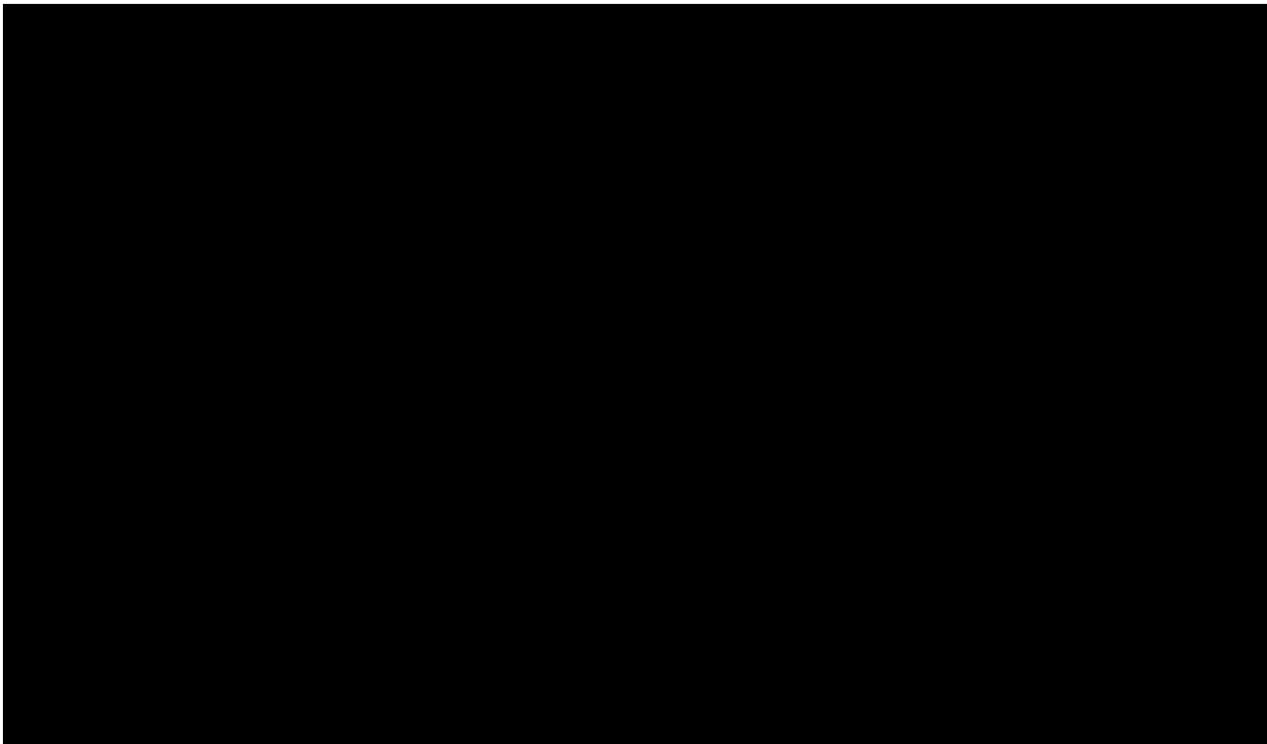


Figure 19. Cost-effectiveness plane with the existing 10% PAS discount (with severity weighting).

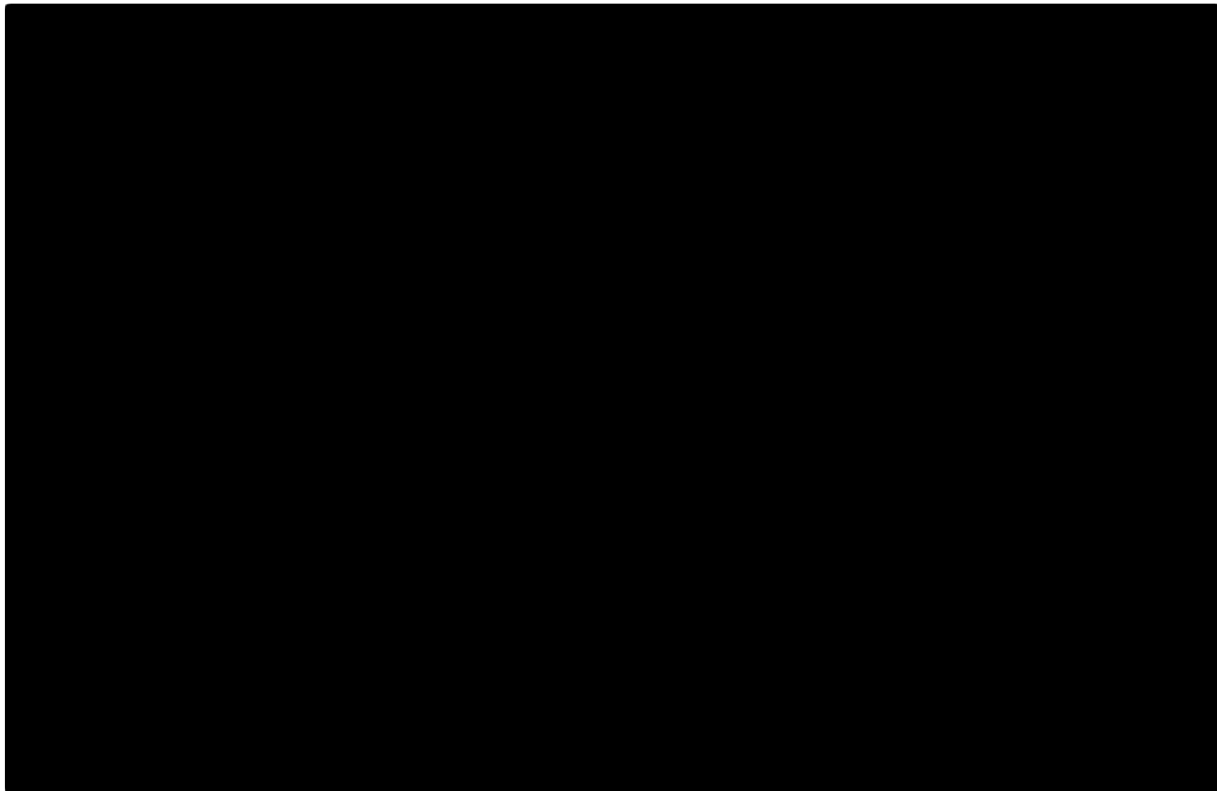


Figure 20. Cost-effectiveness acceptability curve (CEAC) with the existing 10% PAS discount (with severity weighting).

3.9.2 Deterministic sensitivity analysis

3.9.2.1 Univariate sensitivity analysis

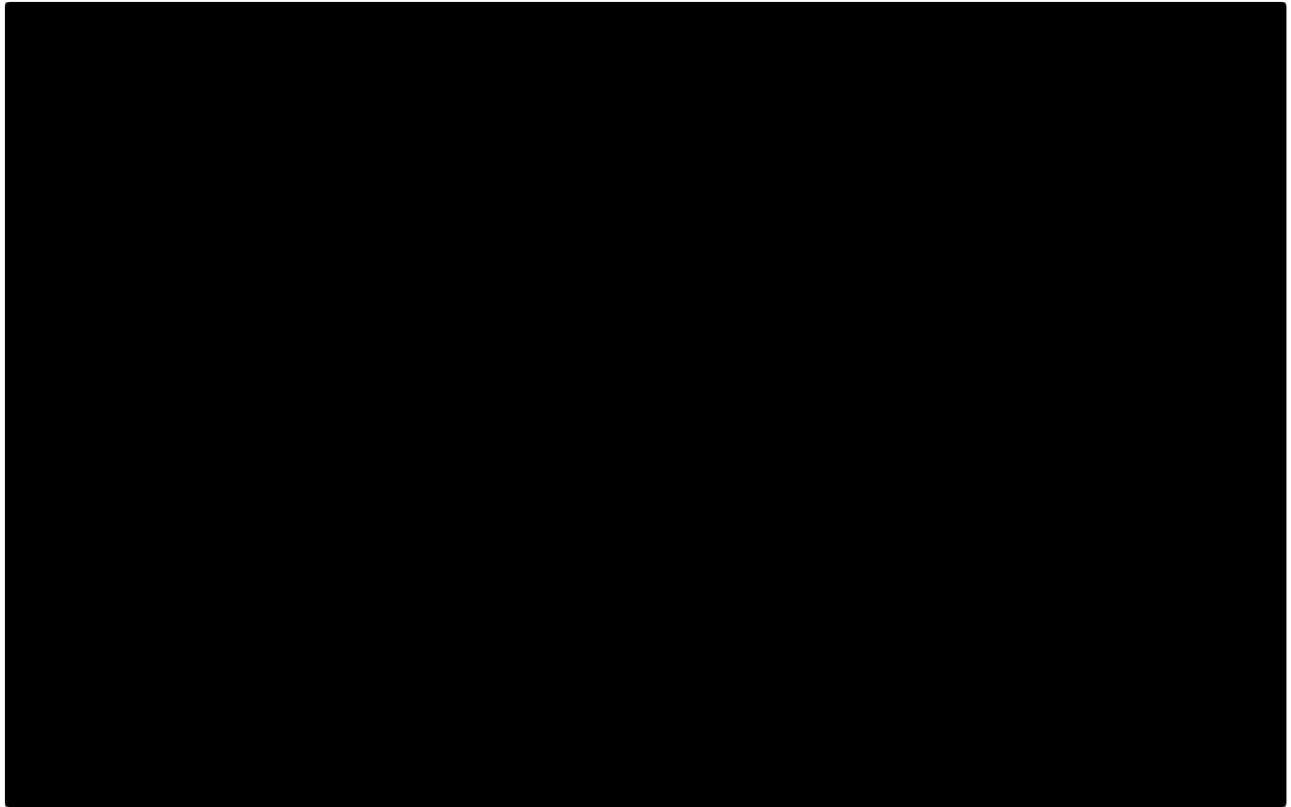
Univariate sensitivity analyses were conducted to test parameter uncertainties, by varying each parameter according to its 95% CI or standard error, while holding all other parameters constant. For those parameters without CI or standard error reported, a 10% variation of the mean estimates was assumed. All parameters with parameter uncertainty were included in these sensitivity analyses. Time-horizon and discount rates were not varied as these were not subject to parameter uncertainty; however, the impact of alternative discount rates and time horizon was examined in scenario analyses, as described below. Similarly, the cemiplimab drug cost per administration is not subject to parameter uncertainty due to the already available PAS discount, and therefore, was not varied in the univariate sensitivity analysis. Non-drug costs were included in sensitivity

analyses as health state costs and total TEAE costs, and not by their component unit costs and resource use used to estimate them.

The 10 parameters for which model results were most sensitive are depicted in a tornado diagram (Figure 21). The model parameters and associated ranges included in the analysis are described in Table 43.

3.9.2.2 Results

The univariate sensitivity analysis tested the effect of extreme (not realistic) values of all inputs with parameter uncertainty. While the ICER estimates with the extreme values are not realistic (and do not include the x1.7 severity weighting), they are useful to determine which parameters the results are most sensitive to. The results on the tornado diagram show that the ICER is most sensitive to the parameters (shape and scale) of the log-normal parametric model used to extrapolate ToT, and the utilities post-progression (Figure 21). Since ToT was almost complete, and the use of alternative utility values resulted in ICERs between £[REDACTED]-£[REDACTED] per QALY when the severity modifier is applied (see Section 3.9.3), this shows that the inputs that are most influential on the results are robust, and the results are associated with low uncertainty.



Abbreviations: TOT, time-on-treatment; PFS, progression-free survival; ICER, incremental cost-effectiveness ratio

Figure 21. Tornado diagram for ICER with the existing ■% PAS discount (without severity weighting)

3.9.3 Scenario analysis

Scenario analyses were conducted to test the robustness of the model to potential alternative structural and methodological assumptions. These include:

- alternative time horizons
- alternative discount rates
- the use of comparator chemotherapies based on clinical expert input (Table 50)
- alternative unit costs for chemotherapies (please see Appendix O)
- adding TEAE disutilities (please see Appendix O)
- the use of alternative health state utilities (Table 30)
- alternative parametric models for extrapolation
- inclusion of wastage.

Table 50. Distribution of 2L chemotherapies used in UK clinical practice according to clinical experts in England and Wales

Chemotherapies included	Percentage of patients receiving
Gemcitabine	5.0%
Topotecan	7.5%
Irinotecan	5.0%
Vinorelbine	5.0%
Weekly paclitaxel	39.0%
Carboplatin + pegylated liposomal doxorubicin	6.3%
Carboplatin + gemcitabine	6.3%
Carboplatin monotherapy	10.0%
Clinical trial or best supportive care	16.0%

Source: Mean of four clinical expert questionnaires from England and Wales^{6-8,51}

3.9.3.1 Results

Scenario analyses demonstrate that the base case model is relatively stable to alternative structural and methodological assumptions (Table 51). Material increases in the ICER only occur with less plausible or less certain assumptions than those adopted in the base case, indicating that the base case assumptions are reasonable and provide plausible estimates of the cost effectiveness of cemiplimab. With the currently available ■% PAS discount price for cemiplimab and the 1.7 severity weighting the ICER was below £22,000/QALY in all scenarios.

The scenario analyses show that (Table 51):

- Decreasing the time horizon substantially (from 33 years to 20 years or to 10 years) reduces the accrual of health benefit for cemiplimab by shortening the life-years over which patients can accumulate a health benefit, while maintaining the higher drug acquisition costs for cemiplimab that accumulate earlier in the time horizon. This therefore biases the analysis against cemiplimab, resulting in a 16% increase

in the ICER. The lifetime horizon used in the base case model remains the appropriate time horizon for decision making in this terminal disease, in line with the NICE reference case.

- Similarly, due to the early accrual of drug costs and more prolonged accrual of health benefits, changing the annual discount rate in the model affects the health benefits more than the costs. Reducing the discount rate to 0% decreases the ICER (by 13%), while increasing the discount rate to 6% increases the ICER (by 8%).
- Due to the low cost generic chemotherapies available as comparator treatments, changing the comparator drug costs has negligible effect on the ICER.
- Due to the high maturity of the OS data from the pivotal trial, selecting alternative clinically plausible parametric models to extrapolate OS changes the ICER only by 0%-7%.
- Extrapolation of ToT with a longer tail (generalised gamma model) increases the drug costs for cemiplimab, and thereby the ICER slightly (by 7%). However, the extrapolation used in the base case is the best fitting model and is most appropriate for decision making.
- Extrapolation of PFS with log-normal model (instead of the generalised gamma model adopted in the base case) increases the drug costs for cemiplimab (as PFS acts as an upper limit for ToT curves) and thereby increases the ICER (by 14%). However, the extrapolation used in the base case was the best fitting model and was confirmed by clinicians to provide clinically plausible extrapolated outcomes.
- Assuming no treatment-specific effect on patient quality of life and using only health state-specific values from the literature, despite the statistically significant difference observed between the treatment arms in the EMPOWER Cervical-1 trial and the views of clinical experts, increased the ICER by 8%. However, based on trial results and clinical expert opinion, an increase in the base case ICER due to use of alternative utility values from the literature would seem implausible.

- Using utility values suggested by the clinical experts to reflect the treatment-specific impacts on patient quality of life decreases the ICER by 12%, demonstrating that the base case approach and results could be conservative.
- Excluding RDI (i.e., assuming 100% dosing for all therapies) increases the ICER by 11% due to the higher acquisition costs of cemiplimab relative to generic chemotherapy. However, as the observed trial outcomes are linked to the observed drug exposure in the trial, assuming 100% RDI is implausible and not reflective of patient experience in trial or clinical practice settings.
- Incorporating wastage for treatments not requiring flat dosing had minimal effect, increasing the chemotherapy costs slightly, and decreasing the ICER by 1%.

Table 51. Scenario analyses with the existing ■% PAS discount (without severity weighting).

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (without severity weighting)
Base case			■	0.79	■
Model characteristics					
Time horizon	Lifetime	10 years	■	0.64	■
		20 years	■	0.69	■
Discount rate	3.5%	0%	■	1.00	■
		6%	■	0.69	■
Comparators	Single-agent chemotherapies	Combination chemotherapies	■	0.79	■
Extrapolations					
Parametric curve for OS chemotherapy	Generalised gamma	Log-normal	■	0.78	■
		Log-logistic	■	0.77	■
Parametric curve for OS cemiplimab	Generalised gamma	Log-normal	■	0.70	■
Parametric curve for ToT for both arms	Log-normal	Generalised gamma	■	0.79	■
Parametric curve for PFS for both arms	Generalised gamma	Log-normal	■	0.75	■
Costs and utilities					
		Mean cost per mg	■	0.79	■

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Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (without severity weighting)
Chemotherapy costs	Minimum costs per mg	Maximum cost per mg	██████	0.79	██████
TEAE disutilities	Excluded	Included	██████	0.79	██████
Age disutilities	Included	Excluded	██████	0.80	██████
Health state utilities	EMPOWER Cervical-1 trial utilities: treatment specific	SMC bevacizumab utilities	██████	0.73	██████
		Clinical expert input	██████	0.90	██████
RDI	Included	Excluded	██████	0.79	██████
Wastage	Excluded	Included	██████	0.79	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SMC, Scottish Medicines Consortium; TEAE, treatment-emergent adverse event; ToT, time on treatment

Table 52. Scenario analyses with the existing ■% PAS discount (with 1.7 severity weighting).

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
Base case			■	1.34	■
Model characteristics					
Time horizon	Lifetime	10 years	■	1.09	■
		20 years	■	1.28	■
Discount rate	3.5%	0%	■	1.70	■
		6%	■	1.18	■
Comparators	Single-agent chemotherapies	Combination chemotherapies	■	1.34	■
Extrapolations					
Parametric curve for OS chemotherapy	Generalised gamma	Log-normal	■	1.33	■
		Log-logistic	■	1.30	■
Parametric curve for OS cemiplimab	Generalised gamma	Log-normal	■	1.20	■
Parametric curve for ToT for both arms	Log-normal	Generalised gamma	■	1.34	■
Parametric curve for PFS for both arms	Generalised gamma	Log-normal	■	1.28	■
Costs and utilities					
		Mean cost per mg	■	1.34	■

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Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
Chemotherapy costs	Minimum costs per mg	Maximum cost per mg	██████	1.34	██████
TEAE disutilities	Excluded	Included	██████	1.35	██████
Age disutilities	Included	Excluded	██████	1.37	██████
Health state utilities	EMPOWER Cervical-1 trial utilities: treatment specific	SMC bevacizumab utilities	██████	1.24	██████
		Clinical expert input	██████	1.53	██████
RDI	Included	Excluded	██████	1.34	██████
Wastage	Excluded	Included	██████	1.34	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SMC, Scottish Medicines Consortium; TEAE, treatment-emergent adverse event; ToT, time on treatment

3.10 Subgroup analysis

In line with the NICE scope⁵⁶ and the clinician and guideline recommended positioning of cemiplimab in clinical practice, no subgroup analysis was conducted.

3.11 Benefits not captured in the QALY calculation

Carer and family benefits: Cemiplimab is proposed as a more effective and better tolerated alternative to chemotherapy in patients with r/m CC and disease progression on or after platinum-based chemotherapy, in line with its licensed indication. As the first and only alternative to chemotherapy, it provides a step-change in the 2L treatment of r/m CC. As CC affects younger women, the better efficacy and tolerability would not only result in better quality of life, but, according to the SMC PACE statement, would also allow “*young women to continue in employment or education or provide ongoing care of young dependants and elderly family members*”.⁸⁶ As a result, the benefit for carers and also family members could be “*considerable*”. These benefits of cemiplimab for patients, carers and family members are not captured in the QALY calculation.

Given that a commonly used treatment in English centres following progression on platinum-based chemotherapy is currently weekly paclitaxel, the three-weekly dosing of cemiplimab is anticipated to confer a particular advantage to patients. Weekly hospital visits are likely to be inconvenient, tiring and expensive for patients, and will often involve a burden for family members, for example the need for childcare or to accompany the patient. In addition, cemiplimab is given by a 30-minute infusion with no requirement in the SmPC for premedication,⁹ whereas paclitaxel requires IV premedication with corticosteroids, antihistamines, and H₂ antagonists and is infused over a period of 3 hours.²⁴ Thus, treatment visits for cemiplimab will be significantly shorter than those required for paclitaxel.

Service-related benefits: the less frequent (3-weekly vs weekly) and shorter (30 minutes without premedication vs 3 hours + IV premedication) administration time for cemiplimab compared with weekly paclitaxel^{9,24} will reduce the demand for chair-time in chemotherapy infusion suites, freeing up staff time and chair capacity and helping

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to reduce waiting times for IV therapies. This is an important consideration at many centres, where pressure on infusion suite capacity can result in delays for patients requiring IV treatment.

3.12 Validation

3.12.1 Validation of cost-effectiveness analysis

3.12.1.1 Conceptual validation

The major assumptions and the inputs for this submission were validated by five clinical experts from the UK, including four clinical experts from England and Wales^{6-8,51} and one expert from Scotland.⁵² An overview of the validation process is given in Appendix R.

3.12.1.2 Clinical/biological plausibility

Median results of the EMPOWER Cervical-1 trial were used for validating the survival predictions from the model, including median PFS, OS, and TOT. Additionally, median PFS and OS were compared to a published real-world study aimed at describing clinical outcomes of patients with advanced CC treated with cemiplimab in Italy (please see Appendix H).⁴¹ The survival predictions were also presented to clinical experts from England and Wales and the cemiplimab results were discussed with a US clinical expert to ensure external validity and clinical/biological plausibility (please see Appendix R).

3.12.1.3 Technical validation

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished. A model validator not involved in the original programming checked the calculation and reference formulas, and an additional team member checked the values of various model inputs. The validation report is available in Appendix Q.

3.13 Interpretation and conclusions of economic evidence

Compared to chemotherapy, cemiplimab resulted in increased duration of the progression-free time and an extended survival when used in adult patients with recurrent or metastatic CC and disease progression on or after platinum-based chemotherapy, who have not received prior immunotherapy. Cemiplimab also conferred important quality of life benefits compared with chemotherapy. With the appropriate severity weighting applied in line with the NICE Manual, the base case ICER is £[REDACTED] per QALY gained at the existing [REDACTED]% PAS price discount, which is below the lower estimate of the threshold used by NICE to indicate the cost-effective use of NHS resources. Extensive sensitivity and scenario analyses confirm the base case results are stable and robust.

In its proposed positioning, cemiplimab provides a clinically and cost-effective immunotherapy option a small group of end-of-life patients who would otherwise have only further chemotherapy available as a treatment option.

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5 Appendices

Appendices are provided in a separate Appendices document, and in stand-alone documents in the case of long reports. A table of appendices is provided below.

Appendix	Location
A1 SmPC	Standalone document
A2 EPAR	Standalone document
B Identification (clin SLR)	Standalone document
C Subgroup analyses	Main appendices document
D Adverse reactions	Main appendices document
E Published cost-effectiveness	Standalone document
F HRQoL studies	Standalone document
G Cost & HCRU studies	Within appendix E
H clinical outcomes and disaggregated results	Main appendices document
I Price details	Main appendices document
J Resource use and unit costs	Main appendices document
K TEAE disutilities	Main appendices document
L Survival analysis	Standalone document
M survival inputs	Main appendices document
N Utility mapping	Standalone document
O Cost-utility detailed results	Main appendices document
P Sensitivity analyses	Main appendices document
Q Technical validation	Main appendices document
R Clinical validation	Main appendices document

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Cemiplimab for treating recurrent or metastatic
cervical cancer that has progressed on or after
platinum-based chemotherapy: ID6610**

Summary of Information for Patients (SIP)

December 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6610_Cemiplimab_Summary info for patients		No	

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Cemiplimab (LIBTAYO®)

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

The population being appraised is adults with recurrent or metastatic cervical cancer (r/m CC) and disease progression on or after platinum-based chemotherapy. Cervical cancer that has come back after treatment is called recurrent. Metastatic means the cancer has spread to other parts of the body.

In line with European clinical guidelines,¹ and evidence from its key clinical trial,² cemiplimab is only expected to be used in NHS clinical practice in patients who have not previously received immunotherapy.

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

Cemiplimab was approved in November 2022 by the European Medicines Agency as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.³ Cemiplimab was granted its UK marketing authorisation in this indication in April 2023.

¹<https://www.ema.europa.eu/en/medicines/human/EPAR/libtayo>

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

Regeneron does not currently have any formal collaborations in place and has not provided any financial support to any cervical cancer patient groups.

SECTION 2: current landscape

2a) The condition – clinical presentation and impact

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

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

What is cervical cancer?

Cervical cancer affects the cervix (the neck of the womb that opens into the vagina) and surrounding tissues; advanced cervical cancer may also affect the bladder, ureters (tubes that carry urine from the kidneys to the bladder), and rectum (the lower part of the large intestine; the back passage). Metastatic cervical cancer means the cancer has spread to distant sites, such as the lung, liver, and bone. Cervical cancer that has come back after treatment is called recurrent.

There are two main types of cervical cancer, named after the type of cell that becomes cancerous: squamous cell carcinoma (80-90% of cases) and adenocarcinoma (10-20% of cases); 3-10% of cervical cancer cases are a mix between the two types (adenosquamous carcinoma).⁴ The two main types are treated in the same way.

In 2022, 2641 cases of cervical cancer were diagnosed in England, and an average of 685 deaths per year from cervical cancer occurred between 2017-2019.^{5,6} Approximately 850 patients per year are diagnosed with r/m CC in England. The main cause of cervical cancer is infection with human papillomavirus (HPV). Risk is increased by smoking.⁴ Cervical cancer affects a younger age group than many other cancers, with the peak age for diagnosis being 30-34 years old.⁶

Symptoms and effects on quality of life

People with r/m CC have a high and complex symptom burden, which can be severely debilitating.^{7,8} They may experience pain, fatigue, gastro-intestinal symptoms (including bowel obstruction), anorexia (loss of appetite), poor wellbeing and mental health problems (anxiety or depression).^{4,8} Many are also living with the complications of previous surgical or systemic treatment, which can include (but are not limited to) menopausal symptoms, altered body image, sexual/vaginal dysfunction, diarrhoea, lymphoedema (swelling caused by lymphatic fluid), peripheral neuropathy (damage to the nerves that carry messages of sensations to the brain), fatigue, and social difficulties.¹ In particular, platinum-based chemotherapy results in persistent peripheral neuropathy for some people.

Outlook for r/m CC

Metastatic cervical cancer is not normally curable.⁷ The EMPOWER Cervical-1 clinical trial of cemiplimab was conducted in people with r/m CC whose disease had progressed or returned on or after platinum chemotherapy. In this trial, the average (median) overall survival (time from randomisation into the trial to date of death) for people treated with current standard treatment (chemotherapy) was 8.5 months.⁹ Similarly, the European Society for Medical Oncology reported overall survival with metastatic cervical cancer on second-line therapy to range from 5.0 to 12.7 months.¹⁰

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

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

People with suspected cervical cancer have a variety of tests to confirm the diagnosis and to find out the stage of cancer, including whether the cancer has spread. These can include internal examinations, scans, and biopsies (where a small sample of tissue is taken to send to a laboratory for further testing).¹¹ Identification of people who would be eligible for treatment with cemiplimab does not require any additional diagnostic tests beyond those that are already routinely carried out.

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

People whose cancer cells are positive for a protein called PD-L1 usually have chemotherapy plus the immunotherapy drug pembrolizumab as their first treatment for r/m CC. For people not eligible to receive pembrolizumab, r/m CC is usually treated with platinum-based chemotherapy as a first treatment. This is usually a combination of a platinum drug and paclitaxel, with or without the targeted cancer drug bevacizumab.⁷

R/m CC is not currently curable, and unfortunately, for most people it will eventually come back or progress after first treatment. There is currently no single recommended treatment for cervical cancer that has progressed on or after platinum-based chemotherapy. Options are limited to various single or combination chemotherapy drugs.⁷ There is currently no alternative to further chemotherapy.

Cemiplimab is approved for the treatment of adult patients with r/m CC and disease progression on or after platinum-based chemotherapy.¹² It is only expected to be used in patients who have not previously had an immunotherapy drug, in line with the patient population in the EMPOWER-Cervical 1 trial and clinical guidelines.^{1,2}

People in Scotland can now receive cemiplimab for r/m CC, as it was accepted by the Scottish Medicines Consortium (SMC) in February 2025.¹³

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

Context:

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

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

Separate PBE has not been collected. However, a range of patient-reported outcomes were assessed in the EMPOWER Cervical-1 clinical trial: see Section 3f.

An insight into the impact of r/mCC on patients and their families and caregivers is provided by the Patient And Clinician Engagement (PACE) meeting from the appraisal of cemiplimab by the SMC.¹³ As well as confirming the high and debilitating symptom burden, the PACE statement notes that patients are generally left unable to work, unable to care for their children, and will require hospital care and symptom control after diagnosis due to severity of symptoms. They worry about the return of the cancer and the future more generally for themselves and for their loved ones.¹³

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Cemiplimab is a type of immunotherapy medicine called an immune checkpoint inhibitor: it works by helping the immune system to fight cancer cells. It is a type of drug called a monoclonal antibody, which recognises and attaches to a receptor on the cancer cells called PD-1. When activated, PD-1 suppresses the functioning of immune system cells around the tumour. By

blocking PD-1, cemiplimab allows immune system cells to recognise and kill cancer cells more effectively.¹⁴

As the first and only alternative to chemotherapy, cemiplimab is an innovative treatment that provides a therapeutic advance in the treatment of r/m CC that has progressed after platinum-based chemotherapy.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

No

3c) Administration and dosing

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

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

Cemiplimab is administered at the hospital as an intravenous infusion (drip into a vein) for 30 minutes once every three weeks.¹⁴ In contrast, some existing chemotherapy treatments, such as paclitaxel, require patients to attend hospital for treatment weekly, and need to receive intravenous treatment for 3 hours. Cemiplimab is therefore given less frequently and requires a shorter administration time than some existing therapies.

Treatment with cemiplimab can continue for as long as the cancer does not progress and the patient does not experience intolerable side effects.³

3d) Current clinical trials

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

A large, international, randomised, controlled trial has been carried out investigating the effectiveness of cemiplimab in treating adult patients with recurrent, persistent and/or metastatic cervical cancer that had progressed after platinum-containing chemotherapy given to treat r/m CC. This is the EMPOWER Cervical-1 trial, registration number NCT03257267.¹⁵

Title: Study of Cemiplimab in Adults With Cervical Cancer.

Study publications: Tewari et al. 2022,² Oaknin et al. 2022,¹⁶ Oaknin et al. 2025.⁹

Locations: 97 sites in 14 countries (Australia, Belgium, Brazil, Canada, Greece, Italy, Japan, Poland, Republic of Korea, Russian Federation, Spain, Taiwan, UK, US); 2 sites in the UK (England).

Completion date: 2023.

Population: Adults with recurrent, persistent and/or metastatic cervical cancer that had progressed after platinum-containing chemotherapy given to treat recurrent or metastatic cervical cancer.

Objective: to compare the efficacy and safety of cemiplimab with that of investigator's choice chemotherapy in this population.

Number of participants: 608 patients were randomised to receive either cemiplimab (304 patients) or investigator's choice chemotherapy (304 patients)

Trial design: Patients were randomly assigned to receive either cemiplimab or chemotherapy. They were regularly evaluated to see their response to treatment, whether their cancer had progressed, the side-effects they had, and how long they lived. They also completed questionnaires about their pain levels and their quality of life (e.g. their symptoms, their ability to carry out their usual activities, and their emotional wellbeing). Treatment with cemiplimab was given at a dose of 350 mg intravenously (IV) every 21 days for up to 96 weeks. Treatment with chemotherapy was available for up to 96 weeks. Chemotherapy was discontinued at disease progression or development of unacceptable toxic effects.²

3e) Efficacy

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

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

The EMPOWER Cervical-1 trial found that cemiplimab significantly improved overall survival compared with investigator's choice chemotherapy. Overall survival is the time from randomisation into the trial to date of death due to any cause. Treatment with cemiplimab also resulted in a significantly higher response rate (percentage of patients whose cancer reduced [partial response] or became undetectable [complete response] following treatment) compared with chemotherapy. Details are given below.

- People in the cemiplimab group had a significantly longer overall survival compared with chemotherapy.⁹ The average (median) overall survival with cemiplimab was 11.7 months, compared with 8.5 months with chemotherapy. This means there was a 33% reduction in the risk of death with the use of cemiplimab compared with chemotherapy (Hazard ratio [HR] 0.67; 95% CI: 0.56, 0.8).

- The estimated probability of being alive at 12 months was 49.0% for people treated with cemiplimab and 34.2% for the chemotherapy group.
- At 24 months, an estimated 28.2% of patients treated with cemiplimab were still alive, compared with 11.9% of those treated with chemotherapy.
- Approximately one-fifth of people in the cemiplimab group were still alive after 36 months (estimated probability of survival 22.0%, compared with 8.3% in the chemotherapy group).
- People treated with cemiplimab had a significantly higher response rate (i.e. a complete or partial response) than chemotherapy.⁹ The objective response rate with cemiplimab was 17.1%, compared with 6.3% with chemotherapy.
 - In addition, 40.5% of people in the cemiplimab group had stable disease (as did 48.7% in the chemotherapy group). Stable disease means that the cancer has not grown or shrunk significantly, and that no new tumours have developed.
- People in the cemiplimab group had a significantly longer duration of response and a significantly reduced risk of disease progression compared with chemotherapy. There was a 26% reduction in the risk of disease progression with the use of cemiplimab compared with chemotherapy (Hazard ratio 0.74).

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

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

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

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

In the EMPOWER Cervical-1 trial, patients in the cemiplimab group generally reported better scores for quality of life measures compared with chemotherapy, as reported using the cancer-specific EORTC QLQ-C30 questionnaire.¹⁶

- Scores for both overall health status/quality of life and physical functioning were generally maintained or improved with cemiplimab during the trial compared with baseline levels, whereas those for chemotherapy generally worsened after patients had received 2-4 cycles of chemotherapy.
- Overall, patients in the cemiplimab group reported significantly better scores than the chemotherapy group for change from baseline in overall health status/quality of life, physical functioning, and also their role functioning, emotional functioning and social functioning.

- Symptom scores for fatigue, nausea/vomiting, pain, insomnia, appetite loss, and constipation all showed a significantly more favourable change from baseline in the cemiplimab group than in the chemotherapy group.
- It also took longer for these symptoms, along with breathlessness, to worsen in the cemiplimab group compared with the chemotherapy group.

These results suggest that treatment with cemiplimab has a positive impact on patients' quality of life compared to treatment with chemotherapy.

3g) Safety of the medicine and side effects

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

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

Like all medicines, cemiplimab can cause side effects, some of which can be serious.¹⁴ Adverse events (any undesirable experience associated with the use of a medical product in a patient) in clinical trials are graded on a scale of 1 (mild) to 5 (leading to death). In the EMPOWER Cervical-1 clinical trial, cemiplimab-treated patients experienced similar rates of adverse events of any grade as the chemotherapy group. However, fewer patients had grade 3 or higher events with cemiplimab than with chemotherapy.⁹ This was despite the fact that patients had a longer average duration of treatment with cemiplimab (15.2 weeks) than with chemotherapy (10.1 weeks).⁹

The most common adverse events of any grade in either treatment group in the EMPOWER Cervical-1 clinical trial were anaemia (25.7% with cemiplimab vs. 44.1% with chemotherapy), nausea (19.0% vs. 34.1%), and fatigue (17.0% vs. 15.5%).⁹ Although a small number of patients in the trial (7 in total) experienced grade 5 adverse events, none of these were considered by the treating investigator to be related to cemiplimab.⁹

Immunotherapy drugs such as cemiplimab tend to cause a different pattern of adverse effects from those seen with chemotherapy. While some side-effects seen with chemotherapy are less likely with immunotherapy, immunotherapy can cause immune-related adverse effects in some people.¹⁴

The most common immune-related effects in cemiplimab-treated patients across all clinical trials (which may affect up to 1 in 10 people) include hypothyroidism (an underactive thyroid gland causing tiredness, weight gain, and skin and hair changes), hyperthyroidism (an overactive thyroid gland causing weight loss, nervousness, rapid heartbeat, and tiredness), pneumonitis (inflammation in the lungs causing shortness of breath and cough), hepatitis (inflammation of the liver), colitis (inflammation of the large bowel), and skin reactions.³

A guide and an alert card will be provided to patients treated with cemiplimab, which will contain information on the signs and symptoms of the immune-related side effects, and instructions on contacting their doctor if they experience symptoms. The summary of product characteristics and the package leaflet also contain recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of cemiplimab.³

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Currently, the only treatment option for r/m CC that has progressed after platinum chemotherapy is to have further chemotherapy. This is usually with different chemotherapy drugs than before. Unfortunately, further chemotherapy has limited effectiveness, with the disease responding poorly to these treatments.¹ It can also have side effects that negatively affect people's quality of life. Because of the side effects, some people may not be able to tolerate more chemotherapy, and so cannot currently have any further treatment.

There is a need for treatment that can help people live longer, while helping to maintain their quality of life and reducing the risk of severe side effects.

Cemiplimab is different from current treatment because it is an immunotherapy rather than a chemotherapy.

The key benefit of cemiplimab is that, compared with the current standard treatment (chemotherapy), it significantly extends both the length of time patients have before their cancer progresses, and how long they live after starting treatment.^{9,17} In the EMPOWER Cervical-1 study, both of these times were significantly increased with cemiplimab compared with the chemotherapy arm. The median survival time was 11.7 months with cemiplimab versus 8.5 months with chemotherapy. At 12 months, an estimated 49.0% of people in the cemiplimab group were still alive vs. 34.2% in the chemotherapy group. At 24 months, these numbers were 28.2% and 11.9%, respectively. At 36 months, an estimated 22.0% of people treated with cemiplimab were still alive, compared with 8.3% treated with chemotherapy.

Additionally, the safety profile of cemiplimab was favourable in the EMPOWER Cervical-1 trial compared to chemotherapy (see Section 3g), and quality of life was better maintained better (see Section 3f). Cemiplimab also requires less frequent trips to hospital for administration, and reduces the amount of time needed for administration in hospital compared with chemotherapy (see Section 3c).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

Both cemiplimab and chemotherapy are given by IV infusion, so patients have to travel to hospital to be treated. Although cemiplimab is significantly more effective than chemotherapy (based on the EMPOWER Cervical-1 study), patients who respond to treatment may have to stay on treatment for longer with cemiplimab. This is because chemotherapy is typically given as a fixed-length course, whereas cemiplimab (like many non-chemotherapy cancer treatments) is taken until the patient has disease progression or intolerable side-effects. The continuing need for regular treatment visits might be seen as a disadvantage by some patients and/or their caregivers. However, this needs to be balanced against the greater efficacy of cemiplimab in prolonging survival compared with chemotherapy. It should also be noted that some chemotherapy options require weekly (or even daily) treatment visits, whereas cemiplimab is given once every three weeks.

3i) Value and economic considerations

Introduction for patients:

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

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

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

What are economic models?

Economic models are a way of capturing the benefits and costs associated with different medical treatments over a patient's lifetime. This allows NICE to estimate how cost-effective a new treatment is compared with existing treatments, and to decide whether paying for a new treatment is good value for money for the NHS. In most cases models look at the overall population of patients who will be using the treatment, rather than looking at individuals.

Models take their information from clinical trials whenever possible. However, clinical trials only last a limited amount of time, so that results can be obtained within a reasonable timescale. This means that models have to extrapolate (project forward) beyond what was seen in the trial, in order to estimate lifetime costs and benefits. Extrapolation involves making some assumptions, and by its nature involves some uncertainty.

How the economic model reflects r/m CC

The type of model used in this appraisal is termed a partitioned survival model. This is a well-established method that is often used in the modelling of cancer. It divides the hypothetical patients into three possible 'health states': either alive without disease progression (i.e., the cancer is stable or responding to treatment), alive with disease progression, or dead. It uses data from the trial on progression-free and overall survival to estimate the proportion of patients who are in each of the health states over time. Beyond the time period of the trial, statistical methods are used to extrapolate the curves until the time when the whole patient group can be expected to have died (even patients whose disease didn't come back).

The model reflects r/m CC by reflecting information from the experience of patients in the EMPOWER Cervical-1 clinical trial. The model structure and inputs were also discussed with expert clinicians to ensure that the disease and patient journey were being properly captured. Inputs were also compared against published values in the scientific literature and previous NICE appraisals. Further information on how life extension, quality of life and treatment cost were modelled is given below.

Modelling how much life is extended

The EMPOWER Cervical-1 trial showed that, compared with patients receiving chemotherapy, people treated with cemiplimab had a significantly longer progression-free survival and overall survival.

At the time of modelling, patients in the EMPOWER Cervical-1 trial had been followed for an average of 47.3 months.⁹ At this cut-off, 493 of the 608 had died.

As discussed above, established statistical methods were used to extrapolate (i.e. project forward) from the progression-free and overall survival results seen in the trial, in order to predict progression-free and overall survival over the lifetime of the entire group of hypothetical patients with r/m CC. The projections were calculated using several different methods and were checked against findings from other studies and with UK clinicians to see which were the most realistic.

Modelling quality of life

To reflect patients' quality of life whilst in the pre-progression and progressed states, each state is assigned a 'utility value'. This is a value between 0 and 1, where 1 corresponds to perfect health and 0 corresponds to death. The European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) was used in the EMPOWER Cervical-1 trial to collect quality of life data.^{16,17} The utility values were then obtained by mapping the results of the EORTC QLQ-C30 onto the EuroQol-5 Dimensions-3 Level (EQ-5D-3L) questionnaire. While the patients are 'on treatment', i.e. in the pre-progression state, the utility values are taken from the separate treatment arms, to reflect any treatment-related differences. In the progressed state, when patients are no longer on the trial treatments, the utility values are lower than in the pre-progression state, reflecting the lower quality of life of patients as their disease has progressed. As

chemotherapy is associated with more longer-term impacts on quality of life, the utility value remains lower with chemotherapy than with cemiplimab.

The model also takes into account the negative effects of adverse events on quality of life, and the cost of treating them. Rates of adverse events of grade 3 and 4 are taken from the trial. For each event, a deduction is made to the quality of life (utility), and the cost of treating the event is added.

Quality-adjusted life years

The model combines the length and quality of life that patients experience into one metric, called quality-adjusted life years (QALYs). The model calculates the number of QALYs that patients would gain on average over the course of a lifetime with cemiplimab and with chemotherapy. As cemiplimab extends life and preserves quality of life to a greater degree than chemotherapy, the model estimates that patients would gain more QALYs with cemiplimab than with chemotherapy.

Modelling costs

The model looks at all the relevant costs to the NHS of buying and administering the different drugs, and treating the side-effects that arise, and the ongoing costs of care. The model calculates the difference in total costs over a lifetime with cemiplimab and with chemotherapy. Cemiplimab is offered to the NHS at a confidential discount on its list price, but as it costs more to buy than chemotherapy, and because it is more effective leading to longer treatment and longer ongoing costs of care, the total costs of cemiplimab are greater than the total costs of chemotherapy.

Uncertainty

To address uncertainty, different scenarios were modelled and are presented to NICE. Expert clinicians were consulted to check whether the model inputs and assumptions were realistic and applicable to UK patients.

Additional factors

There are some benefits not captured by the modelling. Cervical cancer affects a younger age group than many other cancers, with incidence rates in England peaking at age 30-34 years.⁶ People with r/m CC are often young, and many have dependent children or other caring responsibilities. The Patient and Clinician Engagement (PACE) statement from the SMC appraisal of cemiplimab in this indication¹³ notes that “the ability to continue caring for their families [both children and older relatives] is of the upmost importance to this patient group, and minimising time in hospital whilst providing meaningful clinical benefit cannot be underestimated.” The pivotal trial did not measure quality of life impact for families and caregivers arising from the benefits that patients experienced with cemiplimab (e.g. the extended progression-free and overall survival), and this is therefore not captured by the QALY. Additionally, the 3-week dosing interval of cemiplimab means receiving treatment is less disruptive than weekly paclitaxel infusions, which are a common 2L regimen in England. This benefit to patients and families is also not captured by the modelling.

NICE recognises that severe diseases that significantly reduce life expectancy and quality of life should receive a different weighting when making their recommendations than diseases that do not. R/m CC is a severe disease that, compared with people of the same age, significantly reduces life expectancy and quality of life. Based on current treatment with chemotherapy, the economic model predicts that there is an absolute shortfall of 14.61 QALYs and a proportional shortfall of

96% compared with age-matched population expectations. Therefore, based on NICE processes, cemiplimab qualifies for application of a x1.7 QALY weighting when estimating its cost effectiveness as incremental costs per QALY gained vs chemotherapy.

Cost-effectiveness results

With the appropriate application of the x1.7 severity weighting, at the discounted price cemiplimab is offered to the NHS, it represents a cost-effective use of NHS resources.

3j) Innovation

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

Cemiplimab represents an important advancement in the treatment of recurrent/metastatic cervical cancer, as it addresses an important unmet need in this setting. Patients in England who have progressed after platinum-based chemotherapy currently have no option for second-line treatment other than further chemotherapy, which has limited efficacy and negative side effects which may make further chemotherapy intolerable for some people. In addition, many patients will already have received chemotherapy in the neoadjuvant or adjuvant as well as the recurrent/metastatic setting, which may limit their ability to tolerate further chemotherapy cycles.

Cemiplimab offers these patients the option of an immunotherapy instead of more chemotherapy. In the EMPOWER Cervical-1 trial, cemiplimab was shown to significantly improve survival time compared with chemotherapy, with similar or fewer side effects despite a longer duration of treatment.⁹ As the only immunotherapy alternative to chemotherapy, it provides a step-change in the second-line treatment of r/m CC.

The model and resulting QALY calculation captures the main benefits of cemiplimab over chemotherapy. However, it does not take into account the potential benefits to quality of life for patients' caregivers and families that may result from extended progression-free and overall survival with cemiplimab.

3k) Equalities

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

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

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

Cervical cancer disproportionately affects people in more deprived socioeconomic groups. For the period 2013-2017, the incidence rate was 65% higher in the most deprived socioeconomic quintile (as calculated by the Index of Multiple Deprivation) than in the least deprived. A quintile is

a term meaning one-fifth of a population. Cancer Research UK estimates that there are around 520 more cases of cervical cancer each year in England than there would be if all quintiles had the same incidence rates as the least deprived quintile (2013-2017 period).⁶

SECTION 4: Further information, glossary and references

4a) Further information

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

Information on cervical cancer and its treatment in the UK can be found on Cancer Research UK's website:

- <https://www.cancerresearchuk.org/about-cancer/cervical-cancer>

The patient information leaflet for cemiplimab can be found at:

- <https://www.medicines.org.uk/emc/product/10438/pil>

Further information on NICE and the role of patients:

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

4b) Glossary of terms

Adverse event: any undesirable experience associated with the use of a medical product in a patient

Cervix: the neck of the womb that opens into the vagina

CI: confidence interval

Complete response: there are no signs of cancer on scans or tests

HPV: human papillomavirus

IV: intravenous (into the vein)

Median: the middle number in a sorted list of numbers

Metastatic: cancer that has spread to other parts of the body

Overall survival: time from randomisation into the trial to date of death due to any cause

Partial response: the cancer has shrunk by at least one third (30%) and there are no signs the cancer has grown anywhere else in the body

Progression-free survival: time from randomisation into the trial to first documentation of disease progression or death due to any cause (whichever comes first)

R/m CC: recurrent/metastatic cervical cancer

QALY (quality-adjusted life year): A measure in which length of life is adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Rectum: the lower part of the large intestine; the back passage

Response rate: percentage of patients whose cancer met the criteria for response (i.e. reduced or disappeared) following treatment

Ureters: tubes that carry urine from the kidneys to the bladder

4c) References

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

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2. Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. *New England Journal of Medicine* 2022;386(6):544-55.
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4. Cancer Research UK. Cervical cancer (2023). <https://www.cancerresearchuk.org/about-cancer/cervical-cancer> (accessed 8 Apr 2025).
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7. Reed N, Balega J, Barwick T, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: Recommendations for practice. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2021;256:433-65.
8. Kim YJ, Munsell MF, Park JC, et al. Retrospective review of symptoms and palliative care interventions in women with advanced cervical cancer. *Gynecol Oncol* 2015;139(3):553-8.

9. Oaknin A, Monk BJ, de Melo AC, et al. Cemiplimab in recurrent cervical cancer: Final analysis of overall survival in the phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial. *European Journal of Cancer* 2025;216.
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11. NHS. Cervical cancer: tests and next steps for cervical cancer (2024). <https://www.nhs.uk/conditions/cervical-cancer/tests-and-next-steps/> (accessed 20 August 2025).
12. Regeneron UK Ltd. LIBTAYO 350 mg concentrate for solution for infusion: summary of product characteristics (2025). <https://www.medicines.org.uk/emc/product/10438/smpc#gref> (accessed 8 Sept 2025).
13. Scottish Medicines Consortium (SMC). Cemiplimab (Libtayo). Detailed Advice Document, (2025).
14. Regeneron UK Ltd. LIBTAYO 350mg concentrate for solution for infusion - Package leaflet: information for patients (2025). <https://www.medicines.org.uk/emc/product/10438/pil#about-medicine> (accessed 18 September 2025).
15. clinicaltrials.gov. Study of Cemiplimab in Adults With Cervical Cancer (2025). <https://www.clinicaltrials.gov/study/NCT03257267> (accessed 22 August 2025).
16. Oaknin A, Monk BJ, Vergote I, et al. EMPOWER CERVICAL-1: Effects of cemiplimab versus chemotherapy on patient-reported quality of life, functioning and symptoms among women with recurrent cervical cancer. *Eur J Cancer* 2022;174:299-309.
17. Regeneron Pharmaceuticals Inc. An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice Chemotherapy in Recurrent or Metastatic Cervical Carcinoma. Final Clinical Study Report., (2024).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Clarification questions

January 2026

File name	Version	Contains confidential information	Date
ID6610 cemiplimab EAG Clarification Qs 171225 CON_FINAL_readacted	1.0	Yes	20/01/2026

Section A: Clarification on effectiveness data

Decision problem

A1. PRIORITY *The population addressed in the company submission, as described in company submission (CS), Table 1, matches the licensed indication, which specifies that patients must have progressed on or after platinum-based chemotherapy, but does not exclude from the population patients who have received prior immunotherapy. However, the population addressed in the economic evaluation, as described in CS, Section 3.2.1, is described as being restricted to those who have not received prior immunotherapy. In addition, the population enrolled in the pivotal clinical trial (EMPOWER Cervical-1) was restricted to those without prior immunotherapy treatment. The CS also states that it is anticipated that cemiplimab will be used in patients who have not received prior immunotherapy in line with current European guidelines (CS, page 11).*

- a. *Please clarify whether the CS provides any evidence on the clinical effectiveness or cost-effectiveness of cemiplimab in patients who have received prior immunotherapy, and if it does not, please confirm that the population addressed in the CS is restricted to those patients who have not received prior immunotherapy.*

Response: The CS does not provide clinical or economic evidence in patients who have received prior immunotherapy. The population addressed in the submission is restricted to patients who have not received prior immunotherapy, in line with the EMPOWER Cervical-1 trial¹.

As noted by the EAG, the licensed indication and the NICE scope do not specify exclusion of patients who have received prior immunotherapy. The decision to exclude these patients from the submission population was made in order to align with both the trial population and the expected use of cemiplimab in clinical practice, as confirmed by clinical guidelines² and by UK clinical experts³⁻⁵. The decision is explained in detail in section 1.3.4 of the CS. The ESGO/ESTRO/ESP guideline is

described in CS section 1.3.3.3. The guideline states that: *“Patients who progressed after first-line platinum-based chemotherapy should be offered treatment with the anti PD-1 agent, cemiplimab, regardless of PDL-1 tumor status as long as they had not previously received immunotherapy [I, A].”*²

b. Please also clarify, when the population is described as being patients without prior immunotherapy in CS, Section 3.2.1, whether that exclude patients with any prior immunotherapy at any stage of cancer treatment, including neoadjuvant or adjuvant treatment provided prior to the patient being classified as recurrent/metastatic.

Response: Patients were not permitted into the trial if they had received any prior treatment with an agent that blocks the PD-1/PD-L1 pathway, at any stage of their cervical cancer treatment. Immunotherapy is not recommended for use in neoadjuvant or adjuvant use prior to patients being diagnosed with recurrent/metastatic cervical cancer in current clinical guidelines.²

A2. PRIORITY Tisotumab vedotin was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on the 2nd December 2025.⁶ The evidence assessment group (EAG) notes the company’s point that final NICE guidance on tisotumab vedotin is not anticipated to be published until after the first committee meeting for cemiplimab. However, one of the EAG’s clinical experts indicated that there is likely to be uptake of this new treatment within some centres prior to the NICE appraisal being completed. Based on this we are concerned that tisotumab vedotin may be established within clinical practice at the time of the first committee meeting for cemiplimab, irrespective of whether the NICE appraisal for tisotumab vedotin is still ongoing. The EAG notes that tisotumab vedotin was listed as a comparator in the NICE Final Scope. Please provide a comparison of the clinical and cost-effectiveness of cemiplimab versus tisotumab vedotin.

Response: As detailed in CS Table 1, the Company does not consider that tisotumab vedotin (TV) is a relevant comparator in the submission. This remains the case even if there is uptake at some centres prior to the TV NICE appraisal being completed. The selection of TV as a comparator in the appraisal of cemiplimab is not

aligned with the NICE Manual, and would lead to an unfair advantage for TV in the appraisal process, as discussed below.

The selection of Tisotumab vedotin as a comparator is not aligned with the NICE Manual

As noted in the NICE guidance manual⁷ (Section 2.2.12-15), in selecting the most appropriate comparators, the committee will consider:

- established NHS practice in England
- the natural history of the condition without suitable treatment
- existing NICE guidance
- cost effectiveness of the comparator
- the licensing or regulatory status of the comparator.

Based on the extent to which TV is established NHS practice, the availability of existing NICE guidance, and its cost effectiveness, TV should not be considered a relevant comparator for cemiplimab.

- *Tisotumab vedotin cannot be considered established NHS practice in England*

The most recent NHS England National Cancer Drugs Fund List (08 January 2026),⁸ which lists all baseline funded cancer drugs, does not include TV, indicating that TV is not routinely funded by NHS England. Any previous, current or future TV uptake prior to a positive NICE recommendation would presumably be via a manufacturer-funded early access / compassionate use programme, and as such would not constitute established clinical practice. Indeed, a therapy that is subject to NICE appraisal could not be considered established clinical practice until, at a minimum, a final positive recommendation for routine, baseline funding has been issued. Even then, this would not automatically confer its status as established practice.

- *There will not be any existing NICE guidance for tisotumab vedotin at the time of the first appraisal committee of cemiplimab*

The first appraisal committee meeting for TV is scheduled for 10 February 2026 and the earliest possible issuance of final NICE guidance for TV would be 12 June 2026.⁹ Our submission to NICE for cemiplimab was made 2 December 2025, which is >6

months before the earliest possible final NICE guidance can be issued for TV. The first committee meeting for cemiplimab is scheduled for 12 May 2026, which is also well before final NICE guidance will be issued for TV. Therefore, both TV and cemiplimab will have had their first appraisal committee meetings before the other has received final NICE guidance. Neither should therefore be considered to be established clinical practice and relevant comparators to each other.

- *There is no information available on the cost effectiveness of tisotumab vedotin*

As final NICE guidance for TV will not be available until after the first appraisal committee meeting for cemiplimab, there is not currently, and will not be at the time of the cemiplimab appraisal committee meeting, any information on the cost effectiveness of TV. Indeed, at the time of writing, there is no published UK list price for TV.

The scope-listed comparators for the appraisal of cemiplimab and tisotumab vedotin confers an unfair disadvantage for cemiplimab

Whilst the scope for the appraisal of TV appropriately excludes cemiplimab as a relevant comparator, the scope for the appraisal of cemiplimab inappropriately includes TV as a comparator. In addition to being procedurally inconsistent with the NICE Manual, this creates an unfair advantage for TV over cemiplimab in the appraisal process. Given that neither will have final NICE guidance available at the time of their first appraisal meetings, if cemiplimab is not considered to be a relevant comparator to TV, then TV should not be considered a relevant comparator to cemiplimab.

In practice, cemiplimab and tisotumab vedotin may be used in different patient populations.

As noted in CS Table 1, it is likely that TV and cemiplimab may be used in different patient populations in clinical practice, due to differences in their mechanisms of action. Cemiplimab provides a chemotherapy-free immunotherapy option for those patients who have not received first-line immunotherapy. In contrast, TV is a type of chemotherapy rather than an immunotherapy. Given that cemiplimab will only be

used following platinum-based chemotherapy, the alternative use of further chemotherapy with TV, with its attendant adverse event profile, following platinum-based chemotherapy may not be clinically desirable.

For the reasons discussed above and in the CS, the Company does not consider a comparison between cemiplimab and TV to be warranted under NICE appraisal guidance and therefore the comparison has not been supplied.

A3. Treatment pathway: CS, Figure 2. Please clarify why the treatments described for third-line treatment (3L) on the left in Figure 2 differ from the treatments described in the central 3L box in Figure 1. Please also clarify if it is intentional that the 3L treatments following cemiplimab in Figure 2 match the second-line (2L) treatments on the left in Figure 2 or whether they should match 3L treatments in the central box in Figure 1. For clarity, please provide an updated Figure 2 if any errors are identified on review.

Response: Figure 1 describes current treatment pathway ('world without cemiplimab'). Figure 2 describes the pathway with cemiplimab as 2L treatment. Introduction of cemiplimab in 2L after platinum-based chemotherapy results in current 2L treatment being shifted to 3L. The 3L box in Figure 2 is the same as the 2L box in Fig 1, so there is no discrepancy and both figures are correct.

Literature Searches

A4. In the systematic literature review (SLR) described in appendices B, E and F, the search narratives do not explain why it was necessary to conduct multiple phases of searching over several years; nor is this represented in the respective PRISMA flowcharts for each SLR. Please explain why this somewhat unconventional approach was necessary and why you have not provided a separate PRISMA flowchart on each occasion.

Response: The SLRs were originally conducted in 2021 to support reimbursement submissions outside the UK. The scope of the SLRs has remained consistent since the original reviews were conducted. As per best practice the SLRs were updated at appropriate timepoints to ensure that presented data was up to date within ~6 months of a submission. As the results of each update were appended to the results of the SLR a single PRISMA diagram was deemed appropriate.

A5. For the SLRs described in appendices B, E and F, please indicate which version of MEDLINE was searched. Did you include “in process” and “Epub ahead of print” records i.e. the latest to be added to the database?

Response: All versions of MEDLINE were searched, as Embase.com has all versions integrated into their platform. The search also included the “pubmed-not-medicine” database, which includes the “Epub ahead of print” records.

A6. For the clinical SLR described in Appendix B, the narrative description of the search claims that “search strategies were designed using index (MeSH in MEDLINE and Cochrane, and Emtree in Embase)” (CS appendix B, section 3.2.1.1, p.12). However, the EAG notes that in reality the two databases were searched with a single multi-file string (appendix B section 8.1.1) with no apparent attempt to specify which terms were used on which source. Given that this is the case, were the included index terms selected from MeSH or Emtree?

Response: This is a function of searching both MEDLINE and Embase via Embase.com. Embase.com integrates all MEDLINE content within its own database and maps MeSH terms to the EMTREE thesaurus allowing for combined searching of both databases using only the EMTREE terms.

A7. For the clinical SLR described in Appendix B, the CS states that “The search filter for randomised controlled trials used in Medline and Embase is published by the Scottish Intercollegiate Guideline Network (SIGN) adapted for 2mbase.com format by Cochrane.” (CS appendix B, section 3.2.1.1, p12). The EAG is unable to open the Cochrane link provided (which points to: <https://work.cochrane.org/embase>). Please provide a copy of the cited publication so that we may check whether it was designed for multi-database use (as it has been applied here).

Response: Unfortunately the link appears to have been changed since it was used in our SLR and we are also now unable to find where the link originally intended to redirect. The information was on a Cochrane webpage rather than in a publication. But please note the functionality of Embase.com as described in response A6.

Systematic literature review

A8. CS, Appendix B, p14-16. Please confirm whether study selection, data extraction, and quality assessment were undertaken independently by at least two reviewers for each systematic review in the clinical and economic sections. The CS states that any disagreements were resolved by consensus or adjudicated by a third independent reviewer; however, Appendix B lists only two authors. Please clarify the review process undertaken, including how disagreements were managed and whether any additional reviewers were involved.

Response: The two authors listed were the authors of the report, rather than a list of all personnel involved. We can confirm there were additional individuals who supported the study selection process, so there were at least two reviewers who followed the study selection process through, with additional input as required. The description of the approach provided in the CS is correct.

A9. CS, Appendix B, Table 1. For completeness, please comment on the limitations and generalisability of restricting the SLR to English-language publications.

Response: By limiting the SLR to English-language publications there is a risk that articles only published in non-English language exist that would have been excluded from the SLR. However, given the geographical scope of studies which were published in English and included in the SLR, the overall impact on the totality of the evidence base is expected to be limited.

A10. CS, Appendix B, Section 3, Table 1 describes inclusion criteria for a broad SLR limited to clinical trials of systemic therapies in patients with recurrent or metastatic cervical cancer following platinum-based therapy. This review reportedly identified 79 studies, including two phase III trials comparing cemiplimab with investigator's choice (IC) chemotherapy (the number of citations included is unclear). However, the main CS (Section 2.9.2) also presents evidence from real-world evidence (RWE) studies that fall outside the

stated scope of the SLR, and for which the identification methods are not described.

- a. Please clarify the evidence identification process used for this appraisal, including the sources searched and the methods used for study selection, data extraction, quality assessment and data synthesis for the cemiplimab randomised controlled trials (RCTs) and the real-world evidence (RWE) studies.***
- b. Please provide the inclusion and exclusion criteria that were applied specifically for this appraisal.***
- c. Please confirm which studies (with full citations) meet the inclusion criteria for this appraisal. If additional studies meet these criteria beyond those identified in (a), please list them.***
- d. Please confirm whether the following studies were identified through the company's searches. If relevant to the appraisal, please provide further details, including outcomes and results for Hasegawa et al 2024¹⁰ and Renata Pacholczak-Madej et al. 2025¹¹.***
- e. Please confirm whether the authors of the 2024 conference abstract reporting a randomised controlled trial conducted in Uzbekistan (N=180), comparing cemiplimab with IC chemotherapy, were contacted to obtain additional methodological details or results beyond those reported in the conference abstract.***

Response: The scope of the SLR was limited to interventional clinical trials and did not include real-world evidence. The methods and results are fully described in the SLR report (CS Appendix B). The authors of the 2024 Uzbekistan conference abstract were not contacted to obtain additional details.

A systematic search for real-world evidence was not undertaken because comprehensive RCT evidence on cemiplimab versus chemotherapy is available from the EMPOWER Cervical-1, which presents highly mature data: PFS data is nearly complete and OS curves are based on 237 events [78.0%] reported in the cemiplimab arm, and 256 events [84.2%] reported in the chemotherapy arm (see CS

Tables 9 and 10). These data are used in the economic model. As such RCT data represents the gold standard of evidence, a systematic search for real-world evidence, which has a lower standing in the hierarchy of evidence, was considered to be unlikely to add substantial evidence to address the decision problem in this case.

However, the Company was aware of two published sources of RWE, including one from the UK, and these were presented in CS Section 2.9.2 as supporting evidence.

Regarding the two studies highlighted by the EAG in part d:

- The Hasegawa publication was identified in the SLR (see Table 32 of the SLR report). However, it contained only post hoc subgroup data specific to Japanese patients in EMPOWER Cervical-1 (n=56), which is less relevant to the UK than the prespecified ITT analyses used in the submission, and is based on a shorter duration of follow-up (see Hasegawa et al., abstract). Consequently the data were not extracted, as it contained no additional data relevant to the decision problem.
- Thank you for highlighting the Renata Pacholczak-Madej publication (a conference abstract of a RWE series). This was not within the SLR scope and had not been identified as further available evidence at the time of submission. Upon review, this small RWE study appears to be in broad alignment with the RWE presented in section 2.9.2 of the CS.
 - The study reports on 37 patients in Poland. The median age was 58 years. After a median follow-up of 10.2 months the median PFS was 5.7 months (95% confidence interval [CI]: 4.9–6.4), and the median OS was 12.3 months (95% CI: 8.1-6.5 [sic]). The ORR was 21.6% (n=8), with stable disease observed in 40.5% (n=15). Immune-related AEs (irAEs occurred in 45.9% of patients (n=17). The most frequent irAEs were thyroid dysfunction (n=11, 64.7%) and hepatotoxicity (n=3, 17.6%). Most irAEs were mild (grade [G] 1), while moderate toxicities (G2) were reported in 3 cases (17.6%) and severe toxicities (G3) occurred in 2 cases (11.8%), comprising hepatotoxicity and skin rash. Treatment was discontinued due to toxicity in 2 patients (5.4%).

Median overall survival in this small cohort was comparable with that in EMPOWER Cervical-1. Percentages experiencing irAEs should be interpreted with caution due to very small patient numbers.

A11. PRIORITY CS, Appendix B, Section 8.3. Please provide further details of the Cochrane Risk of Bias tool that was used to critically appraise the relevant clinical effectiveness evidence for this appraisal:

a. Please confirm which version of the tool was used;

Response: The Cochrane ROB-2 tool was used.¹²

b. For each response to a signalling question, please provide supporting evidence (e.g., direct quotations from the text of the study report should be used whenever possible) and a score for the answer

Response: an extended ROB assessment for EMPOWER Cervical-1 is provided below.

Unique ID	48	Study ID	EMPOWER-Cervical 1	Assessor	JT
Ref or Label	Tewari 2022	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Cemiplimab	Comparator	IC chemotherapy	Source	Journal article(s) with results of the trial
Outcome	OS	Results		Weight	1
Domain	Signalling question		Response		Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y		"Patients were randomly assigned in a 1:1 ratio to receive either cemiplimab or the investigator's choice of chemotherapy as the control therapy".
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		"Randomization was stratified according to histologic type (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]), geographic region (North America, Asia, or rest of the world), previous bevacizumab exposure (yes or no), and ECOG performance-status score (0 or 1)".

	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	"The demographic and disease characteristics of the patients at baseline were balanced between the treatment groups (Table 1)."
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y	"We conducted EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9, an open-label, multicenter, phase 3 trial..."
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	"Control therapy was discontinued at the onset of disease progression or development of unacceptable toxic effects, with stopping rules for adverse events outlined in the protocol and no crossover allowed."
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle, with patients grouped according to randomized treatment"

			assignment, regardless of adherence."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"304 were assigned to receive cemiplimab and were included in the efficacy analysis."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle".
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	"The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle"
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	"an open-label, multicenter, phase 3 trial"

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Death and date of death are objective and unlikely to be influenced by assessor
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	"The statistical analysis plan is available with the protocol at NEJM.org."
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	"The primary end point, overall survival"
	5.3 ... multiple eligible analyses of the data?	N	"Differences in overall and progression-free survival were assessed with the log-rank test with the use of geographic region and tumor histologic type as stratification factors, as prespecified in the statistical analysis plan."
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

c. To help with the interpretation of the study's overall quality and assist in understanding the reliability of the findings, please provide an overall narrative summary of the results.

Response: The overall risk of bias assessment for EMPOWER Cervical-1 was low. Stratified randomisation was adequately conducted with baseline characteristics balanced accordingly. The trial was open-label, but given the primary outcome was overall survival, this was deemed low risk. The primary outcome was analysed using an ITT analysis including all allocated patients and was as such deemed to be at low risk of bias. The primary publication did not appear to selectively report data, providing information for overall and subgroup populations for the primary outcome, key secondary outcomes as well as adverse events and patient reported outcomes. Supplementary documentation was also provided.

EMPOWER Clinical-1 trial

A12. Prior to randomisation, trial participants were allocated the IC therapy they would receive should they not be allocated to the cemiplimab arm. Please can you provide a breakdown of the intended chemotherapy allocation for the patients who instead went on to receive cemiplimab.

Response: Unfortunately, the planned chemotherapy regimens for patients who were subsequently randomised to cemiplimab were not collected in the trial database. The chemotherapy regimen to which cemiplimab recipients would have been allocated was based on investigator choice, and there are several factors that may influence that choice. However, all patients enrolled in the trial met the same eligibility criteria that required them to be suitable candidates for (randomisation to) chemotherapy, the allocation concealment and randomisation process was robust, and as noted in Table 8 of the CS, the baseline characteristics of the enrolled patients were well balanced between the trial arms. We therefore do not believe the distribution of hypothetical therapies that patients could have received but didn't,

would have influenced the trial outcomes with cemiplimab or the relative treatment effects that were observed.

A13. CS, page 72 describes the proportion of patients who were re-treated with cemiplimab after completing 16 treatment cycles and experiencing progressed disease only in the post-treatment period. However, the study protocol (section 7.1.6) describes re-treatment, with the same chemotherapy agent, as also being possible in the IC chemotherapy arm. Please provide the proportion of patients with progression in the post-treatment period who were re-treated with the same chemotherapy in the IC chemotherapy arm.

Response: Subsequent treatment after progression on study chemotherapy was at the clinician's discretion. Whether or not a patient is rechallenged with a previously used chemotherapy agent depends on the duration of response initially achieved with the agent, and the patient's clinical state, their fitness for treatment and their wishes and priorities regarding further treatment.

Information on the proportion being re-treated with the same chemotherapy agent is not available from the EMPOWER Cervical-1 trial, as post-treatments were not recorded as the specific treatments, only as categories of treatment options (e.g. platinum compounds or combination of antineoplastic agents)¹³. Additionally, given the clinicians' discretion in choosing subsequent treatment, based on the factors noted above, we do not believe this information would aid decision-making in the appraisal, as re-treatment with the same chemotherapy would only be done if clinically appropriate and so would not be a potential source of bias in the trial OS results.

In the cost-effectiveness model, post-progression chemotherapy treatments are included as subsequent treatments. These include treatments that are restarted after progression. For example, in the scenario of comparators provided by clinical experts in England, 39% of patients receive weekly paclitaxel as comparator, and after progression, in the chemotherapy arm, 6.3% of patients receive weekly paclitaxel. Since it is a cohort model, we do not distinguish between patients receiving new treatments and patients restarting previous ones.

A14. CS, Table 5 and Table 32. Please clarify that when a maximum treatment duration of 16 cycles is specified, this is referring to the 6-week cycle length used in the clinical trial, giving a maximum treatment duration of 96 weeks. Please clarify the days of treatment for each intervention within the 6-week cycle implemented in the clinical trial. For example, please confirm if cemiplimab was given on days 1 and 22 of a 42 day cycle, and provide equivalent information for each of the chemotherapies in the comparator arm. Please provide similar clarification for each additional regimen specified in Table 32 as currently it is unclear what cycle length is being applied for each regimen in Table 32.

Response: In the CSR the Brief Description on the title page and Figure 2 describing the Study Design Schematic confirms that the duration of treatment is “16 cycles, each 6 weeks”.¹³ The 6-weekly cycle is able to follow both the 6-weekly cycle of irinotecan and the 3-weekly cycles of all other treatment options in the EMPOWER Cervical-1 trial.

The CSR (Table 2, p. 27) confirms that cemiplimab was given on Day 1 every 3 weeks, for up to 96 weeks (as stated in CS Table 5).

CS Table 32 is shown below, updated to include cycle length for the chemotherapies.

CS Table 32. UPDATE: Dosing regimens for comparator chemotherapies (including regimens included in scenario analysis)

Regimen	Dose			Cycle length (days)	Source
	Mg/administration	Per	Dosing schedule		
Pemetrexed	500.00	mg/m ²	Once every cycle	21	Tewari et al 2022 ¹
Gemcitabine	1,000.00	mg/m ²	Day 1 & 8	21	Tewari et al 2022 ¹
Topotecan	1.00	mg/m ²	Day 1-5	21	Tewari et al 2022 ¹
Irinotecan	100.00	mg/m ²	Days 1, 8, 15, 22, then 10-14-day rest	42	Tewari et al 2022 ¹
Vinorelbine	30.00	mg/m ²	Day 1 & 8	21	Tewari et al 2022 ¹
Paclitaxel	80.00	mg/m ²	Day 1,8,15	21	NHS Chemotherapy protocol ¹⁴
Carboplatin in combination with pegylated liposomal doxorubicin				28	
Carboplatin	750.00*	Flat dose	Day 1	28	NHS Chemotherapy protocol ¹⁵
Pegylated liposomal doxorubicin	30.00	mg/m ²	Day 1	28	
Carboplatin in combination with gemcitabine				21	
Carboplatin	600.00^	Flat dose	Day 1	21	NHS Chemotherapy protocol ¹⁶
Gemcitabine	1,000.00	mg/m ²	Day 1 & 8	21	
Carboplatin monotherapy	750.00*	Flat dose	Day 1	21	NHS Chemotherapy protocol ¹⁷

NOTE: Calvert equation used for calculating carboplatin dose (mg) = AUC (CrCl +25), with CrCl assumed to be 125 based on the clinical expert's estimation.

A15. PRIORITY CS, Table 5. It is stated that patients with an unconventional response consistent with pseudo-progression could be treated beyond progression provided certain conditions were met.

- a. Please confirm whether pseudo-progression was considered in both arms. If this classification of pseudo-progression was allowed only in the cemiplimab arm, please comment on how this**

difference between treatment continuation rules in this unblinded study is reflected in the risk of bias assessment.

Pseudo-progression is a feature seen with immunotherapies, and not with chemotherapies. It refers to an atypical response pattern in which an initial increase in tumour size is observed or new lesions appear, followed by a decrease in tumour burden.¹⁸ The increase in tumour size may be a consequence of T-cells infiltrating and attacking the tumour. Under the standard RECIST criteria, which were developed for assessing response to chemotherapy, this may be falsely designated as disease progression.

Because pseudo-progression is not a recognised feature of chemotherapy treatment and is not biologically relevant to chemotherapy, it was not considered for the chemotherapy arm. Tumour progression was based on RECIST 1.1 criteria in both arms of the trial. RECIST 1.1 criteria count pseudo-progression and progression events, and the first progression is the event in the PFS curve for both arms, including pseudo-progression

This issue only affects PFS, not OS data, and is not considered to be a source of bias in the trial. Indeed, not providing for pseudoprogression in the chemotherapy arm can be considered conservative (i.e. favouring the chemotherapy arm), because pseudoprogression is counted as a PFS event and therefore is detrimental to PFS in the cemiplimab arm.

b. Please clarify how suspected pseudo-progression was managed, including whether treatment beyond RECIST-defined progression was permitted. If pseudo-progression was considered for both arms, please outline the management of this for each arm.

As stated in the study protocol: *“For a small percentage of cancer patients treated with anti-PD-1 therapy, unconventional responses may occur in which radiologic evidence of progression on therapy occurs before subsequent radiologic response. To account for this possibility in the cemiplimab treatment group, treatment beyond progression was allowed after consultation with the medical monitor at Regeneron if the following conditions were met:*

- *The patient had stable performance status*
- *The patient did not have rapid progression of disease*
- *The patient had not experienced adverse events that would require permanent discontinuation of cemiplimab*
- *The patient provided written informed consent prior to resuming treatment by signing the current version of the ICF (eg, the patient repeated the written informed consent that was done prior to initial study enrollment).*
- *It was understood that, if there was further progression after resumption of treatment ($\geq 30\%$ increase in tumor burden from the time of initial progressive disease by RECIST criteria; this includes an increase in the sum of all target lesions and/or the development of new lesions), that cemiplimab would be discontinued.”*

c. Were patients with pseudo progression reported in the progression-free survival (PFS) curves according to the time of pseudo-progression as this was the first documented progression according to RECIST 1.1? If pseudo-progression was considered for both arms, please clearly outline whether the reporting of progression differed between arms.

Response: See response to point 1a. The first event of progression is reported in the PFS curve for both arms, irrespective if it was pseudo progression. Therefore the reporting of progression did not differ between arms.

d. Please provide the proportion of patients with an unconventional response consistent with pseudo-progression who were treated beyond progression in the study. Please provide separate data for each arm. Please also comment on whether these events are primarily occurring early in the treatment.

Response: These data are not available, as a specific analysis on patients considered as ‘pseudoprogessors’ was not conducted. It would be expected that pseudoprogession would primarily occur early in treatment, as it is thought to result

from activation of the T-cells in response to the drug. However, no data on this are available.

- e. ***Please present any data available comparing outcomes in those treated beyond progression versus those not treated beyond progression (e.g. Table 48 from the EPAR¹⁹ and any similar data that the company has presented in publications, has provided to drug regulatory agencies or is available in the clinical study report). Please provide this for both arms if appropriate.***

Response: Table 48 in the EPAR²⁰ (replicated below) provides OS data from the minority (70 [23%]) of patients who fulfilled the criteria for treatment beyond documented progressive disease and the remaining 234 (77%) who did not. This indicates that re-treated patients continued to derive a benefit from cemiplimab; however, the proportion of patients experiencing death was similar in both subgroups (60% vs 60.7%) and, based on the confidence intervals around point estimates, there was no significant difference in median OS or survival probabilities over time. The EPAR notes (page 102) that the re-treated subgroup represents a highly selected patient population. We therefore consider that the results from a minority post hoc subgroup of the trial arm should be interpreted with caution. The ITT results from the trial provide the best estimate of treatment effects for cemiplimab and the comparator arm, and supports the licensed indication for cemiplimab, which permits treatment up to disease progression (or unacceptable toxicity).

Table 48: Overall Survival (FAS) – Patients Treated Beyond Progression Versus Those Who Were Not (Patients with SCC and non-SCC Histology)

	Cemiplimab treated beyond progression (N=70)	Cemiplimab not treated beyond progression (N=234)
Number of deaths, n (%)	42 (60.0%)	142 (60.7%)
Number of censored patients, n (%)	28 (40.0%)	92 (39.3%)
Median (95% CI), (months)[a]	13.9 (11.7, 17.9)	10.5 (8.2, 12.9)
HR (95% CI) [b][c]	0.798 (0.559, 1.141)	
Estimated Survival Probability, % (95% CI)[a]		
6 months	79.8 (68.3, 87.5)	66.5 (60.0, 72.2)
12 months	62.6 (49.8, 73.1)	46.4 (39.5, 53.0)
18 months	36.7 (24.0, 49.5)	32.8 (25.7, 40.0)
24 months	24.7 (13.0, 38.5)	23.9 (16.2, 32.3)
30 months	NE (NE, NE)	23.9 (16.2, 32.3)
36 months	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Jan 4th, 2021.

[a] Based on Kaplan-Meier method.

[b] Stratified by geographic region (North America versus Asia versus ROW) and Histology (SCC versus adenocarcinoma) according to IWRS.

[c] Based on stratified proportional hazards model (cemiplimab vs chemotherapy).

f. Please comment on whether treatment beyond progression is allowed within the license.

Response: The SmPC states that “Treatment may be continued until disease progression or unacceptable toxicity.”²¹ It does not allow for treatment beyond progression.

A16. We understand that patients and investigators were not blinded to treatment allocation for practical reasons. However, please can you confirm if disease progression or any other outcomes were assessed by blinded independent central review (BICR).

Response: Progression and response outcomes were investigator-assessed and not assessed by BICR. These were secondary endpoints in the trial. The primary outcome measure in the trial was overall survival, which is an objective outcome measure.

A17. PRIORITY *Please clarify why Programmed Death-Ligand 1 protein (PD-L1) on Tumour Cells (TC) status was not measured prospectively given the mechanism of action for cemiplimab. Is it correct that many patients had unknown PD-L1 status as their sample was over 6 months old at time of testing (Oaknin 2025).²² Our clinical experts suggested that samples over 6 months old are used in clinical practice to test for PD-L1 status. Please comment on why PD-L1 status could not be measured in all trial participants. Table 9 in the Appendix of the clinical expert interviews,²³⁻²⁶ suggests analyses were previously conducted using PD-L1 determined within or outside of the 6-month window providing a larger sample of 371 patients with known PD-L1 status (Oaknin 2022)²⁷ versus the 254 reported in the final analysis (Oaknin 2025). Please provide a summary of the methods and findings of the analyses reported in Oaknin 2022 and comment on why the data using the larger sample size were not presented in Oaknin 2025.²²*

Response (PD-L1 testing and previous analyses): In the EMPOWER Cervical-1 trial patients were enrolled regardless of PD-L1 expression status. Collection and testing of tumour samples for PD-L1 status before treatment was not required in the trial design, to avoid delay in treatment in this end-of-life condition.²⁸ The objective was to enroll patients regardless of PD-L1 status because of the high unmet need in patients who have progressed after platinum-based chemotherapy. PD-L1 expression status was retrospectively assessed in archived (pre-treatment) tumour samples, and exploratory analysis of OS by PD-L1 status in the final data cut was conducted. It is important to note the following points:

- PD-L1 testing was carried out post-randomisation, so randomisation was not stratified by PD-L1 status.
- Only 61% of patients (371 of 608) had tumour samples evaluable for PD-L1 status (as noted in the final CSR p. 134, 83 samples were not evaluable due to failing assay quality control criteria, 102 samples could not be accessioned per CLIA (US Centers for Disease Control Clinical Laboratory Improvement Amendments) requirements due to missing sample labels, and 52 participants were enrolled without a submitted tissue sample).
- Only 42% of patients (254 of 608, 126 in the cemiplimab group and 128 in the chemotherapy group) had evaluable samples in which staining took place

within the assay manufacturer's recommended 6-month stability window from the sample being mounted.²⁹

- This was considered to be the most appropriate data set for the analysis in both the initial and the final study publications (Tewari 2022¹ and Oaknin 2025²²), because it reflects the manufacturer's instructions for use.¹
- The findings of this analysis conducted in the final data cut are set out in Oaknin 2025.
- Oaknin 2022 also included an exploratory analysis in the 371 patients with samples tested within and outside of the manufacturer's 6-month stability window. For this submission, we have supplied an exploratory analysis in the larger (n=371) PD-L1 tested population in the final data cut (see rationale below), for which the methods are set out in CQ Appendix 1 and comment on the results is given in response A18.

Response (NHS clinical practice and use of n=371 data set for the submission):

Like the EAG, the Company was advised by NHS gynaecologic consultant oncologists practising in England that in NHS practice, only one biopsy is taken, at the beginning of systemic treatment for cervical cancer. Patients are not generally re-biopsied later in their treatment journey, and the initial biopsy is used for all subsequent testing, regardless of time since staining. The data-set of all patients with PD-L1 status available, regardless of staining interval (n=371), is therefore considered most appropriate for use in a scenario analysis to inform the submission, as it best reflects NHS clinical practice and provides the largest sample size. A post hoc exploratory analysis of PFS and OS in this group, adjusted for ECOG PS, was conducted for the submission using individual patient-level data. Time-on-treatment was also analysed. This is described in CQ Appendix 1 and commented on in response A18.

A18. PRIORITY *The EAG understands that the population without prior immunotherapy at 2L is expected to be dominated by those with PD-L1 CPS <1 due to the availability of first-line (1L) pembrolizumab for those with PD-L1 CPS ≥ 1. Please comment on the subgroup analysis results by PD-L1 status (TC < 1% or TC ≥ 1%) available from EMPOWER Cervical-1 and whether the clinical effectiveness from the whole trial intention-to-treat (ITT) population is*

generalisable to the population who will be treated with cemiplimab in clinical practice. In addition to addressing whether any differences in treatment effect would be expected for a predominantly PD-L1 CPS <1 population, please comment specifically on whether PD-L1 TC < 1% is equivalent to PD-L1 CPS <1.

Response (subgroup analysis by PD-L1 status): As discussed in response A17, a post hoc exploratory analysis of overall survival by PD-L1 status in all patients with known PD-L1 status (n=371), was conducted to inform the submission using individual patient-level data. The methods and results are presented in CQ Appendix 1.

Results of the PD-L1 subgroup analysis

The analysis using the larger (n=371) data set with evaluable PD-L1 status found no significant difference in efficacy between the PD-L1 status groups and the HRs are very similar. Please see the details in Table 1. Therefore, there is no generalisability issue. However, we have conducted a scenario analysis, where we have estimated the weighted average ICER using the estimated proportion of PD-L1<1% and PD-L1≥1% patients among those eligible for cemiplimab in response to Question A21. This scenario has decreased the ICER. (Please see results under Question A21 and in Appendix 2.)

Table 1. Comparison of the hazard ratios for the ITT population and the PD-L1 subgroups

Population	n	OS HR	OS Interaction Effect P-Value	PFS HR	PFS Interaction Effect P-Value
All patients with PD-L1 status (N=371)					
ITT					
PD-L1<1	134				
PD-L1≥1	237				

Interpretation and validity of the PD-L1 subgroup analysis

Due to the small sample size in some subgroups, the exploratory subgroup analyses of EMPOWER Cervical-1 by PD-L1 status are underpowered, especially in the PD-L1<1% subgroup where the sample size of patients with known PD-L1 status was only 22% of the overall population (66 and 68 patients in the cemiplimab and chemotherapy arm, respectively). This leads to greater uncertainty and wider confidence intervals. The additional need to adjust for ECOG performance status further increases uncertainty. Therefore, there are challenges to providing robust analyses of OS by PD-L1 status. However, despite uncertainty arising from small subgroup sample sizes, both pre-specified and exploratory subgroup analyses indicate a consistent OS benefit with cemiplimab across all patients meeting the licensed indication, including those with PD-L1 $\geq 1\%$ and those with PD-L1<1%. Given this consistency, and as the EMPOWER-Cervical 1 trial was designed to evaluate the efficacy of cemiplimab in the ITT population, the results based on the ITT population are appropriate to assume across the licensed indication, because:

- they are based on a much larger sample size that is adequately powered for analysis and is balanced for important known treatment-effect modifiers
- they form the basis of the licensed indication for cemiplimab²⁹
- they are the basis of the strong recommendation (level I, A) for the use of cemiplimab in the ESGO/ESTRO/ESP joint clinical guideline, which does not differentiate by PD-L1 status.²

UK clinical experts interviewed by Regeneron deemed the EMPOWER Cervical-1 trial to be representative of the patient population in England and Wales.³⁻⁵ While the proportion of patients with PD-L1<1 status might differ in clinical practice to that in the EMPOWER Cervical-1 trial, the highly similar HRs described above in the different subgroups indicates that the ITT results are generalizable to all patients, including those with PD-L1<1%. It is of note that the ESGO/ESTRO/ESP cervical cancer clinical guidelines recommend the use of cemiplimab irrespective of PD-L1 status,² which is in line with its licensed indication.

Equivalence of different PD-L1 assays

PD-L1 status can be measured using various different assays, and expression can be scored in different ways and to different threshold cut-offs. PD-L1 TC stands for Tumor Cell score, and PD-L1 TC < 1% denotes fewer than 1% positive cells. PD-L1 CPS <1 stands for Combined Positive Score <1; CPS is calculated by dividing the count of PD-L1 positive cells (tumour + immune) by the total number of viable tumour cells, then multiplying by 100, resulting in a score from 0 to 100+. ³⁰ Different assays and scoring systems are not necessarily equivalent. Work has been done in lung cancer to suggest that the two scoring systems may be equivalent, ³¹ but we could not identify similar studies in cervical cancer.

However, the fact that 1st line use of pembrolizumab is determined by PD-L1 by CPS, whilst the testing conducted in the EMPOWER Cervical 1 trial assessed PD-L1 by TC, is irrelevant given that cemiplimab is licensed for use irrespective of PD-L1 status.

A19. PRIORITY Oaknin 2025 presents overall survival (OS) by PD-L1 expression (TC < 1% or TC ≥ 1%) within and without adjustment for Eastern Cooperative Oncology Group performance status scale (ECOG PS).²² Please clarify why the adjustment for ECOG PS was conducted and comment on whether either analysis (with or without ECOG PS adjustment) better predicts the treatment effectiveness of cemiplimab in patients with a PD-L1 CPS < 1.

Response:

Rationale for ECOG adjustment

ECOG PS is a known predictor of outcome for cancer patients and was therefore used as a randomisation stratification factor in EMPOWER Cervical-1, to ensure the two treatment arms were well balanced for ECOG PS. ¹³ Because PD-L1 testing was carried out in archival samples post-randomisation, and results were not available for all patients, this stratification was lost in the data set of patients with known PD-L1 status. This resulted in important differences in the distribution of ECOG PS between the treatment arms within the data set using the 6-month stability window. ¹³ In patients with PD-L1 < 1 % (n = 92), there were more with poorer ECOG PS (PS 1) in

the cemiplimab than in the chemotherapy arm (■■■■■). Because PS is a treatment-effect modifier, the analysis was adjusted for ECOG PS using covariance analysis.

Because there was an imbalance in ECOG PS between treatment groups in the population with known PD-L1 status, the ECOG-adjusted analysis provides the best estimate of treatment effects by PD-L1 status, and confirmed that the ITT results are generalisable to all patients, irrespective of PD-L1 status.

In the larger dataset, that includes all patients with recorded PD-L1 status (n=371) randomisation is also broken, the ECOG imbalance is negligible. In patients with PD-L1 < 1 % (n = 104), the proportion of patients with poorer ECOG PS (PS 1) was ■■■ in the cemiplimab and ■■■ in the chemotherapy arm.

A20. PRIORITY Please can the company provide Kaplan-Meier (KM) plots for PFS, OS and time on treatment (ToT) from EMPOWER Cervical-1 stratified by PD-L1 status. If possible, can this be done both for the group with samples less than 6 months old, reported in Oaknin 2025,²² and for the larger cohort reported in Oaknin 2022.²⁷

Response: Please find the curves below. However please note, as discussed in the response to Question A18, the comparators in these post-hoc analyses are not comparable due to the differences in ECOG PS status, which is an important prognostic factor, and was therefore a stratification factor in the EMPOWER Cervical-1 trial.

Figure 1: Kaplan Meier Plot: OS stratified by PD-L1 status (for patients with samples outside the 6-month stability window, not adjusted for ECOG PS status)

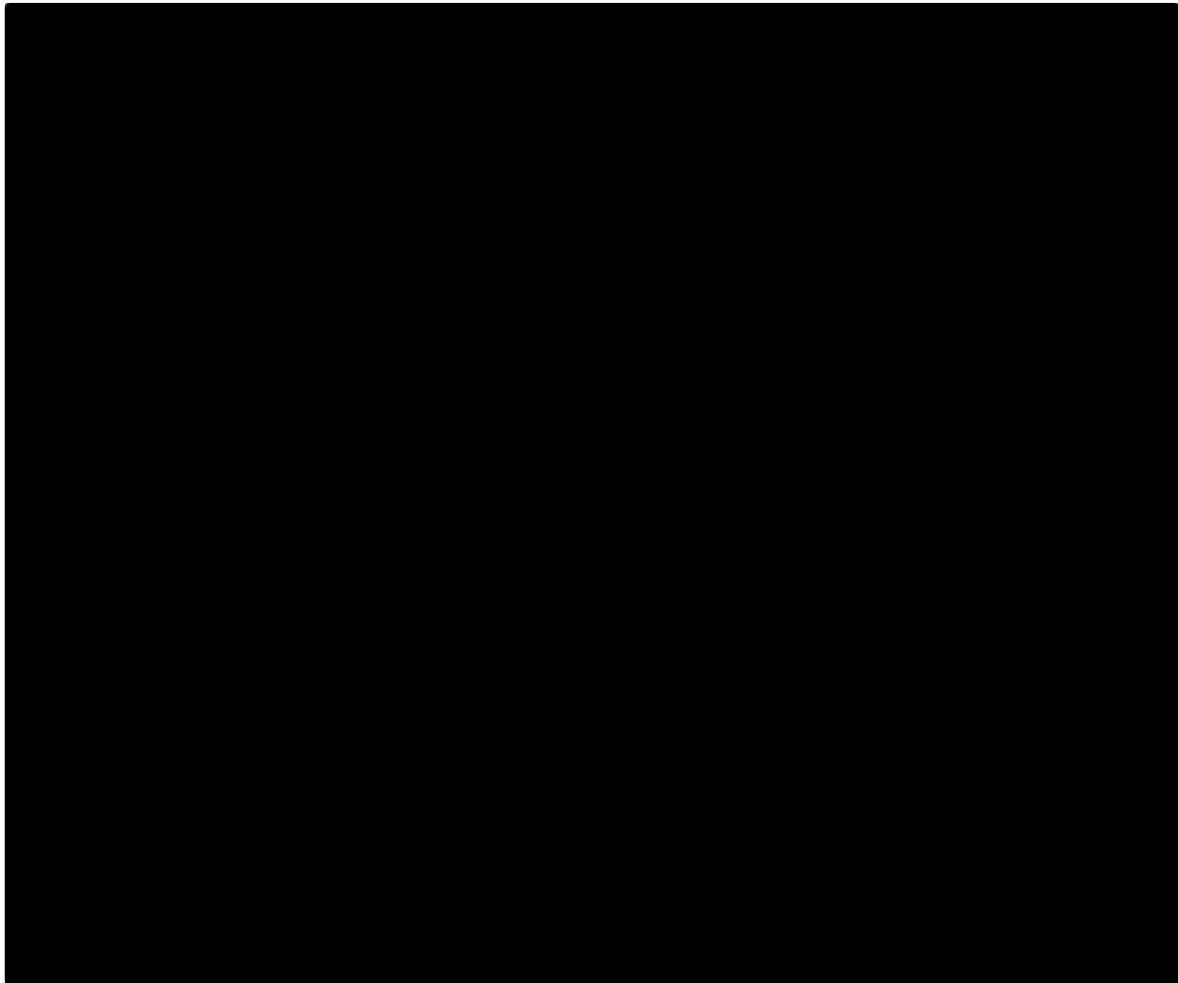


Figure 2: Kaplan Meier Plot: PFS stratified by PD-L1 status (for patients with samples outside the 6-month stability window, not adjusted for ECOG PS status)

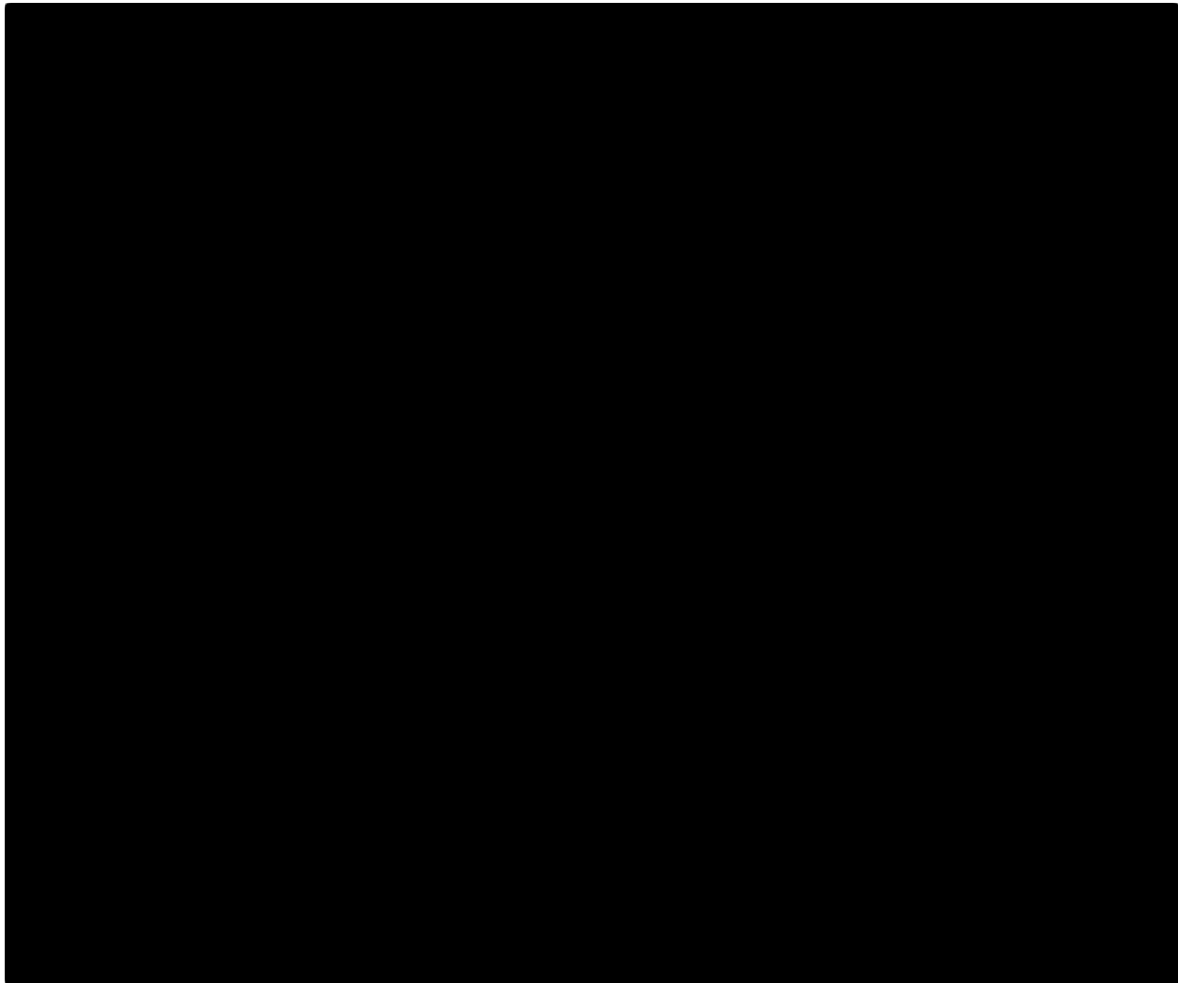


Figure 3: Kaplan Meier Plot: ToT stratified by PD-L1 status (for patients with samples outside the 6-month stability window, not adjusted for ECOG PS status)

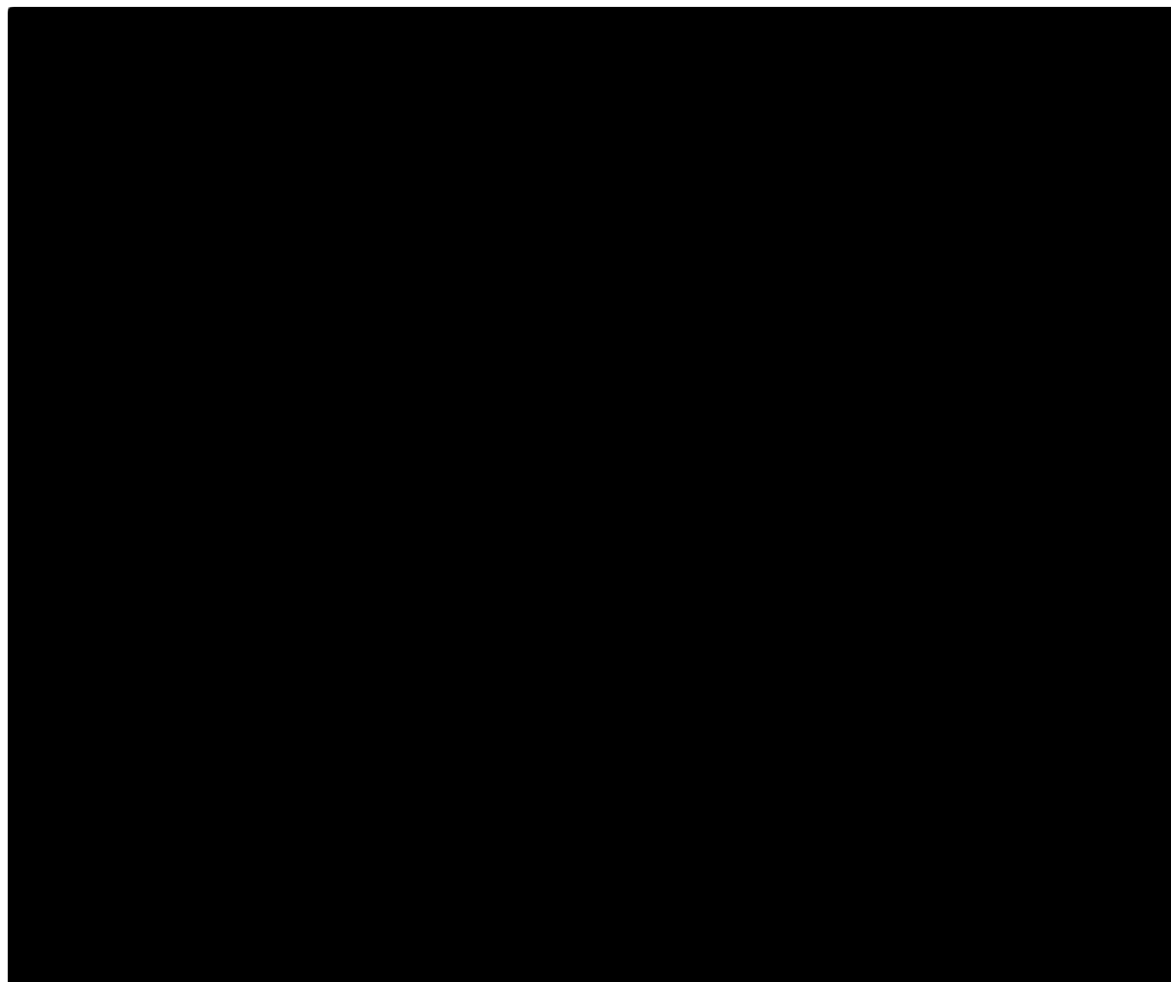


Figure 4: Kaplan Meier Plot: OS stratified by PD-L1 status (for patients with samples within the 6-month stability window, not adjusted for ECOG PS status)

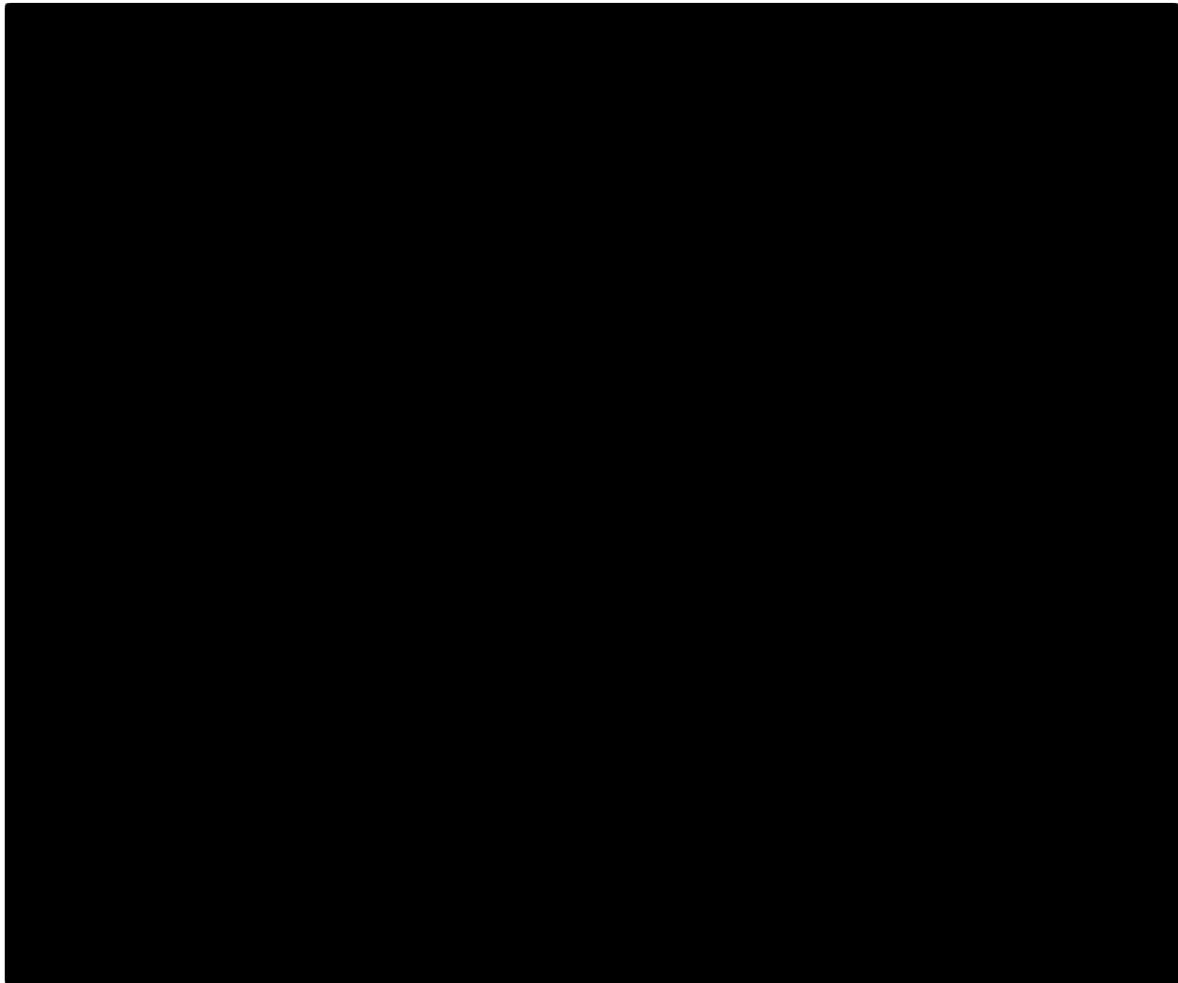


Figure 5: Kaplan Meier Plot: PFS stratified by PD-L1 status (for patients with samples within the 6-month stability window, not adjusted for ECOG PS status)

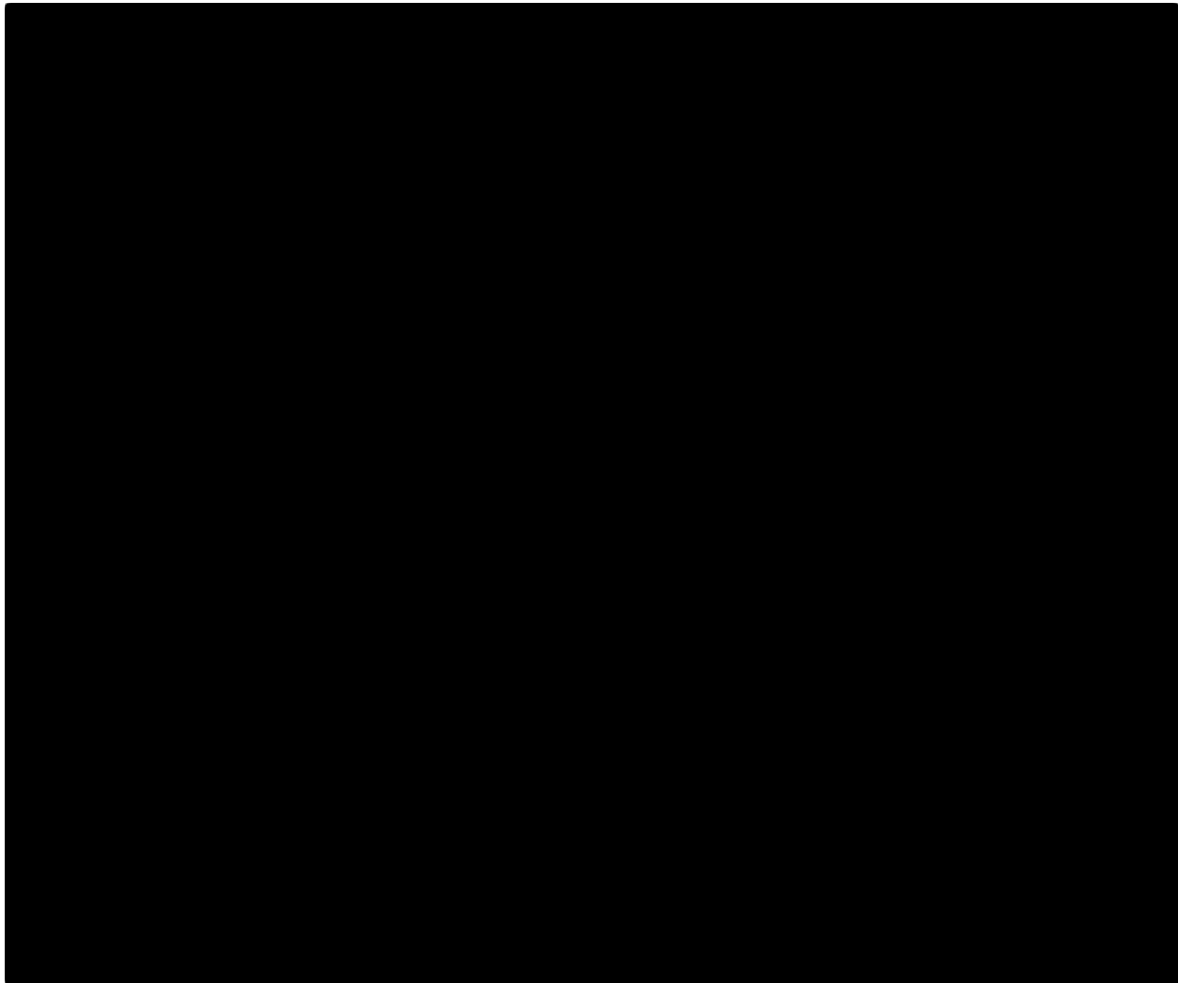
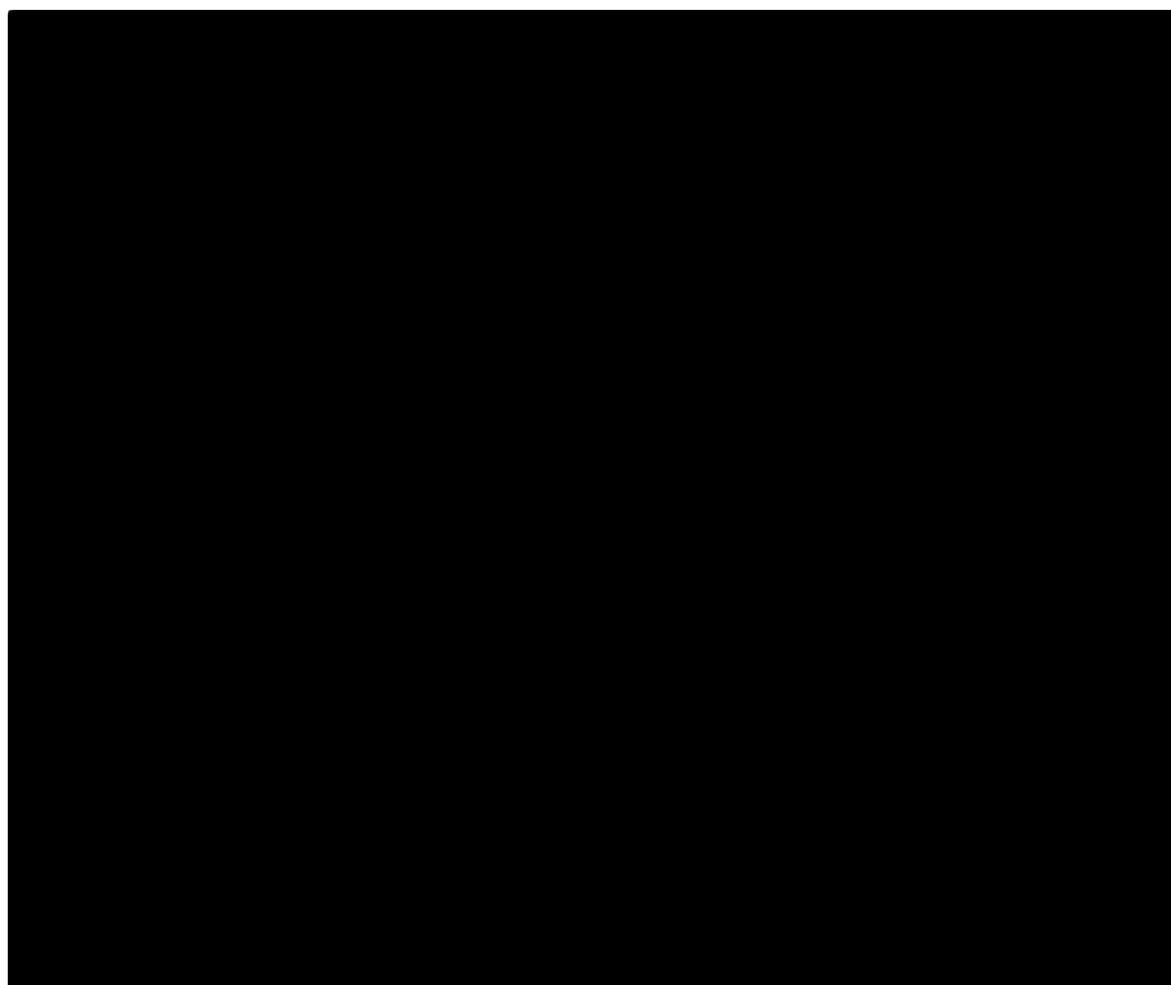


Figure 6: Kaplan Meier Plot: ToT stratified by PD-L1 status (for patients with samples within the 6-month stability window, not adjusted for ECOG PS status)



A21. PRIORITY *The Scottish Medicines Consortium (SMC) advisory document on cemiplimab for this indication describes economic scenario analysis conducted using efficacy for the PD-L1 <1% population and a scenario analysis in which the population was reweighted for PD-L1 status (scenarios 4 and 5 in Table 6.2 of the SMC advisory document).³² Can the company describe these scenarios presented to the SMC in more detail. Can the company present equivalent scenarios for the model provided in its NICE submission.*

Response:

Scenario 4 (PD-L1 <1% population) was provided to SMC as an exploratory analysis but was ultimately not used for decision-making by the SMC, as it is not in line with the licence and the unmet need. As the Patient and clinician engagement

(PACE) statement pointed out, concentrating only on the PD-L1<1% subgroup “leaves a significant gap and a high unmet need”.³³

The use of the PD-L1 < 1% subgroup is inconsistent with the cemiplimab licenced indication, clinical guideline recommendations, the clinical evidence base, and clinical expert recommendations, which all support the use of cemiplimab irrespective of PD-L1 status. It excludes a small, but meaningful proportion of the eligible population who express PD-L1 $\geq$ 1% at the time of relapsed/recurrent disease following platinum chemotherapy but who for a variety of reasons did not have the opportunity to receive pembrolizumab in the first-line setting, and who have a particularly high unmet need. This would have created an equity concern. The scenario was estimated using data from patients whose PD-L1 assessment was within the 6-month stability window, and the results were adjusted for ECOG PS status.

There is no significant difference in the overall survival of cemiplimab by PD-L1 status, and, similarly to Scotland, the use of this subgroup would create equity concerns and is not in line with the cemiplimab licenced indication, clinical guideline recommendations, the clinical evidence base or clinical expert recommendations, and is not required by the NICE scope.³⁴ However, we have estimated this scenario for England and Wales.

In this scenario, the survival analysis was conducted for each ECOG subgroup in the PD-L1<1% population (ECOG 0 vs. ECOG 1) (please see Appendix 1), and then the survival curve for the population was estimated as the weighted average of the ECOG subgroups using the proportion of ECOG 0 vs 1 patients in the population (proportion of patients with ECOG 0: 45.5%). The parametric models used in the base case ITT analysis provide one of the best fits in this scenario. As the patient numbers are low in each ECOG subgroup, and therefore the results of the survival analysis are uncertain, the same parametric models were used as in the ITT population. All patients, who had PD-L1 status were included in the analysis to reflect clinical practice as described by the clinical experts interviewed by both the EAG and Regeneron.

This resulted in a 1.71% decrease in the ICER (by [REDACTED]) without the addition of severity weighting. Please see Appendix 2 for more information. Please see the separate model version also for the implementation.

Scenario 5 was submitted to SMC to represent the full target population for cemiplimab in Scotland, estimated from the budget impact model. This included 74% of patients expressing PD-L1<1% and the 26% patients expressing PD-L1 ≥1%. Results were estimated in three steps:

1. Total costs and total QALYs for the PD-L1<1% and the PD-L1≥1% subgroups were estimated in each subgroup separately using the smaller dataset within the 6-months stability window,
2. Total costs and total QALYs were reweighted using the proportion of expected Scottish patients in each subgroup,
3. The ICER was estimated from the reweighted results.

Please see the same scenario for NICE using the larger dataset (all patients with PD-L1 status) in Appendix 2. According to the calculations in the budget impact model, 96% of patients eligible for cemiplimab are expected to be PD-L1<1% in England and Wales. The parametric models used in the base case ITT analysis provide one of the best fits in this scenario. As the patient numbers are lower in each PD-L1 subgroup, and therefore the results of the survival analysis are more uncertain, the same parametric models were used as in the ITT population. Using this estimate, the ICER decreased by 12.62% (by [REDACTED]) compared to the base case without the severity weighting. Please see separate model version for the implementation.

A22. PRIORITY CS page 20. The CS states that 'NHS gynaecologic consultant oncologist experts practicing in England indicated that there is no standard of care for 2L chemotherapy in the NHS, and clinical practice varies. Weekly paclitaxel monotherapy is a commonly used 2L treatment and single-agent chemotherapy with topotecan, gemcitabine, irinotecan or vinorelbine is also used in some cases. Patients who have had a long interval since the last treatment (> 6-12 months) may be rechallenged with carboplatin + paclitaxel.

Clinical trials are also an option in 2L if available'. Please comment on how generalisable the chemotherapy comparator treatments used in EMPOWER Cervical-1 trial are to current clinical practice in England, and how this variation in practice has been considered in the interpretation of the trial results and the economic analyses?

Response: As noted in the NICE scope and in CS Table 1, CS p. 20 and CS p. 93, in current practice there is no standard of care therapy 2L treatment of r/mCC after platinum-based chemotherapy, and therefore the basket of investigator-chosen single agent chemotherapies used in the EMPOWER Cervical-1 trial is used in the submission base case.

- The generalisability of the trial treatments to NHS clinical practice was discussed with NHS consultant gynaecologic oncologists consulted for the submission. These experts confirmed that the efficacy results of the EMPOWER Cervical-1 trial single-agent chemotherapy arm are representative of expected outcomes with chemotherapy regimens used in UK clinical practice.^{3-5 35}
- This is borne out by the ESMO clinical guideline, as discussed on CS p. 24. The guideline states that “In patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates are low and duration of responses is short. Therefore, no recommendation can be given about the most effective second-line treatment.” A summary table of second-line therapy outcomes in metastatic CC presented in the guideline shows OS ranging from 5.0 to 12.7 months.³⁶ This is in line with the median OS with chemotherapy in EMPOWER Cervical-1 of 8.5 (95% CI 7.5–9.6) months.
- Thus, efficacy is similar regardless of the choice of 2L chemotherapy option. It should also be noted that the 2L chemotherapy options are all low-cost generic agents that are widely used throughout oncology, and the choice of option is therefore not influential for cost-effectiveness.

- An alternative distribution of 2L chemotherapies based on regimens stated by clinical experts as being most commonly used in NHS practice was explored in a scenario analysis (see CS Table 50, p. 146 for treatments used). Due to the low cost generic chemotherapies available as comparator treatments, changing the comparator drug costs had a negligible effect on the ICER (as noted above, efficacy is considered similar between 2L regimens).

A23. In the EMPOWER Cervical-1 trial, approximately 40% of patients had received more than one prior line of systemic therapy for r/m CC, placing these patients at 3L+. Please can the company provide a comment on the potential implications in terms of efficacy for this sub-population who have received more than one prior line of therapy. In Figure 11 of the CS, the sub-group analysis of PFS according to line of therapy is presented, but this is not presented for OS. Please comment on the generalisability of the results from the whole ITT population to patients receiving cemiplimab second line after platinum-based treatment for r/m CC (i.e. only one prior line of treatment).

Response: Some parts of the subgroup analysis forest plot of OS were inadvertently omitted from the CS due to a copy-paste error. We apologise for the confusion. The full forest plot is presented in Figure 6 of the CSR (pages 71-72), and the components missing from the CSR are presented in response A26.

With regard to number of prior lines of therapy for r/mCC, the HR for OS was 0.580 (95% CI 0.455, 0.739) in patients with 1 prior line and 0.794 (95%CI 0.599, 1.052) in patients with >1 prior line. The wider confidence interval for the latter group may be partially due to the smaller sample size (56.9% of patients in the trial had 1 prior line and 42.6% had >1, see CS Table 8, p. 45). However, it is to be expected (as is commonly seen in oncology trials) that patients with >1 prior lines of therapy will, on average, have shorter survival than those with only 1 prior line, because they are further along in the disease course.

Because 42% of patients in EMPOWER Cervical-1 had >1 prior line of therapy, the benefits seen in the ITT trial results are conservative in terms of patients with only one prior line (the group most likely to receive cemiplimab in NHS clinical practice). This is confirmed by the more favourable HR seen in the 1 prior line subgroup.

A24. PRIORITY *Please clarify if the inclusion criteria were originally restricted to those with progression within 6 months of the last platinum-containing chemotherapy.*

- a. If this was the case in the original protocol, please clarify when this was amended, and what proportion of the population were recruited prior to the protocol amendment.*
- b. Please comment on whether the ITT results are generalisable to patients who have progressed more than 6 months after platinum.*
- c. Please also comment on whether the absence of a platinum-rechallenge option in the list of comparator chemotherapy regimens is of significance for patients who have progressed after more than 6 months after finishing their previous platinum-based chemotherapy.*

Response: The original protocol inclusion criterion was for patients who had progressed within 6 months of platinum-containing therapy (see pages 2-12 of the protocol submitted in the CS reference pack). Protocol amendment 4 (as of August 2018) changed this to patients with tumour progression or recurrence that occurred after treatment with cisplatin or carboplatin.¹³

As noted in the EPAR (page 99-100),²⁰ the treatment arms were balanced according to the period after prior platinum (≤ 6 months vs. > 6 months) at which patients were recruited, and by specific platinum compound (i.e., carboplatin, cisplatin). About 88% of patients had a platinum-free interval ≤ 6 months (and 55% of patients recruited to the trial had discontinued platinum-based chemotherapy due to progression while on treatment). The platinum-free interval by longest and shortest duration (some patients were re-treated with platinum) showed a balanced distribution between the arms of the trial, and an ad hoc analysis of efficacy in terms of OS/PFS/ORR/DOR according to platinum-free interval suggests that the benefit of cemiplimab over chemotherapy seems to be maintained regardless of the time interval to progression after prior platinum therapy, even in the ≥ 12 months subgroup (for which retreatment with platinum could potentially be a choice).²⁰

The regulator (EMA) did not limit the licensed indication to progression within 6 months of platinum therapy, and confirmed that the trial data justify the licensed indication. All five choices of chemotherapy in the control arm were deemed acceptable (EPAR page 99).²⁰ Clinical expert opinion sought by the company confirmed that the trial was reflective of the anticipated use of cemiplimab in practice and the outcomes they would anticipate to see with existing chemotherapy options used in practice. We therefore believe the ITT results are generalisable to patients meeting the licensed population, including those with progression ≤ 6 months and > 6 months after prior platinum-containing therapy.

A25. Please provide more information on outcomes in the ECOG PS 2 subgroup in the Multicenter Italian Trials in Ovarian cancer and Gynecologic Malignancies (MITO) 44 study and how these compare to outcomes in the ECOG PS < 2 subgroup which aligns with the EMPOWER Cervical-1 trial. Did the company ask clinical experts whether they would consider patients with an ECOG PS of 2 as being suitable for cemiplimab within their clinical expert interviews.²³⁻²⁶ If so, then please summarise the clinical experts' responses on this issue.

Response: In the MITO 44 study, 24 patients (18.8%) had ECOG PS 2 at the start of cemiplimab. In patients with PS 2, median PFS was 4 months (range 3–6) and median OS was 12 months (range 11-NR).³⁷ This was almost the same as the results for the overall MITO study population (median PFS 4.0 months [range 3.0–6.0], median OS 12.0 months [12.0- NR]). The authors noted that this confirmed the efficacy of cemiplimab in frail patients.

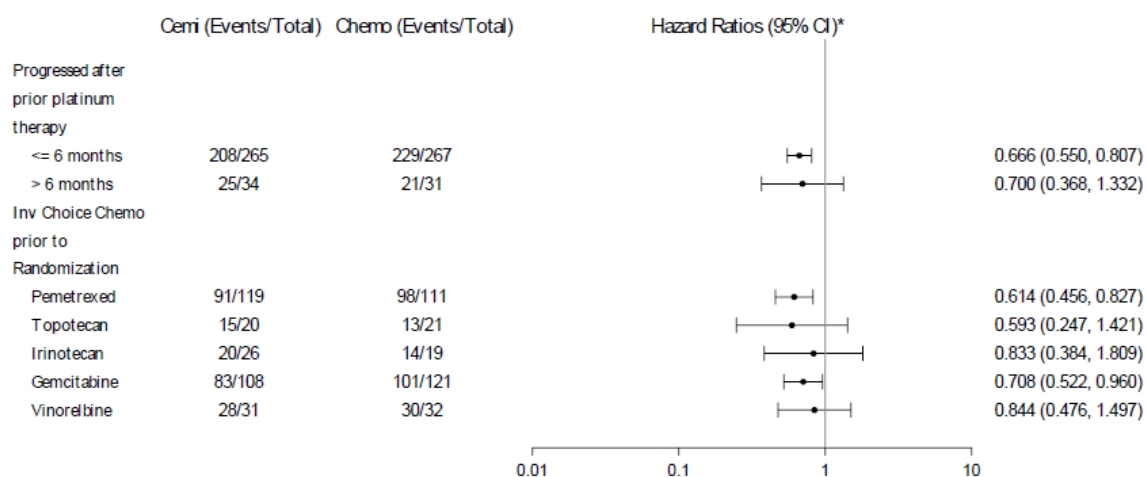
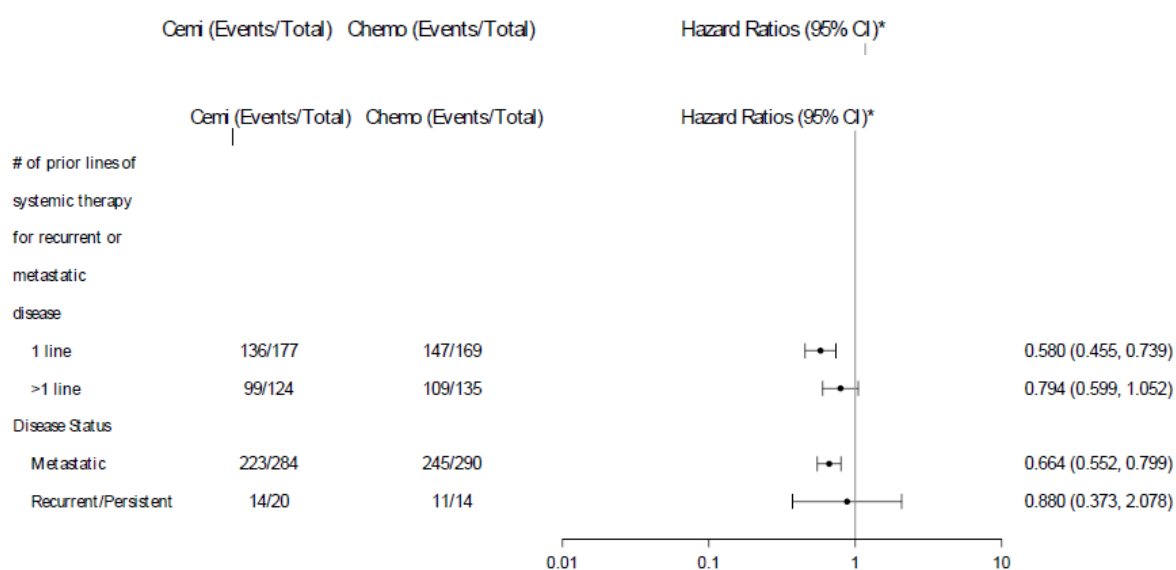
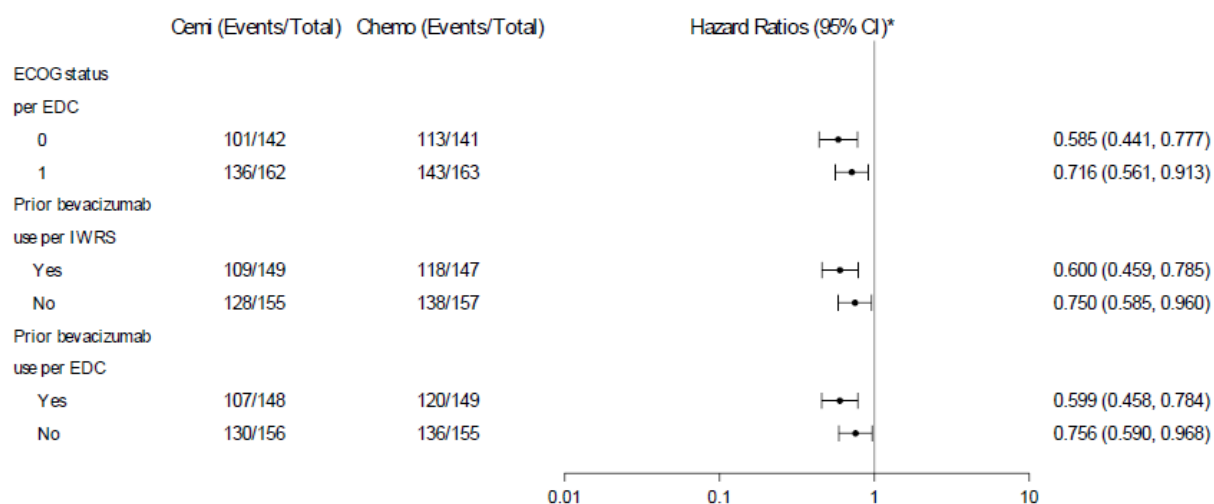
The Company did not ask clinical experts about whether patients with PS 2 would be suitable for cemiplimab. All expert interview questions were submitted with the CS.

Of note, it is common for patients with ECOG PS 2 to be excluded from trials of oncology therapies. Indeed, such patients were also excluded from both the pembrolizumab KEYNOTE-826 trial and the bevacizumab GOG 240 trial.^{38 39} The MITO 44 study suggests that cemiplimab can be effectively used in patients with ECOG PS 2 if deemed suitable by the treating physician.

A26. PRIORITY *In Section 2.8, the company present the pre-specified sub-group analyses for OS and PFS, a summary of the analyses presented is shown below. Please can the company provide the missing sub-group analyses for OS.*

	PFS	OS
Age group 1	✓	✓
Age group 2	✓	✓
Race	✓	✓
# prior lines of systemic therapy for r/m CC	✓	
Disease status	✓	
Time after progressing from prior platinum therapy	✓	
IC chemotherapy prior to randomisation	✓	
Histology (IWRS)	✓	✓
Histology (EDC)	✓	✓
Geographic region group 1	✓	✓
Geographic region group 2	✓	✓
ECOG (IWRS)	✓	✓
ECOG (EDC)	✓	
Prior bevacizumab use (IWRS)	✓	
Prior bevacizumab use (EDC)	✓	

Response: Some parts of the subgroup analysis forest plot of OS were inadvertently omitted from the CS due to a copy-paste error. We apologise for the confusion. The full forest plot is presented in Figure 6 of the CSR (pages 71-72), and the components missing from the CSR are presented below.



A27. In the OS chemotherapy KM curve, Figure 5 of the CS, there is no censoring between 8 months and 24 months, please can the company provide

comment on potential reasons for this, and why this was not observed in the cemiplimab arm.

Response: We confirm that no patients were censored in the chemotherapy arm over the time period between 8 and 24 months; however, many patients experienced death, which precludes the opportunity for censoring. The censoring rate is generally expected to be low up to 24 months given that patients would be expected to remain on follow up unless they choose to withdraw from the study. For the cemiplimab arm there are fewer deaths, reflecting its superior efficacy, and consequently this presents more opportunity for censoring to occur.

A28. Why was earlier data cut-off (DCO) (4 Jan 2021 Primary analysis) used for patient reported outcomes (PRO) when a later DCO is available for other outcomes (3 Oct 2023 for OS, PFS etc)?

Response: The PRO results presented in the CS are from the primary analysis of the trial (4 Jan 2021) and have been fully published in Oaknin 2022.⁴⁰ Results from that primary analysis and from the later DCO presented in the final analysis CSR (03 Oct 2023) are highly consistent, with no evidence of attenuation of the results for cemiplimab versus the results for chemotherapy between the primary and later analysis. However, the PRO results from the final analysis have not been published.

We refer the EAG reviewers to section 5.1.7 of the final CSR for the later DCO PRO results and invite them to compare these with the results presented in the same section of the primary CSR (submitted with these responses),²⁸ to verify that the results and conclusions of the analyses presented in the CS still hold.

A29. CS, Section 2.6.6. When describing the PROs, the figures show timings reported using cycle days e.g. C2D1 for cycle 2, day 1. Please clarify if this is referring to the 6-week cycle implemented in the clinical trial.

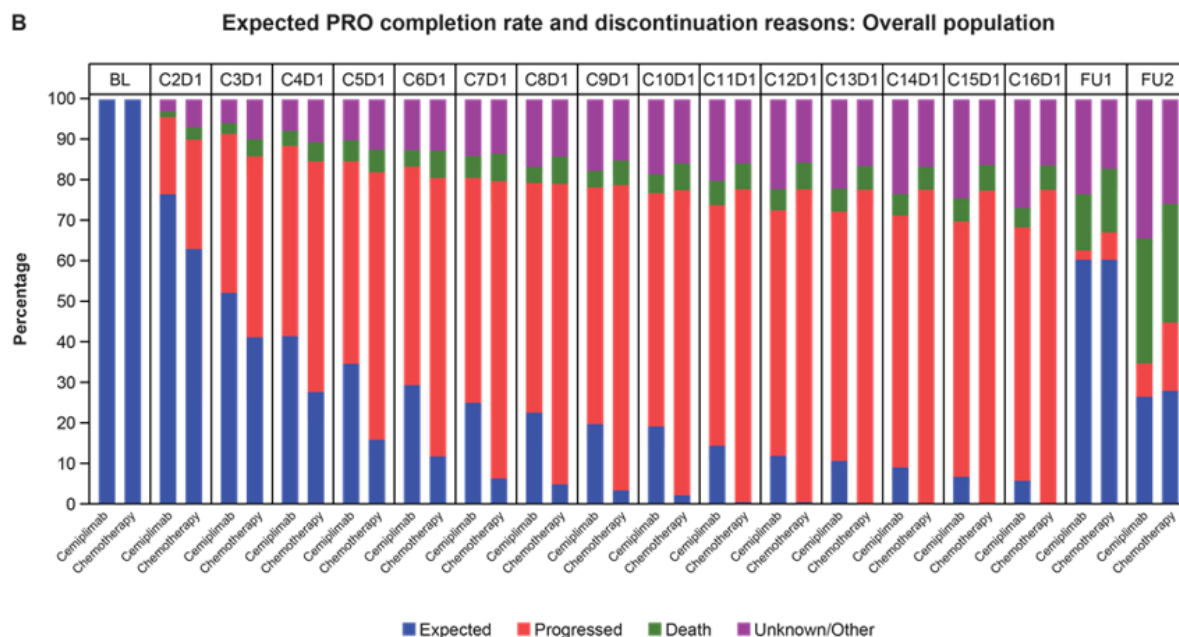
Response: As reported in Oaknin 2022 (p. 301), patients completed the EORTC QLQ-C30 at baseline and on day 1 of each 6-week treatment cycle, up to cycle 16 or disease progression, and then at two post-treatment follow-up visits.⁴⁰ The figures in the CS are taken from this publication and refer to the same timings.

A30. Can the company provide reasoning for why some patients only completed the baseline health-related quality of life (HRQoL) questionnaires and no subsequent follow-up HRQoL questionnaires.

a) Please can the company summarise whether there were any significant differences in these baseline PROs compared with the group who did report subsequent PROs.

Response: Information on reasons for non-completion of PROs is available in the Oaknin 2022 supplementary material, supplied with the CQ responses. In the figure below, disposition is shown as the percentage of patients who were expected to complete the PRO assessment by visit, with reasons patients discontinued the study early (as of the first published data cut). Other reasons included lost to follow-up, patient or physician decision, or withdrawal of consent. As can be seen from the figure, some patients discontinued the study at each visit, and these patients were not expected to complete the PRO questionnaire at that visit. As reported in Oaknin 2022: “Per the PRO statistical analysis plan, between-group comparisons of PRO data were limited to on-treatment analyses. Continued comparison of PROs after the discontinuation of study treatment would have limited generalisability because it would be confounded by the effects of subsequent treatments on QoL and symptoms⁴⁰.”

Among patients still on study and who are expected to complete PRO per protocol, >95% completed at least one PRO scale at baseline and approximately 90% completed at least one PRO scale at each subsequent assessment.⁴⁰ The proportion of patients who completed the baseline PROs but no subsequent PROs is therefore small. Information on PRO differences between this small group and the rest of the study population would be unable to robustly aid decision-making due to the inherent uncertainties in any comparisons.



Abbreviations: BL, baseline; C, cycle; D, day; PRO, patient-reported outcome; SCC, squamous cell carcinoma. Source: Oaknin 2022, Supplementary Figure 3.

b) Please can the company confirm whether the ‘number of patients’ in Figure 7 of the CS corresponds to those who completed the HRQoL questionnaires at baseline and at least one follow-up time point.

Response: We can confirm that the number of patients in figure 7 of the CS corresponds to those who completed the HRQoL questionnaires at baseline and at least one follow-up time point. In Oaknin 2022 Figure 1, from which CS Fig 7 is taken, the footnote states that scheduled visits with <10 patients in either arm, unscheduled visits and off-treatment visits were not included in the analysis.

A31. The company reports that only █ patients out of 396 patients who progressed completed HRQoL questionnaires. Please can the company comment on why so many patients did not complete HRQoL questionnaires following progression. The company also stated that █% of these patients were in the cemiplimab arm. Please can the company further comment on the imbalance of PRO collection following progression.

Response: See response A30 for completion rates and reasons for study discontinuation. In Oaknin 2022, the authors noted that “PRO completion rates in this

study were high and similar in both treatment arms, suggesting low bias. There was a higher dropout rate in the chemotherapy arm due to differences in progression and survival in favour of cemiplimab⁴⁰.” Lower completion rates in patients who have progressed are to be expected, as some of these patients will be in a poor clinical state (both physically and emotionally) and completing questionnaires will not be a priority for such patients or their medical professionals.

The Oaknin 2022 authors also note that PROs collected after the discontinuation of study treatment (which was most commonly due to progression) would be confounded by the effects of subsequent treatments on QoL and symptoms. They noted that sensitivity analysis with PMM partly addressed the concern about the higher dropout rate in the chemotherapy arm by showing that differences also favoured cemiplimab when data were assumed to be missing-not-at-random. These analyses are shown in the Oaknin supplementary material, Supplementary figure 4B and 4D.

Further information on the specific reasons for the difference in PRO collection after progression is not available. It might be expected that patients with better HRQoL would be more likely to attend visits and fill out questionnaires than those patients in poorer health, but no data are available to confirm this.

Section B: Clarification on cost-effectiveness data

Comparator interventions

B1. PRIORITY *The CS states that weekly paclitaxel is a commonly used 2L treatment (CS, pages 20 and 75). Clinical advice to the EAG is that weekly paclitaxel is used widely, with some centres using other single-agent chemotherapies. Please provide a scenario using 100% weekly paclitaxel in the chemotherapy arm. Please consider what the most appropriate assumptions regarding ToT would be for this scenario and justify these.*

Response: We have included a scenario using 100% weekly paclitaxel in the chemotherapy arm. The clinical experts interviewed said that the efficacy and safety of the chemotherapy arm in the EMPOWER Cervical-1 trial is representative of the efficacy of chemotherapies used in current clinical practice in England and Wales.³⁻⁵

As the main reasons for discontinuation were lack of efficacy, treatment-limiting adverse events and finishing the course of treatment, we have assumed the same ToT curves as seen for the chemotherapy arm in the EMPOWER Cervical-1 trial, limiting the course of treatment to 6 cycles as per the NHS chemotherapy protocol.¹⁴

This change decreases the ICER by 3.63% (reduced by [REDACTED]) without the addition of severity weighting. Please see details in Appendix 2.

B2. PRIORITY For the scenario analysis exploring the use of comparator chemotherapies based on clinical expert input (specified in CS, Table 50):

- a) ***Please confirm that TOT remains the same in this scenario and please comment on the face validity of this assumption.***

Response: We can confirm that the same ToT curve is used, however the appropriate caps for the duration of each regimen were also added in line with the relevant NHS chemotherapy protocols. Please see response B1 above for rationale for the assumption.

- b) ***Please clarify how the company derived the proportions in Table 50 from the data provided in the clinical expert interviews.²³⁻²⁶ In particular, please clarify the calculations for carboplatin plus doxorubicin, carboplatin plus gemcitabine, carboplatin and clinical trials***

Response: We have added the calculations in the attached additional Excel file titled 'Cervical cancer NICE model_Updated_Inputs_19Jan2026_CQs.xlsx'.

- c) ***Please explain why 'clinical trials or BSC' (16%) is included in the treatment mix of the comparator arm for this scenario. BSC suggests the patient is not fit enough for active treatment and if that is the case, then they would not have been included in the comparator arm of the EMPOWER Cervical-1 trial. Also patients receiving trial interventions fall outside of routine NHS care and therefore clinical trial enrolment cannot be considered a comparator intervention.***

Response: We have provided the treatment mix for the comparator arm used in a scenario analysis as per clinical expert input. BSC was not included among the comparator treatments. It was only used for subsequent treatments. Clinical trials

however are a common option in some hospitals for this patient population according to the clinical experts interviewed.^{3-5 35} To represent current clinical practice in England and Wales, the use of clinical trials was included. Their exclusion would increase the comparator drug and total costs, and therefore would decrease the ICER. The submitted base case was therefore conservative. For the scenario analysis excluding clinical trials from the comparator arm, please see Question B2e.

d) *Please clarify why BSC and clinical trials would have the same cost as they have very different resource implications for NHS care providers.*

Response: They both have been assumed to have zero drug costs. However, they still incurred both primary and secondary care costs in the model. While patients receiving BSC as a subsequent treatment (patients in the model did not receive BSC as comparator treatment) would incur some additional drug costs as part of the palliative care, since a higher proportion of patients in the chemotherapy arm receive BSC as subsequent treatment than in the cemiplimab arm (68.1% and 50.6% respectively), increasing the BSC costs would result in higher costs for the chemotherapy arm, and therefore a lower ICER for cemiplimab. Our results are therefore conservative.

As subsequent treatments amount to only 4.64% of the incremental costs, this is not a major driver of the ICER.

e) *Please remove 'clinical trials or BSC' from the comparator treatment mix and reweight the treatment mix in the comparator arm accordingly.*

Response: We have updated the comparator arm for this scenario accordingly. This increases the cost of comparator treatments by deleting the comparator with the costs of £0 and replacing it with non-zero cost comparators. In this scenario, this change in itself decreases the ICER by 0.979% (by [REDACTED]) without the severity weighting. Please see updated scenario in Appendix 2.

Survival analysis

B3. In the analysis of time-to-event outcomes (PFS and OS) the standard parametric models according to NICE Decision Support Unit Technical Support Document 14 have been fitted, however these omit the two-parameter gamma distribution. Please can the company explore the use of the two-parameter gamma model to ensure complete assessment of the standard parametric models typically used within survival analysis.

Response:

Use of gamma model in overall survival

For cemiplimab, the gamma model provides the worst fit, while for chemotherapy, it provides the 4th best fit according to AIC/BIC (Table 2). It did not provide a good visual fit to the observed survival in the cemiplimab arm and was similar to the other parametric models in the chemotherapy arm. The predicted hazard with the gamma distribution deviates from the observed hazard for both treatment arms. As a result, the gamma distribution is not an appropriate choice for extrapolating overall survival. Please see Appendix 6 for more details.

Table 2. Statistical criteria for cemiplimab and chemotherapy OS parametric curve fit from the EMPOWER Cervical-1 trial

Functional form	AIC: Chemotherapy	AIC: Cemiplimab 350 mg	BIC: Chemotherapy	BIC: Cemiplimab 350 mg
Exponential	1823.0 (6)	1916.4 (6)	1826.7 (5)	1920.1 (5)
Weibull	1819.4 (5)	1915.6 (5)	1826.8 (6)	1923 (6)
Log-normal	1786.3 (2)	1881.7 (1)	1793.7 (2)	1889.1 (1)
Generalised gamma	1788.1 (3)	1882.4 (2)	1799.2 (3)	1893.6 (3)
Gompertz	1823.4 (7)	1898.2 (4)	1830.8 (7)	1905.7 (4)
Log-logistic	1780.8 (1)	1884.4 (3)	1788.2 (1)	1891.9 (2)
Gamma	1812.1 (4)	1918.0 (7)	1819.5 (4)	1925.4 (7)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

NOTE: Ranking according to fit criteria is given in brackets.

Use of gamma model in progression-free survival

For cemiplimab, the gamma model provides almost the worst fit (6th best fit out of 7), while for chemotherapy, it provides the 4th best fit according to AIC/BIC (Table 3). It did not provide a good visual fit to the observed survival in the cemiplimab arm and was similar to the other parametric models in the chemotherapy arm. The predicted hazard with the gamma distribution deviates from the observed hazard for both treatment arms. As a result, the gamma distribution is not an appropriate choice for extrapolating progression-free survival. Please see Appendix 6 for more details.

Table 3. Statistical criteria for cemiplimab and chemotherapy PFS parametric curve fit from the EMPOWER Cervical-1 trial

Functional form	AIC: Chemotherapy	AIC: Cemiplimab 350 mg	BIC: Chemotherapy	BIC: Cemiplimab 350 mg
Exponential	1408.5 (6)	1704 (7)	1412.2 (6)	1707.7 (7)
Weibull	1396 (5)	1670 (5)	1403.5 (5)	1677.4 (5)
Log-normal	1340.7 (2)	1581.5 (2)	1348.1 (2)	1588.9 (2)
Generalised gamma	1336.7 (1)	1538.7 (1)	1347.9 (1)	1549.9 (1)
Gamma	1383.3 (4)	1690.3 (6)	1390.7 (4)	1697.8 (6)
Gompertz	1410 (7)	1605.6 (4)	1417.4 (7)	1613 (4)
Log-logistic	1353.1 (3)	1583.5 (3)	1360.5 (3)	1590.9 (3)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

NOTE: Ranking according to fit criteria is given in brackets.

B4. In Figures 2, 8, 10, 16, 18, and 24, Appendix L of the CS, the company presents the hazards by arm for OS, PFS and ToT. Please can the company confirm what methods were used to generate the hazard plots, including the smoothing method where appropriate.

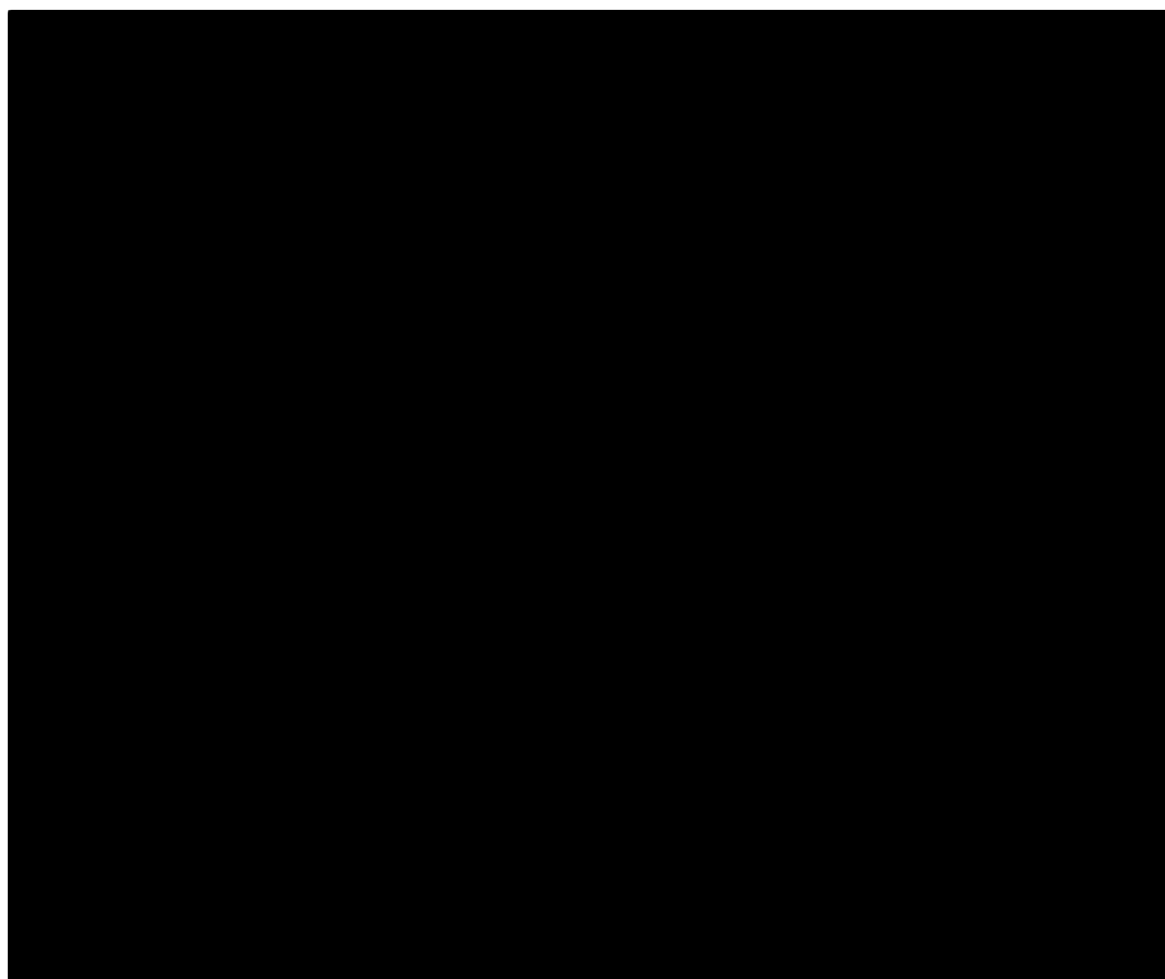
Response: Smoothed plots were derived using the bshazard function from the bshazard package. Hazards are smoothed using B-splines from the perspective of GLM models. Arguments are left as default except for err which was set to 0.01.

B5. In Figures 16 and 24, Appendix L of the CS, the Gompertz model hazard for the chemotherapy arm has atypical behaviour at later time-points (the large spike and variation), please can the company explain this behaviour.

Response: This is due to instability in numeric estimates as predicted survival asymptotes to zero on the chemotherapy arm.

B6. In Figure 16, Appendix L of the CS, the cemiplimab smoothed hazard function is not visible due to the overlaid model hazard plots, please can the company provide an updated figure so that the observed hazard for the cemiplimab arm can be directly compared with the model hazards.

Response: Please see updated graph below.



B7. Flexible parametric models, such as spline models, were not explored for the modelling of OS or PFS. Please can the company explore the use of spline

models on the odds, normal and hazard scales, with 1 to 3 knots. Please present the corresponding model hazard plots, Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) values and discussion of any amendments to the base case model choices if necessary.

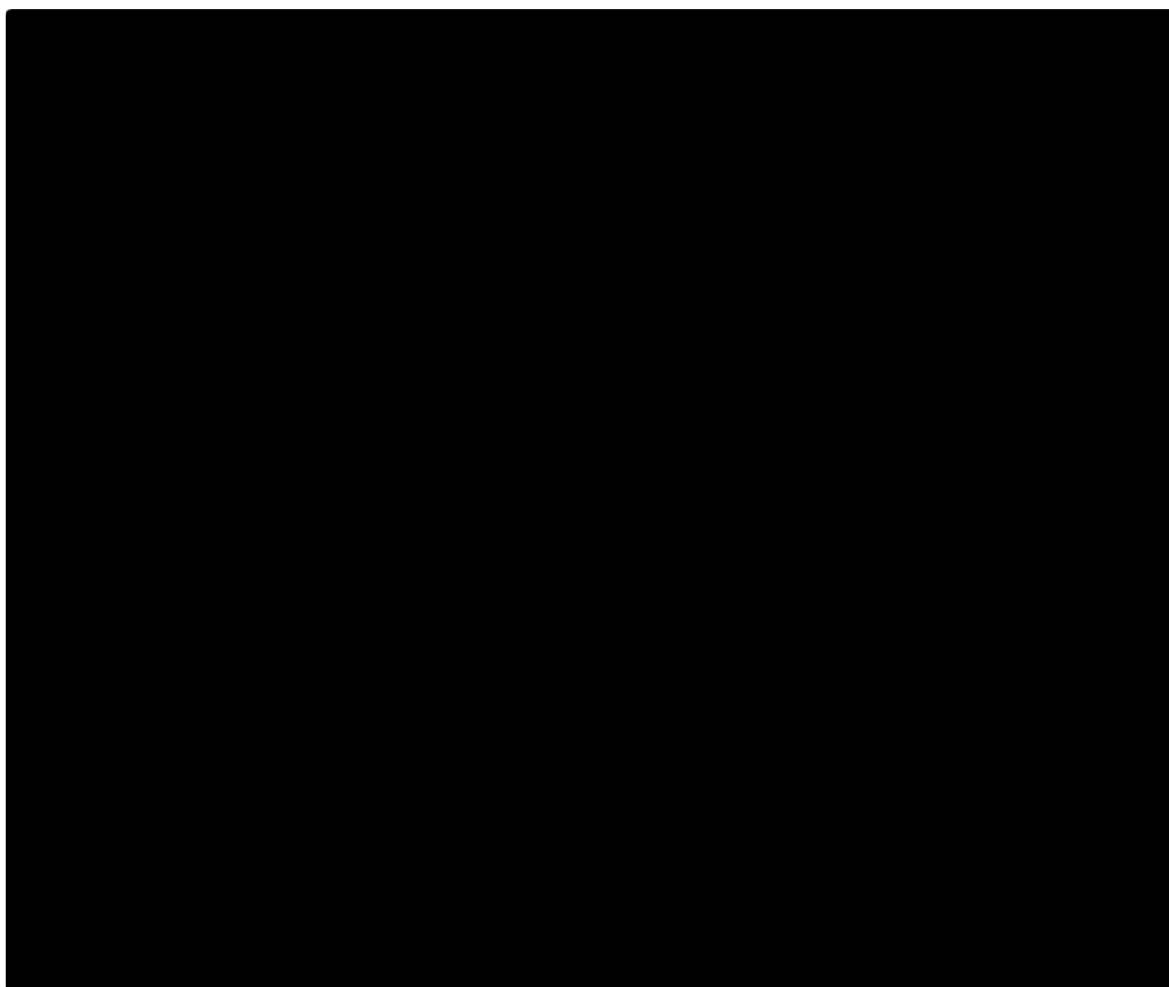
Response: The EMPOWER Cervical-1 trial, on which the model is based, presents highly mature data: PFS data is nearly complete, and OS curves are based on 237 events (78.0%) reported in the cemiplimab arm, and 256 events (84.2%) reported in the chemotherapy arm (see CS Tables 9 and 10). Therefore, there is limited uncertainty. Additionally, the selected base case distributions (generalised gamma for OS and PFS) fit the observed data well.

As seen in Figure 7 below (also CS Appendix L Figure 6), for OS, the generalised gamma model (green line) fits the observed survival in both treatment arms very well throughout the Kaplan-Meier curve. The predicted hazard curves with the generalised gamma model also follow the initial higher and then decreasing hazard for both treatment arms (please see CS Appendix L Figure 8).

Similarly, for PFS, as seen in Figure 8 below (also CS Appendix L Figure 14), the generalised gamma model (green line) fits the observed survival in both treatment arms very well throughout the Kaplan-Meier curve. The predicted hazard curves with the generalised gamma model also follow the decreasing hazard for both treatment arms (please see CS Appendix L Figure 16). (In fact, the fit is so good for cemiplimab, that, as seen in Question B6, it is hard to see the observed curve under the predicted curve as they overlap.) While there is an increase in the observed hazards towards the end of the curve in the chemotherapy arm, this is highly uncertain (shown by the very large confidence interval from 12 weeks onward in CS Appendix L Figure 16), as there are only 23 patients at risk at 12 months (out of 304), and only 4 patients at 18 months in this arm (please see CS Appendix L Figure 9). Fitting this would result in overfitting the data. Additionally, if this highly uncertain increase in hazards were included, it would increase the proportion of patients progressing or dying pre-progression with chemotherapy, and therefore would decrease the LYs and QALYs in the chemotherapy arm, decreasing the ICER.

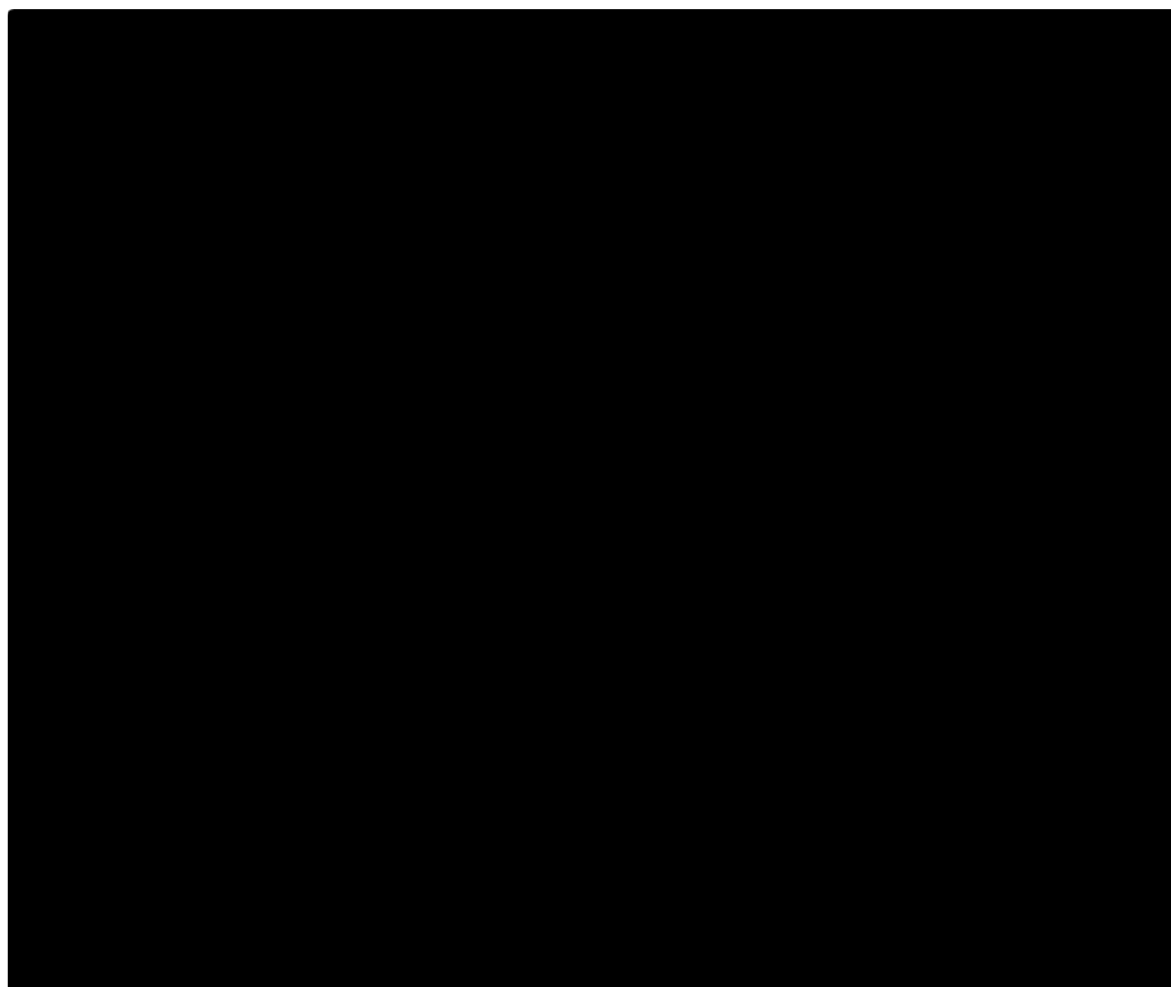
As a result, the spline models would not add value and would bias the results towards cemiplimab.

Figure 7: Parametric Fit Plots OS (ITT) (Figure 6 in Appendix L of the CS)



Abbreviations: OS, overall survival; ITT, intention-to-treat; Ind, independently fitted

Figure 8: Parametric Fit Plots PFS (ITT) (Figure 14 in Appendix L of the CS)



Abbreviations: PFS, progression-free survival; ITT, intention-to-treat; Ind, independently fitted

B8. PRIORITY *Cemiplimab was continued beyond progression in a proportion of patients (70 out of 304, EPAR Table 48),¹⁹ however, the company's base case analysis caps ToT by PFS. Please provide a scenario analysis in which this capping is removed for the cemiplimab arm to reflect the potential for continued use beyond progression.*

Response: The SmPC states that "Treatment may be continued until disease progression or unacceptable toxicity."²¹ This does not allow for cemiplimab treatment to be used beyond progression. Therefore, an artificial scenario, where patients continue cemiplimab treatment beyond progression using an extrapolated curve, is outside the licence and will not reflect potential future clinical practice.

We have, however, implemented this scenario as requested, and have removed capping treatment duration by progression, allowing patients to continue cemiplimab

treatment beyond progression based on the extrapolated ToT curve. This change increases the ICER by 4.14% (by [REDACTED]) without severity weighting, indicating that even with this worst-case scenario (that is outside the licensed indication), cemiplimab remains a highly cost-effective therapy option. Please see details in Appendix 2.

B9. PRIORITY *The curve fits for ToT for cemiplimab are poor due to the models trying to fit across the pre- and post-96 week time periods when there is a large drop in treatment usage at 96 weeks to reflect the treatment duration specified in the trial protocol. According to the EAG's clinical advisors, cemiplimab use would likely be continued beyond 96 weeks for patients who were tolerating treatment and remaining progression-free. The stopping rule imposed within the EMPOWER Cervical-1 trial therefore may not capture the ToT that would be expected within clinical practice. Additionally, within EMPOWER Cervical-1, some patients discontinued cemiplimab at 96 weeks, but were then be permitted to resume treatment with cemiplimab, if they later progressed. It therefore appears that the ToT curve may not reflect the true ToT within the clinical trial either. Please can the company explore the two following approaches to include ToT within the economic model.*

- a. *Please provide a scenario analysis where the ToT data is censored at 96 weeks and refit the data using standard parametric models (and spline models if appropriate). Within this scenario, use this curves beyond 96 weeks to model the potential use of cemiplimab beyond the trial imposed 96 week cut-off.*

Response: We have implemented this scenario. As discussed with NICE at the Clarification question meeting, the ToT needs to be capped by PFS according to the cemiplimab licence. (The SmPC states that "Treatment may be continued until disease progression or unacceptable toxicity."²¹ This does not allow for cemiplimab treatment to be used beyond progression.)

Please note, this scenario does not reflect the trial treatment duration as it allows for patients to take cemiplimab for longer than 96 weeks and therefore is not consistent with the observed efficacy and safety data.

Additionally, the 96 weeks is the total duration of treatment without delays or interruptions. However, in the EMPOWER Cervical-1 trial, █ of patients had at least one dose delay and/or infusion interruption and/or dose modification in the cemiplimab arm. The great majority of these patients had only one delay or one interruption (█ patients out of █ had only one delay and █ patients out of █ had only one interruption).¹³ This is not taken into account in the analysis, as these patients would be still censored at 96 weeks, and instead of having an additional dose, they would be assumed to continue treatment for a longer time using the above extrapolation method, significantly overestimating their treatment duration.

The survival analysis of the censored ToT data is available in Appendix 7. According to AIC, the best fitting model is generalised gamma, followed by the log-normal model, while according to BIC it is either generalised gamma or log-normal depending on the treatment arm (for chemotherapy the log-normal model fits better). Based on the comparison to the observed data, in the cemiplimab arm, the generalised model fits better the artificial, censored end of the observed data.

The use of generalised gamma relies heavily on the fit to the censored, artificial end of the curve (Figure 9). As it relies on an artificial set of data, its extrapolation is unrealistic. As seen in Figure 9, the generalised gamma model predicts patients to be on cemiplimab treatment even at 10 or 20 years. In the short term, ToT consistently runs above the PFS curve (Figure 10) and in the long-term ToT is very similar to PFS (Figure 11). Capping ToT by PFS results in ToT being the same as PFS, as ToT is either higher or the same as PFS.

The use of the second-best fitting log-normal model results in ToT that again consistently runs above the PFS curve in the short term, and in the long-term runs below the PFS curve (Figure 12).

This leads to a scenario that is not just inconsistent with the efficacy and safety data from the EMPOWER Cervical-1 trial, but also leads to unrealistic predictions. In this worst-case scenario, using the log-normal parametric model, the ICER increased by 14.73% (by ██████████), however with the severity weighting, it still remained well below the £35,000/QALY threshold (£████████/QALY). With the highly unrealistic long tail of the generalised gamma model, the mean cemiplimab treatment duration more than

doubled (increased from [REDACTED] months to [REDACTED] months), increasing the ICER by 75.84% (by [REDACTED]) without the severity weighting. With severity weighting this resulted in an ICER [REDACTED].

Please see Appendix 2 for more details.

Figure 9. Parametric Fit Plots with Extrapolation Time on Treatment (Censored) (ITT ToT Censored)

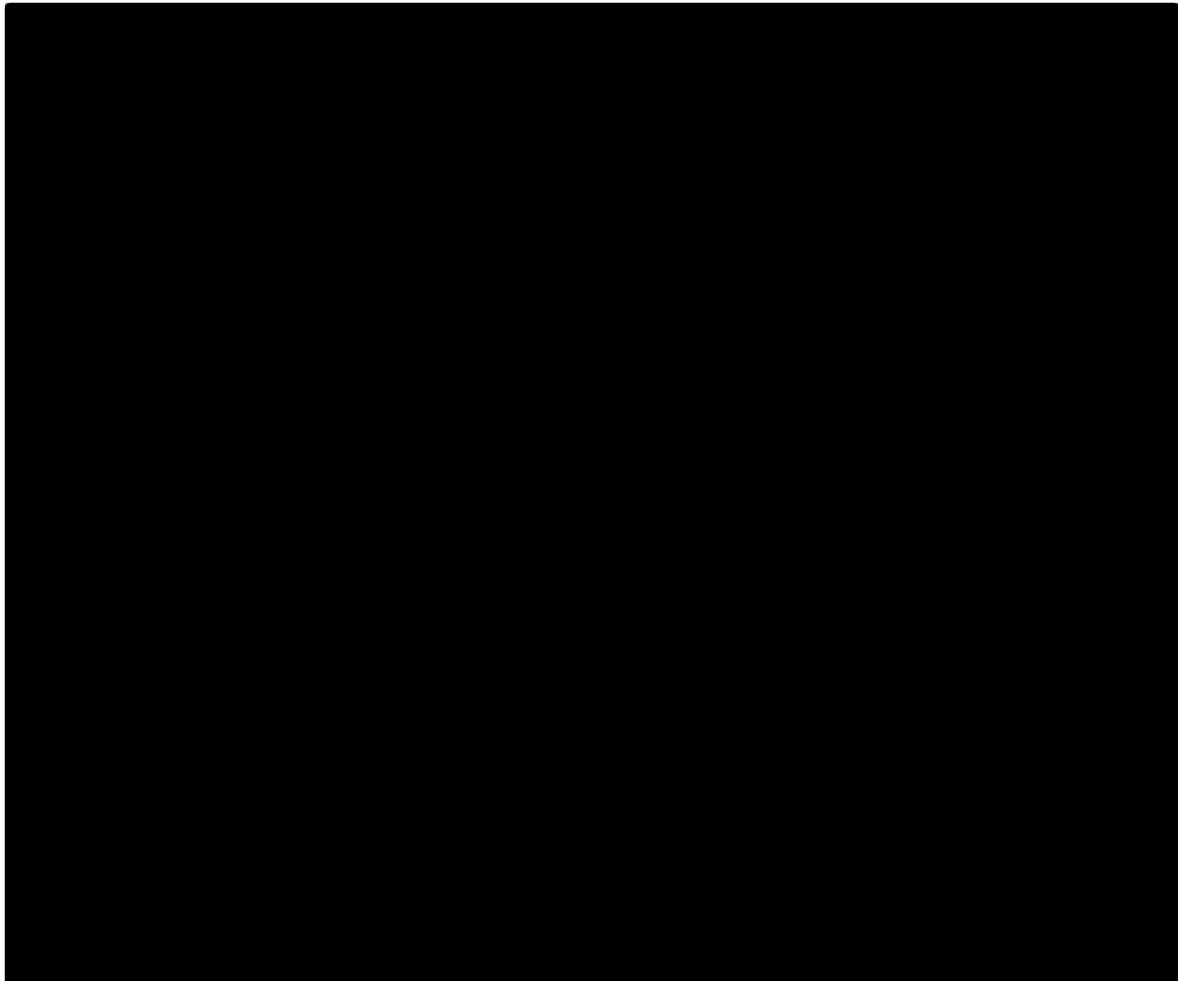


Figure 10. Comparison of extrapolated ToT and PFS curves without capping the ToT by progression (short-term, with generalised gamma model)

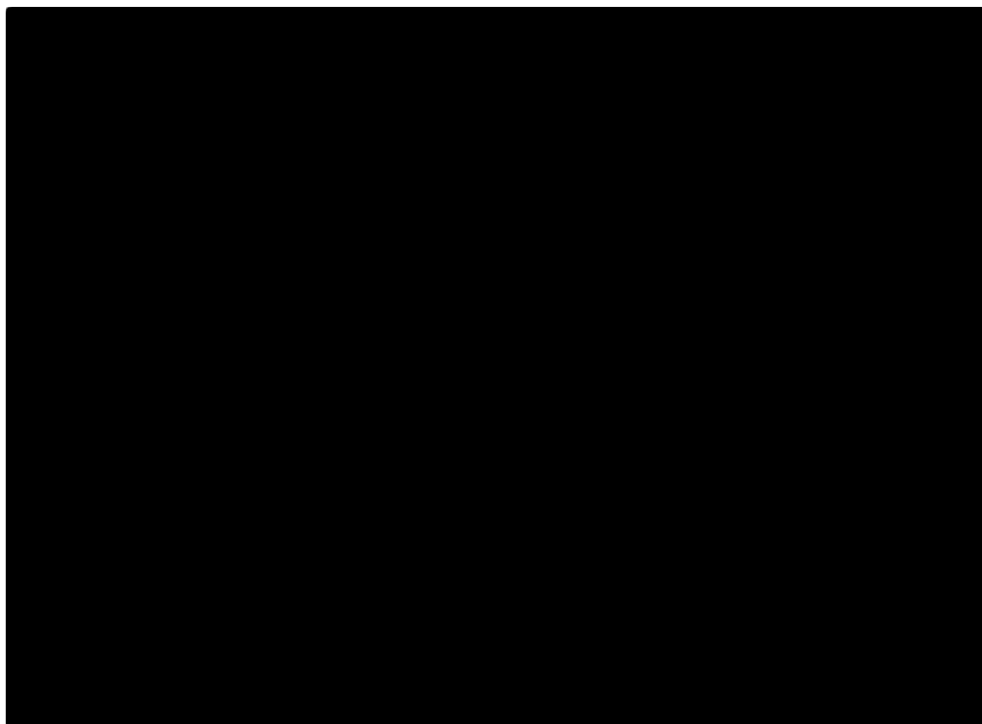


Figure 11. Comparison of extrapolated ToT and PFS curves without capping the ToT by progression (10-year, with generalised gamma model)

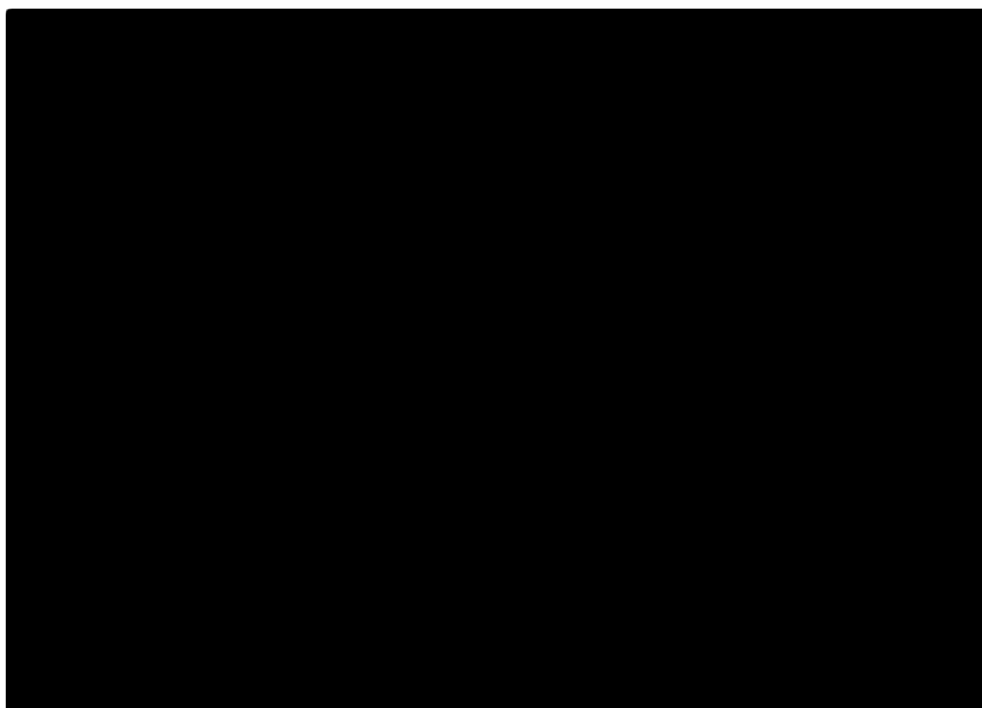
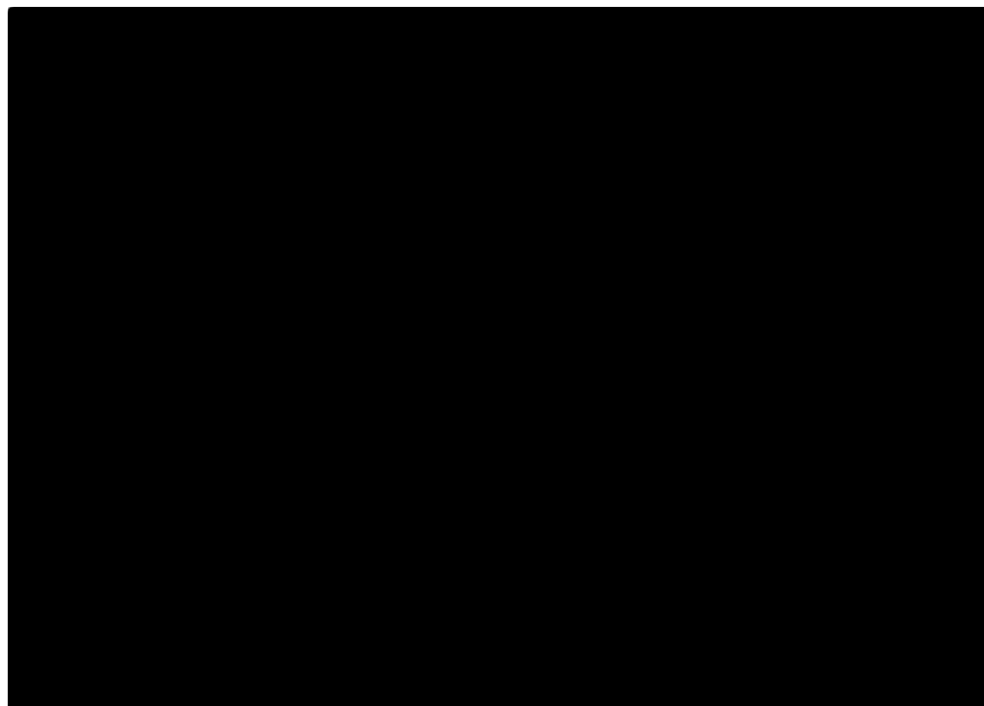


Figure 12. Comparison of extrapolated ToT and PFS curves without capping the ToT by progression (10-year, with log-normal model)



b. Please provide a scenario analysis that uses the KM data to directly inform ToT in the model as these data are relatively mature.

Response: We have incorporated this scenario. As discussed in the Clarifications questions call with NICE (15th January 2026), this is the most appropriate scenario, as it reflects the efficacy and safety observed in the EMPOWER Cervical-1 trial, and the curves are almost complete. This scenario reduced the ICER by 1.20% (by [REDACTED]) without the severity weighting.

Please see Appendix 2 for more details.

c. For both of these approaches, please ensure that appropriate methods to capture uncertainty associated with ToT are also included for use within the probabilistic sensitivity analysis (PSA).

Response: For the first approach in question B9a, the survival curves remain incorporated in the PSA as it was done in the base case. As the scenario in question

B9b had negligible effect on the ICER, this scenario including the KM curves was not incorporated into the PSA.

Adverse events

B10. PRIORITY CS, page 105, states, “Only Grade 3 and 4 TEAEs were included in the CEM since only those AEs are considered to have important cost and quality of life consequences at the population level.” It then goes on to state, “The most common grade 3 or higher AEs, experienced by $\geq 2\%$ of patients in either treatment arm, or by $>5\%$ of patients including all grades, were included in the model.” Please clarify whether the frequencies in Table 28 relate to grade 3 or higher adverse (AEs) or AEs of any grade. Please provide frequencies separately for, i) AEs of grade 3 or higher in more than 2% of either arm, and ii) AEs of any grade occurring in more than 5% of patients.

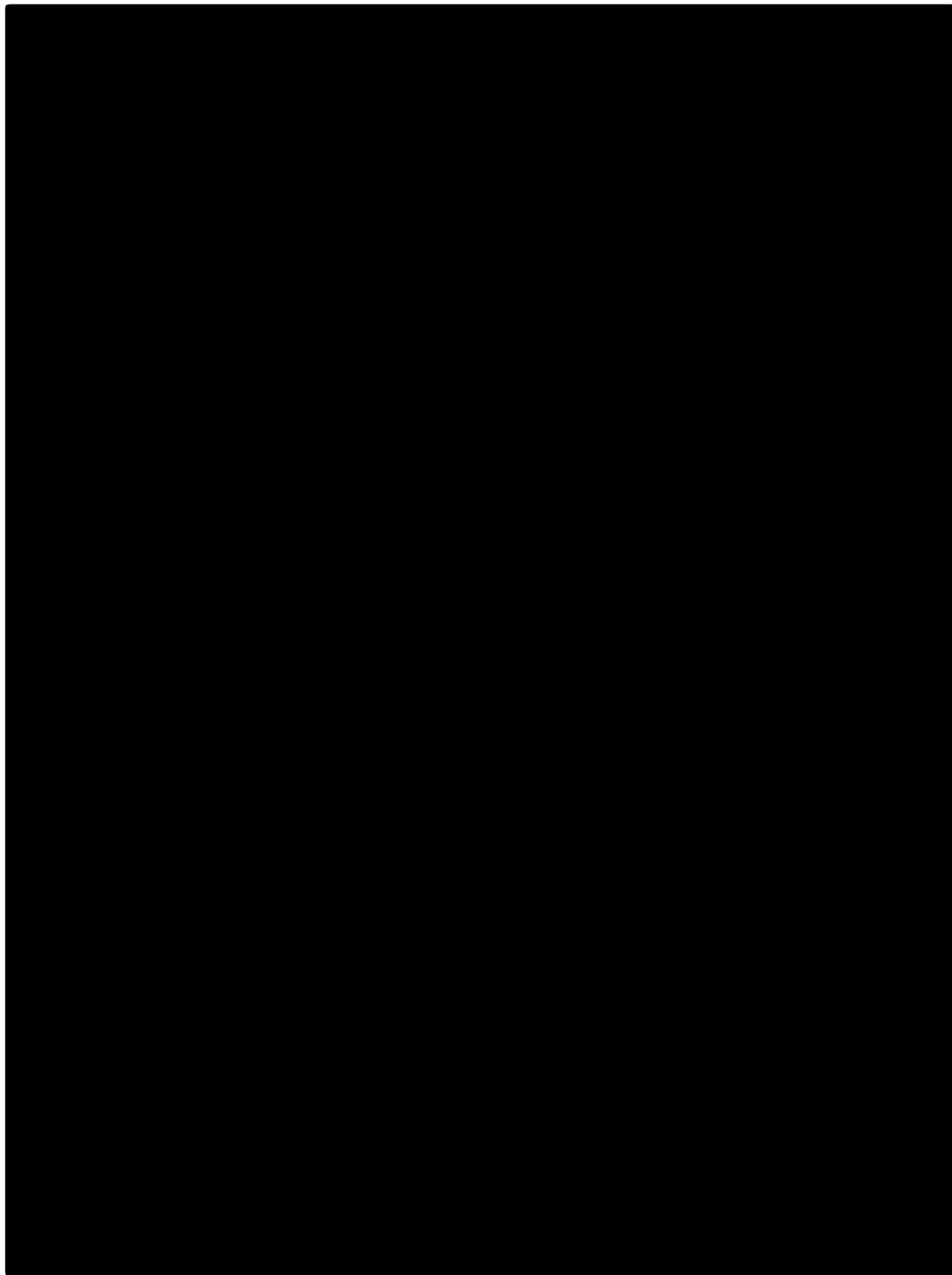
Response: Only Grade 3, 4, and 5 TEAEs were included in the cost-effectiveness model. The frequencies presented in Table 28 of the CS are exclusively for Grade 3+ TEAEs, as used in the model.

The selection criteria for which Grade 3+ TEAEs were included in the model were:

1. Grade 3+ TEAEs that occurred in $\geq 2\%$ of patients in either treatment arm. OR
2. Grade 3+ TEAEs that occurred in $<2\%$ of patients if the rate of that AE of any grade was $>5\%$ in either treatment arm

For example, abdominal pain has a Grade 3+ rate of 1.0% in both arms, which is $<2\%$ and does not meet the first criterion. However, the rate of abdominal pain of any grade was 10.0% with cemiplimab and 11.4% with chemotherapy (i.e., $>5\%$) and meets the second criterion.

The frequencies of adverse events of any grade occurring at a rate $>5\%$, and the frequency of Grade 3+ adverse events occurring at a rate $>2\%$ are provided separately in table 39 of the final CSR, which is reproduced for convenience below.





B11. Our clinical experts have advised that whilst immune-mediated adverse events are rare, when they occur, they can have substantial resource use and HRQoL implications. Please confirm that immune-related AEs were not included in the model and please justify the reason for that. The CS states that immune-related AEs of $\geq$ grade 3 occurred in █% of patients in the cemiplimab arm, but does not tabulate the data for individual immune-related AEs. Please tabulate immune-related AEs and comment specifically on the incidence of grade 3+ AEs for the following specific AEs: hepatitis, pneumonitis, thyroid dysfunction, parathyroid dysfunction, adrenal

insufficiency, myositis, arthritis, nephritis, myocarditis, pericarditis, colitis and diarrhoea, rash and dermatitis, type 1 diabetes.

Response: All grade 3 or higher AEs experienced by $\geq 2\%$ of patients in either treatment arm, or by $>5\%$ of patients including all grades, were assumed to affect costs and quality of life at a population level and were included in the model. This assumption and the list of grade 3/4 treatment-emergent adverse (TEAE) events included in the model was validated by clinical experts.³⁻⁵ The included events were chosen as they were assumed to have important impact on the cost and/or quality of life of patients in this setting. No additional adverse events were suggested by clinical experts.

The immune-related AEs requested are tabulated in the submitted CSR in Table 52 (*Treatment-Emergent Sponsor Identified Immune-Mediated Adverse Events by System Organ Class, Preferred Term and NCI Grade (ImAEs Requiring Systemic Corticosteroids or Immunosuppressants, or Endocrine-related ImAEs Based on Sponsor Provided List (Safety Analysis Set) - Patients with SCC and AC Histology*). The table provides both the numbers and percentages for all grades, and also for grade 3/4/5 adverse events.

The only immune-related AE that meets the validated inclusion criteria for the model is 'Hepatobiliary disorders'. As the model uses a different classification of AEs than the one seen in Question B10, some of the hepatobiliary disorders may have been included in the model already. However, to assess the effect of including all hepatobiliary disorders as described in Table 52 of the CSR, a scenario analysis was conducted. This scenario incorporated [REDACTED] of cemiplimab patients experiencing grade 3/4/5 hepatobiliary disorders, with the average costs of £2,550.22 per AE estimated as the weighted average of the non-elective long- and short stays (Table 4).

This scenario increased the ICER by 0.32% (by [REDACTED]) without the severity weighting.

Please see Appendix 2 for more details.

Table 4. Cost of hepatobiliary AEs

Currency	Activity	Unit cost
Non-Elective Inpatient - Long Stay		
GC17A - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 9+	3,340	£10,896.87
GC17B - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 4-8	2,006	£8,846.72
GC17C - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 0-3	630	£7,125.06
GC17D - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 9+	5,125	£7,193.86
GC17E - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8	6,531	£5,851.50
GC17F - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 0-3	3,606	£5,291.81
GC17G - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 8+	24,749	£4,921.08
GC17H - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 5-7	24,376	£3,907.48
GC17J - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 2-4	39,137	£3,296.36
GC17K - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 0-1	31,019	£2,854.57
Non-Elective Inpatient - Short Stay		
GC17A - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 9+	207	£1,353.03
GC17B - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 4-8	55	£2,230.75
GC17C - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions, with CC Score 0-3	11	£1,828.51
GC17D - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 9+	162	£1,289.82
GC17E - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8	133	£1,159.08
GC17F - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 0-3	54	£1,113.81
GC17G - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 8+	11,179	£852.86
GC17H - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 5-7	16,191	£755.79
GC17J - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 2-4	36,070	£690.55
GC17K - Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 0-1	56,843	£558.91
Weighted average cost		£2,550.22

Source: NHS Reference costs 2024/25

Health Related Quality of Life

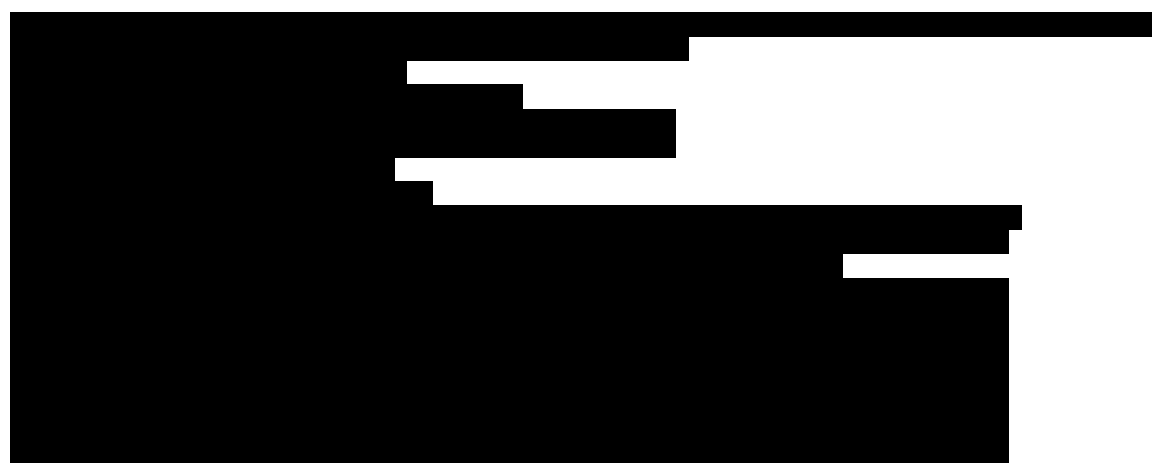
B12. PRIORITY *In CS Appendix N, the use of the linear mixed effect repeated measures model (MMRM) is outlined and the covariates of the regression model described.*

a. Please can the company also justify the choice of covariates and interaction terms within the regression.

Response: The covariates and interaction terms included in the MMRM for the EQ-5D outcome replicated the regression model that was used the main HRQoL outcome (Global Health Status [GHS] from the EORTC QLQ-C30) in the trial. In accordance with the trial statistical analysis plan, the MMRM included covariates for treatment arm, visit number, baseline HRQoL and randomisation stratification factors. It also included interaction terms between treatment arm and visit, and treatment arm baseline HRQoL. Both main effects and the interaction terms remained in the model, regardless of statistical significance, in accordance with the original model fitted for GHS.

b. Can the company summarise the model parameter estimates (with associated uncertainty) along with diagnostic reports of the model fit.

Response: The model parameter estimates from the MMRM used for pre- and post-progression EQ-5D-3L score for the CEM are provided below. Model fit was not conducted as only a single model was trialled, following the specification used for analysing HRQoL in the main trial report.



[REDACTED]

c. Please can the company describe any alternative models that were trialled along with justification for why they were not ultimately used to derive the utility estimates used within the economic analysis.

Response: No other models were trialled. The linear mixed effect repeated measures model (MMRM) is a standard approach for analysing continuous repeated measures within the clinical trial setting, and this was the same approach adopted in the trial statistical analysis plan for the analysis of HRQoL data.

Likelihood estimation (MMRM) is generally an unbiased and efficient method, which incorporates all observed information on the repeated measures of the outcome and accounts for within-patient correlation.

Adjustment for baseline (HRQoL) score and randomisation stratification factors is also recommended standard practice, to increase statistical efficiency and provide unbiased estimates of treatment effects.⁴¹ Variables included in the adjustment should be selected prospectively and prespecified in the trial protocol, and the analysis conducted was aligned with this principle. The treatment interaction terms were included to obtain provide treatment effect estimates for each visit (in addition to the overall treatment effect estimate across visits).

Covariates measured after randomisation e.g. adverse events should not normally be included, as such covariates may be affected by treatment allocation (through either direct causation or association with another factor), and may bias the estimation of the treatment effect.

d. Given the emphasis on differences in utility within the progression-free state being driven by the different adverse effects profiles for immunotherapy versus chemotherapy (CS, page 110), can the company provide a regression analysis including terms for AEs of grade ≥ 3 in addition to terms for progression status.

Response: Unfortunately, we do not have access to the AE patient level data to conduct this analysis. All AE data has been taken from the CSR. However, the lower quality of life observed with chemotherapy in the trial was validated by clinical experts from the UK.^{3-5 35 42} According to the clinical experts, this was due to the AEs: “*Chemotherapy has important side effects. Immunotherapies are very well tolerated, and patients on immunotherapies tend to have good quality of life, that you don’t see on chemotherapy.*”

Three of the experts agreed that utility values estimated from the EMPOWER Cervical-1 trial represent what they see in clinical practice.³⁻⁵ Two of the experts stressed that, while the cemiplimab pre-progression utility value from the EMPOWER Cervical-1 trial reflects what they would expect from a 2L immunotherapy, a lower value than the one observed in the trial would be expected for chemotherapy treatment, due to the range, severity and persistence of side effects.^{35 42} Both clinicians independently commented that a utility value of 0.5 would be closer to what is seen in clinical practice with chemotherapies in 2L pre-progression.^{35 42}

Therefore the utility values included in the model may be conservative.

B13. PRIORITY *Please provide the combined pre-progression mean EQ-5D-3L score based on the EMPOWER Cervical-1 study. To align with the approach taken in TA939,⁴³ please provide a scenario using the treatment-independent health state utility values (derived from the EMPOWER Cervical-1) while incorporating AE-related disutilities as a one-off value in the first model cycle.*

Response: As noted in section 3.4.5 of the CS, assuming equal pre-progression utility value contradicts the clinical trial data, lacks face validity, biases results in favour of chemotherapy and contradicts the opinion of clinical experts:

- **Contradicts the clinical trial data:**
 - The utility for cemiplimab was statistically significantly higher than for the chemotherapy arm (mean difference: [REDACTED]). The difference between treatment arms was also statistically significant across all visits.

- This result was consistent with the benefit of cemiplimab also seen with the EORTC-QLQ30 questionnaire.⁴⁰ (Please see CS section 2.6.6.) Patient-reported outcome scores in the EMPOWER Cervical-1 trial consistently favoured cemiplimab over chemotherapy on a wide range of measures in the overall study population, including mean Global health status/Quality of life (GHS/QoL) scores and physical functioning scores, mean overall changes from baseline in GHS/QoL and physical functioning, symptom scores for fatigue, nausea/vomiting, pain, insomnia, appetite loss and constipation and time to definitive deterioration.⁴⁰
- The different pre-progression utilities are supported by the EMPOWER-Cervical 1 trial results, which showed that a lower proportion of cemiplimab-treated patients (compared with chemotherapy-treated patients) had AEs of any grade (██████████), or grade 3 or higher AEs (██████████), despite a longer duration of treatment exposure. Importantly, treatment-related AEs (██████████), treatment-related AEs of grade 3 or greater (██████████) or AEs leading to dose delay or infusion interruption (██████████), were notably lower.⁵
- Therefore, using the same pre-progression utilities for the cemiplimab and chemotherapy arm would contradict the EMPOWER-Cervical 1 clinical trial data.

- **Lacks face validity:**

- Using the combined pre-progression utility data results in almost the same pre-and post-progression utility values in the chemotherapy arm (progression changed the utility value from ██████ to ██████). This means that patients' quality-of-life would not change with disease progression if they have received chemotherapy.

- **Biases results in favour of chemotherapy:**

- Using the post-progression utility results in a 17% reduction between pre- and post-progression utility in the cemiplimab arm and only a 1% reduction in chemotherapy arm. This contradicts clinical experts, who expected the between-arm difference in utility values seen pre-progression to continue post-progression; one expert additionally stated that “*chemotherapy patients will have more lingering side effects*”.³⁵ Another stated that chemotherapy patients “*have the double whammy, the cancer progressing, and the lingering toxicities*”.⁴²
- The post-progression utility used was estimated from the combined cemiplimab and chemotherapy arm of the EMPOWER-Cervical 1 trial. However due to the very limited number of observations in the chemotherapy arm, this value is more representative of the post-progression utility of the cemiplimab arm (■■■■ of observations).
- **Contradicts the opinion of clinical experts**, who stated they would expect the difference in utility values to continue post-progression. Three of the clinical experts interviewed felt that the health state specific utilities used in the model represent what is expected from cemiplimab and chemotherapy.³⁻⁵ Two of the clinical experts felt that the pre-progression utility value for chemotherapy arm should be lower (0.5).^{35 42} Therefore, the base case may already provide a conservative estimate in this regard.

As the use of the same utilities pre-progression would contradict all available data and clinical expert opinion, we do not consider this to be a plausible assumption to adopt, and have therefore not provided the scenario. The combined pre-progression mean EQ-5D-3L score based on the EMPOWER Cervical-1 study is presented in the CS Appendix N Table 2 (■■■■, 95% CI ■■■■).

Addition of AE disutilities: The base case pre-progression utility values are estimated from the EMPOWER-Cervical 1 trial. No additional adverse event (AE) disutilities are added, as the QoL consequences of AEs are assumed to be captured in the QoL estimates from the trial.

The use of AE disutilities, instead of the clinical trial data, would result in increased uncertainty, by substituting data with the following assumptions:

- Assumption 1: Similarly to most oncology clinical trials, the duration of AEs were not collected in the EMPOWER-Cervical 1 trial, which would require an assumption for their duration.
- Assumption 2: Because of the difficulties in estimating AE disutilities from clinical trials due to the small number of AEs leading to small sample size, multiple values would need to be estimated using direct valuation, which is not recommended in the reference case.⁴⁴
- Assumption 3: Due to the lack of data in cervical cancer, disutilities would have to be taken from treatments for other oncology indications, which involves assuming that the disutilities are independent on the oncology indication.

For the reasons above, we do not consider the use of AE-related disutilities in preference to trial-based utilities to be appropriate, it is however already included as a scenario in the model and the CS (section 3.9.3 Table 51), and in the updated base case in Appendix 2.

B14. In the model, a utility value of 0.092 is assumed for the last 30-days of life. This was however derived from time trade-off values from the French general population based on vignettes. To help validate the choice of this value further, can the company confirm whether any PROs were collected for patients within the EMPOWER Cervical-1 trial within the 30-day period prior to death? Please could the company compare these utility estimates to that used within the model.

Response: Only 14 patients of the 608 recruited to the trial had PRO data collected in the 30-day period prior to death. This is unsurprising given that end-of-life patients are typically at the stage of their illness where completing questionnaires on their quality of life is not considered a priority by patients, their families or their healthcare professionals. Given such small patient numbers, and the fact that the 14 patients providing PRO data within the last 30 days of life are unlikely to be representative of the vast majority of patients who are at the end-of-life stage of cancer, the Company do not consider it appropriate to calculate a value based on these 14 questionnaires.

In any case, to do so would not be informative. All patients in the model go through end of life, regardless of treatment arm, with the only difference being when this stage is reached. Therefore, using a different end-of-life utility value would make no substantive difference, rather there would only be a slight difference between comparators resulting through discounting.

To quantitatively assess the effect of the application of an end-of-life utility value, we have included an additional scenario where we assume no specific utility values for the last 30 days of life. Assuming no end-of-life disutilities, the ICER decreases by 0.721% (by [REDACTED]) without severity weighting, indicating the assumed end-of-life utility value is not a meaningful driver of the results. Please see details in Appendix 2.

B15. Utility values were age-adjusted using Ara and Brazier 2011 in the economic model. Please update the model by using the EQ-5D-3L estimates for the UK reported by Hernández Alava et al.
(<https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d>)

Response: We added the requested utilities, and the user can now toggle between the two options. The revised base case uses the requested values by Alava et al 2022.⁴⁵ See updated base case Appendix 2. This change increased the ICER by 0.988% (by [REDACTED]) without the severity weighting, indicating that this request has marginal impact over the approach used in the CS.

Costs

B16. The end-of-life (EOL) care cost was assumed to be £627.83 per week (£2,729.26 per month) in both arms and the company intends to apply it as a once-only cost in the model (although there were programming errors in the model; see details in Question B27), whereas the corresponding cost was approximately £4,600 in TA939.⁴³ Please comment on the face validity of this assumption. Please also confirm that the EOL cost in Table 36 is the cost per week.

Response: The EAG's interpretation of the EOL costs appears to be incorrect. EOL costs were estimated to be £627.83 for the whole EOL period, which was 30 days and not weeks (please see Table 36 in CS).

The costs were estimated consistently across all health states. Clinical experts were asked about resource use in the pre-progression, the post-progression and the EOL periods.⁴⁶⁻⁴⁹ Resource use elicited was averaged, and the mean resource use was multiplied with the appropriate unit cost. (Please see CS Section 3.5.3 for the details, Table 34 for the resource use and Appendix J for the unit costs.)

TA939 and TA885 took the EOL costs from Round et al. 2015,⁵⁰ which looked at the resource use in lung, breast, colorectal and prostate cancer patients based on literature and multiplied it by unit costs adjusted to 2013-2014.^{50 51} This study was based on much older data and is not directly relevant to the population with cervical cancer. It also used a different definition for EOL. Instead of using a defined time period (30 days in our model), it defined it as “the point at which a patient begins the use of strong opioids”. This meant the use of 372 days for breast cancer, 201 days for colorectal cancer, 180 days for lung cancer and 360 days for prostate cancer.⁵⁰ As a result, for example, the £4,346 health care costs reported for breast cancer was for a period 12.4 times longer than in our model. Adjusting for the time period, using the duration of EOL period by Round et al. 2015 for breast cancer, the only other gynaecological cancer reported (372 days), the costs were almost the same:

- In TA939: £4,611.54⁵¹
- In the CS: $(372 \text{ days} / 30 \text{ days}) * £367.83 = £4,561$

B17. PRIORITY *Recent draft guidance from NICE suggests that many centres are giving chemotherapy as a day case procedure and day case reference costs are more appropriate for decision making, although it also noted that some centres were using outpatient treatment administration. (<https://www.nice.org.uk/guidance/GID-TA11279/documents/consultation-document>) Please use either day case chemo admin costs or the weighted average of outpatient and day case unit costs.*

Response: The NICE guidance to which the EAG refers also noted that to adopt day-case costs only may be conservative given that some centres do use outpatient delivery costs. We have therefore included the weighted average of outpatient and day case unit costs (please see costs below). This, in itself, increased the ICER by

only 0.183% (by ■■■) without severity weighting, indicating this is not an important driver of results.

Administration costs	Day case		Outpatient		Weighted average
Item	Activity	Unit cost (£)	Activity	Unit cost (£)	Unit costs (£)
SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance	163,989	435.51	61,538	256.03	386.53
SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance	86,064	553.43	38,381	300.81	475.52
SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	132,590	571.26	56,260	430.62	529.36

Source: NHS reference costs 2024/25. Available at: <https://www.england.nhs.uk/> (accessed 9 January 2026)

B18. The study protocol specifies that irinotecan is given over 90 mins, whereas the SB12Z Healthcare Resource Group (HRG) code only allows for infusion times up to 60 minutes. Please review all treatments and implement HRGs for administration that reflect total chair time including any premedication. Relevant information can be found in table 1 of this document: https://www.england.nhs.uk/wp-content/uploads/2021/02/20-21NT_Annex_B_Currencies_with_national_prices.pdf

Response: We have revised the administration costs for irinotecan, which requires 90-minute infusion time as per CSR¹³. Similarly for the scenario analysis which includes weekly paclitaxel as comparator, we have revised the administration costs for weekly paclitaxel, which requires over 60 minutes administration. This in itself decreased the ICER by 0.141% (by ■■■) without severity weighting due to the increase in comparator administration costs.

B19. CS, Table 5, describes folate support and vitamin B12 being required for patients receiving pemetrexed, but the EAG cannot identify any costs for these within the economic model. Please adapt the model to account for these supportive medications for patients receiving pemetrexed or alternatively,

please comment on the expected size and direction of any bias from excluding these.

Response: Folate support and vitamin B12 for pemetrexed were not included, as their costs are very low. Their inclusion increases the pemetrexed costs slightly and therefore the comparator drug costs, decreasing the ICER. Therefore, excluding folate and B12 support results in conservative ICER.

Additionally, according to the document referenced by the EAG in Question B18: “The cost of the delivery HRGs now includes the cost of supportive drugs listed on the NHS England and Improvement chemotherapy supportive drugs list”. This is reiterated in the most recent annex: “The cost of the delivery HRGs includes the cost of supportive drugs listed on the NHS England chemotherapy supportive drugs list”.⁵²

We have however included them as requested to demonstrate how this makes very little difference to the ICERs. Please see details in Appendix 2. This change in itself decreased the ICER by 0.006% (■■■■) without severity weighting.

B20. The CS describes the need for premedication in patients receiving paclitaxel and states that this contrasts with a lack of premedication requirement for cemiplimab (CS, page153). However, the EAG can identify no premedication costs within the economic model. Please describe the premedication requirements for each chemotherapy regimen included in the model and include costs for these within the model. Alternatively, please comment on the expected size and direction of any bias from excluding premedication.

Response: Pre-medications for chemotherapy were not included, as their costs are very low. Their inclusion would increase the chemotherapy costs slightly and therefore the comparator drug costs, which would decrease the ICER slightly. Therefore, our exclusion of these premedication costs is a conservative assumption.

B21. The reference (Department of Health 2025, #71) given for the electronic market information tool (eMIT) drug prices included in the submission suggests that it used the dataset covering the 12 month period prior to 31st December 2024. However, the eMIT data were updated in September 2025 to

include data in the 12 months prior to June 2025. Please update the drug costs using the most recent version of eMIT where relevant. Available here:

[<https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>]

Response: At the time of the preparation of the submission, this data was not yet published. We have now updated the model with the new data. This update in itself decreased the ICER by 0.164% (by [REDACTED]) without severity weighting, due mainly to the increase in the topotecan costs.

B22. The CS is informed by NHS Reference Costs from 2023/24, but the NHS Reference Costs 2024/25 have been available since Nov 2025. Please consider updating the unit costs of drug administration, managing adverse events and routine care using the NHS Reference Costs 2024/25. Available here:

[<https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>]

Response: At the time of the preparation of the submission, this data had not been published. We have now updated the model with the new data. This update in itself increased the ICER by 0.431% (by [REDACTED]) without severity weighting.

B23. The CS is informed by unit cost data from PSSRU 2023. The 2024 PSSRU report has been available since April 2025. Please consider updating to use the values from the 2024 report available here:

[<https://research.kent.ac.uk/corec/unit-costs-2022-2027/>]

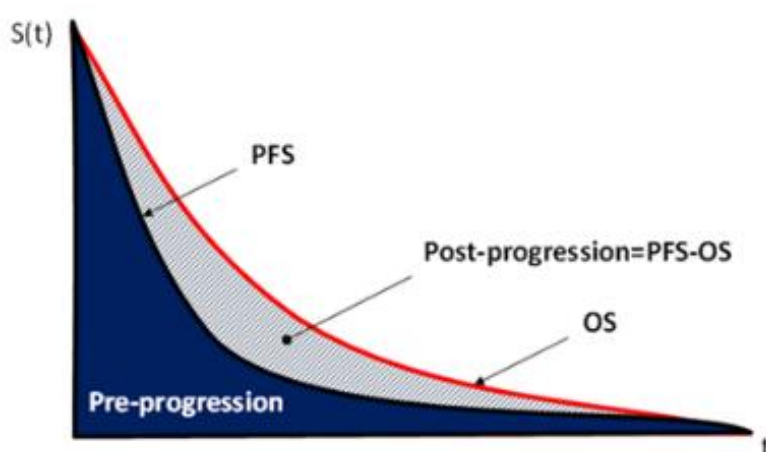
Response: We can confirm that the 2024 PSSRU unit costs were used in the CS. The 2023 date was an error in the reference list. We apologise for the confusion.

Executable model

B24. PRIORITY Executable model, worksheet “Model cemi”, column AE, and worksheet “Model chemo”, column AR. Subsequent treatment costs calculations. The CS states that “The cost of subsequent treatments has been included as a lump sum cost occurring at the time of progression, corresponding to the time at which patients would initiate subsequent treatments”. When calculating the costs of subsequent treatment, the proportion of patients is based on PFS which counts both progression and death as events. This may overestimate costs because only those patients

who do not die should incur these costs. Please correct the model to account for the proportion of PFS events which were deaths.

Response: The model is appropriately based on a partitioned survival approach, commonly used in oncology modelling, which estimates health state occupancy using the area under the curve approach with the help of the OS and PFS curves. This means that the model estimates the proportion of patients who are progression-free in each cycle by calculating the area under the PFS curve and the proportion of patients dead by estimating the area above the OS curve (Figure 13). The area between the PFS and OS curves represent the patients who are alive post-progression.



Abbreviations: OS, overall survival; PFS, progression-free survival; S, survival; t, time

Figure 13. Model structure: Partitioned survival analysis approach

In this approach transition probabilities are not used, therefore we only know the proportion of patients in each health state in each cycle, but not how they got there. This means that the model does not estimate separately the proportion of patients who died pre- and post-progression. It is also not possible to distinguish whether those who left the pre-progression health state died or progressed. This would require a different modelling approach (a state transition model), that would require alternative assumptions.

In the partitioned survival analyses, therefore, assumptions have to be made to estimate the proportion of patients progressing. These could include:

- Assuming that all patients live at least a week after progression (i.e. one cycle), which is the current approach; or

- Assuming a constant proportion for pre- vs post-progression mortality.

Due to the short cycle length (7 days), the first approach was selected as the more minor assumption. However, even with the slight overestimation of the subsequent treatments, as subsequent treatments represent 4.64% of the incremental costs (see response to question B2), the choice of assumption has a negligible effect.

B25. PRIORITY *Please provide the detailed calculations of subsequent treatment (3L) proportions, Table 38, based on the average input from four clinical experts. This is requested as the EAG are unable to replicate the values presented using the data in the source documents.*²³⁻²⁶

Response: Please see the Appendix 3 for the calculations.

B26. PRIORITY *Please clarify why ‘clinical trial or BSC’ has been included as a subsequent treatment option as a clinical trial would take the patient outside of routine NHS care. Please remove the proportion eligible for clinical trials and redistribute to either BSC or one of the other subsequent treatments.*

Response: We have redistributed patients who go into clinical trials to BSC as requested (please note, this does not reflect clinical practice, as in clinical practice a proportion of patients go into clinical trials). However, it should be noted that this revision resulted in no change in the ICER, since both BSC and clinical trials have no costs associated with them in the model.

B27. Executable model, worksheet “Model cemi”, column AD, and worksheet “Model chemo”, column AQ. *When applying the EOL adjustment to the routine care cost of post-progression state, the EAG considers the adjustment to be overestimated. The model erroneously compares the weekly EOL costs with the monthly post-progression management costs.*

- Please confirm this is an error and provide an updated model. Otherwise, please provide rationale for this assumption.*
- Please comment on the face validity of this EOL cost-adjustment for PFS events which were deaths (i.e., those who did not incur post-progression management costs).*

- c. ***Please provide a scenario in which EOL cost is applied as a one-month cost to all new deaths occurring each cycle in addition to disease management costs for pre/post-progression health state occupancy.***

Response: As noted in response to question B16, the EAG's interpretation of the EOL costs appears to be incorrect. The EOL costs are for a 30-day period, and not for a week, and were applied accordingly. Please see CS Table 36 and Section 3.5.3. Therefore, there has been no error in its application.

The model is a partitioned survival analysis, which estimates health state occupancy using the area under the curve approach with the help of the OS and PFS curves. This means that the model estimated the total proportion of patients dead in each cycle by calculating the area above the OS curve (or the proportion of patients alive with the area under the OS curve) and does not differentiate if patients died pre- or post-progression. Therefore, it is not possible to distinguish the proportion of patients dying pre- and post-progression.

In any case, similarly to end-of-life utilities (Question B14), to do so would not be informative. All patients in the model go through end of life regardless of treatment arm, with the only difference being when this stage is reached. Therefore, estimating end-of-life costs differently would make no substantive difference, rather there would only be a slight difference between comparators resulting through discounting.

B28. Executable model, worksheet "Model cemi", column BC and worksheet "Model chemo", column BP. When applying the EOL adjustment to the utility of post-progression state, there is a one-cycle lag in the application of age-adjusted post-progression utility. Please confirm this is an error and correct it in a revised version of the economic model.

Response: We believe the EAG's interpretation is incorrect. The model estimates the EOL adjustment by first estimating the proportion of patients who have died in the current cycle (number of deaths in current minus number of deaths in previous cycle). This is multiplied by the difference between the end of life utility and the age adjusted post-progression utility for the age in the current cycle (adjusted for the

appropriate time period). Both parts of the equation use the current cycle consistently.

This method of estimation is used consistently for both health state occupancy and EOL adjustment. All weekly transitions are assumed to happen in the current cycle, and as a result, all calculations are done using the current cycle. There is therefore no lag included.

B29. Executable model, worksheets “Model cemi” and “Model chemo”, column N. The calculations include a constraint ensuring that the per-cycle risk of death in the target population cannot be lower than that of the age-matched general population. When adding this constraint to the per-cycle OS probabilities by the general population mortality risk, there is a one-cycle lag in the application of general population mortality risk. Please confirm that this is an error and correct it in a revised version of the economic model.

Response: We believe the EAG’s interpretation is incorrect. In the model, the first row on these sheets is cycle 0, the starting point, not the first week of the patients’ journey. The first week is cycle 1. Cycle numbering is shown in column C. The life table is set up similarly. For example, in cycle 4, which is the fifth row in the model engine, it refers to cycle 4 in the life table. As a result, there is therefore no lag included.

B30. Executable model, worksheets “Life tables”. The EAG could not validate the $q(x)$ values in column E. Please update the life table using the most recent values from the Office for National Statistics (ONS) life tables for England.

Response: The life tables that were used were submitted as reference titled: Office for National Statistics 2025 National Life Tables 2021-2023.pdf. These were the latest values at the time of the preparation of the submission. We have now updated the values with the those that have since been published and have included the downloaded life tables as reference.⁵³ This, in itself, decreased the ICER by 0.002% (by ■■■) without severity weighting indicating this did not meaningfully change the model and results.

B31. PRIORITY Drug administration costs for subsequent treatments (those detailed in CS, Table 38) do not appear to have been included in the model

based on the calculations informing cells E51 and E52 of the Treatment costs sheet. Please clarify if the EAG has understood this correctly. If so, then please update the model to include drug administration costs for subsequent treatments or clarify why this is not appropriate.

Response: Drug administration costs for subsequent treatments have not been included as they were expected to be negligible, as subsequent treatment acquisition costs constituted only 0.08% of incremental costs. We have included them as requested. Their inclusion increases the ICER by 4.64% (by £[REDACTED]) without severity weighting, which does not change the conclusions that can be drawn on the cost effectiveness of cemiplimab.

B32. Executable model, worksheet “Model chemo”, columns V to AH.

- a. Please explain why all chemotherapy drugs start at cycle 1 rather than cycle 0. This is slightly underestimating the drug acquisition and administration costs in the comparator arm. Please confirm this is a programming error and update it accordingly.***

Response: Cycle zero is the starting point (i.e. the time prior to starting treatment), not the first cycle of treatment. The first week in the patients' journey is cycle 1.

- b. Please explain why the full drug cost per cycle is applied in the model at the start of each cycle rather than taking into account discontinuation on a weekly basis. This applies particularly to gemcitabine, irinotecan and vinorelbine schedules where treatment is given on days other than day 1 of the treatment cycle. For example, the protocol states that irinotecan was provided on Day 1, 8, 15, 22 followed by 2 weeks rest. Given the weekly cycle length of the model, the EAG believes that drug acquisition and administration costs should be based on the health state occupancy at the relevant time points, rather than applying the full 6-week costs of treatment on Day 1 (week 1), Day 43 (week 7), etc. This would allow for treatment costs to be reduced, in patients discontinuing mid-cycle. Please confirm this is an error and provide an updated model, or clarify why the company's approach is more appropriate.***

Response: We apologise, this was an error, and we have updated the model. This has error made little difference; when corrected the ICER increased by only 0.15% (by [REDACTED] without severity weighting. Please see Appendix 2 for more information.

- c. *The unit cost for vinorelbine was based on the weighted average of injection vials and oral capsules. According to the protocol, it was delivered as an intravenous infusion. Please confirm this is a programming error and update the unit cost of vinorelbine by removing the costs of oral capsules.*

Response: We have removed oral capsules and updated wastage calculations accordingly. This did not result in changes in the base case, as the formulation/size with the lowest costs is used, which was a solution for injection.

B33. PRIORITY *Please clarify that the unit costs of AEs were weighted across both elective and non-elective patient groups. Please update the model to use only non-elective admission data to estimate average unit costs for AEs.*

Response: We have updated the model to use only non-elective costs for AEs. This update in itself resulted in a 0.783% decrease in the ICER (by [REDACTED]) without severity weighting. Please see Appendix 2 for more information.

B34. PRIORITY *CS document, page 122 to 123, Tables 34 and 35*

- a. *Please explain why there is a significant difference in the frequency of hospital-based specialist nurse visits between progressed patients from cemiplimab arm (1.5 per year) and progressed patients from chemotherapy arm (1.5 per month). Please confirm this is a programming error and update the model with correct values. Otherwise, please comment on the face validity of this assumption.*

Response: This is not an error. This was based on the mean input from clinical experts practicing in England.^{3-5 35} Two out of the four clinical experts did not note any specialist nurse visits post-progression, one clinical expert mentioned one or two visits in the post-progression period, and one expert noted frequent visits for chemotherapy patients if they are on treatment again after progression.

In a scenario analyses, we have tested the assumption of patients not having any specialist nurse visit in either treatment arm after progression. This results in a 1.88% increase in the ICER (by [REDACTED]) without severity weighting, indicating the assumption of the base regarding specialist nurse visits is not a meaningful driver of the results. Please see Appendix 2 for more information.

b. Please comment on why the resource use in the post-progression health state is different between treatment arms. Please provide a scenario in which the resource use in the post-progression health state is the same across treatment groups.

Response: The resource use estimates were based on the mean input from clinical experts practicing in England.^{3-5 35} We have implemented the requested scenario, which resulted in a 1.71% increase in the ICER (by [REDACTED]) without severity weighting, indicating the assumption of the base regarding resource use in the post-progression health state is not a meaningful driver of the results. Please see Appendix 2 for more information.

c. Please clarify why the frequencies per year for some resource use in post-progression and EOL were zero even though the proportions of patients requiring these resources were specified (e.g. GP, nurse, specialist nurse).

Response: The resource use estimates were based on the mean input from clinical experts practicing in England.^{3-5 35} The EOL resource use had missing data where experts could not provide even approximate values. However, EOL costs have a negligible effect on the results. All patients in the model go through end of life regardless of treatment arm, with the only difference being the timing of when this stage is reached. Therefore, using a different EOL cost value would make no substantive difference, rather there would only be a slight difference between comparators resulting through discounting.

B35. For the scenario analysis exploring the use of comparator chemotherapies based on clinical expert input,

- a. ***Executable model, worksheet “Model_Interventions”, cells F32:F33. Proportions of patients receiving “combined carboplatin and gemcitabine” and “carboplatin alone” are erroneously set to zero.***

Response: Thank you, this was an error, we have corrected it. It does not affect the base case ICER, and in the scenario using the clinical expert input it decreases the ICER slightly.

- b. ***Executable model, worksheet “Model chemo”, cells AL18:AL1792. Values for carboplatin are missing from the array.***

Response: Thank you, this was an error, we have corrected it. It does not affect the base case ICER. In the scenario analysis using the clinical expert values for comparator distribution, this change in itself decreased the ICER by 0.416% (by [REDACTED]) without severity weighting.

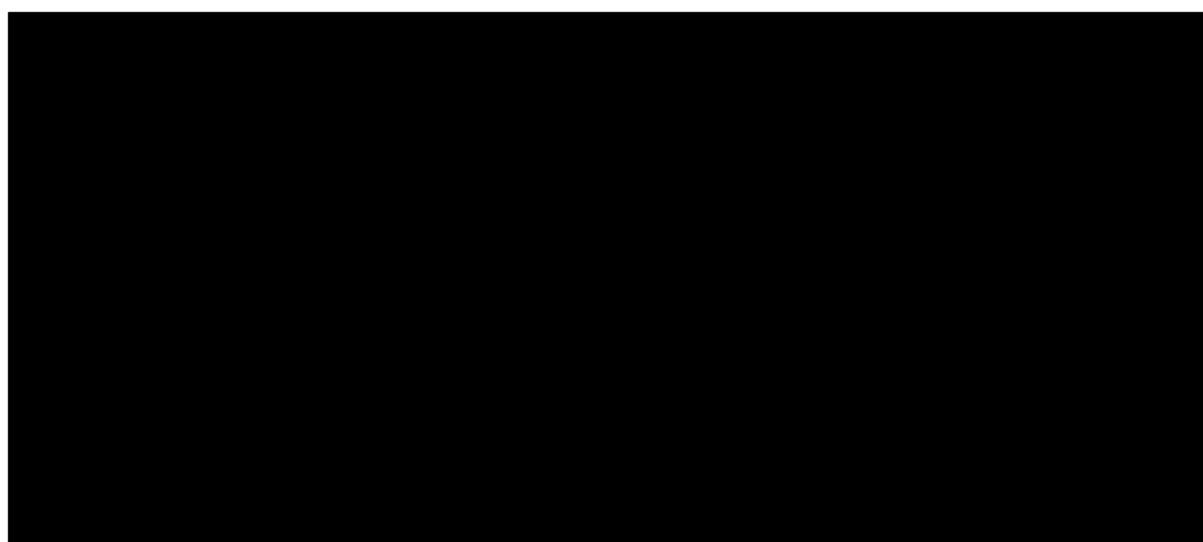
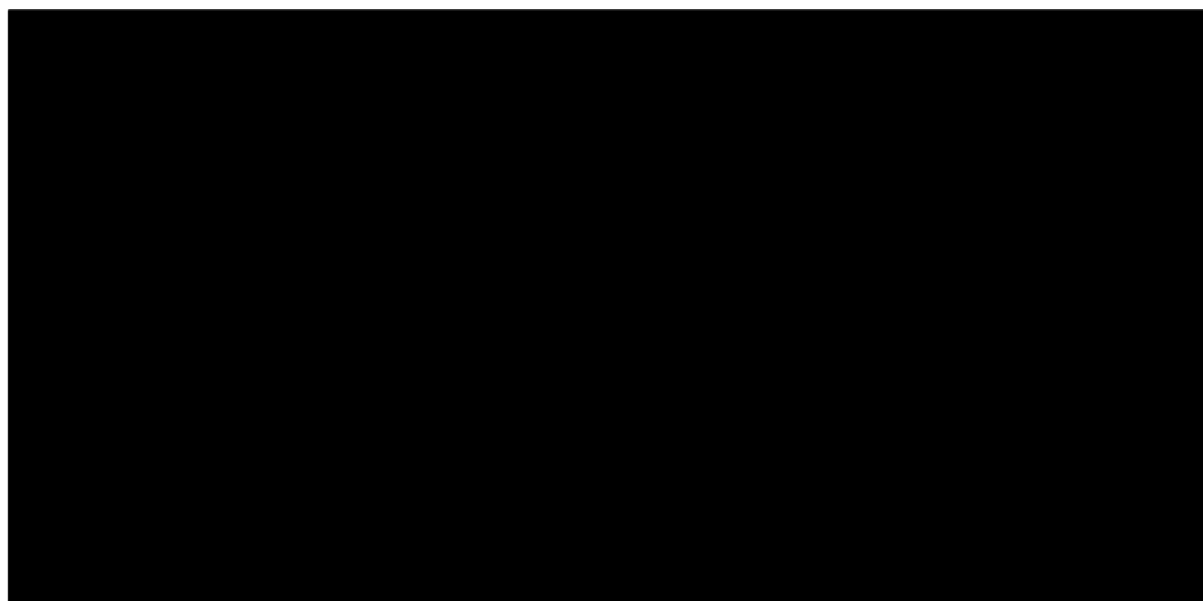
- c. ***Please confirm these are programming errors and update the model accordingly.***

Response: Please see responses above.

B36. PRIORITY Why were the data from the trial not used to inform the proportion having subsequent anti-cancer treatments. Please provide the following data, reported by trial arm, from the EMPOWER Cervical-1 trial:

- a. ***Proportion having any subsequent treatment***
- b. ***Proportion having subsequent immunotherapy***
- c. ***Proportion having subsequent PD-L1 inhibitor***
- d. ***If possible, the specific mix of subsequent treatments received or if the set of treatments received was too diverse, the proportion having the five most common subsequent treatments.***

Response: In the EMPOWER Cervical-1 trial, post-treatments were not recorded as the specific treatments, only as large categories of treatment options (e.g. platinum compounds or combination of antineoplastic agents).¹³ Therefore, the trial data for post-treatments is not suitable to be used for modelling purposes. We have shown CSR post-text table 14.2.5.1 below for additional information.



In total, [REDACTED] and [REDACTED] of patients received subsequent treatment in the cemiplimab and chemotherapy arms, respectively.¹³ PD-1/PD-L1 inhibitors were received as subsequent treatments by [REDACTED] in the cemiplimab and [REDACTED] in the chemotherapy arm.

B37. PRIORITY Executable model, worksheet “Parameters”. Parameter samplings for the PSA.

- a. *Distributions of single-agent chemotherapy drugs were sampled independently resulting in the sum of probabilities exceeding one in some PSA iterations. Please correct this error by sampling those parameters jointly using the Dirichlet distribution.*

Response: The Dirichlet distribution has been added for the distribution of comparator drugs. This does not affect the base case deterministic ICER, however will lower the uncertainty in the sensitivity analyses slightly.

- b. *Health state utility values were sampled independently resulting in some PSA iterations where patients with disease progression could have higher utility than patients without progression, particularly in the chemotherapy arm. Please correct this error.*

Response: This was not an error. Implementing the requested change, while it would lower the reported uncertainty slightly, requires the assumption that even in extreme cases where there is an important severe AE pre-progression, the patient’s quality of life will decrease with radiological progression, even after treatment discontinuation and relief from AEs. This would be unreasonable to assume.

- c. *Please explain why the parameter for relative disutility from the progression-free to post-progression health state, (i.e., ■%, was not included in the PSA).*

Response: The progression disutility was not included in the PSA because the values it was estimated from (pre-progression utility for cemiplimab, post-progression utility for cemiplimab and pre-progression utility for chemotherapy) were included in the PSA, and the value that was estimated with this disutility (post-progression utility for chemotherapy) was also included. If the 17% is also included, the uncertainty would be double-counted. However, we have included it in the revised base case. It does not influence the base case deterministic ICER.

- d. *EOL care costs were sampled independently by treatment arm resulting in some PSA iterations where one treatment arm incurred higher costs than the other. Please correct this error.*

Response: This is not an error. It is possible for EOL costs to vary between patients in clinical practice also and therefore sampling them independently was appropriate. It also allows for flexibility of testing different assumptions regarding the resource use between the two treatment arms. This method also results in greater uncertainty and therefore leads to potentially conservative results. We have however turned off the inclusion of chemotherapy EOL costs in the PDS and DSA, and made it equal to the cemiplimab EOL value.

- e. *For many parameters that are calculated as a function of several inputs, the PSA takes quite a simplistic approach and applies a standard error (SE) of 10% to the total calculated value. For example, the AE costs are a function of the frequency of individual AEs and the unit costs for individual AEs and the total cost is a sumproduct of these two arrays. However, the PSA only varied the combined AE cost across all AEs using a 10% SE. This may overestimate the variance expected if the uncertainty in the frequencies was captured using beta distributions and the unit costs were assumed to have a SE of 10%. We have the same concerns for subsequent treatment costs, routine care costs and drug acquisition costs. For the latter, the total drug acquisition costs are varied with a SE of 10% when the unit costs and the dosing schedule would normally be fixed in the PSA. Ideally only factors associated with uncertainty, such as RDI would be captured in the PSA. Please correct these errors so that the model accounts for the uncertainty in the inputs used to derive total costs in each case. If this is not feasible, please comment on whether the approach used is likely to over or underestimate uncertainty and whether this would introduce any bias into the average costs and QALYs.*

Response: This is a reasonable simplification used for most cancer models, where the AEs or subsequent treatments are not driving the results. Separating out individual aspects would slow the model, would not provide a better understanding of uncertainty (since we are assuming the uncertainty that we are testing), and would incorporate the additional assumption that all aspects of these vary independently (which is incorrect and will overestimate uncertainty). Additionally, any change would be negligible, since subsequent treatments constitute only 4.64% of incremental costs and AEs constitute only 2.17% of incremental costs.

B38. Please confirm that drug wastage was not applied to the subsequent treatments in the scenario analysis including drug wastage and explain why this was not done.

Response: Drug wastage was not applied for subsequent treatments. These are very common treatments used in multiple indications by many patients, and vial sharing is common in clinical practice. Applying a wastage calculation would therefore not reflect clinical practice. Additionally, subsequent treatments have negligible effect on results (as they account for only 4.64% of incremental costs in the updated base case).

Section C: Textual clarification and additional points

C1. CS, Table 8. The data show a high proportion of patients being reported as Hispanic/Latino, which does not correlate with the baseline characteristics presented in Tewari 2022. Please confirm if the data have been reported inverted (i.e. Yes for Hispanic/Latino should be No and vice versa).

Response: Thank you for noticing, this was a typo. The data you mention in Tewari 2022 are the correct data.

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Appendix 1: Survival analysis of PD-L1 subgroups (Question A18)

Please see the separate document title: ID6610_Appendix 1 and 7 – Additional survival analyses for CQs 19Jan2026.doc.

Appendix 2: Revised base case

Changes to the base case

Table 5 shows the summary of the effect of individual changes to the base case on the ICER. Please note all changes are compared to the original base case showing the effect of each individual change in isolation. The effects of individual changes in ICER do not add up to the total consequence of making these revisions concurrently. Each of the individual changes requested by the EAG has negligible and mixed effects, with some marginally increasing the ICER and some marginally decreasing the ICER. The revised base case ICER incorporating all of the requested changes is presented in the tables below.

Table 5. List of changes and their isolated effect on ICER

Change requested	Question	Change in ICER (%)	Change in ICER (£)
Remove 'clinical trials or BSC' from the comparator treatment mix	B2e	-0.98%	■
Include Hernández Alava et al. population utilities	B15	0.99%	■
For administration costs: use of weighted average of day cases and outpatient unit costs	B17	0.18%	■
For chemotherapy administration: update unit costs to reflect longer admin times for some treatments	B18	-0.14%	■
Add folate support and vitamin B12 for patients receiving pemetrexed	B19	-0.01%	■
Update eMIT costs	B21	-0.16%	■
Update NHS Reference costs	B22	0.43%	■
Remove proportion eligible for clinical trials and redistribute to BSC for subsequent treatments	B26	0.00%	£0
Update life tables for most recent one	B30	0.00%	■
Add administration costs for subsequent treatments	B31	4.74%	■
Fix per cycle application of chemotherapy drugs	B32b	0.15%	■
Remove oral vinorelbine from costs	B32c	0.00%	£0
Update AE HRGs to be non-elective	B33	-0.78%	■
Error, "Model_Interventions", cells F32:F33	B35a	0.00%	£0
Error, "Model chemo", cells AL18:AL1792	B35b	-0.42%	■
Use Dirichlet for chemo comparators	B37a	0.00%	£0
Add progression disutility to PSA	B37c	0.00%	£0
Do not allow end-of-life costs to vary independently between treatment arms	B37d	0.00%	£0

Updated base-case results

Results are presented discounted and using the currently available █% PAS discount price for cemiplimab (Table 6). Compared to chemotherapy, cemiplimab resulted in 1.02 discounted additional LYs. The additional LYs are mainly driven by the increased pre-progression period due to the better PFS results with cemiplimab. This is reflected in the QALY results, where cemiplimab resulted in 0.78 discounted QALY gained.

Compared with chemotherapy, the total incremental cost associated with cemiplimab treatment is £█. The total incremental costs are driven by the drug acquisition costs (█); cemiplimab has a higher drug acquisition cost than the comparator chemotherapies, which are mostly generic, and a longer duration of treatment due to its greater efficacy (mean modelled ToT █ months vs. █ months with cemiplimab and chemotherapy, respectively). Additionally, the increased life expectancy came with increased routine care costs due to the greater efficacy in preventing disease progression and prolonging survival with cemiplimab. These are partially offset by savings in TEAE costs.

These incremental costs and QALYs resulted in an ICER (without application of the severity weighting) of £█/QALY gained at the █% PAS discount price of cemiplimab, with a NHB of █ QALYs at the £30,000/QALY threshold (Table 6). At the £35,000/QALY threshold the NHB is █ QALYs.

With application of the 1.7 severity weighting, the ICER is £█/QALY gained using the available █% PAS price discount, with a NHB of █ QALYs at the £30,000/QALY threshold (Table 7). At the £35,000/QALY threshold the NHB is █ QALYs.

Net health benefit (without and with severity weighting) is presented in Table 8 and Table 9, respectively.

The cumulative impact of the updates made to the model at the request of the EAG is a marginal increase to the ICER; with the appropriate application of the x1.7 severity weight, the base case ICER increased by approximately £1000 compared

with the ICER presented in the CS. Nonetheless, at the existing PAS discount price, cemiplimab remains a highly clinically and cost-effective immunotherapy option for a small group of end-of-life patients who would otherwise have only further chemotherapy available as a treatment option.

Table 6. Discounted base-case results with the existing [REDACTED] PAS price discount (without severity weighting).

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Cemiplimab	[REDACTED]	2.09	1.35				
Chemotherapy	16,936	1.08	0.57	[REDACTED]	1.02	0.78	[REDACTED]

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

Table 7. Discounted base-case results with the existing [REDACTED] PAS price discount and x1.7 severity weighting.

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Cemiplimab	[REDACTED]	2.09	2.29				
Chemotherapy	16,936	1.08	0.96	[REDACTED]	1.02	1.33	[REDACTED]

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

Table 8. Net health benefit (without severity weighting).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £25,000	NHB at £30,000	NHB at £35,000
Cemiplimab	[REDACTED]	1.35						
Chemotherapy	16,936	0.57	[REDACTED]	0.78	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: NHB, net health benefit; QALYs, quality-adjusted life years

Table 9. Net health benefit (with x1.7 severity weighting).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £25,000	NHB at £30,000	NHB at £35,000
Cemiplimab		2.29						
Chemotherapy	16,936	0.96		1.33				

Abbreviations: NHB, net health benefit; QALYs, quality-adjusted life years

Exploring updated uncertainty

In line with the ISPOR-SMDM and the NICE Reference case,^{44 54} various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including:

- Parameter uncertainty
- Structural uncertainty
- Methodological uncertainty.

Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess parameter uncertainty; scenario analyses were performed to explore both structural and methodological uncertainty.

Probabilistic sensitivity analysis

PSA was performed to account for joint parameter uncertainty. The probabilistic analyses were run for 1,500 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs, LYs and QALYs. Inputs with parameter uncertainty were varied simultaneously and independently of one another.

Beta distributions were selected for utilities and percentages due to the bounds of the distribution (i.e., 0 to 1 and 0% to 100%). Standard errors were used as the source of variation to calculate alpha and beta parameters of the distribution. Dirichlet distribution was used for the distribution of chemotherapies in the comparator arm. Gamma distribution was chosen for subsequent treatment costs, administration costs, routine care costs, and AEs costs. Parametric distributions were varied using the means and variance-covariance matrices of the parameters applying the Cholesky decomposition method⁵⁵ to help account for the correlation between parameters. Normal distribution was chosen for all other parameters.

Since time horizon and discount rates are not subject to parameter uncertainty, they were excluded from PSA.

Results

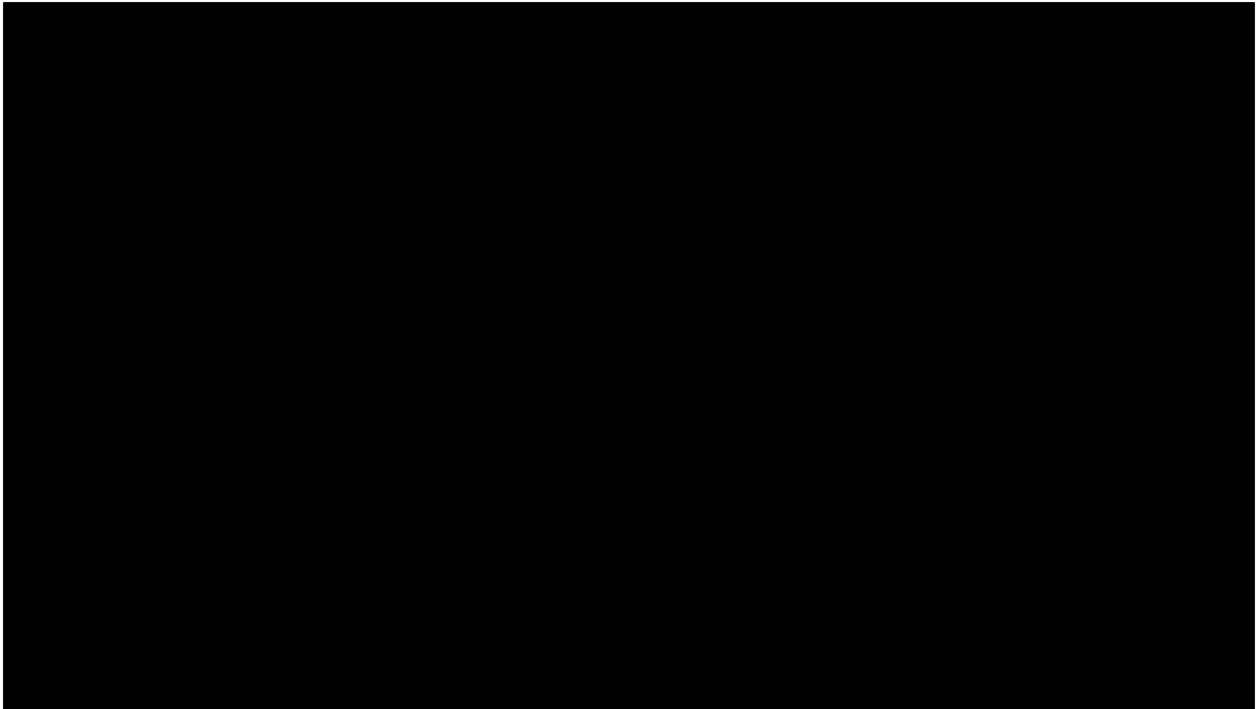
The mean probabilistic results are presented in Table 10 and are highly consistent with the deterministic results.

Table 10. Comparison of the probabilistic and deterministic results with the existing █% PAS discount.

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Without severity weighting				
Deterministic results	████	1.02	0.78	████
Probabilistic results	████	1.05	0.80	████
With the 1.7 severity weighting				
Deterministic results	████	1.02	1.33	████
Probabilistic results	████	1.03	1.34	████

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

All simulations were in the upper right-hand quadrant of the cost-effectiveness plane, where cemiplimab is more effective and more costly than the comparator (Figure 14 and Figure 16). The probability of cemiplimab being cost-effective compared to chemotherapy at the threshold of £30,000 is █% and at the £35,000 threshold is █% without application of the severity weighting (Figure 15). The probability of cemiplimab being cost-effective compared to chemotherapy is █% at the £30,000 threshold and █% at the £35,000 threshold with the application of the severity weighting (Figure 17).



Abbreviations: QALY, quality-adjusted life year

Figure 14. Cost-effectiveness plane with the existing 15% PAS discount (without severity weighting).

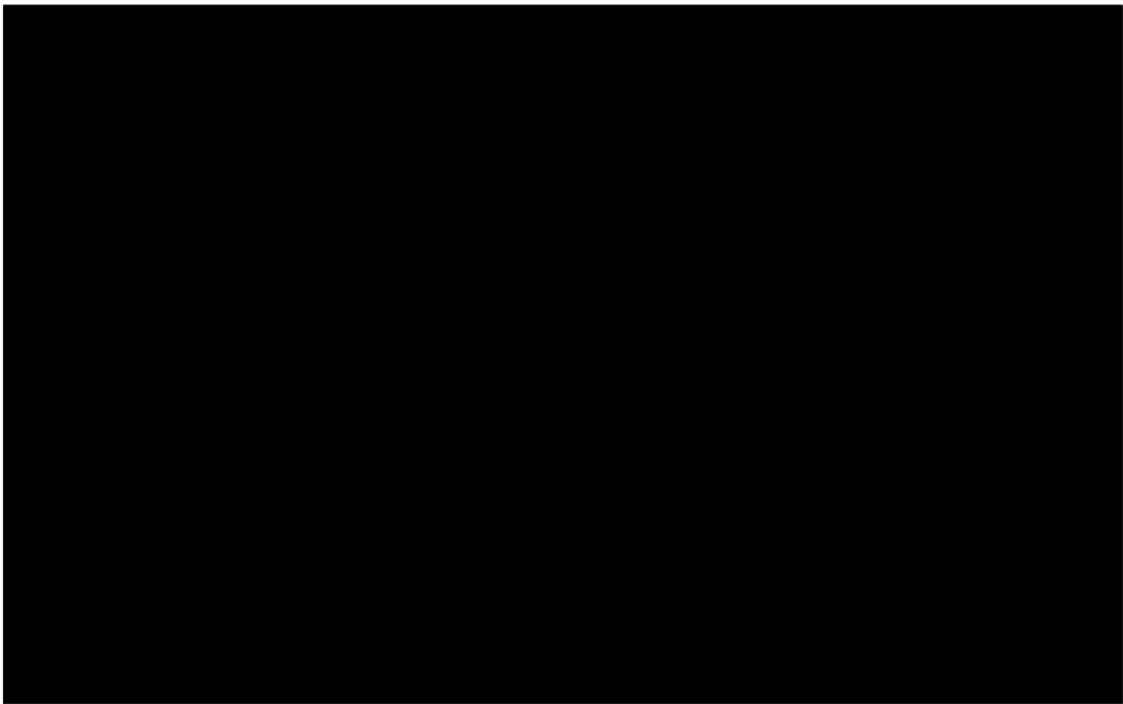


Figure 15. Cost-effectiveness acceptability curve (CEAC) with the existing 15% PAS discount (without severity weighting).

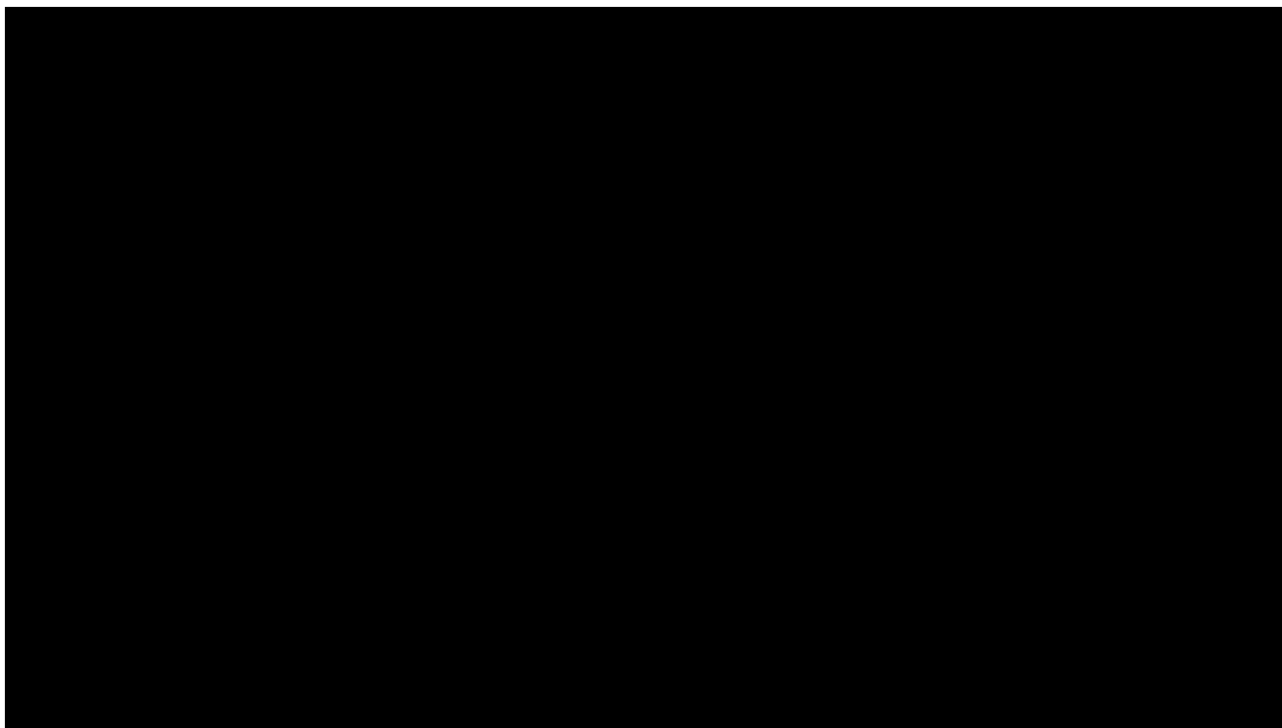


Figure 16. Cost-effectiveness plane with the existing ■% PAS discount (with x1.7 severity weighting).

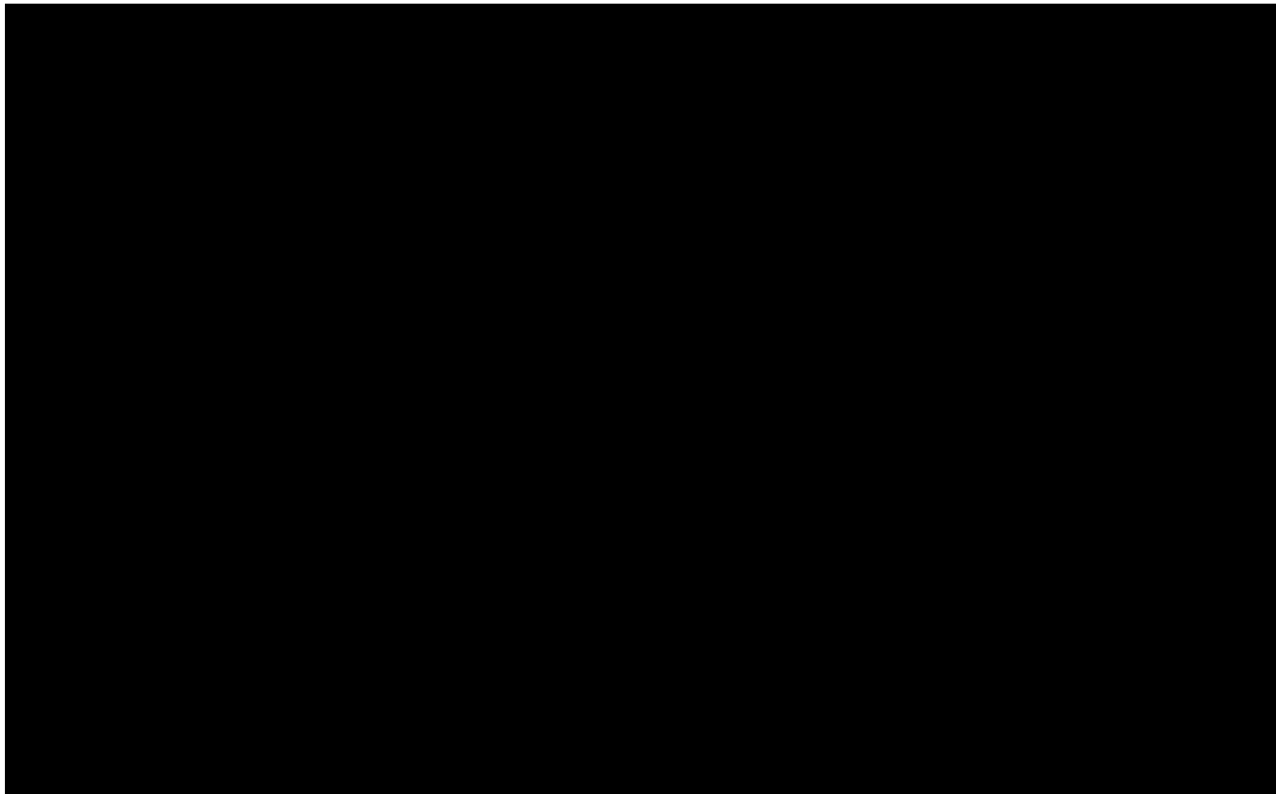


Figure 17. Cost-effectiveness acceptability curve (CEAC) with the existing 10% PAS discount (with x1.7 severity weighting).

Deterministic sensitivity analysis

Univariate sensitivity analysis

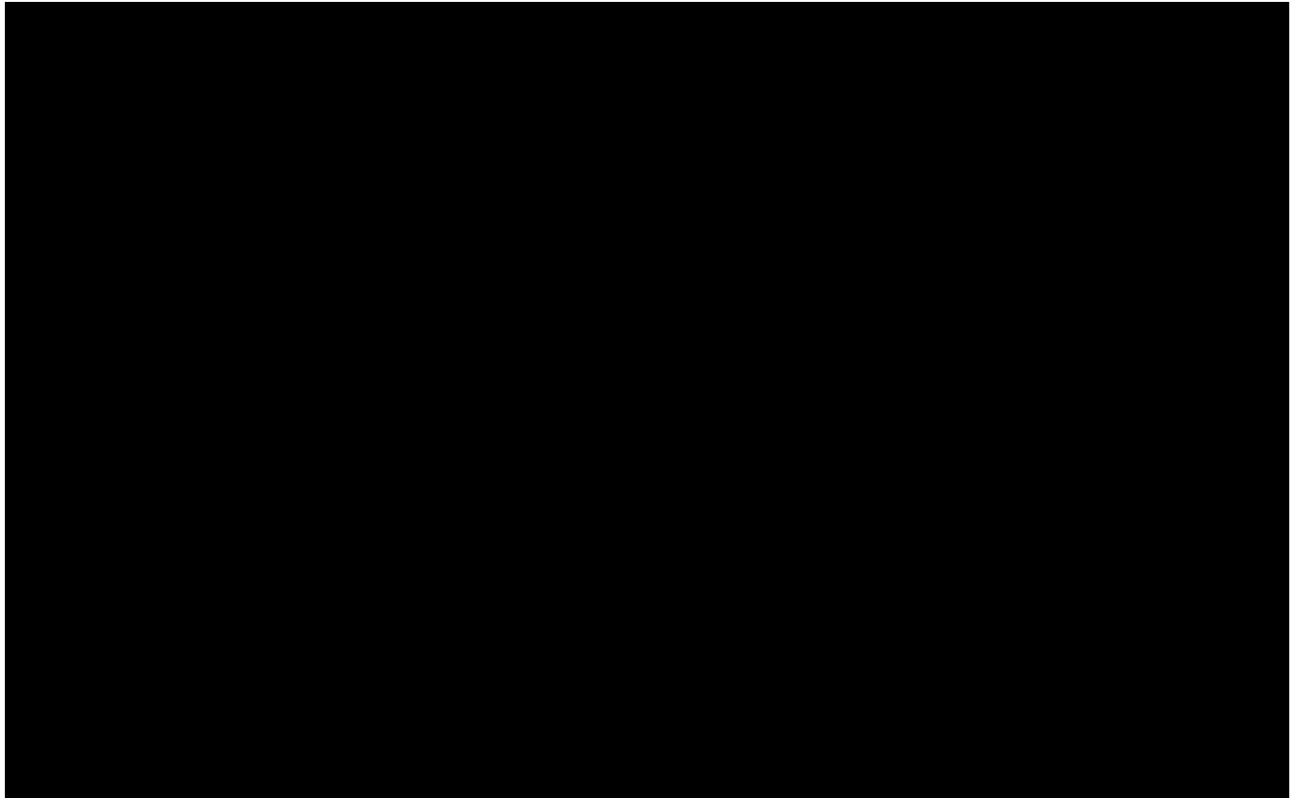
Univariate sensitivity analyses were conducted to test parameter uncertainties, by varying each parameter according to its 95% CI or standard error, while holding all other parameters constant. For those parameters without CI or standard error reported, a 10% variation of the mean estimates was assumed. All parameters with parameter uncertainty were included in these sensitivity analyses. Time-horizon and discount rates were not varied as these were not subject to parameter uncertainty; however, the impact of alternative discount rates and time horizon was examined in scenario analyses, as described below. Similarly, the cemiplimab drug acquisition cost per administration is not subject to parameter uncertainty, and therefore, was not varied in the univariate sensitivity analysis. Non-drug costs were included in sensitivity analyses as health state costs and

total TEAE costs, and not by their component unit costs and resource use used to estimate them.

The 10 parameters for which model results were most sensitive are depicted in a tornado diagram (Figure 18).

Results

The univariate sensitivity analysis tested the effect of extreme (and arguably unrealistic) values of all inputs with parameter uncertainty. While the ICER estimates with the extreme values are not realistic (and do not include the x1.7 severity weighting), they are useful to determine the parameters to which the results are most sensitive. The results on the tornado diagram show that the ICER is most sensitive to the parameters (shape and scale) of the log-normal parametric model used to extrapolate ToT, and the utilities post-progression (Figure 18). Since ToT was almost complete, and the use of alternative utility values resulted in ICERs between £[REDACTED]-£[REDACTED] per QALY when the 1.7 severity modifier is applied, this shows that the inputs that are most influential on the results are robust, and the results are associated with little uncertainty.



Abbreviations: TOT, time-on-treatment; PFS, progression-free survival; ICER, incremental cost-effectiveness ratio

Figure 18. Tornado diagram for ICER with the existing ■% PAS discount (without severity weighting)

Scenario analysis

Scenario analyses were conducted to test the robustness of the model to potential alternative structural and methodological assumptions. These include:

- Scenario analyses included in CS
 - alternative time horizons
 - alternative discount rates
 - the use of comparator chemotherapies based on clinical expert input (Table 11)
 - alternative unit costs for chemotherapies
 - adding TEAE disutilities
 - the use of alternative health state utilities
 - alternative parametric models for extrapolation

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- inclusion of wastage.
- Additional scenarios requested in the clarification questions above
 - The use of weekly paclitaxel only for comparator (Question B1)
 - Removing the PFS cap from ToT (Question B8)
 - Extrapolating ToT with censored ToT using lognormal, and generalised gamma models (Question B9a)
 - Using the Kaplan-Meier curve for ToT (Question B9b)
 - Excluding EOL utilities (Question B14)
 - Assuming no specialist nursing costs post-progression (Question B34)
 - Assuming the same health state costs for chemotherapy arm as for the cemiplimab arm post-progression (Question B34)
 - PD-L1<1% subgroup weighted by ECOG status as done for SMC using all patients with recorded PD-L1 status (Question A21)
 - Weighted average of PD-L1 subgroups as done for SMC using all patients with recorded PD-L1 status (Question A21)

Table 11. Distribution of 2L chemotherapies used in UK clinical practice according to clinical experts in England and Wales

Chemotherapies included	Percentage of patients receiving
Gemcitabine	6.0%
Topotecan	8.9%
Irinotecan	6.0%
Vinorelbine	6.0%
Weekly paclitaxel	46.4%
Carboplatin + pegylated liposomal doxorubicin	7.4%
Carboplatin + gemcitabine	7.4%
Carboplatin monotherapy	11.9%
Clinical trial or best supportive care	0.0%

Source: Mean of four clinical expert questionnaires from England and Wales^{3-5 35}

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Results

Scenario analyses demonstrate that the base case model is relatively stable to alternative structural and methodological assumptions (Table 12, Table 13). Material increases in the ICER only occur with less plausible or less certain assumptions than those adopted in the base case, indicating that the base case assumptions are reasonable and provide plausible estimates of the cost effectiveness of cemiplimab. With the currently available ■% PAS discount price for cemiplimab and the 1.7 severity weighting the ICER was below £24,000/QALY in almost all scenarios. One exception was the highly unrealistic scenario of more than doubling the cemiplimab treatment duration compared to the one observed in the EMPOWER Cervical-1 trial with the ToT curves censored at 96 weeks and extrapolated using generalized gamma model. However, even this unrealistic worst-case scenario resulted in an ICER ■.

The scenario analyses show that (Table 12, Table 13):

- Decreasing the time horizon substantially (from 33 years to 20 years or to 10 years) reduces the accrual of health benefit for cemiplimab by shortening the life-years over which patients can accumulate a health benefit, while maintaining the higher drug acquisition costs for cemiplimab that accumulate earlier in the time horizon. This therefore biases the analysis against cemiplimab, resulting in a 4% or a 16% increase in the ICER. The lifetime horizon used in the base case model remains the appropriate time horizon for decision making in this terminal disease, in line with the NICE reference case.
- Similarly, due to the early accrual of drug costs and more prolonged accrual of health benefits, changing the annual discount rate in the model affects the health benefits more than the costs. Reducing the discount rate to 0% decreases the ICER (by 12%), while increasing the discount rate to 6% increases the ICER (by 8%).
- Due to the low cost generic chemotherapies available as comparator treatments, changing the comparator drug costs has negligible effect on the ICER. Using the comparator mix recommended by clinical experts practicing in England, the ICER decreases by 3%. When weekly paclitaxel is the only comparator used the ICER decreases by 4%.

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- Due to the high maturity of the OS data from the pivotal trial, selecting alternative clinically plausible parametric models to extrapolate OS changes the ICER only by 0%-7%.
- Extrapolation of ToT with a longer tail (generalised gamma model) increases the drug costs for cemiplimab, and thereby the ICER slightly (by 8%). However, the extrapolation used in the base case is the best fitting model and is most appropriate for decision making. While the licence requires patients to stop treatment at progression, not capping ToT with progression increases the ICER by 4%.
- Extrapolation of PFS with log-normal model (instead of the more appropriate generalised gamma model adopted in the base case) increases the drug costs for cemiplimab (as PFS acts as an upper limit for ToT curves) and thereby increases the ICER (by 15%). However, the extrapolation used in the base case was the best fitting model and was confirmed by clinicians to provide clinically plausible extrapolated outcomes.
- Assuming no treatment-specific effect on patient quality of life and using only health state-specific values from the literature, despite the statistically significant difference observed between the treatment arms in the EMPOWER Cervical-1 trial and the views of clinical experts, increased the ICER by 8%. However, based on trial results and clinical expert opinion, an increase in the base case ICER due to use of alternative utility values from the literature would seem implausible.
- Using utility values suggested by the clinical experts to reflect the treatment-specific impacts on patient quality of life decreases the ICER by 12%, demonstrating that the base case approach and results could be conservative.
- Excluding RDI (i.e., assuming 100% dosing for all therapies) increases the ICER by 11% due to the higher acquisition costs of cemiplimab relative to generic chemotherapy. However, as the observed trial outcomes are linked to the observed drug exposure in the trial, assuming 100% RDI is implausible and not reflective of patient experience in trial or clinical practice settings.

- Incorporating wastage for treatments not requiring flat dosing had minimal effect, increasing the chemotherapy costs slightly, and decreasing the ICER by 1%.
- EOL utilities have negligible effect since all patients in the model go through end of life regardless of treatment arm, with the only difference being when this stage is reached. Excluding EOL utilities reduces the ICER by 1%.
- Using the worst-case scenario of highly overestimating ToT resulting in unrealistic treatment duration increases the ICER by 14.73%-75.84% depending on the parametric model used. However, with the severity weighting, the ICER either still remained [REDACTED]. The more realistic use of the Kaplan-Meier curve from the EMPOWER Cervical-1 trial for ToT decreased the ICER by 1%.
- Incorporated hepatobiliary disorders among the AEs had negligible effect by increasing the ICER by <1%.
- Using the weighted average of the PD-L1<1% and PD-L1≥1% subgroups according to the expected proportions in England and Wales decreased the ICER by 13%.
- Focusing on the PD-L1<1% subgroup (adjusted for ECOG status) and therefore excluding a small but meaningful patient population with very high unmet need resulted in increased uncertainty and a reduced ICER (by 1.71%).

Table 12. Scenario analyses with the existing ■% PAS discount (without severity weighting).

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (without severity weighting)
Base case			██████	0.78	██████
Model characteristics					
Time horizon	Lifetime	10 years	██████	0.64	██████
		20 years	██████	0.75	██████
Discount rate	3.5%	0%	██████	0.99	██████
		6%	██████	0.69	██████
Comparators	Single-agent chemotherapies	Combination chemotherapies	██████	0.78	██████
		100% weekly paclitaxel	██████	0.78	██████
Population	ITT population of the EMPOWER Cervical-1 trial	ECOG adjusted PD-L1<1% population	██████	0.96	██████
		Weighted average of PD-L1>1% & PD-L1≥1% patients	██████	0.75	██████
Extrapolations					
Parametric curve for OS chemotherapy	Generalised gamma	Log-normal	██████	0.78	██████
		Log-logistic	██████	0.76	██████
Parametric curve for OS cemiplimab	Generalised gamma	Log-normal	██████	0.70	██████

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (without severity weighting)
Parametric curve for ToT for both arms	Log-normal	Generalised gamma	██████	0.78	██████
Parametric curve for PFS for both arms	Generalised gamma	Log-normal	██████	0.75	██████
Costs and utilities					
Chemotherapy costs	Minimum costs per mg	Mean cost per mg	██████	0.78	██████
		Maximum cost per mg	██████	0.78	██████
TEAE disutilities	Excluded	Included	██████	0.79	██████
Age disutilities	Included	Excluded	██████	0.80	██████
Health state utilities	EMPOWER Cervical-1 trial utilities: treatment specific	SMC bevacizumab utilities	██████	0.72	██████
		Clinical expert input	██████	0.89	██████
RDI	Included	Excluded	██████	0.78	██████
Wastage	Excluded	Included	██████	0.78	██████
TOT capped at progression	Yes	No	██████	0.78	██████
End of life utilities	Included	Excluded	██████	0.79	██████
		Survival analysis of censored EMPOWER	██████	0.78	██████

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (without severity weighting)
Extrapolating ToT with censored ToT	Survival analysis of EMPOWER Cervical-1 trial data	Cervical-1 trial data using log-normal model			
		Survival analysis of <u>censored</u> EMPOWER Cervical-1 trial data using generalised gamma model	██████	0.78	██████
		Using the Kaplan-Meier curve for ToT	██████	0.78	██████
Post-progression health state costs	Based on clinical expert input (cemiplimab £202.50, chemotherapy £217.23)	No specialist nurse visits	██████	0.78	██████
		Same costs for chemotherapy as for cemiplimab (£202.50)	██████	0.78	██████
AE costs	AEs included from Table 39 of the CSR	Addition of hepatobiliary disorders from Table 52 of the CSR	██████	<u>0.78</u>	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SMC, Scottish Medicines Consortium; TEAE, treatment-emergent adverse event; ToT, time on treatment

Table 13. Scenario analyses with the existing ■% PAS discount (with 1.7 severity weighting).

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
Base case			████	1.33	████
Model characteristics					
Time horizon	Lifetime	10 years	████	1.08	████
		20 years	████	1.27	████
Discount rate	3.5%	0%	████	1.68	████
		6%	████	1.17	████
Comparators	Single-agent chemotherapies	Combination chemotherapies	████	1.33	████
		100% weekly paclitaxel	████	1.33	████
Population	ITT population of the EMPOWER Cervical-1 trial	ECOG adjusted PD-L1<1% population	████	1.63	████
		Weighted average of PD-L1>1% & PD-L1≥1% patients	████	1.28	████
Extrapolations					
Parametric curve for OS	Generalised gamma	Log-normal	████	1.32	████
		Log-logistic	████	1.29	████

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
chemotherapy					
Parametric curve for OS cemiplimab	Generalised gamma	Log-normal	██████	1.19	██████
Parametric curve for ToT for both arms	Log-normal	Generalised gamma	██████	1.33	██████
Parametric curve for PFS for both arms	Generalised gamma	Log-normal	██████	1.27	██████
Costs and utilities					
Chemotherapy costs	Minimum costs per mg	Mean cost per mg	██████	1.33	██████
		Maximum cost per mg	██████	1.33	██████
TEAE disutilities	Excluded	Included	██████	1.33	██████
Age disutilities	Included	Excluded	██████	1.37	██████
		SMC bevacizumab utilities	██████	1.23	██████

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
Health state utilities	EMPOWER Cervical-1 trial utilities: treatment specific	Clinical expert input	██████	1.52	██████
RDI	Included	Excluded	██████	1.33	██████
Wastage	Excluded	Included	██████	1.33	██████
TOT capped at progression	Yes	No	██████	1.33	██████
End of life utilities	Included	Excluded	██████	1.34	██████
Extrapolating ToT with censored ToT	Survival analysis of EMPOWER Cervical-1 trial data	Survival analysis of <u>censored</u> EMPOWER Cervical-1 trial data using log-normal model	██████	1.33	██████
		Survival analysis of <u>censored</u> EMPOWER Cervical-1 trial data using generalised gamma model	██████	1.33	██████
		Using the Kaplan-Meier curve for ToT	██████	1.33	██████
		No specialist nurse visits	██████	1.33	██████

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Parameter	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) (with 1.7 severity weighting)
Post-progression health state costs	Based on clinical expert input (treatment dependent: cemiplimab £202.50, chemotherapy £217.23)	for chemotherapy			
		Same costs for chemotherapy as for cemiplimab (£202.50)	██████	1.33	██████
AE costs	AEs included from Table 39 of the CSR	Addition of hepatobiliary disorders from Table 52 of the CSR	██████	<u>1.33</u>	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SMC, Scottish Medicines Consortium; TEAE, treatment-emergent adverse event; ToT, time on treatment

Appendix 3: Subsequent treatments

Please see the requested additional calculations in the attached Excel sheet titled "Cervical cancer NICE model_Inputs_19Jan2026_CQs".

Appendix 4: Updated chemotherapy costs

Table 14. Updated chemotherapy drug costs

Name and pack size	NPC code	Weighted average price	Standard deviation of price
Pemetrexed			
Pemetrexed 100mg powder for solution for injection vials (generic)/pack size 1	DEI019	£55.24	£39.94
Pemetrexed 100mg/4ml solution for infusion vials (generic)/pack size 1	DYC062	£6.83	£1.02
Pemetrexed 1g/100ml infusion bags/pack size 1	DLH024	£96.10	£16.20
Pemetrexed 1g/40ml solution for infusion vials (generic)/pack size 1	DEI018	£112.83	£419.63
Pemetrexed 500mg powder for solution for injection vials (generic)/pack size 1	DEI020	£74.79	£127.78
Pemetrexed 500mg/20ml solution for infusion vials (generic)/pack size 1	DYC063	£23.25	£6.67
Pemetrexed 600mg/100ml infusion bags/pack size 1	DLH025	£103.07	£57.04
Pemetrexed 700mg/100ml infusion bags/pack size 1	DLH026	£77.47	£12.88
Pemetrexed 750mg/100ml infusion bags/pack size 1	DLH027	£120.98	£94.03
Pemetrexed 800mg/100ml infusion bags/pack size 1	DLH028	£75.99	£18.88
Pemetrexed 850mg/34ml solution for infusion vials/pack size 1	DZV051	£42.95	£0.04
Pemetrexed 900mg/100ml infusion bags/pack size 1	DLH029	£136.72	£4.70
Gemcitabine			
Gemcitabine 1200mg/120ml solution for infusion bags / pack size 1	DHB246	£37.01	£0.06
Gemcitabine 1300mg/130ml solution for infusion bags / pack size 1	DQC034	£38.23	£3.90
Gemcitabine 1400mg/140ml solution for infusion bags / pack size 1	DYC085	£38.98	£0.45
Gemcitabine 1500mg/150ml solution for infusion bags / pack size 1	DQC035	£40.12	£2.08
Gemcitabine 1600mg/160ml solution for infusion bags / pack size 1	DHK055	£41.06	£3.17

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Name and pack size	NPC code	Weighted average price	Standard deviation of price
Gemcitabine 1800mg/180ml solution for infusion bags / pack size 1	DHB247	£43.08	£2.69
Gemcitabine 1g powder for solution for infusion vials / pack size 1	DHA151	£20.95	£19.06
Gemcitabine 1g/26.3ml (38mg/ml) concentrate for solution for infusion vials / pack size 1	DYC035	£13.53	£17.74
Gemcitabine 200mg powder for solution for infusion vials / pack size 1	DHA150	£9.98	£4.22
Gemcitabine 200mg/5.26ml (38mg/ml) concentrate for solution for infusion vials / pack size 1	DQC036	£4.82	£0.44
Gemcitabine 200mg/5.3ml (38mg/ml) concentrate for solution for infusion vials / pack size 1	DYC036	£4.96	£3.65
Gemcitabine 2200mg/220ml solution for infusion bags / pack size 1	DHB249	£49.67	£8.68
Gemcitabine 2g/52.6ml (38mg/ml) concentrate for solution for infusion vials / pack size 1	DYC037	£25.52	£32.59
Topotecan			
Topotecan 1mg/1ml concentrate for solution for infusion vials/pack size 1	DXA016	£66.06	£36.22
Topotecan 4mg/4ml concentrate for solution for infusion vials/pack size 1	DXA017	£98.40	£109.22
Topotecan 4mg/4ml concentrate for solution for infusion vials/pack size 5	DXA025	£457.45	£536.51
Irinotecan			
Irinotecan 100mg/5ml solution for infusion vials/pack size 1	DHA208	£5.95	£14.41
Irinotecan 270mg/180ml solution for infusion bags/pack size 1	DLK052	£55.24	£2.56
Irinotecan 300mg/15ml solution for infusion vials/pack size 1	DHA396	£19.39	£28.30
Irinotecan 300mg/200ml solution for infusion bags/pack size 1	DLK051	£59.63	£1.67
Irinotecan 330mg/220ml solution for infusion bags/pack size 1	DLK053	£65.02	£1.78
Irinotecan 360mg/240ml solution for infusion bags/pack size 1	DLK054	£69.96	£0.71
Irinotecan 40mg/2ml solution for infusion vials/pack size 1	DHA207	£3.44	£0.39
Irinotecan 500mg/25ml solution for infusion vials/pack size 1	DHA409	£26.60	£31.04
Vinorelbine			

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Name and pack size	NPC code	Weighted average price	Standard deviation of price
Vinorelbine 10mg/1ml solution for injection vials/pack size 10	DHA220	£79.54	£3.95
Vinorelbine 50mg/5ml solution for injection vials/pack size 10	DHA221	£165.43	£28.46
Paclitaxel			
Paclitaxel 100mg/16.7ml solution for infusion vials/pack size 1	DHA145	£9.79	£32.32
Paclitaxel 150mg/25ml solution for infusion vials/pack size 1	DHA297	£14.23	£37.66
Paclitaxel 300mg/50ml solution for injection vials/pack size 1	DHA210	£23.23	£78.41
Paclitaxel 30mg/5ml solution for infusion vials/pack size 1	DHA144	£3.96	£2.16
Paclitaxel Albumin 100mg powder for suspension for infusion vials (e.g. Abraxane)/pack size 1	DHC068	£123.15	£22.00
Cisplatin			
Cisplatin 100mg/100ml solution for infusion vials/pack size 1	DHA010	£30.50	£13.21
Cisplatin 10mg/10ml solution for infusion vials/pack size 1	DHA013	£3.77	£1.02
Cisplatin 50mg/50ml solution for infusion vials/pack size 1	DHA011	£16.76	£6.36
Carboplatin			
Carboplatin 150mg/15ml solution for infusion vials/pack size 1	DHE001	£6.75	£4.18
Carboplatin 450mg/45ml solution for infusion vials/pack size 1	DHE002	£22.41	£25.72
Carboplatin 50mg/5ml solution for infusion vials/pack size 1	DHE003	£5.26	£3.59
Carboplatin 600mg/60ml solution for infusion vials/pack size 1	DHA162	£21.85	£28.05
Doxorubicin liposomal pegylated			
Doxorubicin liposomal pegylated 20mg/10ml solution for infusion vials (e.g. Caelyx or eqv)/pack size 1	DHA186	£131.06	£52.47
Doxorubicin liposomal pegylated 50mg/25ml solution for infusion vials (e.g. Caelyx or eqv)/pack size 1	DHA268	£254.36	£84.29

Source: eMIT 2026⁵⁶

Abbreviation: NPC, National Product Code

Company evidence submission template for cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Appendix 5: Updated NHS Reference costs (including AE costs)

Please see the updated costs (including the updated AE costs) in the attached Excel sheet titled "Cervical cancer NICE model_Inputs_19Jan2026_CQs".

Appendix 6: Updated graphs for OS/PFS incorporating the gamma distribution

Overall survival

Figure 19 shows the fit for each parametric model within to the observed data.

Figure 19: Parametric Fit Plots OS (B3 ITT)

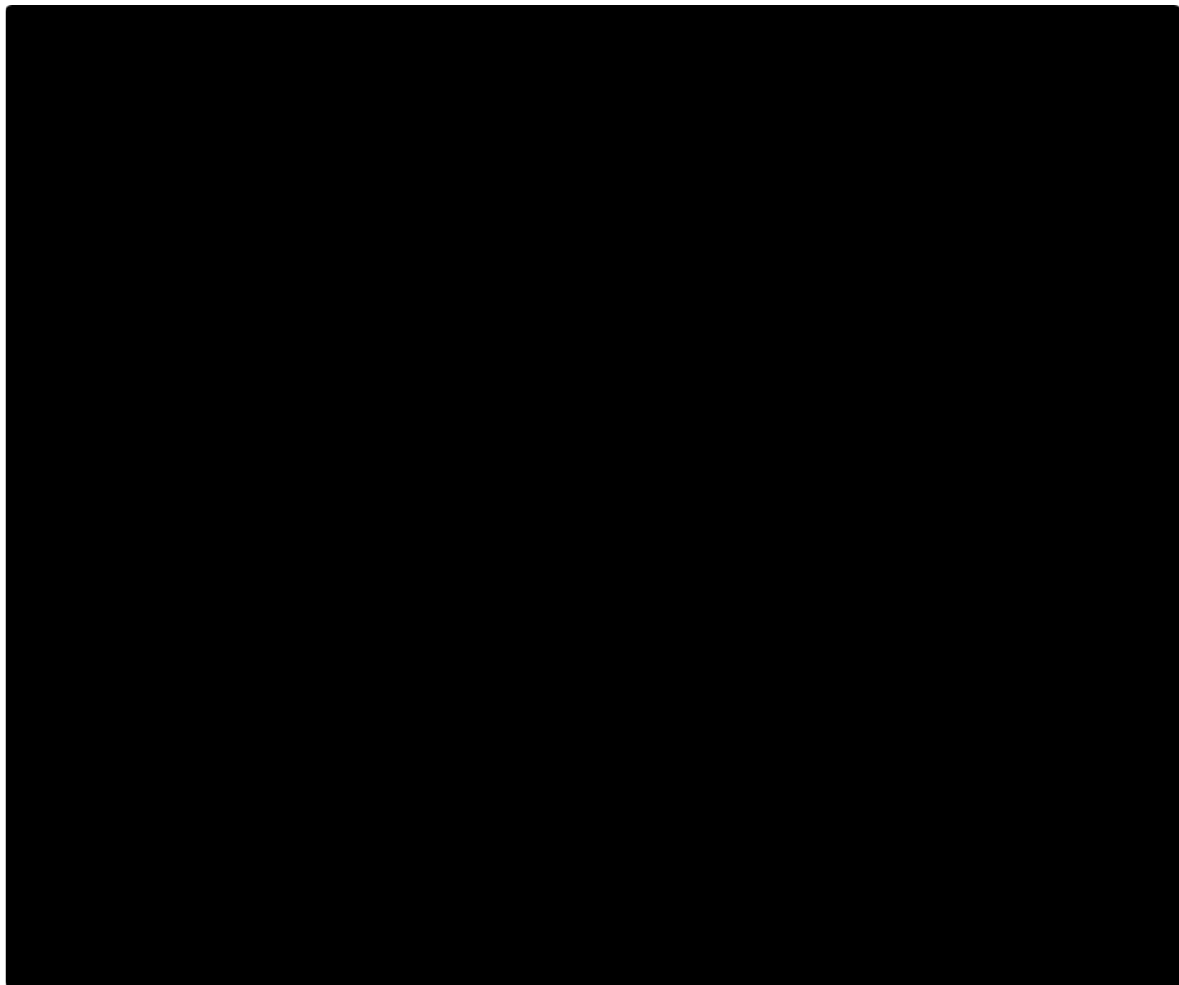
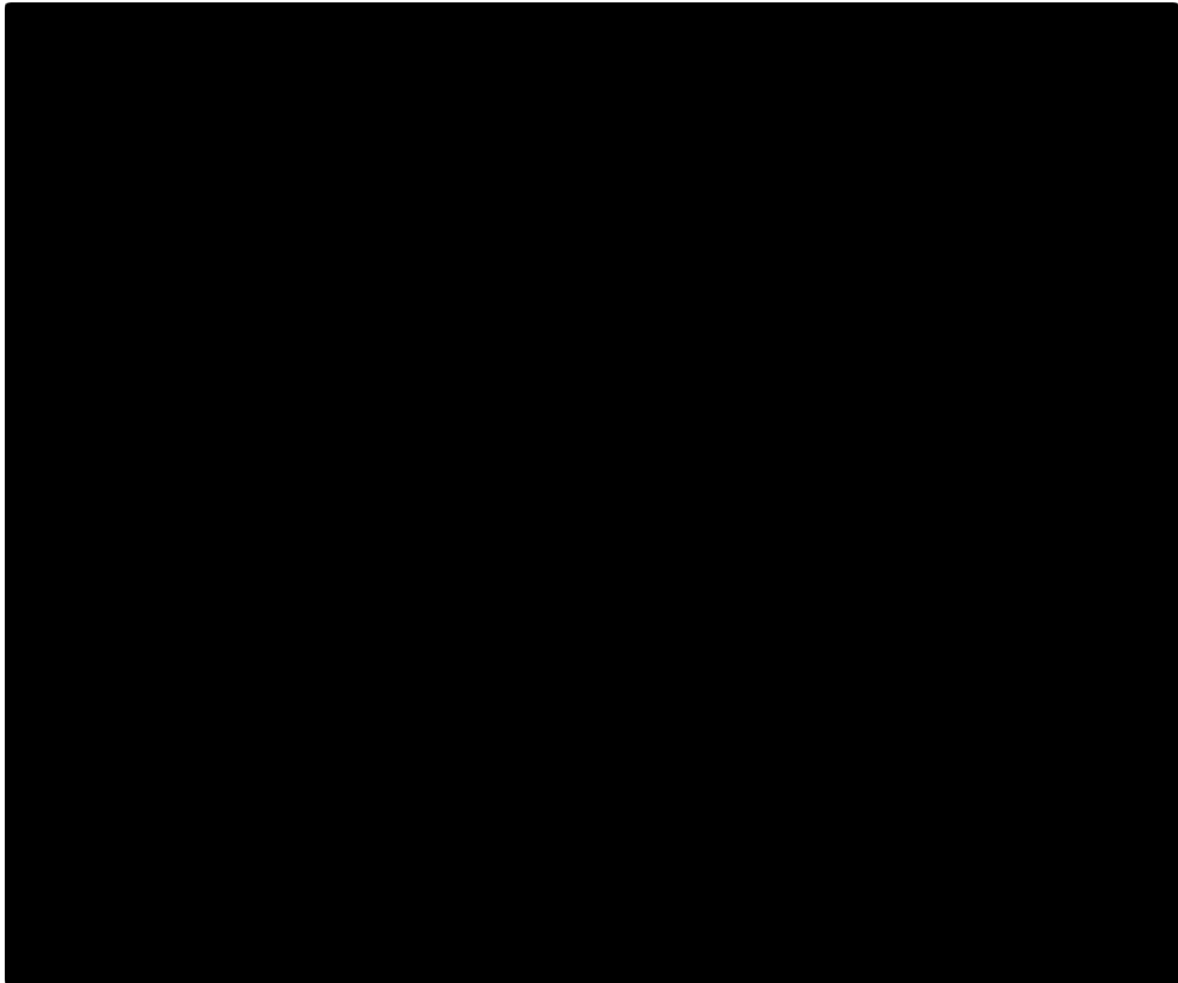


Figure 20 shows the hazards for each parametric model and the observed data.

Figure 20: Parametric Hazard Plots OS (B3 ITT)



Progression-free survival

Figure 21 shows the fit for each parametric model within to the observed data.

Figure 21: Parametric Fit Plots PFS (B3 ITT)

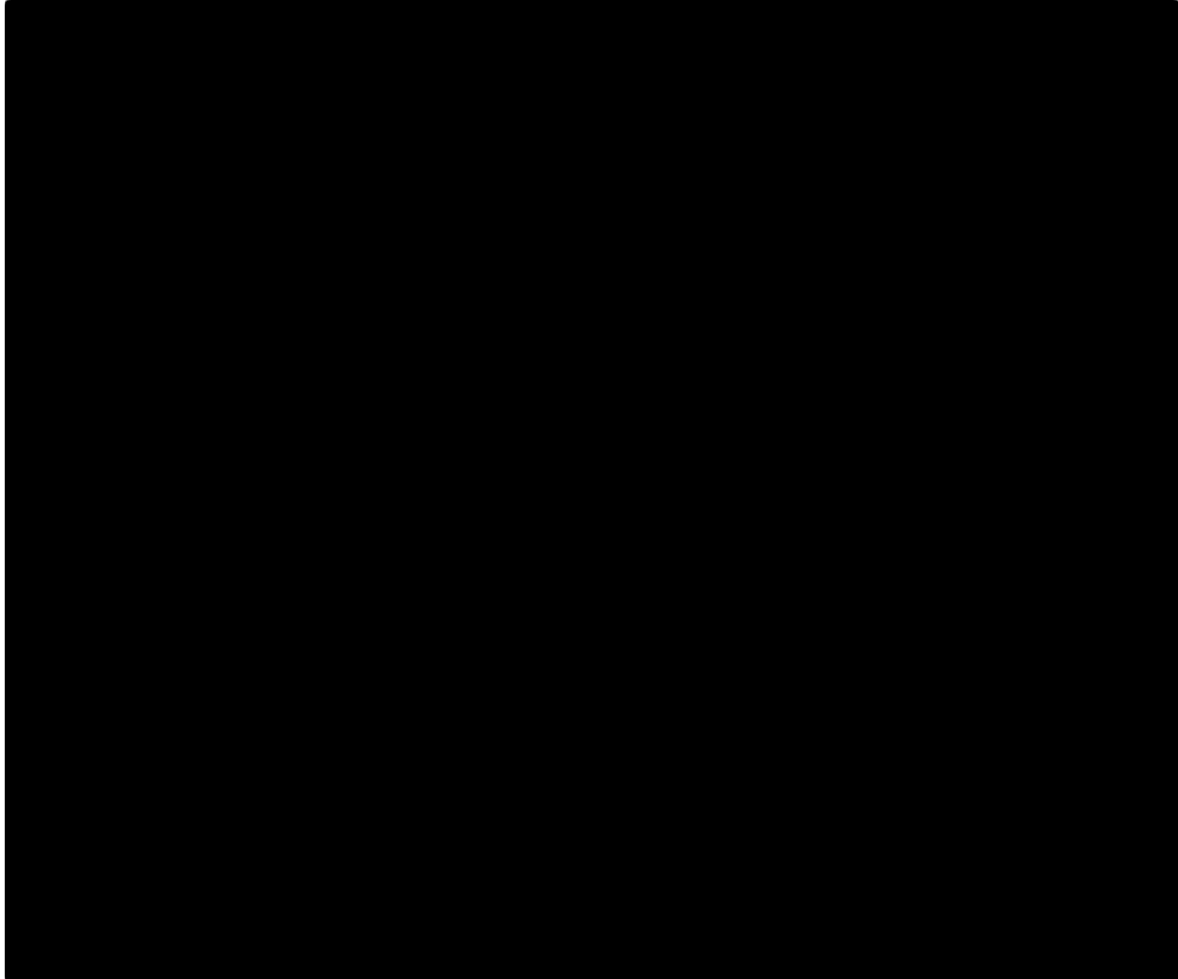
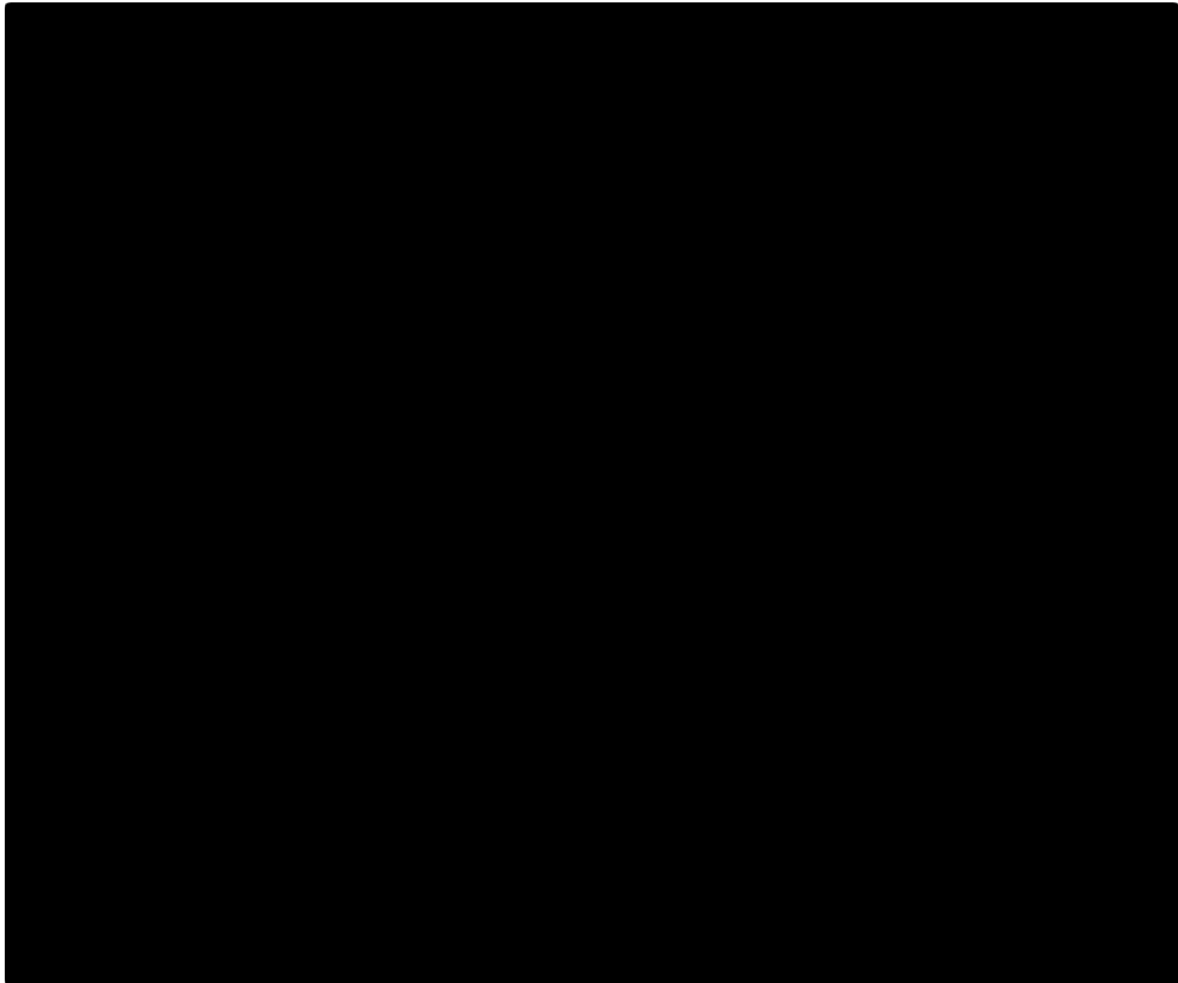


Figure 22 shows the hazards for each parametric model and the observed data.

Figure 22: Parametric Hazard Plots PFS (B3 ITT)



Appendix 7: Survival analysis of the censored Kaplan-Meier curves

Please see the separate document title: ID6610_Appendix 1 and 7 – Additional survival analyses for CQs 19Jan2026.doc.

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 1: Treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alexandra Taylor
2. Name of organisation	The Royal Marsden NHS Foundation Trust
3. Job title or position	Consultant in Clinical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with recurrent or metastatic cervical cancer? ☒ A specialist in the clinical evidence base for recurrent or metastatic cervical cancer or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.) I have not seen the submission.
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To stop disease progression, extend survival and to improve quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Disease regression or stability for at least 6 months Improvement in clinical symptoms – reduction in pain, bleeding, improvement in performance status
10. In your view, is there an unmet need for treatments for this condition?	There is definitely unmet need for recurrent cervical cancer. There is no standard of care for second line treatment and the response rates to non-platinum monotherapy is extremely low. The patients with this condition are frequently young and otherwise fit. When clinical trials become available in this setting (rarely unfortunately), many women are prepared to travel across the country to get treatment and slots are filled very quickly as they have no other option.
11. How is recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Clinical guidelines include ESGO-ESTRO guidelines, ESMO guidelines, BGCS guidelines (2026 update currently in final draft), NCCN guidelines. All clinicians managing patients with recurrent cervical cancer agree that there is a need for better options as the current chemotherapy options are not effective. The drugs used may vary slightly between centres and patients as there is no defined second line option. Cemiplimab would be used for patients who did not have immunotherapy as part of first line systemic therapy - either because the tumour was PDL-1 negative (10-25% relapsed patients) or because their first line treatment was given prior to the availability of pembrolizumab (a small number of patients since it has now

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

	been available for 3 years). It will provide a line of therapy that currently is not available for these women. Tisotumab vedotin is currently available on a named patient access scheme, and is also used for recurrent cervical cancer after platinum chemotherapy. For patients who have previously had immunotherapy, this would be the next line of therapy. For women without prior immunotherapy cemiplimab would be the preferred option as it has less toxicity and potentially there will be a greater number of patients with a prolonged response. Tisotumab vedotin would then be a subsequent option.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This will be used in the same way as current care in NHS clinical practice. The use of checkpoint inhibitors is now very common for patients with gynaecological cancer and the oncology teams will have significant experience of the treatment and managing potential toxicities. All oncology units will already have pathways in place for management of immunotherapy-related toxicities.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I would expect this treatment to both increase length of life and improve quality of life compared to current care.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be straightforward to use, and no specific practical implications.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be stopped in the event of definite disease progression. Imaging would be undertaken to assess response as per usual practice with all systemic therapy.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	It is much easier to deliver than weekly taxol or gemcitabine– less visits, less blood tests. No hair loss which is really important to women with this disease.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The improvement in QoL and longer time to definitive deterioration in symptoms such as pain compared to standard of care in the EMPOWER study is striking and really supports using this drug.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

- Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	It is a step-change to be able to use immunotherapy for women currently who would not receive this option.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are potential immunotherapy-related toxicities but severe toxicity with monotherapy is rare.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The EMPOWER trial is in keeping with UK practice. The median OS of only 8.5 months in the chemotherapy arm underlines the poor prognosis for this patient cohort - and obviously these were patients selected for a trial so the outcomes for the whole UK population would be even worse. The main outcomes were improvement in overall survival which was maintained at 2 years (28.2% versus 11.9%) with the tail of more than 10% very long term survivors typical of immunotherapy and not seen with chemotherapy. In addition the improvement in quality of life is very important, particularly as palliation of uncontrolled pelvic disease is extremely challenging.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The MITO 44 study is real world data on efficacy and safety of cemiplimab in 135 patients in a nominal use programme.
22. How do data on real-world experience compare with the trial data?	This study showed outcomes that are comparable to the clinical trial. It is also reported no significant differences in response for tumours that were PDL1 positive or negative.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Cervical cancer more frequently affects women from deprived socio-economic populations and immigrants from countries that have a much higher incidence of cervical cancer including Africa, parts of Asia and Eastern Europe.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Cemiplimab is already available for second line treatment of cervical cancer in Scotland.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Current treatment options for recurrent cervical cancer are limited and not effective.

Cemiplimab is an important treatment option for women who have not previously had access to immunotherapy

In addition to improved survival outcomes, importantly it improves quality of life for women.

Click or tap here to enter text.

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Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

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Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 1: Treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Gemma Eminowicz
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with recurrent or metastatic cervical cancer? ☐ A specialist in the clinical evidence base for recurrent or metastatic cervical cancer or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

8. What is the main aim of treatment for recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim is symptomatic benefit and improvement in quality of life with addition of survival if possible. Often patients with metastatic or recurrent cervical cancer are young with young families and quality of life to be able to spend with family is a priority.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in survival amount depends upon burden of the treatment as only a few months survival does make a big difference providing it is accompanied by good quality of life. Symptomatic improvement with increase in quality of life on treatment more important.
10. In your view, is there an unmet need for treatments for this condition?	Treatment options very limited in this cohort and often young patient population (with young families) with high symptom burden. In patients with PDL1-ve disease they are usually excluded from trials due to not being exposed to immunotherapy so this is huge unmet need. Standard of care is weekly paclitaxel which has poor response rates.
11. How is recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The standard treatment used in the UK is single agent chemotherapy, most commonly weekly paclitaxel with other options including topotecan, vinorelbine, gemcitabine etc. Due to the poor outcomes in general with these treatments, any fit patients are often referred for trials where possible including phase 1 or 2 trials. However, in the PDL1 negative population trials often exclude these patients as they have not previously received immunotherapy. Cemiplimab could be used as an alternative to weekly paclitaxel or as an option after weekly paclitaxel and use of this may also open up other trial opportunities which would have otherwise not be available to PDL1 negative patients.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Cemiplimab would be given on chemotherapy day unit which is the same as standard of care and would only be used in the specialist tertiary setting. No new facilities/equipment/training needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. In comparison with single agent chemotherapy, cemiplimab provides an improvement in PFS, OS, ORR and most importantly quality of life. Patients having this treatment had a more than 3 month increase in overall survival with a 31% reduction in risk of death. This was also associated with less severe toxicity than chemotherapy (45% G3 or higher tox, compared with 53%) and an improvement in quality of life, most obvious in pain and role functioning.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Equally as effective in the PDL1 positive and negative subgroups
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Would be similar to current standard of care Centres and clinicians in general are familiar now with managing immunotherapy.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usual stopping rules ie progression on imaging or symptomatic progression or unmanageable toxicity No additional imaging compared with standard of care
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The only point here is to say that this is often a cohort of patients who are contributing to society and have jobs which they do return to when feeling well and they often have young children who are attending school etc and if they are not looked after as well they may need more support/health services too.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	This is a significant change in the treatment of metastatic/recurrent cervical cancer as it provides improved outcomes and additional treatment options especially in the PDL1 negative group who have no other access to immunotherapy and very limited treatment options
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This causes less toxicity than standard single agent chemotherapy and does not detrimentally affect quality of life, if anything there are improvements and quality of life outcomes are much more favourable than single agent chemotherapy.
20. Do the clinical trials on the technology reflect current UK clinical practice? If not, how could the results be extrapolated to the UK setting?	The trial did not include paclitaxel in the investigators choice standard of care arm. It is unlikely that there is a significant survival difference between the standards used in the trial compared with paclitaxel but there is no good data comparing these.

Clinical expert statement

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Otherwise the trial outcomes and recording of AEs etc was all in line with UK practice and no AEs have come to light that are in addition to those published. Within the gynae community we are also becoming more confident in managing patients with immunotherapy and therefore should feel confident managing most of the toxicities here.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	Real world data similar eg Beatson presented their cohort of 28 patients who had similar outcomes as the trial
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Nil specific to consider in relation to this treatment but overall in cervical cancer, incidence is higher in lower socioeconomic class and non white ethnicity.

Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

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Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patients who progress after first line systemic therapy for metastatic cervical cancer have minimal good treatment options and can have a high symptom burden. This is therefore an area of significant unmet need, especially in patients who are PDL1 negative and cannot access immunotherapy.

Cemiplimab offers a treatment option with improved survival and quality of life compared with single agent chemotherapy

Cemiplimab offers an additional line of treatment to PDL1 negative patients who have very little other effective options

Click or tap here to enter text.

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Clinical expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In [part 1](#) we are asking you about living with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy or caring for a patient with the condition The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 1: Living with this condition or caring for a patient with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

Table 1 About you, the condition, current treatments and equality

1. Your name	Katrina Cowley
2. Are you (please tick all that apply)	☐ A patient with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): A former cervical cancer patient (now no evidence of disease)
3. Name of your nominating organisation	Self-nominated
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I work in an evidence team at Cancer Research UK and have done some basic reading around Cemiplimab ☐ I have not completed part 2 of the statement
6. What is your experience of living with recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy? If you are a carer (for someone with this condition, please share your experience of caring for them)	I do not have recurrent or metastatic cervical cancer, but I do have experience of cervical cancer as a patient. I was diagnosed with cervical cancer stage 1b1 in summer 2018, following routine cervical screening. I was treated at University College London Hospital. I had a radical hysterectomy with ovarian preservation, followed by chemoradiotherapy for 5 weeks, then brachytherapy. I have had no evidence of disease since my treatment ended. I have some long-term effects of the treatment: early menopause due to the impact of the radiotherapy on my ovaries, and lymphoedema in one leg. My surgery was surprisingly problem-free, but I found chemoradiotherapy very difficult physically and emotionally. At the time, my children were of preschool age, and I was frequently unable to care for them either because I was out of the house having treatment, or because I felt too unwell to do so. I had nausea and vomiting throughout the treatment period, and was eating and drinking very little. This, coupled with travelling for treatment (a 2-hour round trip every day) and the physical effects of the treatment itself, meant I was absolutely drained during treatment and for around a month afterwards. I came very close to stopping treatment in around week 3 of chemoradiotherapy, as I didn't feel able to continue. I was anxious and depressed through the treatment period and for a time afterwards – I couldn't stop thinking about the possibility of the cancer returning. I still struggle with this now, and my anxiety increases markedly around the time of my annual follow-ups.

Patient expert statement

7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a: My understanding is that the prognosis for recurrent or metastatic cervical cancer is fairly bleak – suggesting that current treatment options are not particularly effective. The side effects of chemotherapy are obviously well-known, and to have to go through these side effects knowing that the treatment will likely not extend your life for very long, would be very difficult I think. Also the specific side effect profile of chemotherapy – including nausea, anaemia, and fatigue – I think makes this treatment particularly difficult for the cervical cancer patient population, many of whom will have caring responsibilities (given their age). Not being able to care for my young children properly while going through my treatment, certainly made everything harder for me – it added to my feeling that I was losing my identity because of the cancer and the treatment. I think it's disappointing that there have been relatively few developments in the treatment of a cancer that affects women often quite early in their adult life, when they have so much time ahead of them to lose. 7b: People I have spoken to about cancer treatment, either relating to their own experience or that of their loved ones, agree that going through chemotherapy is usually very difficult.
8. If there are disadvantages for patients of current NHS treatments for this condition (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As above, I think the side effects of chemotherapy are well-known. I haven't been through the chemotherapy regimens given for metastatic or recurrent cervical cancer myself, so I cannot speak from experience. I would imagine though that going through such a gruelling treatment knowing that another treatment could give you more time if it were available, would make everything even more difficult
9a. If there are advantages of cemiplimab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	9a: As far as I am aware (e.g. based on https://www.sciencedirect.com/science/article/abs/pii/S0959804924017532, https://www.nejm.org/doi/full/10.1056/NEJMoa2112187), cemiplimab has been shown to extend median survival in comparison with single-agent chemotherapy regimens, in the situation under consideration here. So I think the biggest advantage is longer survival, and the benefit to quality of life that comes with the knowledge that you have more life ahead of you. I believe also that the side effect

Patient expert statement

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does cemiplimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	profile of cemiplimab is less debilitating than that of standard chemotherapy, and those side effects are likely to be manageable for the majority of the cervical cancer patient population. The lower incidence of nausea and diarrhoea with cemiplimab versus standard chemotherapy is I think particularly important in terms of impact on quality of life and ability to continue with daily activities which make life meaningful. 9b: The survival benefit is the most important advantage in my opinion. 9c: I believe cemiplimab addresses all the main disadvantages of standard chemotherapy – though I recognise that it doesn't completely overcome them, and does come with its own disadvantages.
10. If there are disadvantages of cemiplimab over current treatments on the NHS please describe these. For example, are there any risks with cemiplimab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As I understand it, the side effects profile of cemiplimab is different to that of standard chemotherapy. For some patients, specific side effects may be harder to tolerate than others, so I think it's very difficult to say how those different side effects compare in terms of overall disadvantage.
11. Are there any groups of patients who might benefit more from cemiplimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I wouldn't identify any specific groups of patients for whom the impact and side effects of cemiplimab would be particularly good or bad, in comparison with other patient groups. I would always advocate for individual patients to be involved in decision-making about their care, and to be provided with all the relevant information they might need to make the best decision for their own specific circumstances.
12. Are there any potential equality issues that should be taken into account when considering this condition and cemiplimab? Please explain if you think any groups of people with this condition are particularly disadvantage	I don't feel able to comment on this from lived experience, in terms of inequality within the cervical cancer patient population. In terms of potential inequality between cervical cancer patients and other groups in the population, obviously issues of sex and gender are relevant.

Patient expert statement

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13. Are there any other issues that you would like the committee to consider?	No, thank you.

Patient expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I have experience of early-stage cervical cancer treated with radical hysterectomy, chemoradiotherapy and brachytherapy; for me chemoradiotherapy was very difficult emotionally and physically, and the side effects had a huge impact on my quality of life.
- For me, the survival impact of treatment was the main focus, and I was able to 'justify' the side effects to myself on the basis that the treatment gave me the best chance of survival. That sense of 'it'll be worth it in the end' was really central to me persevering with the treatment, without it I think my quality of life would have been substantially poorer during and after treatment.
- Frequency of adverse effects is broadly similar between cemiplimab and standard chemotherapy, but for me personally the lower incidence of nausea and diarrhoea with cemiplimab would be particularly impactful on quality of life. That, coupled with the higher survival impact of cemiplimab, mean that it would absolutely be my preference if my cancer recurred.
- I believe patients should always be able to play an active part in decision-making about their own care, having more treatment options available is generally a positive thing for patients in my opinion

Thank you for your time.

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Patient expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy
(review of TA901) [ID6610]

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Patient expert statement

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy
(review of TA901) [ID6610]



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Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]. A Single Technology Appraisal

Produced by Sheffield Centre for Health and Related Research (SCHARR), School of Medicine and Population Health (SMPH), Division of Population Health, University of Sheffield

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Rider on responsibility for report

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Contributions of authors

Sarah Davis acted as project lead. Mark Clowes critiqued the company's search strategy. Abdullah
Pandor and Beauty Igein summarised and critiqued the clinical effectiveness data reported within the
company's submission. Sarah Davis, Mon Mon Yee and Andrew Rawdin critiqued the health economic
analysis submitted by the company. Jessica Forsyth critiqued the statistical aspects of the submission
and contributed to the summary and critique for both clinical and cost-effectiveness evidence. Asma

Sarwar and Peter Hoskin provided clinical advice. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

AE	Adverse Event
AIC	Akaike Information Criterion
ASA	Additional sensitivity analysis
BIC	Bayesian Information Criteria
BICR	Blinded Independent Central Review
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CPS	Combined Positive Score
CR	Complete response
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
dMMR/MSI-H	Deficient mismatch repair or high microsatellite instability
DOR	Duration of response
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic data capture
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EOL	End-of-life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol 5-Dimensions 3-Level
EQ-5D-5L	EuroQol 5-Dimensions 5-Level
FACT-G	Functional Assessment of Cancer Therapy – General
GHS	Global Health Status
GP	General Practitioner
HbA1c	Glycated hemoglobin

HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LS	Least squares
MHRA	Medicines and Healthcare products Regulatory Agency
mg	Milligrams
MMRM	Mixed-effects repeated measures model
m ²	Square meter
N/A	Not applicable
NE	Not evaluable
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rates
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
Q-Q plots	Quantile-quantile plots
Q3W	Every 3 weeks
Q6W	Every 6 weeks
r/m CC	Recurrent or metastatic cervical cancer
RCT	Randomised controlled trial

RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SCC	Squamous cell carcinoma
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TSD	Technical support document
TTE	Time-to-event
WTP	Willingness-to-pay threshold

1 EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses cemiplimab as monotherapy for treating recurrent or metastatic cervical cancer (r/m CC) that has progressed on or after platinum-based chemotherapy. The key study informing the CS is the EMPOWER Cervical-1 randomised controlled trial (RCT) which compared cemiplimab with investigator's choice of chemotherapy. Trial investigators pre-selected patients for one of five single-agent chemotherapy regimens specified in the protocol prior to randomisation: pemetrexed, gemcitabine, topotecan, irinotecan, and vinorelbine. This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). The results presented in the EAG report include the patient access scheme (PAS) price for cemiplimab. None of the comparator technologies or other technologies given as subsequent treatments have confidential prices.

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. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. A summary of the results of the EAG's exploratory analyses, including its preferred base case ICER is provided in Section 1.6. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not necessarily the opinion of National Institute for Health and Care Excellence (NICE).

1.1 Overview of EAG's key issues

The key issues identified in the EAG's critique of the CS are summarised in Table 1 and presented in more detail in Section 1.3. A more limited discussion is also provided in Section 1.4 of additional secondary issues explored by the EAG in its additional analyses, which were not included in Table 1 as they were not considered to be key issues.

Table 1: Summary of key issues

ID 6610	Summary of issue	Impact on results	Report sections
1	Tisotumab vedotin has not been included as a comparator in the company submission	Unknown	2.3.3
2	Distribution of patients by programmed cell death-ligand 1 (PD-L1) tumour expression status within the population expected to receive cemiplimab in clinical practice	Moderate impact on the ICER	2.3.1; 2.3.5; 3.2.1.3; 3.3.3.2; 4.2.6.2 to 4.2.6.5
3	Uncertainty regarding time on treatment for cemiplimab in clinical practice	Moderate impact on the ICER	4.2.6.1; 4.2.6.4 and 4.2.6.5
4	Treatment beyond progression in the cemiplimab arm	Small impact on the ICER	3.2.1.3; 3.3.2.1; 3.7; 4.2.6.4 and 4.2.9.8
5	Application of treatment dependent utilities particularly for the post-progression state	Moderate impact on the ICER.	4.2.8.4

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

- Using the Kaplan-Meier (KM) data to inform time on treatment (ToT) with removal of progression-free survival (PFS) capping in the cemiplimab group to account for treatment beyond progression in the cemiplimab arm of the EMPOWER Cervical-1 RCT
- Applying the same post-progression utilities for the cemiplimab and chemotherapy arms whilst maintaining the company's preference for different pre-progression utilities
- Adjusting PFS to account for fatal events when subsequent treatment costs are applied
- Assuming the same resource use in post-progression health states in both treatment groups
- Including immune-related treatment-emergent adverse events (TEAEs)

However, none of the alternative assumptions had a significant impact on the ICER

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival [OS]) 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:

- Extending OS by increasing life-years gained in both the pre-progression and post-progression health states.
- Providing a higher health-related quality of life (HRQoL) for patients in both the pre-progression and post-progression health states.

Overall, the technology is modelled to affect costs by:

- Increasing drug acquisition costs during treatment with cemiplimab with minimal impact on drug administration costs
- Moderately increasing health state management costs
- Slightly increasing the downstream costs of subsequent treatments for progressed disease
- Slightly reducing the management costs of TEAEs

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

- Whether it can be assumed that the intention-to-treat (ITT) data from the EMPOWER Cervical-1 trial are generalisable to the population likely to receive treatment in clinical practice, which is expected to be dominated by PD-L1 negative patients.
- Whether it is better to use PD-L1 subgroup specific estimates and generate a weighted ICER that reflects the expected distribution of PD-L1 status in the cohort likely to receive cemiplimab in clinical practice.
- Whether it can be assumed that utility values within the pre-progression and post-progression health states would be expected to vary depending on whether the patients received cemiplimab or chemotherapy, particularly for the post-progression health state.
- Whether treatment with cemiplimab will be stopped at 96 weeks in clinical practice to match the trial protocol or whether clinicians will treat according to the licensed indication which allows treatment until disease progression or unacceptable toxicity.
- The mix of second-line chemotherapies used in clinical practice and whether these are restricted to 6 cycles (18 weeks) or offered for up to 96 weeks.

1.3 EAG's key issues

The EAG's key issues related to the clinical effectiveness and cost-effectiveness of cemiplimab are summarised below as issues 1 to 5. Further secondary issues are presented in Section 1.4. For those uncertainties where it was possible to estimate the impact on the ICER (Issues 2 to 5), the uncertainty was generally found to have a moderate impact on the ICER. However, the EAG notes in particular that it is not possible to quantify the potential impact on the ICER of the company having not presented a comparison against tisotumab vedotin (Issue 1).

It should be noted that when discussing the impact of a particular uncertainty on the ICER in this section, the EAG has quoted the ICERs as calculated when applying a disease severity modifier of 1.7. ICERs both with and without the severity modifier applied are available in Table 2 for the EAG's exploratory analyses (EA), Table 3 for the EAG's additional sensitivity analysis (ASA), and Table 48 for the

company's scenario analyses. The EAG was satisfied that a severity modifier of 1.7 was supported by the company's calculation of the proportional QALY shortfall (see Section 5.3.1).

Issue 1 Tisotumab vedotin has not been included as a comparator in the company submission

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The final NICE scope included tisotumab vedotin as a comparator treatment, although this was noted to be “<i>subject to NICE evaluation</i>,” as there is an ongoing appraisal of tisotumab vedotin in this indication (ID3753). The company does not consider tisotumab vedotin to be a relevant comparator as it does not believe that it is currently part of established clinical practice in the NHS. It also notes that final guidance on tisotumab vedotin is not expected until after the first committee meeting for the cemiplimab appraisal. The company has therefore not provided any evidence on the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin despite being asked to do so within the EAG's clarification request. The EAG notes that tisotumab vedotin has now received a UK marketing authorisation for this indication. The EAG also notes that if both appraisals proceed according to their scheduled timelines there is the potential for tisotumab vedotin to have received final guidance before the committee finalises its guidance on cemiplimab. The EAG considers that due to the overlapping technology appraisal (TA) timeframes, there is uncertainty regarding whether tisotumab vedotin will be part of established clinical practice at the time the committee makes its final decision on cemiplimab.
What alternative approach has the EAG suggested?	The EAG would have preferred the company to have provided evidence on the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin for the NICE committee to consider should the NICE committee determine that tisotumab vedotin is part of established clinical practice, and therefore a relevant comparator, at the time the committee finalises its guidance for cemiplimab.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of cemiplimab versus tisotumab vedotin is unknown due to the lack of evidence provided by the company.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could adapt their model to estimate the cost-effectiveness of cemiplimab relative to tisotumab vedotin. This could be achieved using published data on the clinical effectiveness of tisotumab vedotin and indirect treatment comparison methods. The EAG acknowledges that there is not yet a published list price for tisotumab vedotin, however, the cost-effectiveness analysis could be populated with an arbitrary list price which could then be updated by the EAG once the relevant price for tisotumab vedotin is available to NICE.

Issue 2 Distribution of patients by PD-L1 tumour expression status within the population expected to receive cemiplimab in clinical practice

Report sections	2.3.1; 2.3.5; 3.2.1.3; 3.3.3.2; 4.2.6.2 to 4.2.6.5
Description of issue and why the EAG has identified it as important	The CS states that cemiplimab is expected to be used as a second-line treatment in patients who have not received prior immunotherapy treatment. It also states that its clinical experts have advised that a high proportion ($\geq 95\%$) of patients who are PD-L1 positive (combined positive score [CPS] ≥ 1) will have received pembrolizumab in combination with platinum-based chemotherapy as a first-line treatment. This implies that the population likely to receive second-line cemiplimab in clinical practice will be dominated by patients who are PD-L1 negative (CPS < 1). However, the licensed indication for cemiplimab is not restricted by PD-L1 status and the EMPOWER Cervical-1 trial recruited patients irrespective of PD-L1 status. Furthermore, patients recruited to the trial were not required to have PD-L1 status assessed before being randomised and could have PD-L1 status assessed using archival tumour samples. This meant that PD-L1 status was not a stratification factor for randomisation and a subgroup analysis by PD-L1 status was not pre-specified. Furthermore, PD-L1 status was not obtained for 39% of patients recruited. In the cohort which did have PD-L1 status assessed, 36% were PD-L1 negative in both trial arms. The company argues that the subgroup analyses by PD-L1 status from EMPOWER Cervical-1 demonstrate a consistent benefit across both the PD-L1 positive and PD-L1 negative subgroups. They consider that the effectiveness of cemiplimab should be based on the whole trial population because the subgroup analyses are underpowered and the license is not restricted by PD-L1 status. However, in response to a clarification request, the company did provide an updated model programmed to allow cost-effectiveness to be estimated separately for PD-L1 negative and PD-L1 positive patients. They then used these subgroup specific estimates to provide an estimate of cost-effectiveness for a mixed cohort of patients in which 96% are PD-L1 negative. The latter was obtained by populating the model separately for the PD-L1 negative and PD-L1 positive subgroups and calculating a weighted average of the overall lifetime costs and QALYs obtained for each subgroup.
What alternative approach has the EAG suggested?	The EAG believes that it is informative to estimate the cost-effectiveness of cemiplimab within a cohort dominated by PD-L1 negative patients as this is likely to better predict its cost-effectiveness when used in clinical practice. It therefore welcomed the company's attempt to present estimates for a hypothetical cohort who are 96% PD-L1 negative. However, the EAG disagreed with the company's choice of curves to extrapolate outcomes within the PD-L1 subgroups. This was because the company selected parametric models for the subgroups that matched the best fitting curves used for the ITT population analyses. The only justification provided for this was that "<i>the parametric models used in the base case ITT analysis</i>

	<i>provide one if [sic] the best fits in this scenario”</i> and that the subgroup data are more uncertain due to the smaller sample size. The EAG therefore selected alternative curves within its own analysis for this scenario which were based on the fit to the subgroup specific data.
What is the expected effect on the cost-effectiveness estimates?	Although the company’s additional analysis shows a lower ICER for the hypothetical cohort who are 96% PD-L1 negative (£█████ versus £█████), the EAG notes that this is due to the company selecting the best fitting curves in the ITT population to extrapolate OS and PFS in the PD-L1 negative and positive subgroups, rather than the best fitting curves for the subgroup specific data. In the EAG’s scenario analysis (ASA2), the ICER for a cohort who are 96% PD-L1 negative is substantially higher than the EAG’s base case ICER which uses the data from the whole ITT trial population unweighted by PD-L1 status (£█████ vs ██████). The EAG also reports the ICER for a 100% PD-L1 negative subgroup (ASA3; £█████) as a means of assessing the maximum impact on the ICER of uncertainty regarding the mix of PD-L1 status in the cohort likely to be treated in clinical practice.
Could any additional evidence or analyses be provided to resolve this key issue?	No additional analyses are suggested. However, it may be worthwhile seeking further data or clinical expert opinion on the expected mix of PD-L1 status in the population likely to receive cemiplimab as the analyses demonstrate that using the subgroup specific data has a moderate impact on the ICER.

Issue 3 Uncertainty regarding time on treatment for cemiplimab in clinical practice

Report sections	4.2.6.1; 4.2.6.4 and 4.2.6.5
Description of issue and why the EAG has identified it as important	The EMPOWER Cervical-1 trial restricted patients to 16 six-week cycles of cemiplimab (equivalent to 96 weeks of treatment when given without delays or interruptions). However, the Summary of Product Characteristics (SmPC) states that cemiplimab may be continued until disease progression or unacceptable toxicity. The EAG’s clinical experts indicated that the duration of treatment in clinical practice would be driven by the wording in the SmPC and they would be reluctant to stop treatment at 96 weeks (or after 16 six-week cycles) if a patient had not progressed and was still tolerating treatment. The EAG is therefore concerned that the cost of treatment over the lifetime of a patient could be substantially higher in clinical practice. Whilst it acknowledges that any extension in duration of treatment has the potential to provide further OS and PFS benefits, the size of these is unknown, meaning the impact on the ICER of extending treatment beyond 96 weeks is uncertain.
What alternative approach has the EAG suggested?	The EAG’s preferred approach to modelling the ToT in its base case was to use the ToT KM directly as the most accurate representation of treatment received in the trial. It also acknowledges that modelling treatment beyond 96 weeks would introduce a disconnect between the cost of cemiplimab predicted

	by the model and the OS and PFS outcomes in the model which reflect the duration of treatment received in the trial. However, the EAG also believes it is necessary to explore the potential impact on the cost-effectiveness estimates of extended use of cemiplimab beyond 96 weeks in clinical practice. It therefore requested that the company provide an analysis in which the ToT data were re-censored at 96 weeks and curves were fitted to the re-censored data to extrapolate ToT. The company provided this analysis which also included capping of ToT by PFS. The company describes this as a “ <i>worst-case scenario</i> ” because it includes the additional cost of prolonged cemiplimab use without adjusting the OS and PFS estimates to allow for any potential benefit derived from treatment beyond 96 weeks.
What is the expected effect on the cost-effectiveness estimates?	The company’s scenario analysis using a log-normal curve to extrapolate from the 96-week censored ToT KM increased the ICER from £[REDACTED] to £[REDACTED], whereas the ICER increased to £[REDACTED] when using the generalised gamma curve. The EAG notes that the company describes the generalised gamma both as better fitting to the censored end of the KM data and as having a highly unrealistic long tail. It therefore preferred the log-normal which it described as the second-best fitting curve. When the EAG conducted a similar exploratory analysis (ASA10) using its own base case as the starting point and using the log-normal curve to extrapolate ToT, the ICER increased from £[REDACTED] to £[REDACTED]. The EAG considers that these analyses demonstrate the sensitivity of the cost-effectiveness estimates to uncertainty regarding the likely duration of treatment in clinical practice, but that they should not be considered to represent a plausible alternative to the EAG’s base case ICER due to the lack of adjustment to OS and PFS and the high uncertainty regarding whether the tail of the 96-week censored ToT KM predicts future cemiplimab use in clinical practice. Although the EAG notes the latter is somewhat mitigated by the capping of ToT by PFS (see Issue 4).
Could any additional evidence or analyses be provided to resolve this key issue?	This uncertainty could be resolved by real world evidence examining the pattern of treatment discontinuation after 96 weeks in clinical practice, and/or by formally eliciting such estimates from a broader group of clinical experts along with estimates on how OS and PFS may be affected with extended treatment.

Issue 4 Treatment beyond progression in the cemiplimab arm

Report section	3.2.1.3; 3.3.2.1; 3.7; 4.2.6.4 and 4.2.9.8
Description of issue and why the EAG has identified it as important	Within the EMPOWER Cervical-1 trial, patients in the cemiplimab arm were allowed to continue treatment beyond progression if the progression was considered to be an unconventional response to treatment consistent with pseudo-progression. Pseudo-progression is where radiologic evidence of progression on therapy occurs before subsequent radiologic response, and it is a recognised feature of immunotherapy treatment, but not chemotherapy treatment. Treatment beyond

	progression was therefore not permitted within the comparator chemotherapy arm. As any progression that met the Response Evaluation Criteria in Solid Tumours (RECIST) criteria was recorded as progression for the purposes of assessing PFS, this meant that some patients in the EMPOWER Cervical-1 trial were recorded as having progressed for the purposes of PFS assessment, but they were judged by the investigator to have experienced a pseudo-progression and thereby continued treatment. The EAG's clinical experts considered that treatment in clinical practice would mimic the trial protocol in that patients would continue treatment if a change in tumour size was considered to be pseudo-progression and would only stop treatment if further progression was observed. Based on this the EAG believes that the ToT in the model should reflect the actual use of cemiplimab within the clinical trial including any treatment beyond progression. However, in the company's base case, the proportion of patients remaining on treatment was restricted to always remain below or equal to the proportion remaining progression-free. The EAG did not agree with this given that the PFS curve did not exclude progression events that were considered to be a pseudo-progression by the investigator.
What alternative approach has the EAG suggested?	The EAG prefers not to apply a restriction to the ToT curve to ensure it stays under the PFS curve as it considers that using the actual ToT recorded in the trial better reflects both the outcomes measured in the trial and the expected use of cemiplimab within clinical practice.
What is the expected effect on the cost-effectiveness estimates?	In the company's base case analysis, removing the capping of ToT by PFS increased the ICER from £[REDACTED] to £[REDACTED]. However, the EAG notes that its exploratory analysis (EA2) which combined removal of the ToT capping by PFS with the EAG's preferred method of capturing ToT, which was to use the KM ToT data directly, only increased the ICER to £[REDACTED]. The EAG also conducted a scenario analysis using the EAG base case as its starting point, whereby it maintained the use of the ToT KM to directly estimate ToT, but it reapplied the capping of ToT by PFS (ASA9) to see how important the capping was in isolation. This decreased the ICER from [REDACTED] in the EAG base case to [REDACTED]. These analyses demonstrate that uncertainty regarding whether or not clinicians will continue treatment beyond progression when pseudo-progression is suspected, is of some importance to the cost effectiveness estimates, although it is much less important than uncertainty regarding whether clinicians will continue treatment beyond 96 weeks and what impact this would have on the OS and PFS estimates (see Issue 3).
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG does not consider that any further additional analyses are necessary. However, it believes that it would be worthwhile asking a broader group of clinical experts whether they observe pseudo-progression on immunotherapies within clinical practice and whether they would allow patients to continue treatment if pseudo-progression was suspected and only stop treatment if further progression was observed.

Issue 5 Application of treatment dependent utilities particularly for the post-progression state

Report section	4.2.8.4
Description of issue and why the EAG has identified it as important	The company has used treatment-dependent utility values for both the progression-free and post-progression health states. In its base case the utility values were obtained from the EMPOWER Cervical-1 trial by mapping from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) responses to the EuroQol 5-Dimensions 3-Level (EQ-5D-3L) utilities. The pre-progression utility values were estimated separately for each arm of the trial and there was a statistically significant difference between arms for patients who remained progression-free. The post-progression utility values for cemiplimab were based on the pooled estimates across both arms. However, the post-progression utility values for chemotherapy were estimated by assuming that the proportionate decrement in utility occurring due to progression (■) was similar between arms. The company considered this approach to be necessary because the pre-progression utility for chemotherapy was very similar to the pooled post-progression utility value and the company considered that this lacked clinical face validity. The company also stated that different pre-progression utility values were consistent with clinical expectations of poorer quality of life for patients receiving chemotherapy versus immunotherapy due to immunotherapy being better tolerated with a lower rate of adverse events (AEs). The company's clinical experts also noted the potential for some AEs, such as peripheral neuropathy, to have a persistent impact on HRQoL after treatment is stopped which might lead to lower utility post-progression for patients having chemotherapy. The EAG notes that the company did not present arm specific estimates of post-progression utility values. It also did not conduct a regression analysis including covariates for progression and presence of AEs. It is therefore difficult to determine whether the model should include differential estimates of post-progression utility. Based on this, the EAG considers that there is some uncertainty regarding the appropriate post-progression utility values for chemotherapy due to the company's inadequate exploration of this issue and its reliance on the assumption that the proportionate decrement associated with progression will be consistent across treatment arms.
What alternative approach has the EAG suggested?	The EAG is reasonably satisfied with the company's decision to use treatment-dependent utilities for the pre-progression state. However, it considers that it may be incorrect to assume the same proportionate decrement associated with progression in both arms. It notes in particular that if the lower pre-progression utility for chemotherapy observed in the EMPOWER Cervical-1 trial is being driven by AEs associated with the chemotherapy

	treatment itself, then this AE related utility decrement may be reversed when patients stop chemotherapy treatment. This would mean that patients who have stopped chemotherapy due to disease progression may have a similar quality of life to patients who have stopped cemiplimab due to disease progression, and their post-progression utilities would then be likely to be similar. Although the EAG acknowledges that some specific chemotherapy related AEs may not be reversible, e.g., peripheral neuropathy, this is infrequently reported, and many of the most common treatment-related AEs reported in the EMPOWER Cervical-1 chemotherapy arm (anaemia, nausea, fatigue, vomiting, constipation, decreased appetite) are likely to be reversible. The EAG believes that the difference in pre-progression utilities between the trial arms observed in the EMPOWER Cervical-1 trial are plausible because they may reflect differences in the incidence and type of AEs experienced across these two different types of treatment. However, it does not believe that the company has provided sufficient evidence to support its assumption that the proportionate decrement in utility from pre-progression to post-progression is consistent across arms leading to lower post-progression utilities for chemotherapy. The EAG prefers to assume the same post-progression utility across arms, on the basis that any pre-progression utility differences due to AEs may be reversed when treatment is stopped at the time of progression. The EAG has therefore conducted an exploratory analysis (EA3) in which the pre-progression utilities are informed by the treatment arm specific estimates from EMPOWER Cervical-1, but the post-progression utility values in both arms are informed by the pooled post progression utility from EMPOWER Cervical-1 with no application of the proportional decrement to the chemotherapy utility. It has also included this assumption within the EAG's preferred base case. Whilst the EAG has included the pre-progression treatment-arm specific utilities from EMPOWER Cervical-1 in its preferred base case, it has also presented a scenario analysis in which treatment independent utility values have been applied both pre- and post-progression, with QALY losses related to TEAEs applied as a one-off value in the first model cycle. This is provided because the EAG still considers there to be some uncertainty regarding the factors driving the difference in pre-progression utility between arms which it considers have not been adequately explored in the company's regression analysis.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis applying the same post-progression utility values across arms (EA3), but maintaining treatment-dependent utilities for the pre-progression state, increased the ICER for the company's base case from £[REDACTED] to £[REDACTED]. It should be noted that this one change accounted for the majority of the difference between the company's preferred base case and the EAG's preferred base case. The EAG's scenario analysis assuming treatment-independent utilities both pre- and post-progression but maintaining the other

	changes included in the EAG's preferred base case, increased the ICER from £[REDACTED] to £[REDACTED]. This demonstrates that the ICER is also sensitive to whether treatment-dependent utilities are considered plausible for the pre-progression health state.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could conduct a regression analysis on the mapped utility estimates from the EMPOWER Cervical-1 trial including coefficients such as treatment allocation, progression status, presence or absence of grade ≥ 3 AEs, and relevant interaction terms. This would provide a better understanding of whether the pre-progression utility differences are being driven by differences in treatment-related AEs that may be reversible when treatment is stopped. This would help determine whether the post-progression utility is likely to be similar between patients who have progressed on or after receiving cemiplimab treatment and patients who have progressed on or after receiving chemotherapy.

1.4 Secondary issues identified by the EAG

The EAG identified three secondary issues, which are described in detail in the issue boxes below. The EAG found that these issues generally had a low impact on the ICER when explored in ASAs.

The EAG also notes that it made two adjustments in its base case that had minimal impact on the ICER and therefore the rationale for these adjustments is not discussed in detail here. These were the adjustment of subsequent treatment costs to account for PFS events that are deaths rather than progressions (EA4, see Sections 4.2.9.8 and 5.2.2), and the inclusion of immune-mediated TEAEs (EA6, see Sections 4.2.7.1 and 5.2.2.)

Issue 6 Uncertainty regarding the second-line chemotherapy treatments likely to be used within clinical practice

Report sections	2.2.2, 2.3.3, 4.2.9.1 and 4.2.9.8
Description of issue and why the EAG has identified it as important	The EAG notes that there is a lack of clear consensus on second-line treatments for r/m CC. The EAG considers that the mix of treatments used in the EMPOWER Cervical-1 clinical trial may not be reflective of the treatments used in current clinical practice. For example, weekly paclitaxel, which is described in the CS as a commonly used treatment, was not included as an option in the comparator arm of the clinical trial. Furthermore, some of the included treatments were described as not being used in NHS clinical practice by the EAG's clinical experts. However, this is somewhat mitigated by clinical expert advice that the outcomes may be equally poor across all currently available second-line treatments, therefore the risk of bias for OS and PFS outcomes may be minimal.

	Furthermore, in EMPOWER Cervical-1, patients randomised to the chemotherapy arm could receive treatment for up to 96 weeks. The EAG is concerned that this does not reflect clinical practice as NHS treatment protocols for many of the second-line chemotherapies included in the comparator arm specify a maximum duration of 6 cycles, equivalent to 18 weeks of treatment. The company's scenario analysis in which it explored the assumption that 100% of second-line treatment is weekly paclitaxel included a maximum 18-week (6 cycle) duration for paclitaxel, but a similar restriction was not applied to any other second-line treatments in the company's base case analysis.
What alternative approach has the EAG suggested?	The EAG has presented a scenario analysis in which the maximum duration of second-line treatment for the chemotherapy comparator arm is restricted to 18 weeks to better reflect the expected treatment duration in clinical practice (ASA8). It has also conducted a scenario analysis in which it adapted the company's scenario assuming that 100% of patients receive weekly paclitaxel to remove the 18-week restriction for paclitaxel to bring it in line with the approach used for the other chemotherapies in the company's base case (ASA7). This was because the EAG clinical expert whose preferred second-line treatment was weekly paclitaxel reported using it for up to 8 to 12 months in patients who continued to respond.
What is the expected effect on the cost-effectiveness estimates?	The company's scenario analysis using weekly paclitaxel as the only second-line chemotherapy treatment decreased the company's ICER from £[REDACTED] to £[REDACTED]. The EAG's scenario analysis applying this change to the EAG base but not restricting weekly paclitaxel to 18 weeks (ASA7) decreased the ICER from [REDACTED] to [REDACTED]. The EAG's scenario analysis restricting the second-line chemotherapy treatments applied in the company's base case to 18 weeks (ASA8) increased the ICER using the EAG's preferred assumptions from [REDACTED] to [REDACTED]. It is not possible to assess the uncertainty associated with the assumption that the OS and PFS outcomes observed in the EMPOWER Cervical-1 trial will reflect the OS and PFS outcomes expected for chemotherapy treatments used in clinical practice. However, the EAG's clinical experts did not expect any bias due to differences in clinical effectiveness to be large (see Section 2.3.3).
Could any additional evidence or analyses be provided to resolve this key issue?	Real-world evidence could be sought on the mix of treatments currently offered in NHS clinical practice to patients requiring second-line treatment for r/m CC and whether any restrictions are applied to the number of cycles offered for these regimens.

Issue 7 Uncertainty regarding resource use following disease progression

Report sections	4.2.9.8

Description of issue and why the EAG has identified it as important	The company has assumed that the resource use following disease progression will differ for patients who progressed on chemotherapy versus those who progressed on cemiplimab. These are based on data elicited from clinical experts. However, the EAG's clinical experts advised that similar post-progression resource use would be expected regardless of whether the patient received cemiplimab or chemotherapy as their second-line treatment and that resource use post-progression would be driven by whether the patient was receiving active systemic treatment or only best supportive care (BSC). The EAG is therefore concerned that the company did not separately elicit estimates for patients having systemic post-progression treatment and those receiving BSC.
What alternative approach has the EAG suggested?	The EAG prefers to assume the same resource use post-progression regardless of the treatment received at second-line. The EAG therefore amended post-progression resource use for chemotherapy to match that estimated for cemiplimab in its base case (EA5). This assumption was also incorporated in the EAG's preferred base case. In addition, the EAG's clinical experts noted that resource use post-progression will be mainly driven by whether the patient was receiving active treatment or BSC. Therefore, the EAG conducted an additional analysis (ASA5) to explore the impact of assuming that post-progression resource use for patients having active treatment is the same as pre-progression resource use, whilst post-progression resource use for patients having BSC is limited to the estimates provided by the company's clinical experts for palliative care.
What is the expected effect on the cost-effectiveness estimates?	Setting the post-progression resource use the same across arms had a small impact on the ICER increasing it from the company's base case of £[REDACTED] to £[REDACTED]. The EAG's additional sensitivity analysis exploring the impact of applying pre-progression resource use to patients having active third-line treatment and palliative care costs only to patients having BSC third-line (ASA5) decreased the ICER to [REDACTED] relative to the EAG's base case ICER of [REDACTED].
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG does not consider that additional analyses would be worthwhile to resolve this secondary issue.

Issue 8 Uncertainty regarding OS extrapolation

Report sections	4.2.6
Description of issue and why the EAG has identified it as important	Both the company and the EAG have applied a generalised gamma model for OS in their base case analyses. Additionally, both the company and the EAG have also explored the use of a log-normal/log-logistic model for cemiplimab OS and a log-logistic model for chemotherapy OS in scenario analyses as these were considered to be plausible alternative extrapolations (ASA1a and ASA1b).

What alternative approach has the EAG suggested?	In addition to the scenarios presented by the company, the EAG also explored using a two-knot spline on the hazards scale in both arms in scenario analysis (ASA1c).
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER of applying these alternative OS extrapolations is not large for either the company or the EAG's scenario analyses. The largest impact on the ICER was in ASA1a in which the EAG applied the log-normal curve for cemiplimab OS and the log-logistic curve for chemotherapy OS. This increased the EAG's ICER from ██████ in its base case to ██████ in its scenario analysis. These analyses demonstrate that whilst the uncertainty associated with the use of alternative OS curves is not large, the ICER is still sensitive to this choice.
Could any additional evidence or analyses be provided to resolve this key issue?	No additional evidence or analyses are suggested by the EAG.

1.5 Company's modelling errors identified by the EAG

The EAG identified the following minor programming errors within the company's model, and none of them have a substantial impact on the ICER (see EA1, Table 2).

- (a) The programming error related to starting treatment in the chemotherapy group, as detailed in Section 4.2.9.8, was corrected. All patients now initiate chemotherapy at cycle 0, rather than cycle 1, to align with cemiplimab group.
- (b) The end-of-life (EOL) care cost was amended to reflect a 30-day costs of £3,081 (Section 4.2.9.8).
- (c) The drug administration costs of (i) carboplatin plus paclitaxel and (ii) carboplatin plus gemcitabine were included in the calculation of expected subsequent treatment costs (Section 4.2.9.8).

These corrections were all incorporated in the EAG's preferred base case.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 provides the results from the EAG's EAs where each analysis shows the individual changes to the company's base case ICER. When including all the changes preferred by the EAG (EAs 1 to 6), it can be seen that the ICER in the EAG's preferred base case is higher than the ICER in the company's base case; £█████ versus £█████ for the deterministic analysis (when applying a severity modifier of 1.7). The probabilistic ICER for the EAG's preferred base case is similar at £█████.

The EAG has also presented its ASAs which explore areas of remaining uncertainty in Table 3. These analyses use the EAG's base case as their starting point. For the whole ITT trial population, ICERs ranged from ██████ to ██████ when a severity modifier of 1.0 is applied, and from ██████ to ██████

██████ with a severity modifier of 1.7. When considering the analyses adjusted for PD-L1 status, the highest ICER presented is for the scenario assuming that 100% of patients treated are PD-L1 negative, ██████ (with a severity modifier of 1.0) and ██████ (with a severity modifier of 1.7).

Table 2: Summary of EAG’s preferred assumptions and ICER

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Company’s base case: deterministic model								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,936					
EA1: Correction of minor programming errors								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£20,185					
EA2: Using the KM data to inform ToT with no PFS capping on ToT in the cemiplimab group								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,682					
EA3: Assuming same post-progression utility value across treatment groups based on EMPOWER Cervical-1 (0.613)								
Cemiplimab	2.45	1.35	█	1.32	0.73	█	█	█
Chemotherapy	1.13	0.62	£16,936					
EA4: Adjustment of PFS to account for fatal events								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,664					
EA5: Assuming same resource use in post-progression health state in both arms								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,481					
EA6: Inclusion of immune-related TEAE								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,936					
EAG’s base case (combined EA1-6): deterministic model								
Cemiplimab	2.45	1.35	█	1.32	0.73	█	█	█
Chemotherapy	1.13	0.62	£19,043					
EAG’s base case (combined EA1-6): probabilistic model								
Cemiplimab	2.51	1.37	█	1.42	0.74	█	█	█
Chemotherapy	1.09	0.63	£19,172					

Abbreviations: ICER - incremental cost-effectiveness ratio; KM – Kaplan-Meier; LYG - life year gained; PFS – progression-free survival; QALY - quality-adjusted life year; TEAE – treatment emergent adverse events; ToT – time on treatment. * undiscounted

Table 3: Results of EAG's scenario analyses using EAG's preferred assumptions

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
EAG's base case: deterministic								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£19,043					
ASA1a: OS cemiplimab = log-normal, OS chemotherapy = log-logistic, Population = ITT								
Cemiplimab	2.21	1.26	██████	1.00	0.61	██████	██████	██████
Chemotherapy	1.21	0.65	£19,566					
ASA1b: OS cemiplimab = log-logistic, OS chemotherapy = log-logistic, Population = ITT								
Cemiplimab	2.35	1.30	██████	1.15	0.65	██████	██████	██████
Chemotherapy	1.21	0.65	£19,566					
ASA1c: OS cemiplimab = 2-knot hazard RCS model, OS chemotherapy = 2-knot hazard RCS model, Population = ITT								
Cemiplimab	2.41	1.34	██████	1.18	0.68	██████	██████	██████
Chemotherapy	1.23	0.67	£19,826					
ASA2: OS cemiplimab and PFS chemo arms in PD-L1 < 1% group = log-normal, PFS chemo arm in PD-L1 ≥ 1% group = log-normal, Population = PD-L1-weighted (PD-L1 < 1% = 96% of the population) †								
Cemiplimab	1.97	1.12	██████	0.85	0.51	██████	██████	██████
Chemotherapy	1.12	0.61	£19,041					
ASA3: OS cemiplimab and PFS chemo arms in PD-L1 < 1% group = log-normal, Population = PD-L1-weighted (PD-L1 < 1% = 100% of the population)								
Cemiplimab	1.93	1.10	██████	0.81	0.49	██████	██████	██████
Chemotherapy	1.12	0.61	£19,040					
ASA4a: Assuming treatment-independent health state utility values (pre-progression utility = █████, post-progression utility = 0.613)								
Cemiplimab	2.45	1.29	██████	1.32	0.65	██████	██████	██████
Chemotherapy	1.13	0.64	£19,043					
ASA4b: Assuming treatment-dependent health state utility values in both pre- and post-progression health states								

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Cemiplimab	2.45	1.35	██████	1.32	0.78	██████	██████	██████
Chemotherapy	1.13	0.57	£19,043					
ASA5: Post-progression resource use costs applied only to patients receiving active subsequent treatment, assumed same resource use as in pre-progression health state - on treatment, patients with BSC incur only palliative treatment costs								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£17,597					
ASA6: Proportion of patients receiving active subsequent treatment based on EMPOWER Cervical-1								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£19,901					
ASA7: Assuming 100% paclitaxel for comparator group, with removal of treatment stopping rule at 18 weeks								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£22,262					
ASA8: Assuming all chemotherapy treatments stopped at 18 weeks								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£17,974					
ASA9: Using KM ToT for both groups with cemiplimab ToT capped by PFS								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£19,043					
ASA10: Using ToT data fitted to censored data at 96 weeks, removal of PFS capping before 96 weeks								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£19,306					

Abbreviations: ASA, additional sensitivity analysis; BSC – best supportive care; ICER - incremental cost-effectiveness ratio; ITT; intention-to-treat; KM – Kaplan-Meier; LYG - life year gained; OS - overall survival; PD-L1 – Programmed cell death-Ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; RCS – restricted cubic splines; ToT – time on treatment

*undiscounted

†a detail breakdown of each component of this scenario is provided in Appendix 2.

1.7 Outline of confidential comparator or subsequent treatment prices

The PAS discount for cemiplimab is applied within the model. None of the interventions that form part of the comparator or subsequent treatments have confidential discounts.

2 BACKGROUND

This External Assessment Group (EAG) report critiques the company submission (CS) for cemiplimab as monotherapy for treating recurrent or metastatic cervical cancer (r/m CC) that has progressed on or after platinum-based chemotherapy.¹

2.1 Critique of the company's description of the underlying health problem

The cervix is the lower part of the womb, often referred to as the neck of the womb, which opens into the vagina.² Cervical cancer originates in the cells lining the cervix, with the two main types being squamous cell carcinoma (SCC), which accounts for 80-90% of cases, and adenocarcinoma, accounting for 10-20% of cases.² A small minority of tumours (3-10%) present with mixed (adenosquamous) histology.² Patients whose cancer has returned following previous treatment are described as having recurrent disease. Metastatic disease is when the cancer has spread beyond the cervix into surrounding tissues, or to more distant sites, either at recurrence or at the time of first diagnosis.

The CS describes r/m CC as a health condition with a high and complex symptom burden and poor life-expectancy.¹ The CS describes the symptoms of r/m CC as commonly including pain, fatigue, anorexia, gastrointestinal symptoms, anxiety and depression.³ It also describes the potential for ongoing morbidity from previous surgical or systemic treatment, with persistent peripheral neuropathy in particular being a recognised issue in patients who have previously received platinum-based chemotherapy.⁴ Other symptoms related to previous treatment include menopausal symptoms, altered body image, sexual dysfunction, lymphoedema, diarrhoea and social difficulties.⁵ The CS presents estimates of overall survival ranging from 5.0 to 12.7 months in patients receiving second-line treatments for r/m CC.⁶ Cervical cancer incidence peaks in women aged 30-34 years,⁷ which is a time when many women would otherwise be working and / or looking after children or elderly relatives, but many patients with r/m CC are left unable to work or care for others due to the severity of their symptoms.⁸ The company estimates that the high symptom burden, combined with the poor life-expectancy, results in an expected life-time QALY gain that is only 4% of that expected in age-matched members of the general population without r/m CC (see Section 5.3.1).¹

The CS states that there were 2641 cases of cervical cancer diagnosed in England in 2022,⁹ with an average of 685 deaths per year in England from cervical cancer in the 2017-2019 time period.⁷ Although the CS does not cite a published estimate for the incidence of r/m CC, it states that it expects between 850 and 880 patients to be diagnosed with r/m CC in England over the next 5 years based on its Budget Impact calculator.¹

Overall, the EAG is generally satisfied with the company's description of the underlying health problem, although the EAG identified two minor concerns. Firstly, it was not able to corroborate the exact figure given for the age-standardised incidence rate for females in England (years 2017 to 2019) from the cited source, although the number the EAG identified was similar 9.5 (95% confidence interval [CI] 9.3 to 9.7) versus 9.9 (95% CI 9.7 to 10.1). Secondly, when describing the symptom burden of r/m CC the CS cites a study by Kim *et al.*,³ which recruited patients from a palliative care service with over 50% being inpatients at the time of referral and over 50% having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≥ 3 . Based on these factors the EAG is concerned that the symptoms described in this study may be biased towards those expected in patients who would not be considered fit enough to receive further systemic therapy in the UK.

2.2 Critique of the company's overview of current service provision

The CS presents two figures, one showing the current treatment pathway for r/m CC (CS, Figure 1) and the other showing the proposed positioning of cemiplimab (CS, Figure 2).¹ The EAG has amalgamated these within Figure 1. The proposed positioning for cemiplimab is as a second-line treatment consistent with its license specifying it is to be used in patients with r/m CC who have progressed on or after platinum-based chemotherapy.

2.2.1 First-line treatment for r/m CC

The CS states that for first-line treatment of r/m CC, a high proportion of patients ($\geq 95\%$) with a programmed cell death ligand-1 (PD-L1) combined positive score (CPS) ≥ 1 will receive pembrolizumab in combination with chemotherapy, with or without bevacizumab, as recommended in TA939.¹⁰ Patients ineligible for pembrolizumab, are offered platinum-based chemotherapy with or without bevacizumab. Reasons for being ineligible for pembrolizumab may include negative PD-L1 status (PD-L1 CPS = 0), unknown PD-L1 status due to a delay or failure in PD-L1 testing, contraindication to immunotherapy or concerns regarding the patient's fitness to tolerate immunotherapy combined with chemotherapy.

The CS describes carboplatin with paclitaxel as the usual chemotherapy regimen for patients not having pembrolizumab. Furthermore, the National Cancer Drugs Fund List specifies that bevacizumab can only be given in combination with a chemotherapy regimen of paclitaxel combined with either carboplatin or cisplatin. Although the licensed indication for pembrolizumab does not specify the chemotherapy regimen to be used in combination with pembrolizumab, the chemotherapy regimen used in the key clinical trial informing TA939 (KETNOTE-826) was platinum (cisplatin or carboplatin) combined with paclitaxel.¹¹ The alternative chemotherapy regimens specified in the scope for TA939 were platinum combined with either topotecan or etoposide. The EAG's clinical experts indicated that the usual chemotherapy regimen for first-line treatment of r/m CC was carboplatin with paclitaxel. It is

therefore anticipated that all patients will receive platinum-based chemotherapy as first-line treatment, with the addition of bevacizumab and/or pembrolizumab according to eligibility.

2.2.2 Second-line treatment for r/m CC

The CS states that there is no clear standard of care for patients who have progressed on first-line platinum-based chemotherapy. Figure 1 of the CS describes the options as “*various single-agent; combination or platinum-paclitaxel rechallenge for selected patients.*”¹ The CS states that weekly paclitaxel monotherapy is the most commonly used second-line treatment, with topotecan, gemcitabine, irinotecan or vinorelbine, used in some cases. It also describes the potential for patients to be rechallenged with platinum-based chemotherapy (carboplatin with paclitaxel) if they have been progression-free for more than 6 to 12 months since completing platinum-based chemotherapy.

Docetaxel and mitomycin/fluorouracil (5-FU) are also mentioned as potential second-line single-agent chemotherapy options in CS, Section 1.3.3.¹ Cisplatin with topotecan is mentioned as an alternative platinum-based combination treatment. The EAG notes that topotecan with cisplatin was recommended in TA183¹² only for patients without prior cisplatin treatment. Although not mentioned in the description of current clinical practice provided in CS, Section 1.3.3, carboplatin with pegylated liposomal doxorubicin, carboplatin with gemcitabine, carboplatin monotherapy and enrolment in clinical trials were other treatment options identified by the company’s clinical experts (CS, Table 50).¹

The CS states that pembrolizumab is theoretically available for r/m CC as neither the licensed indication nor the NICE recommendation specifies whether or not patients must have received previous treatment for r/m CC.¹ However, the CS also acknowledges that this possibility is likely to apply only to a small minority of patients given that a high proportion of pembrolizumab eligible patients are described as receiving this option first-line.¹

The EAG’s clinical advisors acknowledged a lack of consensus on second-line treatment options in clinical practice, with both gemcitabine and paclitaxel being described as potential options used across different centres. One clinical expert described paclitaxel as their preferred option, whilst the other described preferring gemcitabine as patients will already have received paclitaxel first-line. One clinical expert described no longer being able to access topotecan for this indication, despite it being their preferred option. Neither described using vinorelbine or irinotecan, but one described sometimes offering doxorubicin as an alternative monotherapy. Both agreed that there was the potential for rechallenge with platinum-based chemotherapy (platinum plus paclitaxel) if the patient had been progression-free for a sufficient period since completing first-line platinum-based treatment.

The EAG's clinical experts also indicated that some NHS treatment centres are making preparations to offer tisotumab vedotin through a compassionate use programme, and that when this treatment becomes accessible, they would use it either second-line or third-line.

2.2.3 Third-line treatment for r/m CC

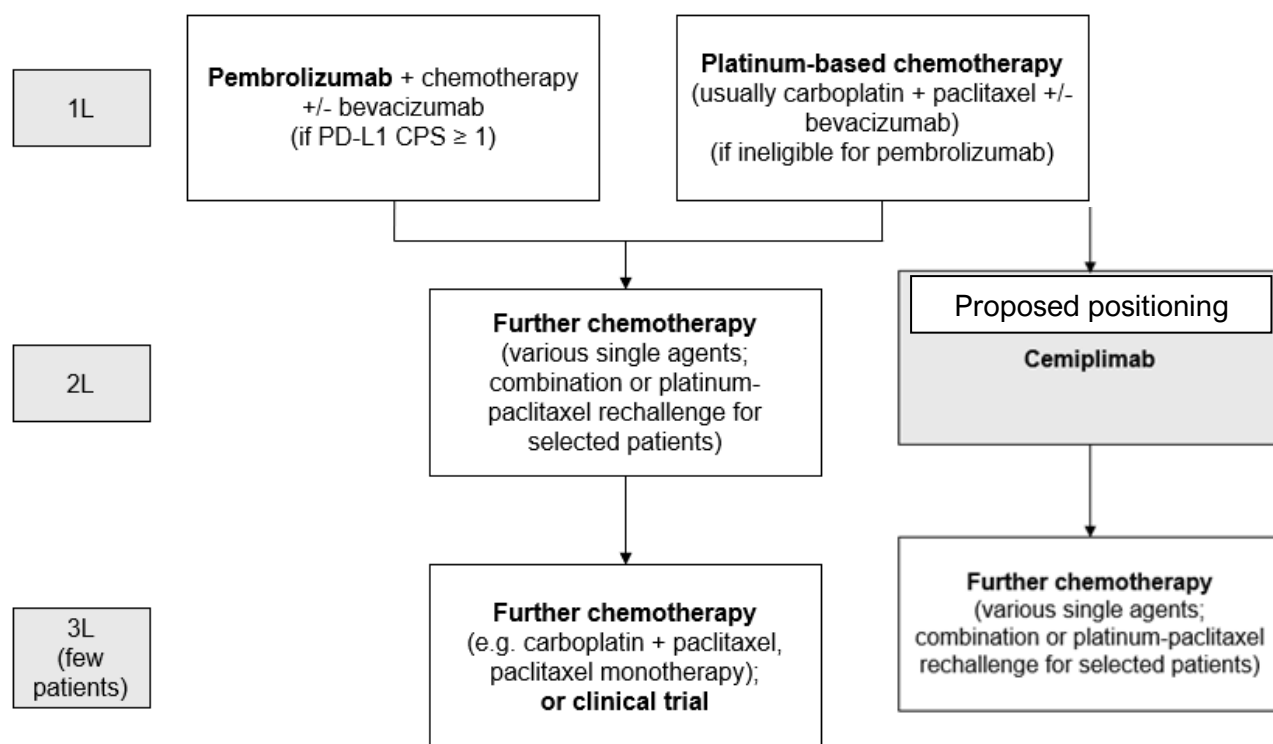
The CS states that according to its clinical experts, few patients are fit enough to receive third-line treatment. However, carboplatin with paclitaxel, paclitaxel monotherapy or clinical trials are described in the CS as potential options in those fit enough to continue systemic treatment. The EAG's clinical experts broadly agreed with those third-line options, although one expert noted that carboplatin with gemcitabine was a more likely third-line combination treatment than carboplatin with paclitaxel. They stated that single-agent treatments not previously used at second-line would also be an option for third-line treatment.

The EAG notes that a broader range of third-line treatments were incorporated in the economic modelling, based on clinical expert interviews conducted by the company. These included carboplatin with gemcitabine, carboplatin monotherapy and topotecan. The EAG's clinical experts noted that these probably reflected regimens that clinicians are familiar with from treating other gynaecological cancers. However, it was noted that topotecan is not commonly used, with one expert not having access to topotecan locally and the other choosing not to use it.

2.2.4 Positioning of cemiplimab and the impact on subsequent treatments

The proposed positioning of cemiplimab within the current pathway, as shown in Figure 1, is as a second-line treatment after platinum-based chemotherapy in those patients who have not had pembrolizumab first-line. The EAG notes that this figure also shows the current second-line treatment options being moved back to third-line in patients having cemiplimab (see clarification response A3).¹³

Figure 1: The current UK treatment pathway for r/m CC and the proposed positioning of cemiplimab (adapted from CS, Figures 1 & 2)



Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; CPS, combined positive score; PD-L1, programmed cell death-ligand 1.

2.3 Critique of the company’s definition of the decision problem

A summary of the company’s adherence to the decision problem set out in the NICE scope is provided in Table 4. The EAG’s critique of the company’s deviations from the NICE scope are discussed in Section 2.3.

2.3.1. Population

In CS, Table 1, the company stated that the patient population is, “*adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy*”.¹ This is in-line with the population specified in the NICE scope and the licensed indication for cemiplimab in cervical cancer.

The EAG notes that the licensed indication for cemiplimab is not restricted by whether patients have previously received prior immunotherapy. However, the key clinical trial for cemiplimab in cervical cancer (EMPOWER Cervical-1) excluded patients who had received prior immunotherapy. The CS

states that it, “*is anticipated cemiplimab will be used in practice in this second-line setting in patients who have not received prior immunotherapy.*” Furthermore, the target population for the economic analysis is described in CS, Section 3.2.1, as being restricted to those who have not received prior immunotherapy.¹ In its clarification request, the EAG requested further clarity from the company as to whether the population addressed in the CS should be considered to reflect only those without prior immunotherapy, to match both the population in the key clinical trial, and the modelled population in the economic evaluation. In response, the company confirmed that the population addressed in the CS is, “*restricted to patients who have not received prior immunotherapy*” (see clarification response, A1).¹³ The EAG notes that this population is narrower than the licensed indication.

The licensed indication for cemiplimab is not restricted by PD-L1 status, but the CS states that over 95% of patients who are PD-L1 positive ($CPS \geq 1$) will have had pembrolizumab at first-line. Combining this information with the company’s statement that cemiplimab is likely to be used only in individuals without prior immunotherapy, means that the population likely to be offered cemiplimab in clinical practice is expected to be dominated by patients who are PD-L1 negative. Furthermore, those patients who are PD-L1 positive and who have not received prior immunotherapy may not be eligible for cemiplimab if their reason for not having pembrolizumab was immunosuppressant treatment for an autoimmune condition that is still ongoing. The EAG was concerned that the CS did not adequately explore the implications for clinical and cost-effectiveness of the population treated in clinical practice being dominated by PD-L1 negative patients. It therefore requested at clarification that the company comment firstly on the subgroup results by PD-L1 status available from EMPOWER Cervical-1 trial and secondly on whether the clinical effectiveness data from the whole trial cohort (the intention-to-treat [ITT] population) are generalisable to the cohort likely to receive cemiplimab in clinical practice. In response to this request, the company provided additional analyses exploring the clinical effectiveness by PD-L1 status (see clarification response, A18).¹³ It also presented two additional economic model scenarios (see clarification response, A21).¹³ The first addressed the cost-effectiveness in the PD-L1 negative subgroup and the second addressed the cost-effectiveness in a mixed population where 96% of the patients treated are PD-L1 negative.

The EAG notes that the licensed indication for cemiplimab is not restricted by ECOG PS despite patients with a ECOG PS > 1 being excluded from the EMPOWER Cervical-1 trial. The EAG is therefore concerned about the generalisability of the clinical effectiveness evidence presented in the CS to patients with an ECOG PS of >1, although the CS does present some real-world evidence that included patients with ECOG PS of 2.

The EAG also notes that the original protocol for the EMPOWER Cervical-1 trial required patients to be platinum-refractory, defined as having progressed within 6 months of their last dose of platinum-containing treatment. Although this inclusion criteria was removed in a later protocol amendment, a high proportion (88%) of the trial population were platinum-refractory and 55% had progressed whilst still on platinum treatment (see clarification response A24).¹³ This combined with the lack of platinum-rechallenge as a comparator treatment option (see section 2.3.3) meant that the EAG was concerned about the generalisability of the evidence presented in the CS to patients who have progressed more than 6 months after their previous platinum-based treatment, and the EAG asked the company to comment on this in its clarification request (question A24).¹³ In its response the company cites a discussion in the European Public Assessment Report (EPAR) which describes ad-hoc analyses suggesting that, *“the benefit of cemiplimab over chemotherapy seems to be maintained regardless of the time interval to progression after prior platinum therapy, even in the ≥ 12 months subgroup (for which retreatment with platinum could potentially be a choice).”* The company cites the discussion in the EPAR and the European Medicines Agency (EMA) decision not to restrict the license to platinum-refractory patients as being supportive of the evidence from EMPOWER Cervical-1 being generalisable to the whole licensed population. Despite these statements, the EAG considers that there is greater uncertainty regarding the clinical and cost-effectiveness of cemiplimab in this subgroup of patients due to their underrepresentation in the trial and due to rechallenge with platinum-based chemotherapy not being included in the comparator arm (see Section 2.3.4). However, it acknowledges that a minority of patients having second-line treatment would be eligible for platinum-rechallenge.

2.3.2. Intervention

The CS states that the licensed indication for cemiplimab in cervical cancer is as a monotherapy for the treatment of adult patients with r/m CC and disease progression on or after platinum-based chemotherapy. The marketing authorisation for cemiplimab was granted in April 2023, but when cemiplimab was previously appraised for this indication (TA901), NICE was unable to make a recommendation as the technology sponsor at the time (Sanofi) did not provide a submission.¹⁴

Cemiplimab is an immune checkpoint inhibitor (immunotherapy) that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Despite this mechanism of action, PD-L1 testing is not required for cemiplimab in its cervical cancer indication, as the licensed indication is not restricted by PD-L1 status.¹⁵

The recommended dose of cemiplimab is 350 mg every 3 weeks (Q3W) which is administered by intravenous (IV) infusion over 30 minutes.¹⁵ Although no dose reductions are recommended in the Summary of Product Characteristics (SmPC), treatment modifications in the form of dosing delays or

discontinuation are recommended to manage adverse reactions (SmPC, Table 1).¹⁵ Cemiplimab is contraindicated in women who are pregnant or breastfeeding.¹⁵ In addition, the SmPC notes that there are limited data for cemiplimab in patients with severe renal impairment or severe hepatic impairment.¹⁵

The SmPC states that treatment may be continued until disease progression or unacceptable toxicity with no maximum duration of treatment specified in the SmPC.¹⁵ In the EMPOWER Cervical-1 trial the duration of the study treatment period was 96 weeks. There was the option for repeated treatment within the trial, in those completing 96 weeks of treatment without progression, who then progressed in the post-treatment period. However, in practice this was limited to a small minority of patients (■%). The EAG notes that re-treatment after disease progression would fall outside of the licensed indication.¹⁵

2.3.3 Comparator

The comparator addressed in the CS is single-agent chemotherapy, which the company considers to be the only relevant comparator treatment strategy. The comparator arm in the company's key clinical trial was investigator choice of single-agent chemotherapy, with investigators able to choose from one of five regimens specified in the trial protocol which were as follows:

- Pemetrexed (500 mg/m² body-surface area IV every 21 days), with vitamin B12 and folate support as needed; or
- Topotecan (1 mg/m² IV daily for 5 days, every 21 days); or
- Irinotecan (100 mg/m² IV weekly for 4 weeks, every 42 days); or
- Gemcitabine (1000 mg m² IV on days 1 and 8 every 21 days); or
- Vinorelbine (30 mg/m² IV on days 1 and 8 every 21 days).

The clinical effectiveness of single-agent chemotherapy as a comparator strategy is therefore based on the clinical effectiveness of the mix of treatments provided in the comparator arm of the trial. As previously discussed in Section 2.2.2, the EAG's clinical advisors acknowledged a lack of consensus on second-line treatment options in clinical practice. The specific monotherapy interventions they thought were in common use across different centres were gemcitabine and weekly paclitaxel, with the latter not being one of the five options included in the company's basket of single-agent chemotherapies. However, both experts acknowledged that treatment outcomes for single-agent chemotherapies given at second-line are generally poor, and the treatment outcomes would be unlikely to differ substantially according to the specific chemotherapy agent used. Therefore, the basket of single-agent chemotherapy regimens offered in the trial might be expected to lead to similar outcomes to the mix of treatments used in current clinical practice.

The EAG also notes that rechallenge with platinum-based chemotherapy was not identified as a comparator treatment option in the final NICE scope, despite being identified as a viable option in selected patients by both the company and the EAG's clinical experts. This may reflect the fact that the protocol for the EMPOWER Cervical-1 study originally included progression within 6 months of the last dose of platinum-containing chemotherapy as an inclusion criterion, meaning that platinum-rechallenge would not have been a relevant treatment option for the trial's original target population.

The EAG notes that the final NICE scope included best supportive care (BSC) as a comparator. The company argued that BSC was not a relevant strategy in the population likely to be considered eligible for cemiplimab. The EAG's clinical experts agreed that BSC would only be offered in those not considered fit enough for further treatment, or who were declining further treatment, and therefore it was not a relevant comparator.

The final NICE scope also included tisotumab vedotin as an additional comparator, although this was described as being subject to NICE evaluation, as the appraisal of tisotumab vedotin (ID3753)¹⁶ is currently ongoing with an anticipated publication date in June 2026. The company argued that tisotumab vedotin is not a relevant comparator because it is not currently in routine use in clinical practice, and that even if it were approved in the ongoing appraisal, it would still not be established clinical practice at the time of the first committee meeting for the appraisal of cemiplimab, which is scheduled for May 2026. It therefore did not include an assessment of the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin in the CS. However, tisotumab vedotin received its Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation on 2nd December 2025.¹⁷ The EAG's clinical experts have advised that some centres are already preparing to offer tisotumab vedotin via a compassionate use scheme whilst awaiting final guidance from NICE. The EAG also noted that if both appraisals proceed according to their scheduled timelines, there is the potential for tisotumab vedotin to have received positive guidance by the time the final guidance for cemiplimab is published. The EAG therefore considered that there was some uncertainty as to whether the committee would consider tisotumab vedotin to be part of established NHS practice. The EAG asked the company to provide an assessment of the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin at clarification. The company declined to do so, reiterating its argument that tisotumab vedotin is not yet part of established NHS practice.¹³ The company noted in particular that tisotumab vedotin is absent from the NHS England National Cancer Drugs Fund list indicating that it is not currently routinely funded and that any use prior to the NICE appraisal would be via a manufacturer-funded early access / compassionate use programme and would therefore not constitute established clinical practice. The company also stated that there is no information available on the cost-effectiveness of tisotumab

vedotin and no published list price. The EAG does not consider the latter point to be an absolute barrier to the company presenting evidence on their relative clinical and cost-effectiveness, as the company could construct a cost effectiveness model including tisotumab vedotin as a comparator using the publicly available information on the clinical effectiveness of tisotumab vedotin and employ an arbitrary list price. This would allow the EAG to provide confidential analyses to the committee using the relevant price which would be available to NICE. Given that tisotumab vedotin is listed as a relevant comparator in the NICE scope, and it has the potential to become part of established NHS practice by the time the final guidance for cemiplimab is due to be published, the EAG would have preferred the company to have submitted evidence on the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin for the committee to consider, should it decide that tisotumab vedotin is a relevant comparator.

2.3.4 Outcomes

The outcomes reported in the CS were generally consistent with those specified in the final NICE scope. The key outcomes specified in the scope that directly inform the economic modelling are overall survival (OS), progression-free survival (PFS), treatment emergent adverse events (TEAEs) and health-related quality-of-life (HRQoL). To inform the utility values included in the economic analysis, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scores measured in the trial were mapped on to the EuroQol 5-Dimensions 3-Level (EQ-5D-3L) using individual patient-level data (IPD) and a published mapping algorithm. Time on treatment (ToT) is also a key input to the economic analysis, which is adequately addressed in the CS, despite not being specified in the NICE scope. Information on overall response rates (ORR) and duration of response (DOR) are reported in the CS, but do not inform the economic modelling.

2.3.5 Subgroups

Although CS, Table 1, states that the submission relates to the whole licensed population which is irrespective of PD-L1 status, pre-specified subgroup analyses are presented for key clinical outcomes (OS and PFS) in CS, Section 2.8.¹ Some results of the pre-specified subgroup analyses were not included in the CS or clinical study report (CSR) available to the EAG and these were requested and provided at the clarification stage (question A26).¹³

The pre-specified subgroup analyses did not include any presentation of subgroup analyses by PD-L1 status. However, the population treated with cemiplimab is anticipated to be dominated by PD-L1 < 1% patients. The EAG therefore requested (clarification questions A18 and A21) that the company provide additional data stratified by PD-L1 status for the key outcomes informing the economic model (OS, PFS). These data were provided in the company's clarification response.¹³

2.3.6 Special considerations

The CS states that the incidence of cervical cancer is higher in more deprived socioeconomic groups, and that people from more deprived groups are more likely to be diagnosed with more advanced cervical cancer. It goes on to state that, “*making cemiplimab available would represent a positive step towards addressing this inequality in r/m CC.*” However, the company has not provided a specific analysis, such as a distributional cost-effectiveness analysis, demonstrating that recommending cemiplimab has the potential to reduce health inequalities.

Table 4: Summary of decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Population	Adults with r/m CC that has progressed on or after having platinum-based chemotherapy.	Adult patients with r/m CC and disease progression on or after platinum-based chemotherapy (in line with the licensed indication for cemiplimab)¹⁸ In response to clarification, the company confirmed that the population addressed in the CS is those who have not received prior immunotherapy.¹³	The population addressed in the CS is narrower than the population specified in the final NICE scope because it excludes patients who have received prior immunotherapy. The EAG considers that this is reasonable as it aligns with the population recruited to the key clinical trial (EMPOWER Cervical-1) The EAG notes that patients with an ECOG PS > 1 were excluded from the key clinical trial (EMPOWER Cervical-1) meaning that the findings from the trial may not be generalisable to those with ECOG PS > 1. In addition, whilst the licensed indication is not restricted by PD-L1 status, other information presented in the CS regarding the current treatment pathway and the anticipation that cemiplimab will be used in patients without prior immunotherapy treatment suggests that the population is likely to be dominated by patients who are PD-L1 negative. The EAG also notes that the EMPOWER Cervical-1 trial predominantly recruited patients who had progressed within 6 months of completing platinum-based therapy.
Intervention	Cemiplimab	Cemiplimab	Intervention addressed in the CS is consistent with the final NICE scope
Comparator(s)	• Single-agent chemotherapy • BSC	Basket of single agent chemotherapy regimens.	The EAG's clinical experts agreed that BSC is not a relevant comparator in the population eligible to receive cemiplimab, as BSC would only be offered if the patient was not fit enough

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
	Tisotumab vedotin monotherapy (subject to NICE evaluation)	The company provided the following rationale for its choice of comparator treatments: <i>“As noted in the NICE scope, there is no standard of care therapy in this setting, therefore the basket of investigator-chosen single agent chemotherapies observed in the EMPOWER Cervical-1 trial is used in the base case. An alternative distribution of second-line chemotherapies based on regimens stated by clinical experts as being most commonly used in NHS practice is explored in a scenario analysis.</i> <i>BSC is not considered a relevant comparator, as the minority of patients who are not suitable for active second-line treatment with existing chemotherapy options are also not anticipated to be eligible for cemiplimab.</i> <i>Although their licensed indications theoretically overlap, tisotumab vedotin is not considered a relevant comparator for cemiplimab in this appraisal. According to the NICE Reference case,¹⁹ tisotumab vedotin would not constitute a relevant comparator, as its use cannot be considered to be established clinical practice for the following reasons:</i> <i>It is not currently in routine use in NHS clinical practice,</i> <i>It does not currently have a positive recommendation for use by NICE,</i> <i>NICE guidance for tisotumab vedotin is not scheduled to be published until 25th June 2026,¹⁶ which is >6 months after the scheduled</i>	to receive further treatment or was declining further treatment. The EAG considers that due to the overlapping timelines of the appraisals for tisotumab vedotin and cemiplimab, there is some uncertainty regarding whether tisotumab vedotin will be part of established NHS practice when the final guidance for cemiplimab is being decided upon by the committee. Therefore, the EAG would have preferred the company to have provided a comparison of the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin, as requested at clarification. The CS argues that tisotumab vedotin may be used in a different population to cemiplimab because it is a chemotherapy and not an immunotherapy. The CS argues that this means that tisotumab vedotin may be more likely to be offered to patients who have previously received immunotherapy and less likely to be offered to those who have previously received chemotherapy. However, the EAG notes that the key trial that supported the marketing authorisation for tisotumab vedotin (innovaTV 301) was conducted in a population previously treated with doublet chemotherapy.²⁰ Therefore, the EAG considers it likely that tisotumab vedotin would be used in NHS practice in patients who have progressed having received platinum-based chemotherapy and this should not preclude it being considered a comparator.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		<i>submission date for cemiplimab, and >1 month after the scheduled appraisal committee meeting for cemiplimab, and</i> <i>Even if NICE makes a positive recommendation for tisotumab vedotin, it cannot reasonably be considered to have become established clinical practice within the planned timescale of the appraisal of cemiplimab.</i> <i>Furthermore, we anticipate that, in practice, cemiplimab and tisotumab vedotin may be used in different populations. Cemiplimab provides a chemotherapy-free immunotherapy option for those patients who have not received first-line immunotherapy. In contrast, tisotumab vedotin is a type of chemotherapy, rather than an immunotherapy, and as such could be offered to patients who have received prior immunotherapy. Given that cemiplimab will only be used following platinum-based chemotherapy, the alternative use of further chemotherapy with tisotumab vedotin following platinum-based chemotherapy may not be clinically desirable.”</i>	The EAG notes that platinum-rechallenge was not included as a comparator in the CS. Whilst this is consistent with the final NICE scope, the EAG notes that the licensed indication does not exclude patients who have progressed more than 6 months after stopping platinum treatment, and some of these patients would be eligible for platinum-rechallenge in clinical practice.
Outcomes	• PFS • OS • Response rates • Adverse effects of treatment • HRQoL	• PFS • OS • Response rates • Adverse effects of treatment • HRQoL Response rates are not modelled but are presented narratively.	The outcomes addressed in the CS are consistent with NICE scope. The EAG notes that the CS presents DOR in addition to ORRs.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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.	CS, Table 1, does not include information on the alignment between the economic analysis in the CS and the specifications for economic analysis in the final NICE scope.¹ However, the EAG notes that the following information provided later in the CS:¹ • The analysis calculates incremental cost-effectiveness ratios (ICERs) as incremental costs per QALY gained. • A life-time horizon is taken • An NHS and Personal Social Services (PSS) perspective is taken • The analysis applies a confidential Patient Access Scheme (PAS) price for cemiplimab	A more detailed assessment of alignment between the economic analysis presented in the CS and the NICE reference case is presented in Section 4.2.1. However, it is noted that here that no major concerns were identified. In addition to applying the PAS price for cemiplimab, the company's economic analysis uses prices for relevant generic products that form part of the comparator treatments or subsequent treatments included in the analysis. None of the interventions that form part of the comparator or subsequent treatments have confidential discounts and therefore the company's approach is appropriate.
Subgroups	• N/A, the final scope does not specify any subgroups	As NICE scope. The submission relates to the whole licensed population.	Although CS, Table 1, states that the submission relates to the whole licensed population, pre-specified subgroup analyses are presented for key clinical outcomes (OS and PFS) in CS, Section 2.8. However, the original CS did not include any presentation of subgroup analyses by PD-L1 status. As discussed above, the EAG was concerned that the population who would receive cemiplimab in clinical practice would be dominated by PD-L1 negative patients as PD-L1 positive patients

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
			would be unlikely to be immunotherapy naïve. The EAG therefore requested at clarification that the company provide results stratified by PD-L1 status, and comment on the generalisability of the evidence presented in the CS to the PD-L1 negative population. The company provided additional clinical and economic analyses including key clinical outcomes stratified by PD-L1 status and adapted the economic model to present outcomes for subgroups defined by PD-L1 status. ¹³
Special considerations including issues related to equity or equality	None specified.	Cervical cancer disproportionately affects people in more deprived socioeconomic groups (see Section 1.5). These groups are therefore disproportionately affected by the current lack of effective and well tolerated treatments after platinum-based chemotherapy, and by decision-making on new treatments.	The company has not provided a specific analysis, such as a distribution cost-effectiveness analysis, to demonstrate that recommending cemiplimab would be expected to reduce the health inequalities they have described in CS, Section 1.5. ¹

Abbreviations: BSC, best supportive care; CPS, combined positive score; DOR, duration of response; HRQoL, health-related quality-of-life; ICER, incremental cost-effectiveness ratio; ORR, overall response rate; OS, overall survival; PAS, patient access scheme; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PSS, Personal Social Services.

3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical effectiveness evidence included in the CS. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work done by the EAG and Section 3.7 presents the conclusions of the clinical-effectiveness section.

3.1 Critique of the methods of review

The clinical evidence submitted by the company for cemiplimab in the treatment of r/m CC that has progressed on or after platinum-based chemotherapy is comprised of:

- A systematic literature review (SLR).
- A summary and results of an open label, randomised, multicentre, phase III trial (Tewari *et al.* 2022,²¹ Oaknin *et al.* 2022,²² Oaknin *et al.* 2025²³)
- Additional evidence from a conference abstract of a small RCT²⁴ (not subject to full peer review) and real-world evidence.²⁵⁻²⁷

Full details of the company's SLR are presented in Section 2 of the CS and CS Appendix B. In general, the EAG noted that appropriate methods were used in the conduct of the clinical effectiveness review, while also identifying some concerns regarding certain aspects of the review process. Further details are provided below.

3.1.1 Searches

Searches to identify evidence for the SLR of clinical effectiveness are presented in Appendix B of the CS.¹ Sources included all the core databases expected by NICE, though the EAG notes that MEDLINE was only searched as part of a multi-file search of Embase.com with no attempt to optimise the search for MEDLINE's own features (e.g., MeSH) – contrary to the company's own claims (CS Appendix B, section 3.2.1.1, p.12). When questioned about this, the company revealed that they relied on Embase's automated mapping from Emtree (clarification response A6)¹³ – thereby losing some of the key benefits of searching multiple sources. This decision could potentially have affected the retrieval performance of the Scottish Intercollegiate Guidelines Network RCT filter, since these filters are not designed for multi-database use.

Somewhat confusingly, the searches are presented in several phases, though reported in a single Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart. When the EAG queried this during the clarification process, the company clarified that though the earlier searches (from as far back as 2020) were originally conducted for the purpose of a different evidence

submission, the scope itself had not changed; and, moreover, the new search results from each update (the most recent being June 2025) had been appended to those from the previous searches (clarification response A4).¹³

In spite of the above points, the search strategies are broadly well-designed and appear to have been competently executed. The company also executed complementary searches of trial registers (ClinicalTrials.gov and ICTRP) and relevant conference proceedings, as would be expected for a SLR of this type. Therefore, the EAG concludes that it is unlikely any relevant RCT evidence will have been missed.

3.1.2 Inclusion criteria and study selection

The CS describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria to citations identified by the searches. Any disagreements were resolved through discussion or arbitration by a third reviewer (see CS Appendix B.3.3 and clarification response, question A8).¹³ The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS (Appendix D.1.1 and Appendix D.1.2, Table 3) initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria for the SLR (i.e., all potentially relevant trials of systematic therapy in women aged ≥ 18 years with recurrent, persistent and/or metastatic cervical cancer, that had progressed after platinum-containing chemotherapy) but then restricted the SLR only to those studies which were directly relevant to the decision problem (i.e., cemiplimab only - see CS, Section 2.2).¹ Following a clarification request to question A10, the CS did not provide sufficient detail on how the inclusion/exclusion criteria were applied during the study selection process. A fundamental prerequisite for a SLR is to have clearly focused research questions and pre-specified inclusion/exclusion criteria at the outset to minimise bias and enhance transparency and reproducibility.^{28, 29} In addition, the company states (clarification response to question A10)¹³ that ‘*a systematic search for real-world evidence was not undertaken*’, further limiting the transparency and robustness of the evidence base presented in support of the CS.

3.1.3 Data extraction

The data extracted and presented in the CS for the SLR of clinical effectiveness evidence appear to be appropriate and comprehensive. As noted in Appendix B (Section 3.4) and the company’s clarification response (question A8),¹³ all relevant data were extracted by a single reviewer and checked for accuracy by a second independent reviewer. Despite the lack of clarity in the company’s clarification response, the EAG assumes that any discrepancies were resolved through discussion.

3.1.4 Quality assessment

Quality assessment was conducted using an appropriate critical appraisal tool. The CS (Appendix B, Section 4.5, Section 8.3.1 and the company's clarification response to question A11)¹³ used the revised Cochrane risk of bias tool (RoB 2) to assess the included RCT.³⁰ Due to the lack of detail in the CS (including the company's clarification response to question A10),¹³ it is unclear how the quality assessment process was undertaken. According to the Cochrane Handbook (Section 7.3.2),³¹ this should ideally be conducted independently by at least two reviewers to minimise the risk of error and subjective bias, with disagreements resolved via consensus or arbitration.

3.1.5 Evidence synthesis

The company conducted a narrative synthesis of the evidence for cemiplimab; however, the CS did not provide sufficient methodological detail on how this approach was undertaken. Ideally, the narrative synthesis approach should be justified, transparent, and conducted in a way that avoids selective reporting or undue emphasis on particular findings to minimise potential bias.^{32, 33}

The EAG agrees with the company (CS section 2.10) that a meta-analysis comparing cemiplimab and chemotherapy is not appropriate, as only a single relevant trial was identified.^{21, 23} Additional evidence was limited to an inadequately reported conference abstract of an RCT conducted in Uzbekistan,²⁴ which lacked key information including full author contact details and a trial registration number, thereby preventing further verification or information retrieval. The EAG also notes that this study could not be located in accessible public trial registries (e.g., WHO ICTRP, ClinicalTrials.gov) and the abstract indicated that the study was unfunded. There is ongoing debate regarding the inclusion of non-peer-reviewed (or unpublished) data in quantitative syntheses, as such evidence sources often provide insufficient detail to permit robust assessment of internal validity and may have uncertain impact on meta-analysed results.³⁴⁻³⁶

3.2 Summary and critique of the methods of the trials of the technology of interest

The clinical effectiveness review presented in the CS identified only one fully published RCT (NCT03257267),³⁷ reported across three key peer-reviewed publications (Oaknin *et al.* 2025²³; Tewari *et al.* 2022²¹; Oaknin *et al.* 2022²²). As noted in Section 3.1.5, additional RCT evidence was available from a conference abstract.²⁴ However, due to the limited information, the absence of a full publication, and lack of trial registration details, this evidence is summarised separately in Section 3.3.5 (Additional evidence). Furthermore, the CS (Section 2.13) states that there are no ongoing RCTs of cemiplimab in r/m CC

3.2.1 Main supporting evidence – EMPOWER Cervical-1

3.2.1.1 Study design

The company's SLR of cemiplimab in the treatment of r/m CC that has progressed on or after platinum-based chemotherapy identified and included one pivotal study: the EMPOWER Cervical-1 trial.^{21, 23} A summary of this study is provided in Table 5.

Table 5: Summary of the trial design - EMPOWER Cervical-1^{21, 23, 38} (adapted from CS, Table 3 and Table 5)

Study details	EMPOWER Cervical-1
Role in this evaluation	This trial is the key source of clinical effectiveness evidence for cemiplimab in the treatment of r/m CC that has progressed on or after platinum-based chemotherapy. It is used to inform both the assessment of clinical efficacy and the economic evaluation. Overall survival (OS), progression-free survival (PFS), and time on treatment (ToT) informed the partitioned survival economic model, which estimates the patient distribution across the pre-progression, post-progression, and death health states. HRQoL was collected using the EORTC QLQ-C30 questionnaire, mapped to EQ-5D-3L utilities, and used to derive treatment-specific utility values for the pre-progression and post-progression health states. Costs and resource use were not directly informed by the trial, relying instead on expert opinion and published literature.
Study type	Phase 3, open label, randomised controlled trial.
Setting and location	Multicentre international trial conducted across 97 sites in 14 countries (Australia, Belgium, Brazil, Canada, Greece, Italy, Japan, Poland, Republic of Korea, Russian Federation, Spain, Taiwan, UK [2 sites in England], US).
Patient group	Adults with r/m CC whose disease progressed after platinum-containing chemotherapy; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
Exclusion criteria	Key exclusions included candidates for pelvic exenteration, significant autoimmune disease requiring systemic immunosuppression within the past 5 years, prior treatment with PD-1/PD-L1 or other immune-modulating agents, use of immunosuppressive corticosteroids within 4 weeks prior to enrolment, and active or untreated brain metastases
Intervention	Cemiplimab, intravenous (IV), 350 mg every 3 weeks for up to 96 weeks (or until disease progression/unacceptable toxicity) with an option of repeat

	treatment for patients completing 16 six-week treatment cycles who then had progressive disease in the post-treatment follow-up period Patients with an unconventional response consistent with pseudo-progression could be treated beyond progression provided the following conditions were met: no increase in ECOG PS score, no rapid disease progression and, no severe adverse events (AEs) warranting cemiplimab discontinuation.
Comparator	Investigator's choice of single-agent chemotherapy. Options, determined for each patient prior to randomisation, included (all for up to 96 weeks): • Pemetrexed (500 mg/m² body-surface area IV every 21 days), with vitamin B12 and folate support as needed; or • Topotecan (1 mg/m² IV daily for 5 days every 21 days); or • Irinotecan (100 mg/m² IV weekly for 4 weeks, every 42 days); or • Gemcitabine (1000 mg m² IV on days 1 and 8 every 21 days); or • Vinorelbine (30 mg/m² IV on days 1 and 8 every 21 days) Investigator's choice chemotherapy was discontinued at disease progression or development of unacceptable toxic effects. Crossover was not permitted.
Outcomes	Primary endpoints • Overall survival (OS; time from randomisation to date of death). Key secondary endpoints • Progression-free survival (PFS; time from randomisation to the date of the first documented tumour progression using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, or death due to any cause). Assessed on day 42 (+/- 7 days) of the 6-week cycle, in cycles 1-4, 6, 8, 10, 12, 14 and 16 and follow-up visits 1 and 2 and survival follow-up assessments). • Objective response rate (ORR; number of patients with a best overall response of confirmed complete response (CR) or partial response (PR) divided by the number of patients in the efficacy

	analysis set). Assessed by the investigator by RECIST 1.1. Assessment schedule as for PFS. Other secondary endpoints • Duration of response (DOR; time between the date of first response (CR or PR) to the date of the first documented tumour progression (per RECIST 1.1) or death due to any cause. • Quality of life measured by the EORTC QLQ-C30 instrument (administered at screening visit and on Day 1 of each 6-week cycle, and follow-up visits 1 and 2) • Safety and tolerability
Subgroups	Pre-specified subgroup analyses of the primary and key secondary endpoints were performed on the following factors. • age group (<65, ≥65) • race (White, Non-white) • geographic region (North America, Asia and Rest of World) • geographic region (Japan, outside of Japan) • histology (Squamous, Adenocarcinoma/adenosquamous) • prior bevacizumab use (Yes, No) • baseline ECOG PS (0, 1) • choice of IC chemotherapy • number of prior lines of systemic therapy for recurrent or metastatic disease (1 line, >1 line)
Exploratory variables (PD-L1 biomarker)	Exploratory analyses were performed on archival tumour samples to evaluate associations between efficacy endpoints and biomarkers, including PD-L1 expression in tumour cells (detected using the SP263 monoclonal antibody [Ventana]). PD-L1 expression status was categorized as either ≥ 1% or < 1% in tumour cells.
Duration of study	Treatment for up to 96 weeks or until disease progression or unacceptable toxicity; survival follow-up continued beyond treatment.

Abbreviations: AEs, adverse events; CR, complete response; ECOG PS, ECOG performance status; DOR, duration of response; Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL, health-related quality-of-life; IC, investigator choice; IV, intravenous; ORR, Objective response rate; OS, overall survival; PD-L1, programme cell death ligand-1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; r/m CC, relapsed or metastatic cervical cancer; ToT, time on treatment

The EMPOWER-Cervical 1 study^{21, 23, 38} is an international, multicentre, open-label, randomised, phase III trial designed to assess the efficacy cemiplimab (a PD-1 blocking antibody) compared with investigator's choice of single-agent chemotherapy in women with r/m CC. Eligible patients were adults with recurrent or metastatic squamous-cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the cervix whose disease had progressed after first-line platinum-containing chemotherapy for recurrence or metastases. Participants were required to have previously received bevacizumab and paclitaxel therapy unless these treatments were declined, deemed unsuitable, or unavailable. Additional eligibility criteria included an ECOG performance status of 0 or 1, measurable disease, and adequate renal, hepatic, and bone marrow function. Key exclusion criteria included candidacy for curative pelvic exenteration, recent or active moderate-to-severe autoimmune disease, clinically significant immunosuppression, and active infections requiring systemic therapy. Previous anti-PD-1 or anti-PD-L1 therapy was not permitted.

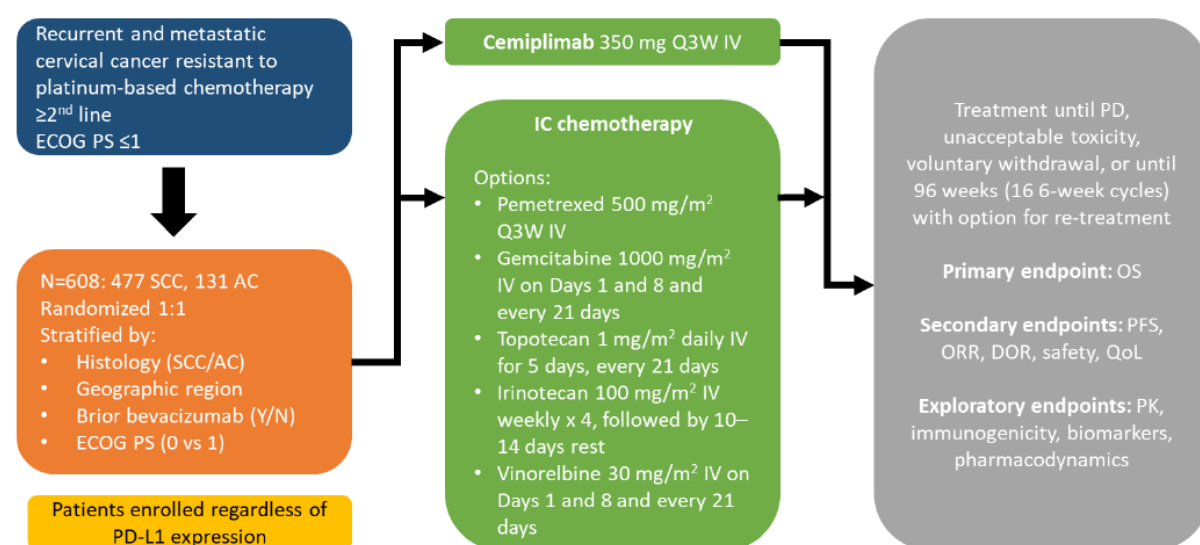
Randomisation was performed centrally in a 1:1 ratio to cemiplimab or chemotherapy and stratified by histologic type (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]), geographic region, previous bevacizumab exposure, and ECOG performance-status score. Between July 2017 and August 2020, 608 patients were enrolled and randomised to either the treatment arm (cemiplimab; n=304) or the investigator's choice of chemotherapy (n=304) arm across 97 sites in 14 countries (Australia, Belgium, Brazil, Canada, Greece, Italy, Japan, Poland, Republic of Korea, Russian Federation, Spain, Taiwan, UK [2 sites in England], US).

Participants allocated to the treatment arm received cemiplimab at a flat dose of 350 mg IV every 3 weeks for up to 96 weeks, with an option for repeat treatment for patients who completed 16 six-week treatment cycles and then had progressive disease in the post-treatment follow-up period. Treatment beyond progression was allowed in selected cases of suspected pseudo-progression provided clinical status remained stable (i.e., no increase in ECOG performance-status score, no rapid disease progression and, no severe AEs warranting cemiplimab discontinuation). Those in the chemotherapy arm received one of several single-agent options chosen by the investigator, including pemetrexed, gemcitabine, topotecan, irinotecan, or vinorelbine, administered according to protocol-specified dosing schedules and discontinued on progression or unacceptable toxicity. No crossover to cemiplimab was permitted.

The pre-specified primary endpoint was overall survival (OS), analysed in a hierarchical fashion with OS first tested in the squamous-cell carcinoma subgroup and, if significant, then in the overall trial population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), HRQoL assessed with the EORTC QLQ-C30 global health status/quality-of-life scale, and safety (TEAEs up to 90 days after last dose or before subsequent

therapy). The sample size plan required approximately 460 patients with squamous-cell carcinoma, which was expected to yield about 340 deaths. The total planned enrolment for the overall study population was approximately 590 patients, including both histologic subtypes). This sample size provided 90% power to detect a $\geq 30\%$ reduction in risk of death, with group-sequential stopping boundaries and two planned interim analyses. Analyses of OS and PFS were conducted using stratified log-rank tests and Cox models. Longitudinal QLQ-C30 data were analysed using mixed-effects models for repeated measures. All primary and key secondary efficacy analyses were conducted on the ITT population, with safety evaluated in the as-treated population. The median duration of follow-up from randomisation to the data cutoff (primary analysis) was 18.2 months (range, 6.0 to 38.2) for all patients. At the time of the final analysis, the median follow-up was 47.3 months. A diagram summarising the study design is reproduced in Figure 2.

Figure 2: Summary diagram of the EMPOWER Cervical-1 trial²¹ (reproduced from CS, Section 2.3.1, Figure 3)



AC: adenocarcinoma/adenosquamous cell carcinoma; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; IC: investigator's choice; IV: intravenous; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; PK: pharmacokinetics; Q3W: every three weeks; QoL: quality of life; SCC: squamous cell carcinoma; Y/N: yes/no.

3.2.1.2 Baseline and disease characteristics

The baseline demographic and disease characteristics of the overall study population in the EMPOWER-Cervical 1 trial are presented in Table 6. The two treatment arms were generally well balanced at baseline across key demographic and clinical variables, including age, ECOG performance status, histologic subtype, disease extent, prior treatment history.

Table 6: Baseline characteristics of the overall study population (reproduced with minor amendments from CS Section 2.6.1, Table 8)

Characteristic	Cemiplimab (N = 304)	Chemotherapy (N = 304)	Overall (N = 608)
Age			
Median, yr (range)	51 (22-81)	50 (24-87)	51 (22-87)
<65 years, n (%)	269 (88.5)	264 (86.8)	533 (87.7)
Race or ethnic group, n (%)*			
White	193 (63.5)	192 (63.2)	385 (63.3)
Black	9 (3.0)	12 (3.9)	21 (3.5)
Asian	88 (28.9)	88 (28.9)	176 (28.9)
American Indian or Alaska Native	2 (0.7)	1 (0.3)	3 (0.5)
Other	8 (2.6)	4 (1.3)	12 (2.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Not reported	3 (1.0)	6 (2.0)	9 (1.5)
Hispanic or Latino			
No†	251 (82.6)	250 (82.2)	501 (82.4)
Yes†	47 (15.5)	44 (14.5)	91 (15.0)
Not reported	6 (2.0)	10 (3.3)	16 (2.6)
Region of enrolment, n (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of the world	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance status score, n (%)*‡			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)
Histologic type, n (%)*‡			
Squamous-cell carcinoma	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma or adenosquamous carcinoma	64 (21.1)	71 (23.4)	135 (22.2)
Extent of disease, n (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent or persistent	20 (6.60)	14 (4.6)	34 (5.6)
Previous lines of therapy for recurrent or metastatic disease, n (%)			
One	177 (58.2)	169 (55.6)	346 (56.9)
More than one	124 (40.8)	135 (44.4)	259 (42.6)
Previous bevacizumab use, n (%)§			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)
Previous paclitaxel use, n (%)§			
Yes	273 (89.8)	287 (94.4)	560 (92.1)
No	31 (10.2)	17 (5.6)	48 (7.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group

* Information is from the electronic data-capture system;

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability;

‡ Typo amended by EAG (company's clarification response, question C1)¹³

‡ At the time of randomization, discrepancies between the electronic data-capture system and interactive Web response system in the distribution of histologic types were introduced. According to the electronic data-capture system, 77.8% of the patients had squamous-cell carcinoma and 22.2% had adenocarcinoma or adenosquamous carcinoma. According to the interactive Web response system, 78.5% of the patients had squamous-cell carcinoma and 21.5% had adenocarcinoma or adenosquamous carcinoma

§ Information is from the interactive Web response system.

The median age of patients was 51 years (range 22–81 years) in the cemiplimab group and 50 years (range 24–87 years) in the chemotherapy group, with approximately 88% of patients aged <65 years in both arms. ECOG performance status was well matched between groups, with 53.3% and 53.6% of patients having an ECOG score of 1 (indicating some functional impairment) and the remainder an ECOG score of 0 in the cemiplimab and chemotherapy groups, respectively.

Histologic subtype was similarly distributed between groups, with squamous-cell carcinoma accounting for 78.9% of patients in the cemiplimab arm and 76.6% in the chemotherapy arm, and adenocarcinoma or adenosquamous carcinoma comprising approximately 22% overall. The majority of patients had metastatic disease at baseline (>93% in both arms), with only a small proportion presenting with recurrent or persistent disease. Baseline disease extent was therefore comparable across treatment groups.

All patients had previously experienced disease progression after platinum-containing therapy used to treat recurrence or metastases. Approximately 40% of patients in each group had received more than one previous line of systemic therapy for r/m CC, placing a substantial proportion of the study population in the third-line or later treatment setting. Approximately 50% in each group had previously received bevacizumab and prior paclitaxel exposure exceeded 90% overall. In 87.8% of patients, disease progression had occurred ≤6 months after prior platinum chemotherapy, emphasising the poor prognosis in a heavily pretreated population.

The geographic distribution of patients was similar between groups, with around 11% enrolled in North America, 27% in Asia, and approximately 62% in the rest of the world. However, the small number of UK sites (n=2) and patients (not explicitly reported in the CS or Tewari *et al.*)²¹ may limit direct applicability to the NHS setting, although UK clinical experts consulted by the company considered that the trial was generalisable to the NHS.

Overall, no clinically meaningful imbalances were observed between treatment groups at baseline, and the randomisation appears to have been effective. However, the EAG has several concerns that may

affect the generalisability. First, the requirement for ECOG performance status 0–1 excludes patients with poorer functional status, who may present in real-world practice. Second, as the objective was to enrol patients independent of PD-L1 expression status, collection and testing of tumour samples for PD-L1 was not required before treatment and PD-L1 expression status was retrospectively assessed in archived samples. This meant that baseline PD-L1 data were only available for a subset of patients (371 patients with evaluable samples: 182 in the cemiplimab group and 189 in the chemotherapy group), limiting interpretation of biomarker-defined subgroups. Finally, given the majority of patients were platinum-refractory (disease progression within ≤ 6 months), generalisability of the evidence to patients who have progressed >6 months after their previous platinum-based treatment is unclear.

3.2.1.3 Summary and critique of the company's quality assessment

The company's (and the EAG's) assessment of the design, conduct, and internal validity of the EMPOWER-Cervical 1 study^{21, 23, 38} is summarised in Appendix 1. This appraisal was conducted using a recognised methodological instrument - the Cochrane RoB 2 tool.³⁰

Overall, the EAG broadly agrees with the company's assessment that the EMPOWER-Cervical-1 study was a generally well-conducted RCT, and that the primary outcome of OS is at low risk of bias. Although the study was open-label, OS is an objective endpoint (time from randomisation to death) and is unlikely to be significantly influenced by the lack of blinding. However, as noted in company's clarification response (question A16) "*Progression and response outcomes were investigator-assessed and not assessed by BICR [blinded independent central review]*".¹³

As a result, these secondary outcomes (e.g., PFS, ORR) are more susceptible to detection bias and should be interpreted with caution. In addition, patients receiving cemiplimab who had an unconventional response consistent with pseudo-progression were allowed to continue treatment beyond radiologic progression, provided ECOG performance status did not worsen, there was no rapid disease progression, and no severe AEs warranting discontinuation were encountered. This was not permitted in the chemotherapy arm. While pseudo-progression is a recognised phenomenon associated with immunotherapy and not with chemotherapy, this could have resulted in prolonged treatment duration and continued benefit in a subset of cemiplimab-treated patients. Retreatment with cemiplimab was also permitted for patients who completed the planned treatment period and subsequently experienced disease progression. Although retreatment was allowed in both arms, re-exposure to chemotherapy agents was considered subsequent therapy rather than an extension of the study intervention (clarification response, A13).¹³ Retreatment with cemiplimab after disease progression would also fall outside the licensed indication and the differential handling of treatment beyond progression and retreatment may therefore have favoured the cemiplimab arm and could have resulted

in more favourable OS estimates than might be expected in routine clinical practice. Although retreatment with cemiplimab after progression was limited to a small proportion of patients (■%), treatment beyond progression occurred in a sizable minority (23%) and therefore has a greater potential to impact the OS and PFS estimates. The EAG notes that patients with pseudo-progression will have been recorded as progressed at the time they first met the progression criteria, even if that event was then considered by the investigator to be a pseudo-progression, potentially leading to PFS being underestimated in these patients.

Patient-reported outcomes (PROs) are also subject to limitations inherent to the open-label design. As noted in the EMA assessment report (p99) *‘The fact that PROs [patient reported outcomes] were collected is acknowledged, but since their clinical relevance in an open-label trial remains questionable, inclusion of their results in section 5.1 of the SmPC is not endorsed’*.^{18, 21} In addition, PRO completion rates declined over time due to treatment discontinuation and disease progression. Consequently, later quality-of-life estimates may be driven by a selected subset of patients who remain on treatment and are likely to have a better prognosis, increasing uncertainty of any quality-of-life benefit. The company further notes (clarification response to question A31) that *‘specific reasons for the difference in PRO collection after progression is not available. It might be expected that patients with better HRQoL would be more likely to attend visits and fill out questionnaires than those patients in poorer health, but no data are available to confirm this.’*¹³

The EAG notes several issues relevant to the generalisability of the trial results to clinical practice in England. The majority of patients experienced disease progression within 6 months of prior platinum-based therapy, and therefore the applicability of the evidence to patients relapsing >6 months after previous platinum treatment remains uncertain. In addition, patients with an ECOG performance status greater than 1 were excluded from the trial, limiting generalisability to less fit patients commonly encountered in routine practice, although the CS does present some supportive real-world evidence including patients with ECOG PS 2. Finally, although the licensed indication for cemiplimab does not restrict use by PD-L1 expression status or prior immunotherapy, the CS suggests that cemiplimab will mainly be used in patients who have not received pembrolizumab first-line. The CS further states that most PD-L1-positive patients ($\geq 95\%$) are now offered pembrolizumab-based therapy at first-line. As a result, cemiplimab may be used predominantly in patients with PD-L1-negative tumours in routine clinical practice. This raises some uncertainty regarding the applicability of the trial evidence to the full licensed population, particularly as the EMPOWER-Cervical-1 trial did not include patients previously treated with an anti-PD-L1 agent.

3.3 Critique of the results of the trials of the technology of interest

This section briefly summarises the key findings of the analysis from Oaknin *et al.* 2025²³ based on information reported in the CS (Section 2.6) and the company's clarification response to questions A28–31.¹³ This analysis focuses on the overall population with r/m CC after chemotherapy. Further details and results of the full study (ITT) population and relevant subgroups are provided in brief for completeness. Full details of all reported results are available in Section 2.6 of the CS.¹

3.3.1 Primary endpoint: OS in the overall population

A summary of the OS results is presented in Table 6 and the corresponding Kaplan-Meier (KM) estimates in Figure 3. In the overall population, at the final analysis (data cut-off 3 October 2023; median follow-up 47.3 months), cemiplimab was associated with a 3.2-month improvement in median OS compared with chemotherapy (11.7 vs 8.5 months), corresponding to a 33% reduction in the hazard for death (hazard ratio [HR]: 0.67, 95% CI: 0.56 to 0.80; $p < 0.00001$). Although the HR is presented here, the EAG notes that the company's assessment of the proportional hazards assumption suggested it may be violated. Therefore, the HR should be interpreted with caution. This is further supported by the Kaplan-Meier curves, which begin to diverge at approximately six months, indicating that the underlying hazards may change differently over time between the two treatment arms.

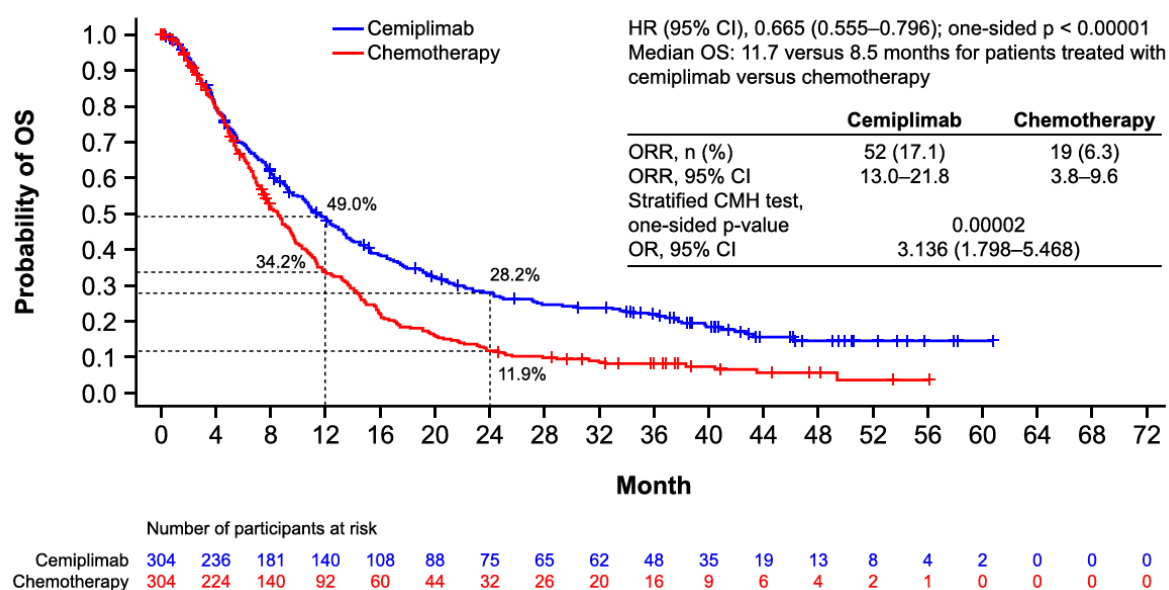
Table 7: Overall survival in final analysis (overall population)²³ (reproduced from CS, Table 9)

	Cemiplimab (n = 304)	Chemotherapy (n = 304)
Deaths, n (%)	237 (78.0)	256 (84.2)
Censored patients, n (%)	67 (22.0)	48 (15.8)
Median OS (95% CI), months ^a	11.7 (9.6–13.4)	8.5 (7.5–9.6)
Stratified log-rank test one-sided p-value ^{b,c}	<0.00001	
HR (95% CI)^{b,d}	0.67 (0.56–0.80)	
Estimated survival probability, months, % (95% CI) ^a		
6	69.6 (64.0–74.5)	66.1 (60.3–71.3)
12	49.0 (43.2–54.6)	34.2 (28.6–39.8)
24	28.2 (23.0–33.5)	11.9 (8.4–16.1)
36	22.0 (17.3–27.0)	8.3 (5.3–12.0)
48	14.7 (10.3–19.9)	5.7 (3.0–9.7)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

^aBased on the Kaplan-Meier method; ^bStratified by geographic region (North America vs Asia vs rest of world) and histology (squamous cell carcinoma vs adenocarcinoma); ^cOne-sided p-value converted from a stratified log-rank test two-sided p-value; ^dBased on a stratified proportional hazards model (cemiplimab vs chemotherapy).

Figure 3: Kaplan-Meier Plot of Overall Survival in the overall population, final analysis²³
(reproduced from CS, Figure 5)



Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival

Note: One-sided nominal P value was converted from stratified log-rank test 2-sided nominal P value.

3.3.2 Other secondary outcomes

3.3.2.1 PFS

A summary of the PFS results is presented in Table 7 and the corresponding KM estimates are shown in Figure 4. PFS was defined as the time from the date of randomisation to the date of the first documented tumour progression using RECIST v1.1 (including progression events deemed by the investigator to be consistent with pseudo-progression, see Section 3.2.2.1). The final analysis of the cemiplimab regimen in the overall population indicates an improvement in PFS compared with the chemotherapy group (HR, 0.741; 95% CI: 0.62–0.88; one-sided $P=0.0003$). However, the EAG notes that the median PFS was similar across both groups (2.8 months with the cemiplimab group and 2.9 months in the chemotherapy group). Although the HR is presented here, the EAG notes that as part of the submission, the company assessed whether the proportional hazards assumption holds and found that it may be violated. Therefore, the HRs should be interpreted with caution. This is further supported by the divergence of the KMs at approximately four months, thus indicating underlying hazards that change differently for the two arms.

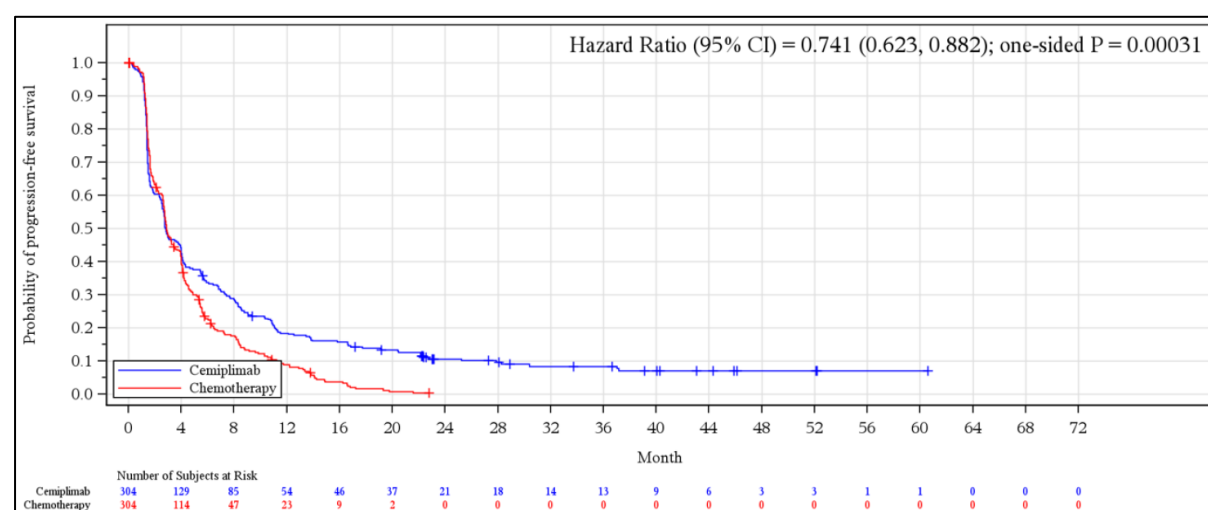
Table 8: PFS in the overall population (n= 608) (adapted from CS, Table 10)

	Cemiplimab (n=304)	Chemotherapy (n=304)
Number of events, n (%)	272 (89.5%)	278 (91.4%)
HR (95% CI); p-value	0.741 (0.62–0.88); one-sided P=0.00031	
Median PFS (95% CI); months	2.8 (2.6–3.9)	2.9 (2.7–3.5)

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Source: EMPOWER Cervical-1 Trial Final Clinical Study Report

Figure 4: Kaplan-Meier curves of PFS in the overall population (n=608) (reproduced from CS, Figure 6)



Abbreviation: CI, confidence interval

Note: One-sided nominal P value was converted from a stratified log-rank test 2-sided nominal P value

Source: EMPOWER Cervical-1 Trial Final Clinical Study

Pseudo-progression

Pseudo-progression is a phenomenon frequently observed when treating with immunotherapies. It refers to an atypical response pattern following treatment whereby an initial increase in tumour size is observed or a new lesion appears, followed by a decrease in tumour burden. When treating with immunotherapies these tumour observations may in fact be a consequence of T-cells infiltrating and attacking the tumour. These initial increases in tumour size can be falsely designated as disease progression under the RECIST criteria. Pseudo-progression is not a recognised phenomenon when treating with chemotherapies.

Within the EMPOWER Cervical-1 trial, tumour progression was assessed according to the RECIST 1.1 criteria in both arms of the trial. Under the RECIST 1.1 criteria, potential initial pseudo-progression in the cemiplimab arm were therefore counted as the first progression events in the PFS data. In the

EMPOWER Cervical-1 trial, treatment beyond suspected pseudo-progression was permitted in the cemiplimab arm, provided certain criteria were met (see Table 5).

Within EPAR Table 48,³⁹ and the company response to clarification question A15,¹³ a comparison of OS within the cemiplimab arm, comparing the 70 patients who continued cemiplimab treatment beyond documented progression, and the remaining 234 patients who did not was presented. These results are reproduced in Table 9. No statistically significant differences in median OS or the proportion of deaths were identified. However, these results are from a post hoc analysis of a subgroup within the trial, and should be interpreted with appropriate caution.

Table 9: Comparison of OS in patients who were treated beyond documented progression and those who were not, cemiplimab arm only (Reproduced from Table 48 of the EPAR and clarification response question A15a)

	Cemiplimab treated beyond progression	Cemiplimab not treated beyond progression
	(N=70)	(N=234)
Number of deaths, n (%)	42 (60.0%)	142 (60.7%)
Number of censored patients, n (%)	28 (40.0%)	92 (39.3%)
Median (95% CI), (months) ^[a]	13.9 (11.7, 17.9)	10.5 (8.2, 12.9)
HR (95% CI) ^{[b][c]}	0.798 (0.559, 1.141)	

Abbreviations: CI – confidence interval; SCC – squamous cell carcinoma; IWRS - Interactive Web Response System

^a Based on Kaplan-Meier method

^b Stratified by geographic region (North America vs Asia vs rest of world) and histology (SCC versus adenocarcinoma) according to IWRS

^c Based on stratified proportional hazards model

3.3.2.2 ORR and DOR

A summary of the ORR results is presented in Table 8, and the DOR results in Table 9. The final analysis in the overall population indicated that treatment with cemiplimab resulted in a significantly higher ORR (defined as rate of best overall response of complete response or partial response) than with chemotherapy (17.1% [95% CI: 13.0, 21.8]) vs. 6.3% [95% CI: 3.8 to 9.6], respectively; odds ratio 3.1 [95% CI: 1.8, 5.5]). The median DOR was longer in the cemiplimab group than in the chemotherapy group based on a low number of confirmed CR or PR across both groups (mDOR 18.7 months vs 7.2 months).

Table 10: ORR in final analysis (overall population) (reproduced from CS, Table 11)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Odds ratio (95% CI)
Complete response			-
Partial response			
Stable disease			
ORR % (95% CI)	17.1 (13.0–21.8)	6.3 (3.8–9.6)	3.1 (1.8–5.5)

Abbreviations: CI, confidence interval; ORR, objective response rate (based on patients with confirmed CR or PR)

Table 11: DOR in the overall population (adapted from CS, Table 12)

	Cemiplimab	Chemotherapy
N*	52	19
mDOR, months (95% CI) *	18.7 (16.4–NE)	7.2 (5.1–9.9)

Abbreviations: CI, confidence interval; DOR, duration of response; NE, not evaluable

*Based on patients with confirmed CR or PR.

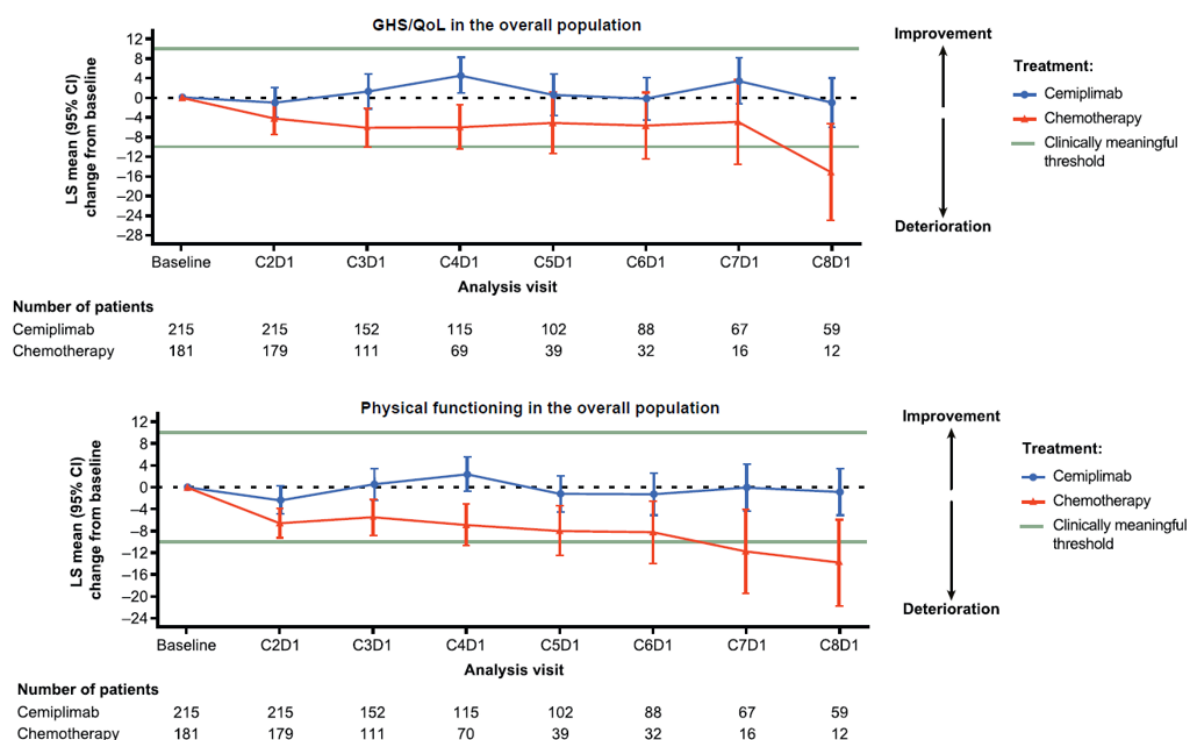
3.3.2.3 HRQoL

The HRQoL outcome was measured by patient responses to the EORTC QLQ-C30. The EORTC QLQ-C30 assesses five function scales (physical, role, cognitive, emotional and social), eight symptom scales and a global health status and quality-of-life scale (GHS/QoL), with total scores ranging from 0 to 100. Higher scores on function and GHS/QoL scales reflect better health status, while higher scores on symptom scales reflect more symptoms. Patients were required to complete PRO questionnaires at baseline, on day 1 of each treatment cycle up to cycle 16 or disease progression, and at two post-treatment follow-up visits, with a recall period of “*during the past week*”.²² According to Oaknin *et al.* (2022),²² among patients remaining on study, PRO completion was high, with >95% completing at least one PRO scale at baseline and approximately 90% completing at least one PRO scale at each subsequent assessment. However, the number of patients contributing evaluable PRO data declined substantially over time due to disease progression, treatment discontinuation (e.g. lost to follow-up, patient or physician decision, withdrawal of consent) and death. For example, PRO results were evaluable for at least 10 patients per treatment group only up to cycle 8 in the overall population. After disease progression, PRO data were available for only a limited number of patients (█%), the majority of whom were in the cemiplimab group (CS, pg. 111).¹ The company further notes (clarification response to A31) that “...Lower completion rates in patients who have progressed are to be expected, as some of these patients will be in a poor clinical state (both physically and emotionally) and completing questionnaires will not be a priority for such patients or their medical professionals.”¹³ The EAG views the lower completion rates as a limitation. Specifically, the HRQoL estimates at these later time points are likely to reflect a select subgroup of patients who remained well enough to complete the questionnaires. It also notes that patients in the cemiplimab arm who met the criteria for disease

progression, but who remained on treatment because they were considered to have an unconventional response consistent with pseudo-progression, will have contributed to the post-progression utilities.

HRQoL outcomes were reported at two separate data cut-offs, and both showed differences between treatment groups for PROs of GHS/QoL and physical functioning in numerical favour of cemiplimab (Figure 5 and Table 12). While the EAG acknowledges that the findings were consistent across analyses (clarification response to question A28)¹³, the EAG notes that the differences at both data cutoffs did not meet the predetermined 10-point threshold to be considered clinically meaningful. Furthermore, low PRO completion rates may lead to the overestimation of HRQoL outcomes and should therefore be interpreted with caution.

Figure 5: GHS/QoL and physical functioning in the overall population (reproduced from CS, Figure 7)



Abbreviations: C, cycle; CI, confidence interval; D, day; GHS, global health status; LS, least squares; QoL, quality of life
 Note: Scheduled visits with <10 patients in either arm, unscheduled visits, and off-treatment visits were not included in the analysis.

Table 12: GHS/QoL and physical functioning in the overall population (adapted from CS, pg. 53 and CSR, pg. 96)

HRQoL	Primary cutoff (04 Jan 2021)	Final cutoff (03 Oct 2023)
Overall LS mean changes from baseline for GHS/ QoL, difference (95% CI)	7.81 (3.30-12.33)	
Overall LS mean changes from baseline for physical functioning, difference (95% CI)	8.26 (4.29-12.22)	

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; GHS, global health status; LS, least squares; QoL, quality of life

3.3.3 Subgroup analyses

3.3.3.1 Pre-specified sub-group analyses

Pre-specified sub-group analyses of OS and PFS included comparisons of age groups, race, number of lines of prior therapy, disease status, time after progressing from prior platinum therapy, IC chemotherapy prior to randomisation, histology (according to Interactive Web Response System [IWRS] and electronic data capture [EDC]), geographical region, ECOG (according to IWRS and EDC) and prior bevacizumab use (according to IWRS and EDC). These sub-group analyses were provided by the company for PFS in the CS. Some of the subgroup analyses for OS presented in Table 13 were provided at the clarification stage as they were inadvertently omitted from the CS (clarification response A23 and A26).¹³ The available subgroup analyses for OS and PFS are shown in Table 13 and Table 14 respectively. The benefit of cemiplimab versus chemotherapy in terms of OS and PFS appears to be consistent across prespecified subgroups: although small sample sizes in some subgroups (such as older patient groups (65 years), patients in Japan, patients who have progressed >6 months after prior platinum therapy, recurrent/persistent disease) resulted in broader CIs; the results of those analyses should therefore be interpreted with appropriate caution. Comparisons of OS and PFS HRs for the subgroups corresponding to investigator's choice of chemotherapy showed some variation and non-significant effects, however the subgroups with non-significant HRs similarly had small numbers of patients (topotecan, irinotecan, and vinorelbine) and should also be interpreted with caution.

Table 13: OS pre-specified sub-group analyses (constructed from CS Figure 10 and clarification response A26)

	Cemiplimab (Events/Total)	Chemo (Events/Total)	HR (95% CI)
All patients	237/304	256/304	0.665 (0.555-0.796)
Age group 1			
<65	211/269	222/264	0.664 (0.548-0.806)
>=65	26/35	34/40	0.587 (0.334-1.033)
Age group 2			
<65	211/269	222/264	0.664 (0.548-0.806)
>=65 and <75	21/30	24/29	0.587 (0.300-1.147)
>=75	5/5	10/11	0.362 (0.073-1.803)
Race			
White	151/193	164/192	0.672 (0.536-0.841)
Non-white	84/107	86/105	0.661 (0.480-0.911)
#lines of prior systemic therapy for r/m disease			
1 line	136/177	147/169	0.580 (0.455, 0.739)
>1 line	99/124	109/135	0.794 (0.599, 1.052)
Disease status			
Metastatic	223/284	245/290	0.664 (0.552, 0.799)
Recurrent/persistent	14/20	11/14	0.880 (0.373, 2.078)
Time of progression after prior platinum therapy			
<=6 months	208/265	229/267	0.666 (0.550, 0.807)
> 6 months	25/34	21/31	0.700 (0.368, 1.332)
Investigator choice chemo prior to randomisation			
Pemetrexed	91/119	98/111	0.614 (0.456, 0.827)
Topotecan	15/20	13/21	0.593 (0.247, 1.421)
Irinotecan	20/26	14/19	0.833 (0.384, 1.809)
Gemcitabine	83/108	101/121	0.708 (0.522, 0.960)
Vinorelbine	28/31	30/32	0.844 (0.476, 1.497)
Histology per IWRS			
SCC	186/239	201/238	0.698 (0.570-0.855)
Non-SCC	51/65	55/66	0.552 (0.372-0.819)
Histology per EDC			
SCC	187/240	197/233	0.684 (0.558-0.838)
Non-SCC	50/64	59/71	0.598 (0.404-0.886)
Geographic region group 1			
North America	21/32	26/34	0.523 (0.290-0.941)
Asia	66/83	67/83	0.625 (0.439-0.892)
Rest of world	150/189	163/187	0.705 (0.564-0.883)
Geographic region group 2			
Japan	23/29	22/27	0.887 (0.491-1.606)
Outside of Japan	214/275	234/277	0.652 (0.540-0.788)
ECOG status per IWRS			
0	105/146	119/146	0.568 (0.431-0.749)
1	132/158	137/158	0.736 (0.576-0.941)

ECOG status per EDC			
0	101/142	113/141	0.585 (0.441, 0.777)
1	136/162	143/163	0.716 (0.561, 0.913)
Prior bevacizumab use per IWRS			
Yes	109/149	118/147	0.600 (0.459, 0.785)
No	128/155	138/157	0.750 (0.585, 0.960)
Prior bevacizumab use per EDC			
Yes	107/148	120/149	0.599 (0.458, 0.784)
No	130/156	136/155	0.756 (0.590, 0.968)

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EDC, Electronic Data Capture; HR, hazard ratio; IWRS, Interactive Web Response System; SCC, squamous cell carcinoma

Table 14: PFS pre-specified sub-group analyses (reproduced from CS Figure 11)

	Cemiplimab (Events/Total)	Chemo (Events/Total)	HR (95% CI)
All patients			
Age group 1			
<65			
>=65			
Age group 2			
<65			
>=65 and <75			
>=75			
Race			
White			
Non-white			
#lines of prior systemic therapy for r/m disease			
1 line			
>1 line			
Disease status			
Metastatic			
Recurrent/persistent			
Time of progression after prior platinum therapy			
<=6 months			
> 6 months			
Investigator choice chemo prior to randomisation			
Pemetrexed			
Topotecan			
Irinotecan			
Gemcitabine			
Vinorelbine			
Histology per IWRS			
SCC			
Non-SCC			
Histology per EDC			
SCC			

Non-SCC			
Geographic region group 1			
North America			
Asia			
Rest of world			
Geographic region group 2			
Japan			
Outside of Japan			
ECOG status per IWRS			
0			
1			
ECOG status per EDC			
0			
1			
Prior bevacizumab use per IWRS			
Yes			
No			
Prior bevacizumab use per EDC			
Yes			
No			

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EDC, Electronic Data Capture; HR, hazard ratio; IWRS, Interactive Web Response System; SCC, squamous cell carcinoma

3.3.3.2 *PD-L1 < 1% and PD-L1 ≥ 1% sub-group analyses*

Subgroup analyses of PD-L1 < 1% versus PD-L1 ≥ 1% were not presented explicitly in the CS or supporting documents but were provided by the company in clarification response, Appendix 1.¹³ Patients in the EMPOWER Cervical-1 trial were enrolled irrespective of their PD-L1 status. Therefore, collection and testing of samples for PD-L1 status was not required for entry into the trial. PD-L1 status was assessed retrospectively using pre-treatment samples with the use of archival samples allowed to avoid delay in treatment (clarification response A17) and was not a pre-specified subgroup analysis.¹³ Only 61% (371 out of 608) of patients had samples available for PD-L1 testing of which only 68% (254 out of 371) were stained within the assay manufacturer's recommended six month stability period. In previous published analyses of PD-L1 subgroups, the smaller PD-L1 tested population was used (i.e., samples testing within the 6-month window). However the company in clarification response A17 highlighted that they received further recommendation from NHS gynaecologic consultant oncologists that samples would be tested irrespective of the time between sample collection and staining.¹³ Therefore, only the PD-L1 sub-group analyses corresponding to the larger sample (n=371 PD-L1 tested samples) are presented here.

The proportion of PD-L1 < 1% and PD-L1 ≥ 1% patients (with samples tested any time after collection) appeared to be balanced across both arms, see Table 15. The OS and PFS HRs are presented in Table

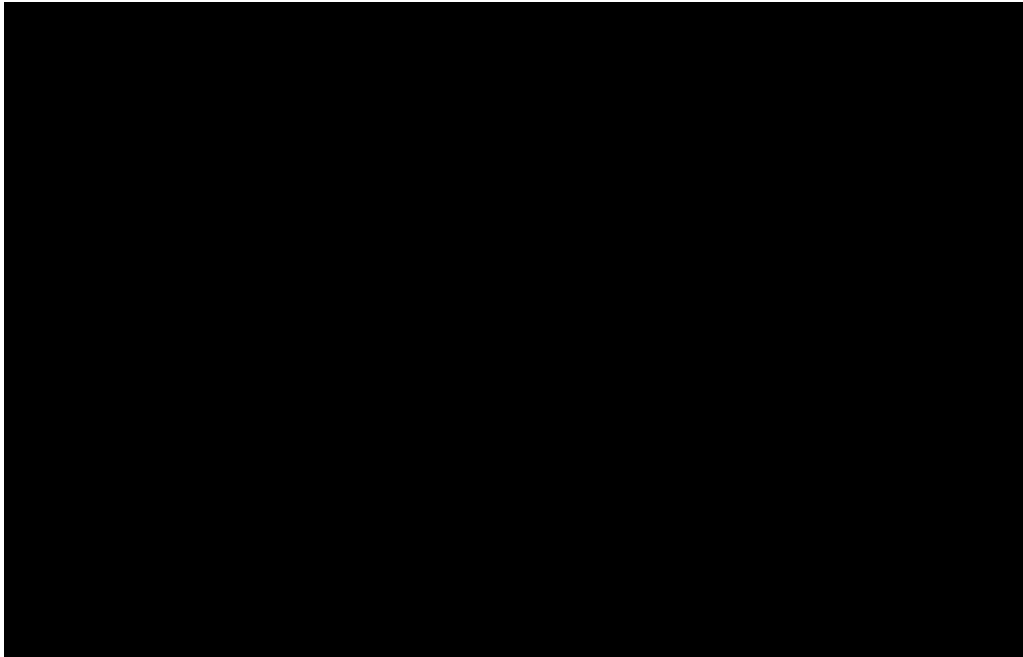
15 and the OS and PFS KM curves for the PD-L1 < 1% and PD-L1 ≥ 1% sub-groups presented in Figure 6 and Figure 7 respectively. The OS HRs in both the PD-L1 < 1% and PD-L1 ≥ 1% groups demonstrate that there is a statistically significant clinical benefit of cemiplimab compared to chemotherapy alone in terms of OS in both groups. The associated p-value for the OS interaction effect suggests there is no statistically significant difference in OS HR between these groups. The PFS HR for the PD-L1 ≥ 1% group similarly supports the statistically significant benefit of cemiplimab compared to chemotherapy alone in terms of PFS. However, in the PD-L1 < 1% group the 95% CI of the PFS HR spans 1, indicating a clinical effect that is not statistically significant. Given that these analyses use a sub-proportion of the patients from the EMPOWER Cervical-1 trial and thus have a reduced number of patients these analyses should therefore be interpreted with appropriate caution.

Table 15: Comparison of HRs for the PD-L1 sub-groups using samples tested at any time since collection (adapted from clarification response A18, Table 1)

Population	n (Cemiplimab)	n (chemotherapy)	OS HR	OS interaction effect p- value	PFS HR	PFS interaction effect p- value
PD-L1 < 1%						
PD-L1 ≥ 1%						

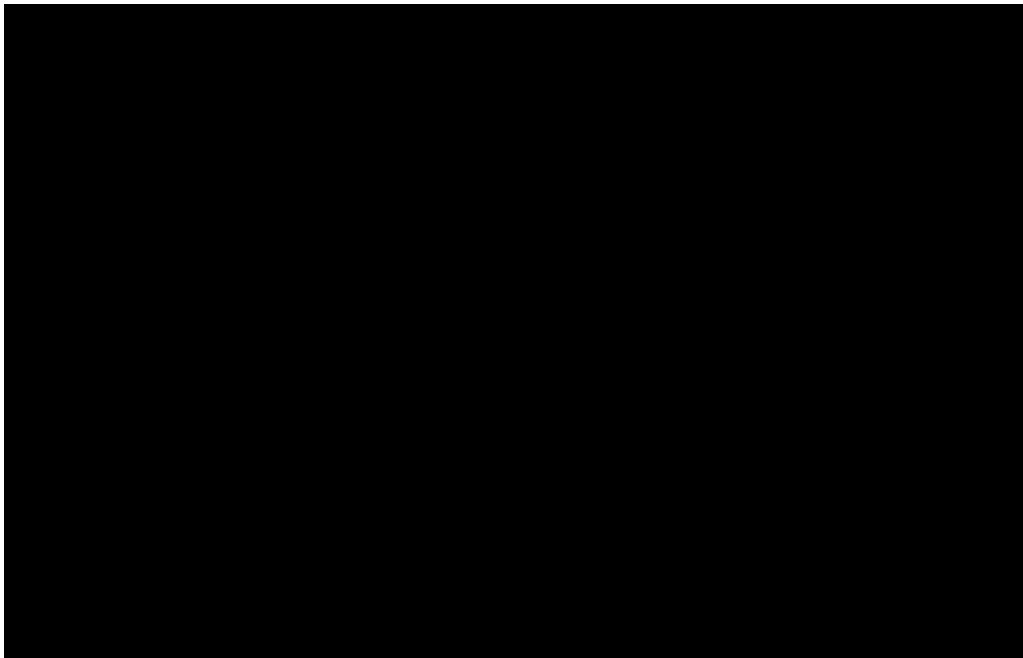
Abbreviations: OS, overall survival; HR, hazard ratio; PFS, progression-free survival; PD-L1, Programmed cell death-ligand 1

Figure 6: OS Kaplan-Meier curves for cemiplimab and chemotherapy PD-L1 sub-groups (reproduced from clarification response, Figure 1)



OS – overall survival; PD-L1 - Programmed cell death-ligand 1

Figure 7: PFS Kaplan-Meier curves for cemiplimab and chemotherapy PD-L1 sub-groups (reproduced from clarification response, Figure 1)



PFS – progression-free survival; PD-L1 - Programmed cell death-ligand 1

3.3.4 Safety

This section presents the main safety evidence from the CS and the CSR, based on the safety population comprising all randomised patients who received at least one dose of the assigned therapy.^{1, 40} As a result, 590 patients were included in the safety population: 300 in the cemiplimab treatment arm and 290 in the chemotherapy arm.

Patients in the cemiplimab group received a longer median exposure of 15.2 (range: 1.4 to 107.7) weeks compared to the chemotherapy group, and 38 patients completed the full planned 96-week course of therapy (

Table 16). Treatment-emergent adverse events (TEAEs) resulting in discontinuation of trial treatment occurred in 27 patients (9.0%) receiving cemiplimab and in 15 patients (5.2%) receiving chemotherapy.

Table 16: Treatment discontinuation (reproduced from CS, Table 7)

	Cemiplimab (N=304)	Chemotherapy (N=304)
Randomized but Never Treated, n (%)	5 (1.6%)	13 (4.3%)
Treatment ongoing, n (%)	0	0
Off treatment, n (%)	299 (98.4%)	291 (95.7%)
Treatment completed (per study protocol)	38 (12.5%)	0
Treatment discontinued	261 (85.9%)	291 (95.7%)
Primary reason for treatment discontinuation		
Adverse event*	28 (9.2%)	15 (4.9%)
Death	14 (4.6%)	18 (5.9%)
Non-compliance with study drug(s)	0	2 (0.7%)
Subject decision	8 (2.6%)	10 (3.3%)
Physician decision	0	2 (0.7%)
Disease progression	208 (68.4%)	233 (76.6%)
Withdrawal of consent	3 (1.0%)	10 (3.3%)
Other	0	1 (0.3%)

Source : Oaknin *et al.* 2025 (Suppl)

Note: * discontinuations due to adverse events not adjusted for treatment exposure.

The frequency of AEs is shown in Table 17. Most patients in both groups experienced AEs of any grade (89.7% of the patients who received cemiplimab and in 91.7% of those who received chemotherapy) (Table 17Error! Not a valid bookmark self-reference.). The most common AEs were anaemia, nausea, fatigue, vomiting, constipation, decreased appetite. The SmPC¹⁵ reported that the most common adverse reactions (listed in descending order of frequency) experienced by patients treated with cemiplimab monotherapy were fatigue, musculoskeletal pain, rash, diarrhoea, anaemia, nausea, decreased appetite, pruritus, constipation, abdominal pain, upper respiratory tract infection, and cough.

Asthenia	35 (11.7%)		44 (15.2%)	
Diarrhoea	34 (11.3%)		39 (13.4%)	
Arthralgia	33 (11.0%)		8 (2.8%)	
Back pain	32 (10.7%)		28 (9.7%)	
Abdominal pain	30 (10.0%)		33 (11.4%)	
Neutropenia	6 (2.0%)		45 (15.5%)	

* None of the AEs leading to death were considered by the treating investigator to be related to cemiplimab.

†The events are listed in descending order of frequency in the cemiplimab group. The data are not exposure-adjusted.

Source: Tewari *et al.* 2022 Final Clinical Study Report to reflect final analysis;⁴⁰ Oaknin *et al.* 2025

3.3.5 Additional evidence

In addition to the EMPOWER-Cervical-1 trial, the CS provided supporting evidence from an RCT from Uzbekistan (reported as a conference abstract)²⁴ and from real-world studies in the UK,²⁵ Italy,²⁷ and Poland²⁶ (identified by the EAG). The conference abstract reported results from a trial (n=180) comparing cemiplimab with physician's choice chemotherapy in patients whose disease progressed after first-line platinum-containing chemotherapy, regardless of CPS status. The study showed improvements in OS, PFS, and response rates that were broadly consistent with the EMPOWER-Cervical-1 study. For further details see CS, Section 2.9.1.¹ Interpretation is limited by the absence of a full peer-reviewed publication, incomplete reporting, lack of trial registration details and full investigator contact details, thereby preventing further verification or information retrieval.

Real-world evidence from the UK (a single-centre case series of 28 patients),²⁵ Italy (nominal use programme including 128 patients across 12 centres),²⁷ and Poland (37 patients treated under a national rescue access programme)²⁶ also showed outcomes in OS, PFS, and response rates broadly in line with the pivotal trial, including for patients with ECOG PS 2. For further details see CS, section 2.9.2 and the company's clarification response to question A10.^{1, 13} While these data provide supportive evidence, interpretation is limited by small sample sizes, short or immature follow-up, and the non-comparative observational design.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The CS states that “*no indirect treatment comparison versus chemotherapy is required, as direct evidence versus the only relevant comparator (i.e. chemotherapy) is available from the pivotal RCT*”. Whilst the EAG agreed that an indirect treatment comparison was not relevant when limiting the comparators to single-agent chemotherapy, the EAG considered that this approach would have been necessary had the CS provided a comparison against tisotumab vedotin.

3.5 Critique of the indirect comparison or multiple treatment comparison

Not applicable as an indirect comparison or multiple treatment comparison was not presented in the CS.

3.6 Additional work on clinical effectiveness done by the EAG

The EAG has not conducted any additional clinical effectiveness analyses. The EAG has conducted further survival analyses using the PD-L1 subgroup specific data provided by the company in response to clarification,¹³ but these are described in Section 4.2.6.2, as they were conducted to inform the economic analysis.

3.7 Conclusions of the clinical-effectiveness section

The pivotal clinical effectiveness evidence for cemiplimab is derived from a single international, multicentre, open-label, randomised phase III trial, EMPOWER-Cervical-1. This study compared cemiplimab with investigator's choice of single-agent chemotherapy in adult women with r/m CC whose disease had progressed after platinum-containing therapy. Between July 2017 and August 2020, 608 patients were randomised 1:1 across 97 centres in 14 countries, including two sites in England. OS was the primary endpoint and was aligned with the NICE final scope, with PFS, ORR, PROs and safety assessed as secondary endpoints.

The EMPOWER-Cervical-1 trial was generally well conducted and was judged by both the company and the EAG to be at low risk of bias for the primary outcome of OS. Although the study was open-label, OS is an objective endpoint and is unlikely to be significantly influenced by the lack of blinding. Randomisation appears to have been effective, with no clinically meaningful imbalances between treatment arms at baseline. The EMPOWER Cervical-1 trial found that cemiplimab significantly improved OS compared with investigator's choice chemotherapy. At final analysis (data cut-off 3 October 2023; median follow-up 47.3 months), cemiplimab was associated with a 3.2-month improvement in median OS compared with chemotherapy (11.7 vs 8.5 months) in the overall population, corresponding to a 33% reduction in the hazard for death (HR: 0.67, 95% CI: 0.56 to 0.80; $p < 0.00001$). However, the magnitude of benefit should be interpreted with caution, as certain trial design features may have favoured the cemiplimab arm, including allowance for treatment beyond progression and retreatment in a small minority of patients, which would fall outside the licenced indication. There were also statistically significant improvements with cemiplimab compared with chemotherapy, in several secondary outcomes, including PFS (HR, 0.741; 95% CI: 0.62–0.88; one-sided $P = 0.0003$) and ORR (odds ratio 3.1; 95% CI: 1.8, 5.5). However, PFS and tumour response outcomes were investigator-assessed and were not assessed by BICR, increasing the risk of detection bias for these secondary endpoints. In addition, as described in Section 4.2.6, testing of the proportional

hazards assumption, which underpins the evaluation and interpretation of a constant HR, suggested that this assumption may not hold for OS and PFS. Therefore, assessment of cemiplimab effectiveness relative to chemotherapy should not be based on the OS and PFS HRs alone.

In the cemiplimab arm, pseudo-progression was considered due to this being a phenomenon frequently associated with immunotherapy treatment. Treatment could continue beyond suspected pseudo-progression given that specific criteria were met and a post hoc analysis of the patients who continued treatment beyond their documented progression versus those who did not was conducted. No significant differences in OS between these groups were identified. The median OS in the groups treated beyond the documented progression events and those who were not treated beyond progression was 13.9 months (95% CI: 11.7, 17.9) and 10.5 months (95% CI: 8.2, 12.9). However, these results are from a post hoc analysis of a subgroup within the trial and should be interpreted with appropriate caution. As pseudo-progression was not considered to be relevant for the chemotherapy arm, all documented progressions that met the RECIST criteria in the chemotherapy arm were counted as true progressions which incurred cessation of treatment.

Pre-specified subgroup analyses were conducted, as summarised in Section 3.3.3.1, these analyses largely demonstrated clinical benefit of cemiplimab compared to chemotherapy (in terms of OS and PFS) within these subgroups, with overlapping 95% CIs. As expected, the subgroups with lower numbers of participants were associated with greater uncertainty and broader 95% CIs. A post hoc exploratory analysis of PD-L1 < 1% and PD-L1 ≥ 1% groups was conducted using retrospectively tested archived samples. Enrolment into the EMPOWER Cervical-1 trial did not require a PD-L1 test result, due to the intended use of cemiplimab across all PD-L1 status patients. As a result, not all participants in the EMPOWER Cervical-1 trial had an evaluated PD-L1 status, and thus these subgroup analyses do not utilise the entire trial population. Only 371 out of 608 patients had tested samples, with 134 of these corresponding to the PD-L1 < 1% group and 237 in the PD-L1 ≥ 1% group. Within the subgroups, there was no indication of imbalance between the cemiplimab and chemotherapy arms. The HRs for OS for the PD-L1 < 1% and PD-L1 ≥ 1% groups were [REDACTED] and [REDACTED] respectively. The HRs for PFS for the PD-L1 < 1% and PD-L1 ≥ 1% groups were [REDACTED] and [REDACTED] respectively. No significant differences in efficacy (OS and PFS) between PD-L1 status groups was found. This comparison of PD-L1 status groups was conducted as an exploratory analysis and uses smaller sample sizes, therefore these comparisons may be underpowered which may lead to greater uncertainty and broader CIs. As such, these results should be interpreted with appropriate caution.

Patient-reported outcomes were also collected in an open-label context, with completion rates declining substantially over time due to treatment discontinuation and disease progression. As a result, later quality-of-life estimates are likely to be based on a progressively smaller and more selected subset of patients who were well enough to complete the HRQoL questionnaires.

The safety profile in the EMPOWER Cervical-1 trial indicates that although AEs were common, cemiplimab was generally tolerable and manageable for patients with r/m CC. Despite a longer median duration of exposure to cemiplimab (15.2 weeks) compared with chemotherapy (10.1 weeks), patients receiving cemiplimab experienced similar rates of AEs of any grade to those who received chemotherapy (89.7% vs 91.7%), and lower rates of grade 3 or higher AEs (47.0% vs 53.8%), treatment-related AEs (57.3% vs 81.7%) or AEs leading to dose delay or infusion interruption (■% vs ■%). The most common TEAEs of any grade, regardless of attribution, were anaemia (25.7% vs. 44.1%), nausea (19.0% vs. 34.1%), fatigue (17.0% vs. 15.5%), vomiting (16.7% vs. 23.4%), constipation (15.0% vs. 20.0%), and decreased appetite (15.3% vs. 15.9%) in the cemiplimab and chemotherapy groups, respectively.

■
■
■ Although a small number of patients in the trial (5 in the cemiplimab arm and 2 in the chemotherapy arm) experienced AEs leading to death (grade 5), none of the deaths in the cemiplimab arm were considered by the treating investigator to be related to cemiplimab. Chemotherapy was reported to be related to the deaths of 2 (0.7%) of patients in the chemotherapy group.

Immunotherapy drugs such as cemiplimab tend to cause a different pattern of AEs from those seen with chemotherapy. While some AEs seen with chemotherapy are less likely with immunotherapy, immunotherapy can cause immune-related AEs in some people. Immune-related AEs, regardless of attribution, occurred in ■% of patients receiving cemiplimab and ■% of those receiving chemotherapy. Most of these events in the cemiplimab group were grade 1 or 2: with ■ patients (■%) experiencing grade ≥ grade 3 events compared with ■ patients (■%) in the chemotherapy group.

In general, the EAG's main concern with the clinical evidence is its limited applicability and generalisability to current UK practice. In the EMPOWER Cervical-1 trial, most patients had experienced disease progression within 6 months of prior platinum-based therapy, leaving uncertainty about the applicability of the evidence to patients relapsing more than 6 months after prior platinum treatment. Additionally, patients with an ECOG performance status greater than 1 were excluded from the trial, limiting generalisability to less fit patients commonly seen in routine practice, although the CS

does present some supportive real-world evidence, including patients with ECOG PS 2. Finally, cemiplimab is expected to be used as a second-line treatment in patients who have not received prior immunotherapy, representing a narrower subset of the full licensed population. While the marketing authorisation is not restricted by PD-L1 status, the CS suggests that routine practice will be dominated by PD-L1-negative patients (CPS <1), as $\geq 95\%$ of PD-L1-positive patients (CPS ≥ 1) are now offered first-line pembrolizumab-based therapy. Consequently, the EMPOWER-Cervical-1 trial evidence may not fully reflect anticipated routine practice, as the trial excluded patients previously treated with anti-PD-L1 agents and did not stratify by PD-L1 status.

4 COST EFFECTIVENESS

4.1 Critique of the review of cost-effectiveness evidence

4.1.1 Search strategy

Appendices E and F of the CS report the searches for the SLR of economic evidence and HRQoL studies, respectively.¹ Searches meet the minimum requirements expected by NICE in terms of databases and sources of grey literature (conferences, HTA reports etc). As with the clinical SLR, searches were completed in multiple phases between 2020 and 2025 and are reported with a single PRISMA flowchart for each review.

Once again, MEDLINE has only been searched as part of a multi-file search of Embase.com, which is likely contrary to the intended use of the Canadian Agency for Drugs and Technologies in Health filters applied to identify eligible types of study (though as the cited web page from which the filters were taken no longer exists, it was not possible for the EAG to confirm this). For future systematic reviews, the EAG would encourage the company to search databases one at a time, adapting the search strategy to make the best use of each source and only using filters as advised by their published validation study. However, since it is not possible within the short timelines of the present TA for the EAG to repeat the study selection process, it is unable to ascertain whether any relevant evidence was missed.

4.1.2 Identified studies

The company identified four studies which included an economic evaluation in a population of patients with r/m CC (Liu *et al.*,⁴¹ Huo *et al.*,⁴² Phippen *et al.*,⁴³ and Shi *et al.*⁴⁴). However, only two of these studies addressed second-line treatment, with Huo *et al.* addressing previously treated patients and Liu *et al.* addressing patients previously treated specifically following platinum-based treatment.^{41, 42} Liu *et al.* compared cemiplimab to single-agent chemotherapy, whilst Huo *et al.* compared tisotumab vedotin to single-agent chemotherapy.^{41, 42} The other two studies addressed patients having first-line treatment for r/m CC and therefore the treatments compared were not relevant for patients having second-line treatment.^{43, 44} The four included studies are described in Table 18. All of the included studies related to a United States setting and used a third-party payer perspective. The EAG has converted both the cost of interventions and the ICER to £ Sterling using the online Campbell & Cochrane Economics Methods Group and the EPPI (CCEMG-EPPI) Centre cost conversion tool.⁴⁵

Table 18: Summary list of published cost-effectiveness studies (adapted from CS, Table 17)

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)	Comments / relevance to decision problem
Liu 2023 ⁴¹	2023	Cost-utility analysis which the authors described as a Markov model with survival based on a partitioned survival analysis.	Patients with recurrent cervical cancer previously treated with platinum-based chemotherapy. The mean age of the patients was not reported.	Cemiplimab: 1.704	Cemiplimab: \$141,700 (£100,568)*	\$111,212 (£78,930)*	Same indication. US-based model with efficacy inputs based on aggregate published efficacy data, and non-cervical cancer utilities
				Chemotherapy: 1.107	Chemotherapy : US \$75,296 (£53,439)*		
Huo 2024 ⁴²	2023	Cost-utility analysis which the authors described as a Markov model with survival based on a partitioned survival analysis.	Patients with a median age of 50 years with previously treated r/m CC.	Tisotumab vedotin: 1.15	Tisotumab vedotin: \$293,641 (£203,787)*	\$839,108 (£582,341)*	Same indication. US-based model with efficacy inputs based on aggregate published efficacy data, and non-cervical cancer utilities
				Chemotherapy: 0.90	Chemotherapy : \$86,862 (£60,282)*		
Phippen 2013 ⁴³	2012	Cost-utility analysis based on a decision tree structure.	Patients with inoperable recurrent cancer of the uterine cervix who have received prior chemoradiation	Not reported (Due to the lack of utility studies published at the time of model	Home hospice for all: \$10,890 (£10,019)*		Population and comparators not relevant to decision problem, US-based model with

				development the authors estimated that the QALY was 1 for all treatment options)	Single-agent chemotherapy with home hospice for all: \$15,818 (£14,553)*	\$44,392 (£40,842)*	utilities based on assumptions
					Selective chemotherapy: \$29,112 (£26,784)*	\$78,404 (£72,134)*	
					Standard doublet chemotherapy for all: \$33,368 (£30,699)*	\$275,630 (£253,587)*	
Shi 2022 ⁴⁴	2020	Cost-utility analysis with survival based on a partitioned survival analysis	Adults of at least 18 years of age with persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix who had not received systemic chemotherapy and were not amenable to curative treatment	Pembrolizumab: 2.23	Pembrolizumab: \$432,196 (£318,017)*		Both arms received chemotherapy (platinum with paclitaxel) with or without bevacizumab. Population and comparators not relevant to decision problem. US-based model with non-cervical cancer utilities
				Placebo: 1.50	Placebo: \$249,925 (£183,899)	\$247,663 (£182,234)*	

Notes *:The study's and the CS presented results in terms of US Dollars these have been converted to £ Sterling values using the online CCEMG-EPPI Centre cost conversion tool.⁴⁵

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; r/m CC, relapsed or metastatic cervical cancer; US, United States

4.1.3 Interpretation of the review

In CS, Section 3.1, the company does not provide any commentary on how the findings of the studies included in the review should be interpreted.¹ In CS, Appendix E, which reports the SLR of economic studies in full, the interpretation given for the two most relevant analyses presented by Liu *et al.* and Huo *et al.* is that cemiplimab is cost-effective in a US setting because the ICER falls under \$150,000 per QALY gained and tisotumab vedotin is not cost-effective in US setting because the ICER is above this threshold. However, the interpretation of these estimates within a UK context is not discussed. Instead the CS provides a *de novo* economic evaluation.

4.1.4 Critique of the company's review of published cost-effectiveness studies.

The EAG has some concerns regarding the presentation of the SLR findings within CS Section 3.1. Firstly, CS Appendix E describes a Japanese adaptation of the model reported by Lui *et al.* which concluded that cemiplimab was not found to be cost-effective in a Japanese setting (when applying a JPY15 million per QALY threshold),⁴⁶ which is not mentioned in the CS. Although this Japanese adaptation is only reported in abstract form, it is unclear why it is discussed alongside the study by Liu *et al.* in CS, Appendix E, but not mentioned at all in the CS, Section 3.1, given that conference proceedings reporting adaptations of the model described by Shi *et al.* are mentioned in the CS. In addition, the EAG notes that the full SLR in Appendix E describes the ICERs from Liu *et al.* for both the full EMPOWER Cervical-1 trial population and for the PD-L1 ≥ 1 subgroup. However, it does not comment on the ICERs in the PD-L1 < 1 subgroup reported by Liu *et al.* which were substantially higher than the cited threshold of \$150,000 per QALY.⁴¹ Secondly, there appears to be inconsistencies in the selection of studies that were considered relevant. Two studies in r/m CC populations were included in the four discussed in CS, Section 3.1, despite them examining first-line treatment.¹ However, another study by Richardson *et al.* identified in CS, Appendix E, was not discussed in the CS, Section 3.1, despite examining treatment sequences for patients having first-line treatment for r/m CC.⁴⁷ The EAG considers that this study does provide a relevant comparison, despite modelling patients starting first-line treatment. This is because it compares platinum-based chemotherapy with bevacizumab followed by chemotherapy to platinum-based chemotherapy with bevacizumab followed by cemiplimab.

Overall, the EAG considered that the company's presentation of the published cost-effectiveness literature to be potentially open to bias because there is not a clear logical rationale for selecting the four studies presented in CS, Section 3.1. However, given that none of the studies included in the full SLR reported in CS, Appendix E presented a relevant comparison conducted from a UK NHS and PSS perspective, the EAG considers that the company's decision to provide a *de novo* economic analysis is reasonable.

4.2 Critique of the submitted economic evaluation

As part of its submission to NICE,¹ the company submitted a fully executable model programmed in Microsoft Excel®. Section 4.2 provides a summary and critique of the methods of the economic evaluation submitted by the company, with results summarised in Section 5.1. Unless otherwise stated, the description and critique of the company's model provided here reflects the version submitted following the clarification request.¹³ The EAG's exploratory analyses to explore areas of uncertainty identified in the company's analysis are summarised in Section 5.2.

4.2.1 NICE reference case checklist

Table 19 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 2.

Table 19: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
The decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is narrower than the final NICE scope. ⁴⁸ The company's model excludes patients with prior immunotherapy. Following the clarification round, the company provided two subgroup analyses: a weighted PD-L1 < 1% and PD-L1 ≥ 1% subgroup, and an ECOG-adjusted PD-L1 < 1% subgroup. ¹³
Comparator	As listed in the scope developed by NICE	The economic analysis includes single-agent chemotherapy as the sole comparator: this is not consistent with the final NICE scope which also lists BSC and tisotumab vedotin monotherapy as comparators. The EAG's clinical advisors did not consider BSC to be a relevant comparator. However, for tisotumab vedotin, it is unclear whether this treatment will be part of established clinical practice at the time final guidance for this appraisal is published and therefore the EAG would have preferred the company to have provided a comparison against

Element of health technology assessment	Reference case	EAG comment on company's submission
		tisotumab vedotin (see Section 2.3.3. for further discussion).
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and Personal Social Services	Costs include those borne by the NHS and PSS.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for cemiplimab monotherapy versus single-agent chemotherapy. A full incremental analysis is not required as there is only a single comparator in the company's economic analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 33-year (lifetime) time horizon which the EAG considers to be sufficient.
Synthesis of evidence on health effects	Based on systematic review	PFS, OS, ToT and TEAEs for both treatment groups were informed by the final analysis of the EMPOWER Cervical-1 study which is the pivotal trial of cemiplimab monotherapy identified from the company's SLR. The EAG considers the data sources to be relevant to the decision problem.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Treatment-specific health-state utility values were based on the EQ-5D-3L mapped from the EORTC QLQ-C30 collected in the EMPOWER Cervical-1 study. ²³ A one-off QALY loss related to TEAEs was applied in the first model cycle in the scenario analysis.
Source of data for measurement of HRQoL	Reported directly by patients, carers or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	The economic model provides estimates of QALY shortfall which lead to a decision modifier of 1.7 (see Section 5.3.1).
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Drugs costs were valued at current prices using BNF 2025 ⁴⁹ and eMIT

Element of health technology assessment	Reference case	EAG comment on company's submission
	valued using the prices relevant to the NHS and PSS	2025. ⁵⁰ Other resource use costs were valued using estimates from the NHS Cost Collection 2024/25 ⁵¹ and the PSSRU 2024. ⁵²
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects were discounted at a rate of 3.5% per annum.

Abbreviations: BNF, British National Formulary; EAG, evidence appraisal group; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; eMIT, electronic market information tool; EQ-5D-3L, EuroQoL 5-Dimensions 3-Level; NHS, national health service; OS, overall survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; PFS, progression-free survival; QALY, quality adjusted life year; SLR, systematic literature review; TEAE, treatment emergent adverse events

4.2.2 Population

The population included in the company's economic model reflects the population of the EMPOWER Cervical-1 Study²³ which included patients with r/m CC who have progressed on or after platinum-based chemotherapy. At model entry, patients are assumed to have a mean age of 51.14 years and 100% are female. These characteristics are used to estimate general population mortality risks and to adjust utility values for increasing age. Patients are assumed to have a mean body weight of 63.87 kg and body surface area (BSA) of 1.66 m², based on the EMPOWER Cervical-1 study. Following the clarification round, the company provided two additional executable economic models exploring subgroup analyses: one based on a weighted population of PD-L1 < 1% and PD-L1 ≥ 1% patients, and one restricted to an ECOG-adjusted PD-L1 < 1% population.¹³ Further details are discussed in Sections 4.2.6.2 and 4.2.6.3.

4.2.3 Interventions and comparators

Intervention

The intervention evaluated within the economic analysis is cemiplimab monotherapy. The recommended dose of cemiplimab in adults is a flat dose of 350 mg every 3 weeks (Q3W) administered as an IV infusion over 30 minutes. Section 4.2 of the SmPC⁵³ states that cemiplimab can be administered until disease progression or unacceptable toxicity.

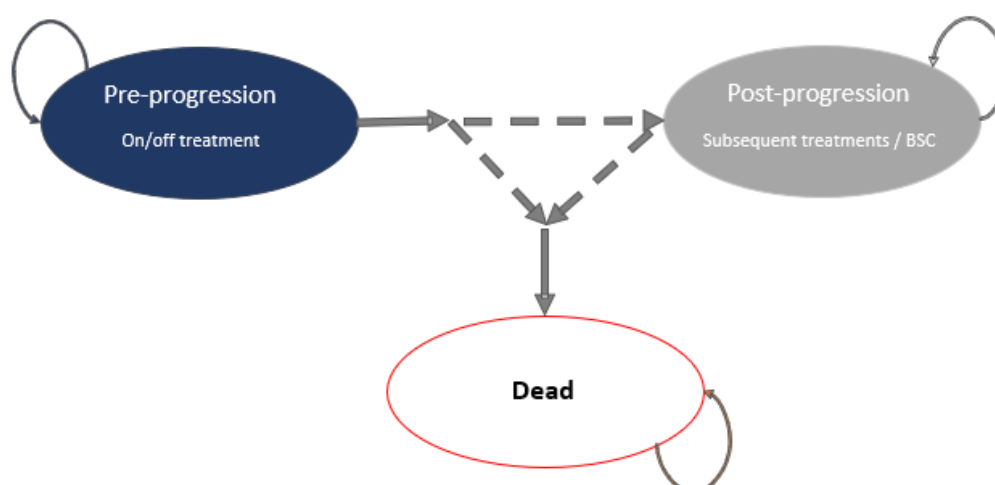
Comparator

The comparator is single-agent chemotherapy which is represented in the model by the 'basket' of investigator-chosen single agent chemotherapies offered in the EMPOWER Cervical-1 trial, which included: pemetrexed, gemcitabine, topotecan, irinotecan and vinorelbine. The dosing schedules and distributions of each treatment are based on the EMPOWER Cervical-1 study protocol³⁸ and presented in Table 20.

Chemotherapy	Distribution	Dosage	Route	Schedule
Pemetrexed	36.51%	500 mg/m ²	IV infusion	Day 1, Q3W
Gemcitabine	39.80%	1000 mg/m ²	IV infusion	Days 1 and 8, Q3W
Topotecan	6.91%	1 mg/m ²	IV infusion	Days 1-5, Q3W
Irinotecan	6.25%	100 mg/m ²	IV infusion	Days 1, 8, 15, and 22, Q6W
Vinorelbine	10.53%	30 mg/m ²	IV infusion	Days 1 and 8, Q3W

4.2.4 Model structure

Figure 8: Model structure (reproduced from CS, Figure 12)



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ToT cannot be higher than the cumulative probability of PFS at any timepoint, (ii) the cumulative probability of PFS cannot be higher than the cumulative probability of OS at any timepoint, and (iii) the per-cycle risk of death in the target population cannot be lower than that of age-matched general population. Patients are assumed to be in an end-of-life (EOL) state for the last month of post-progression survival. Costs and health utility values are assigned to each alive health state and weighted based on health state occupancy to calculate overall costs and QALYs. The cost-effectiveness of cemiplimab monotherapy versus single-agent chemotherapy was evaluated using pair-wise comparisons over a 33-year (lifetime) time horizon.

Key assumptions employed in the economic model

The company's base case model employs the following key assumptions:

- The average baseline characteristics of trial population (age, sex, body weight and BSA) adequately reflects the anticipated population in clinical practice.
- Single-agent chemotherapy is the only comparator for cemiplimab monotherapy.
- Clinical outcomes for the mix of single-agent chemotherapy options included in the EMPOWER Cervical-1 trial (pemetrexed, gemcitabine, topotecan, irinotecan and vinorelbine) are reflective of expected clinical outcomes for the single-agent chemotherapies used in clinical practice.
- Outcomes for patients receiving intervention and comparators are informed by EMPOWER Cervical-1 (final analysis).²³
- PFS and OS are modelled using the generalised gamma parametric survival models fitted to the data from each arm in EMPOWER Cervical-1.
- ToT is modelled using the log-normal parametric survival model fitted to the data from each arm in EMPOWER Cervical-1.
- Modelled PFS and OS probabilities are structurally unrelated to the receipt of subsequent treatments in the model.
- Following disease progression, patients receive a form of subsequent treatment, including active treatments, clinical trials or BSC.
- HRQoL is determined by the type of treatment and the presence or absence of disease progression. Patients receiving cemiplimab are assumed to have higher utility values than those treated with single-agent chemotherapy. In both treatment groups, the utility value for pre-progression health state is higher than that for the post-progression health state. Post-progression utility value for single-agent chemotherapy group is assumed to reflect a 10% reduction from pre-progression utility as observed in the cemiplimab arm of study. Utility values are assumed to decline with increasing age. An EOL utility is applied for the last month spent in the post-progression health state.

- Disutilities related to Grade ≥ 3 TEAEs resulting from cemiplimab or single-agent chemotherapy are not considered in the base case as these effects are assumed to have been captured within the treatment-specific utility values.
- Caregiver disutilities are not considered.
- Drug wastage is not included for both second- and subsequent-line treatments.
- Relative dose intensity (RDI) and frequencies of TEAEs from EMPOWER Cervical-1 are reflective of the RDI and TEAEs expected for treatments used in clinical practice.
- Additional costs associated with Grade ≥ 3 TEAEs are included as one-off values in the first model cycle. TEAEs related to subsequent treatments are not included in the model.
- Health state resource use depends on the type of treatment received, treatment discontinuation and the health status (pre-progression or post-progression or EOL). The resource use data were based on the company's clinical input.
- The decision severity modifier is assumed to be 1.7 based on the company's calculation of the absolute and proportional QALY shortfall (see Section 5.3.1).

4.2.4.1 EAG's critique of the model structure

The EAG considers the company's model structure to be generally appropriate. The EAG notes that the company did not apply a half-cycle correction and the EAG considers this to have a minimal impact on the ICER, given the one-week model cycle length. The EAG has some concerns regarding the company's approach in modelling ToT and modelling assumptions applied to health state utility values and resource use, and these issues are discussed in detail under the relevant critique sections later in the report.

4.2.5 Summary of evidence sources used to inform the company's model parameters

Table 21 summarises the evidence sources used to inform the parameters of the company's base case model. The derivation of the model parameter values using these sources is described in further details in the following sections.

Table 21: Summary of evidence sources used to inform the model parameters for the company's base case

Parameter type	Source
Patient characteristics	Mean age, body weight and BSA taken from EMPOWER Cervical-1 ²³
PFS, OS	Generalised gamma parametric survival model fitted to PFS and OS data for each arm of EMPOWER Cervical-1
ToT	Log-normal parametric survival model fitted to ToT data for each arm of EMPOWER Cervical-1
General population mortality risk	General population life tables for England and Wales, 2022-2024 ⁵⁴
AE frequencies	Grade ≥ 3 TEAEs from EMPOWER Cervical-1
Health state utility values	Health-state utility values based on the EORTC QLQ-C30 from the EMPOWER Cervical-1 study which are mapped to the EQ-5D-3L. Pre-progression utility value for each treatment group derived from the corresponding arm of EMPOWER Cervical-1. Post-progression utility value for cemiplimab group based on the combined post-progression mean score across arms of the study. Post-progression utility value for single-agent chemotherapy group assumed to reflect a ████ reduction from pre-progression utility as observed in the cemiplimab arm of study. EOL disutility for the last 30 days taken from Chevalier <i>et al.</i> ⁵⁵
General population utility	Hernández Alava <i>et al.</i> ⁵⁶
Drug acquisition costs	Treatment dosing schedules and RDI of both cemiplimab and comparator chemotherapies, as well as the distribution of comparator chemotherapies based on EMPOWER Cervical-1. Drug prices taken from BNF 2025 ⁴⁹ and eMIT 2025. ⁵⁰ PAS provided by the company for cemiplimab.
Drug administration costs	NHS Reference Costs 2024/25 ⁵¹
Health state costs, EOL costs and TEAE management costs	Resource use data for pre-progression, post-progression and EOL based on clinical input. ⁵⁷⁻⁶⁰ Unit costs taken from PSSRU 2024 ⁵² and NHS Reference Costs 2024/25 ⁵¹
Subsequent therapies following disease progression	Usage of therapies informed by clinical input. Treatment dosing schedules informed by the EMPOWER Cervical-1 ³⁸ protocol for topotecan and NHS chemotherapy protocols for all other treatments. ⁶¹⁻⁶⁵ Unit costs taken from eMIT 2025 ⁵⁰ and NHS Reference Costs 2024/25 ⁵¹

Abbreviations: BSA, body surface area; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; TEAE, treatment-emergent adverse event; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D-3L, Euroqol 5-Dimensions 3-Level; EOL, end-of-life; RDI, relative dose intensity; BNF, British National Formulary; eMIT, electronic market information tool; PAS, Patient Access Scheme; PSSRU, Personal Social Services Research Unit

4.2.6 Treatment effectiveness and extrapolation

In the company base case and scenarios, OS, PFS and ToT were estimated by fitting standard parametric curves to the cemiplimab monotherapy and single-agent chemotherapy arms IPD corresponding to the ITT population. All fits used data from the final data cut-off of the EMPOWER Cervical-1 clinical trial (3 October 2023).²³ Six standard parametric models (exponential, Weibull, log-normal, log-logistic,

Gompertz and generalised gamma) were initially fitted to the trial IPD, and at the clarification stage, fits for the two-parameter gamma model were also provided. The two-parameter gamma model was included for all subsequent fitting performed by the company. The company did not fit more complex models to any of the time-to-event (TTE) outcome data, such as piecewise fits or polynomials, as it was believed by the company that the standard parametric fits were appropriate and that the fitting of more complex models would have increased the risk of overfitting to the data.

For OS, PFS and ToT, the company evaluated whether joint or independent models should be employed through the assessment of Schoenfeld residuals plots, a statistical test of the proportional hazards assumption, quantile-quantile (QQ)-plots and assessment of model-specific diagnostic plots. These assessments can be found in CS Appendix L. For all TTE outcomes, it was deemed by the company that it was most appropriate to fit the models independently to the cemiplimab monotherapy and single agent chemotherapy groups due to the indication of non-proportional hazards. The EAG agrees with this conclusion and thus the joint models and diagnostics relating to this decision are not considered further within this report.

Selection of the base case parametric model for each TTE outcome was performed according to Technical Support Document (TSD) 14.⁶⁶ This included the assessment of the Akaike information criterion (AIC)⁶⁷ and Bayesian information criterion (BIC)⁶⁸ statistics and visual inspection of goodness of fit to the KM. For PFS and OS the company also considered the clinical/biological plausibility of the extrapolations based on clinical expert opinion (5 experts). Clinical expert opinion was collected in advisory board meetings and questionnaires, and the responses used to help inform the company's selection of models. The empirical hazard plots were also provided by the company for each TTE outcome, along with the hazards for the fitted models. However, these did not appear to have been used when selecting the appropriate model for use within the economic model, but for completeness these are included in the following sections.

The company provided two additional scenarios at the clarification stage which explicitly explored PD-L1 status subgroup efficacy.¹³ The treatment efficacy for these two scenarios was based on assessment of the following

- OS, PFS and ToT for the PD-L1 < 1% and PD-L1 ≥ 1% groups (using the larger PD-L1 tested group, which includes samples tested after 6 months n=371: n=237 PD-L1 ≥ 1% and n=134 PD-L1 < 1%),
- OS, PFS and ToT for the PD-L1 < 1% group (using the larger PD-L1 tested group, n=134) adjusted for ECOG status.

For both scenarios, standard parametric models were fitted independently to the cemiplimab monotherapy and single agent chemotherapy groups as for the ITT analysis. The company chose to use the same parametric models used in the base case (using the ITT population) for OS, PFS and ToT. The company justified this approach by stating that in these scenario analyses the number of patients is reduced and there is potentially an increased uncertainty when selecting the most appropriate model. The company provided further clarification at the factual accuracy and confidential information (FAC) check that it had based its decision by considering both the best fitting curves in the ITT population and the best fitting curves in the relevant subgroup.

In the company base case and scenarios PFS was constrained by OS and ToT constrained by PFS to avoid implausible crossing of the curves.

In the following sections the AIC/BIC statistics, visual comparisons of model fit vs KM curves and hazard plots are presented for the ITT population and the PD-L1 < 1% and PD-L1 ≥ 1% subgroups. The EAG does not consider the OS, PFS and ToT data used in the ECOG-adjusted scenario analysis further as the ECOG-weighted curves were sufficiently similar to the overall PD-L1 < 1% curves when appropriate parametric models were chosen, this is explained further in Section 4.2.6.5.

4.2.6.1 TTE outcomes (ITT population)

A summary of the company base case and scenario curve choices for OS, PFS and ToT when using the data from the ITT population are summarised below in Table 22. The rationale behind these choices is presented in the following sections.

Table 22: Summary of models used for TTE outcomes in the company base case and scenarios using the ITT dataset

	Cemiplimab	Single agent chemotherapy
OS	Base case: Generalised gamma Scenario(s): Log-normal	Base case: Generalised gamma Scenario(s): Log-logistic; log-normal
PFS	Base case: Generalised gamma Scenario(s): Log-normal	Base case: Generalised gamma Scenario(s): Log-normal
ToT	Base case: Log-normal Scenario(s): generalised gamma; KM; re-censoring of ToT data at 96-weeks fitted using log-normal	Base case: Log-normal Scenario(s): Generalised gamma

OS – overall survival; PFS – progression free survival; ToT – time on treatment

Overall survival

Comparisons of observed and predicted OS using parametric survival models for cemiplimab and single-agent chemotherapy are presented in Figure 9 and Figure 10, respectively. The AIC and BIC

statistics of the fitted parametric survival models for each group are shown in Table 23. Empirical hazard plots and corresponding hazard plots, produced by the company, of the parametric models for cemiplimab and single-agent chemotherapy are presented in Figure 11. The EAG notes that the formatting of the empirical hazard plots and corresponding model-predicted hazards makes them difficult to interpret and critically evaluate; however, they are included for completeness.

For the chemotherapy arm, the lowest AIC/BIC values were associated with the log-logistic model, followed by the log-normal and generalised gamma models (both within AIC/BIC 5 points, indicative of similar statistical fit).⁶⁹ These three models provided good visual fit to the KM curve, however clinical experts advised the company that the log-logistic model may provide extrapolations that were considered too optimistic for chemotherapies. All the company's clinical experts suggested that the generalised gamma model would be an appropriate and representative choice, and some of the experts also suggested the use of the log-normal distribution. Therefore, the generalised gamma was chosen for the company base case, and the log-normal and log-logistic models explored in scenario analyses as plausible alternatives when modelling OS for the single-agent chemotherapy arm.

The lowest AIC/BIC values for the cemiplimab arm corresponded to the log-normal model but the AIC/BIC values for the log-logistic and generalised gamma model fits were also within 5 points of the log-normal model, suggesting similar statistical fit to the data. The generalised gamma, log-logistic and log-normal curves were all deemed to provide superior fits compared with the alternative models. The company used clinical expert opinion, to further support this as experts believed that the Gompertz model was too optimistic and that the estimated survival proportion (3-4%) at 10 years according to the three candidate models was plausible. For consistency with the chemotherapy arm, the generalised gamma was chosen for the company base case, and the log-logistic model explored in a scenario analysis as a plausible alternative.

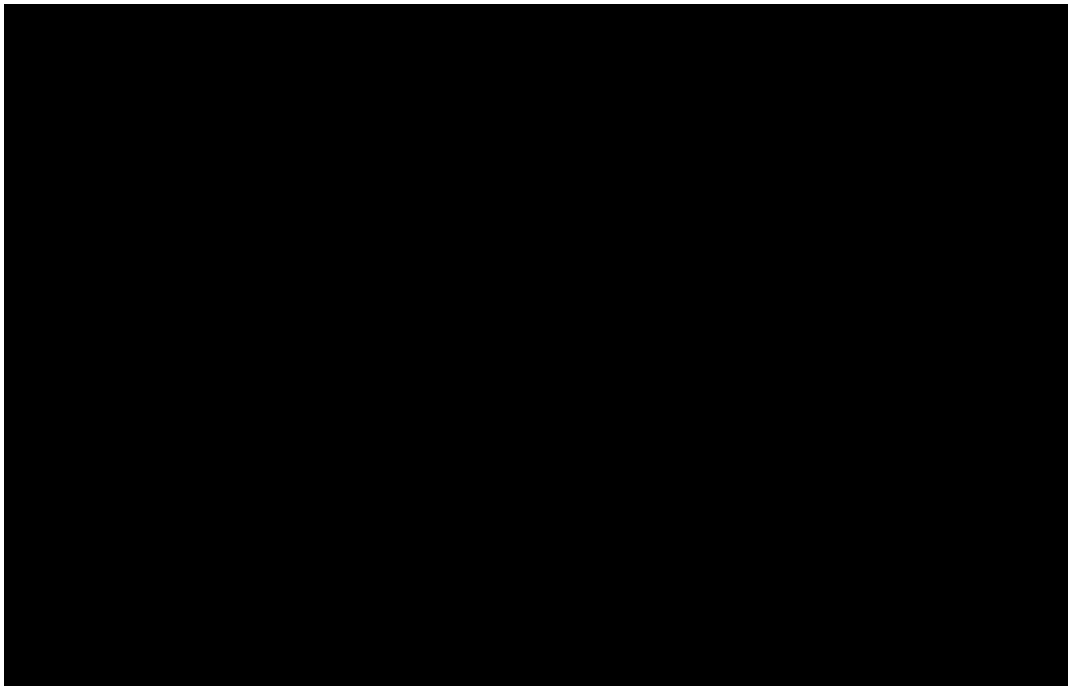
Table 23: AIC and BIC statistics for parametric survival models of OS (adapted from CS, Table 23)

Distribution	Cemiplimab		Single-agent chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	1916.4 (6)	1920.1 (5)	1823.0 (6)	1826.7 (5)
Weibull	1915.6 (5)	1923 (6)	1819.4 (5)	1826.8 (6)
Log-normal	1881.7 (1)	1889.1 (1)	1786.3 (2)	1793.7 (2)
Generalised gamma	1882.4 (2)	1893.6 (3)	1788.1 (3)	1799.2 (3)
Gompertz	1898.2 (4)	1905.7 (4)	1823.4 (7)	1830.8 (7)
Log-logistic	1884.4 (3)	1891.9 (2)	1780.8 (1)	1788.2 (1)
Gamma	1918.0 (7)	1925.4 (7)	1812.1 (4)	1819.5 (4)

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

Company's selected base case model highlighted in bold. Ranking provided in brackets.

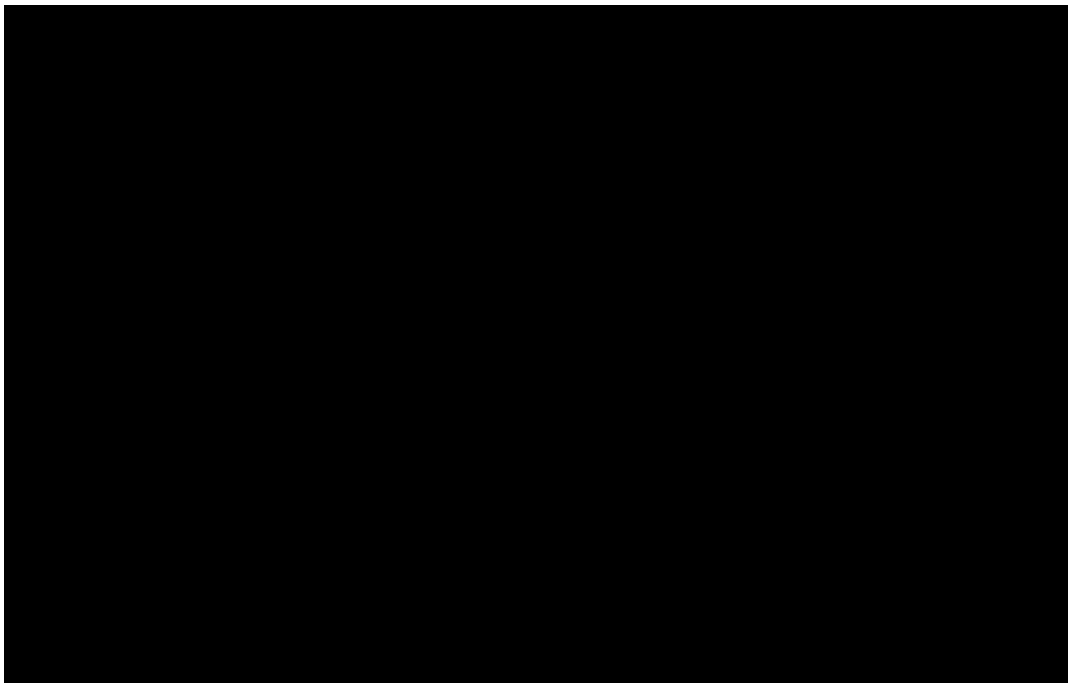
Figure 9: Observed and model-predicted OS, cemiplimab (plotted by the EAG)



OS, overall survival; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

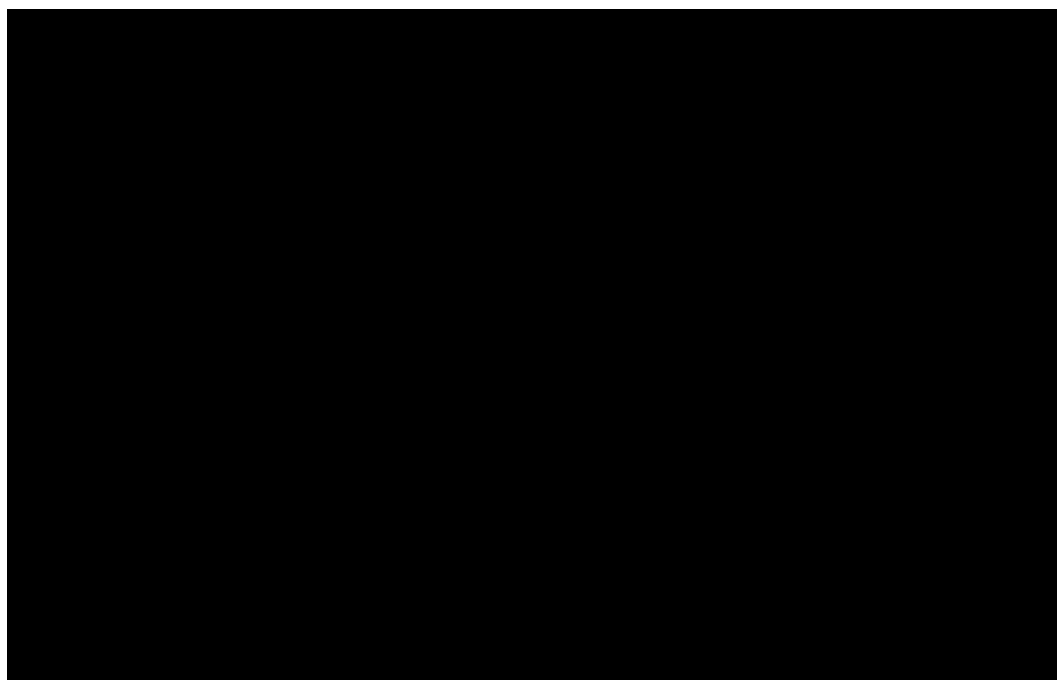
Figure 10: Observed and model-predicted OS, single-agent chemotherapy (plotted by the EAG)



OS, overall survival; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

Figure 11: Empirical and modelled hazard plots for OS, cemiplimab and chemotherapy arms (reproduced from CS Appendix L, Figure 8)



OS – overall survival; ITT – intention to treat; Ind – independently fitted; tx – treatment

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

Progression-free survival

Comparisons of observed and predicted PFS using parametric survival models for cemiplimab and single-agent chemotherapy are presented in Figure 12 and Figure 13, respectively. The AIC and BIC statistics of the fitted parametric survival models for each group are shown in Table 24. Empirical hazard plots and corresponding hazard plots of the parametric models for cemiplimab and single-agent chemotherapy are presented in Figure 14. The EAG notes that, as for the OS hazard plots, the formatting of the empirical hazard plots and corresponding model-predicted hazards makes them difficult to interpret and critically evaluate; however, they are included for completeness.

For both the cemiplimab monotherapy and single-agent chemotherapy arms, the generalised gamma model had the lowest AIC and BIC values and provided a good visual fit to the KM curves. The company’s clinical experts stated that PFS in the single-agent chemotherapy group would likely be close to zero at 5 years, and all standard parametric models were consistent with this clinical expert opinion. The company stated that one expert expressed their agreement with the 2% PFS at 2 years predicted by the generalised gamma and log-normal models. For cemiplimab, clinical experts believed that a “tail is expected” and thus did not believe the exponential or Weibull models to be representative of this expected behaviour. Clinical experts believed that the generalised gamma and Gompertz models were most plausible. However, given that the Gompertz model was not considered plausible in the single-agent chemotherapy group this was not considered to be an appropriate choice for the

cemiplimab arm. The company therefore chose the generalised gamma distribution for the base case analysis for both arms and tested the log-normal distribution in a scenario analysis as this model has the second lowest AIC/BIC values.

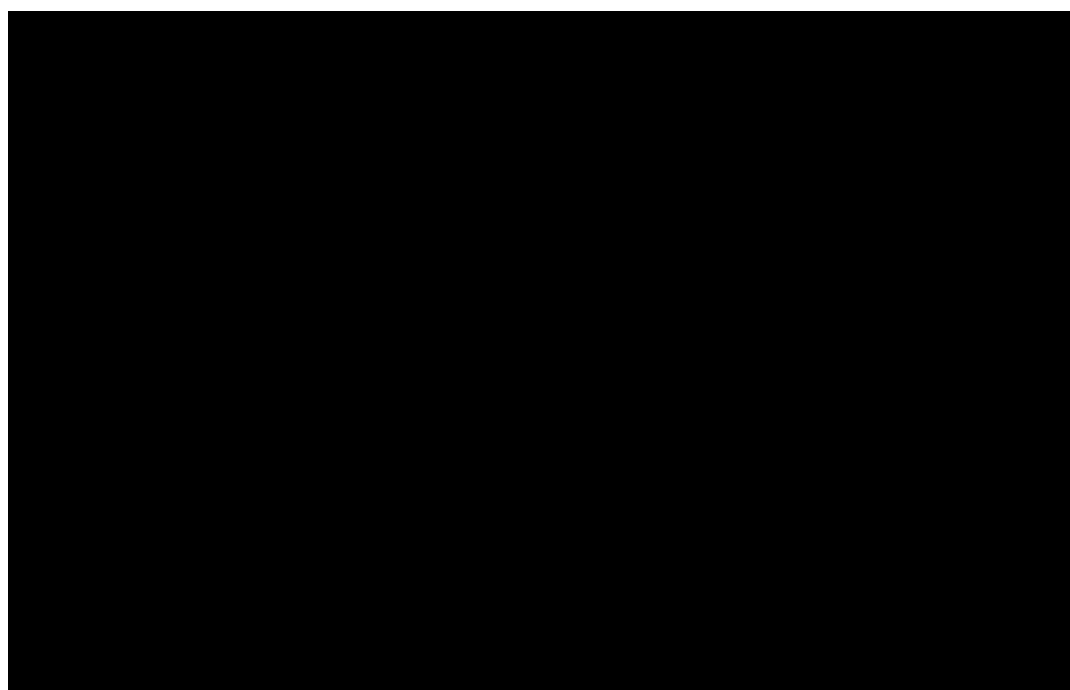
Table 24: AIC and BIC statistics for parametric survival models of PFS (adapted from CS, Table 25)

Distribution	Cemiplimab		Single-agent chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	1704.0 (7)	1707.7 (7)	1408.5 (6)	1412.2 (6)
Weibull	1670 .0(5)	1677.4 (5)	1396 (5)	1403.5 (5)
Log-normal	1581.5 (2)	1588.9 (2)	1340.7 (2)	1348.1 (2)
Generalised gamma	1538.7 (1)	1549.9 (1)	1336.7 (1)	1347.9 (1)
Gompertz	1690.3 (6)	1697.8 (6)	1383.3 (4)	1390.7 (4)
Log-logistic	1605.6 (4)	1613 (4)	1410 (7)	1417.4 (7)
Gamma	1583.5 (3)	1590.9 (3)	1353.1 (3)	1360.5 (3)

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

Company's selected base case model highlighted in bold. Ranking provided in brackets.

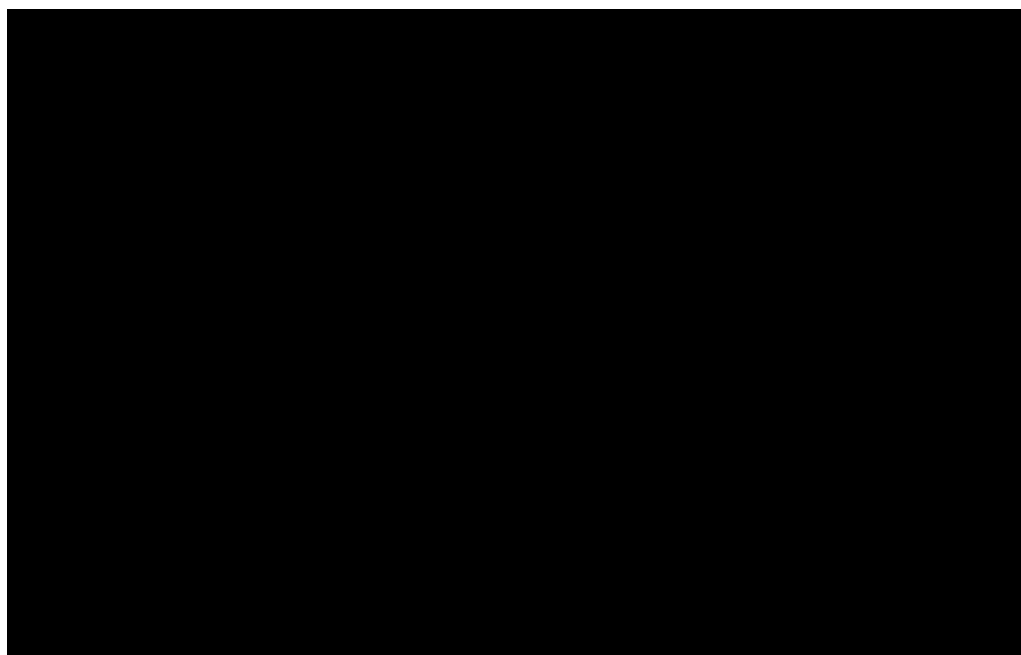
Figure 12: Observed and model-predicted PFS, cemiplimab (plotted by the EAG)



PFS, progression-free survival; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

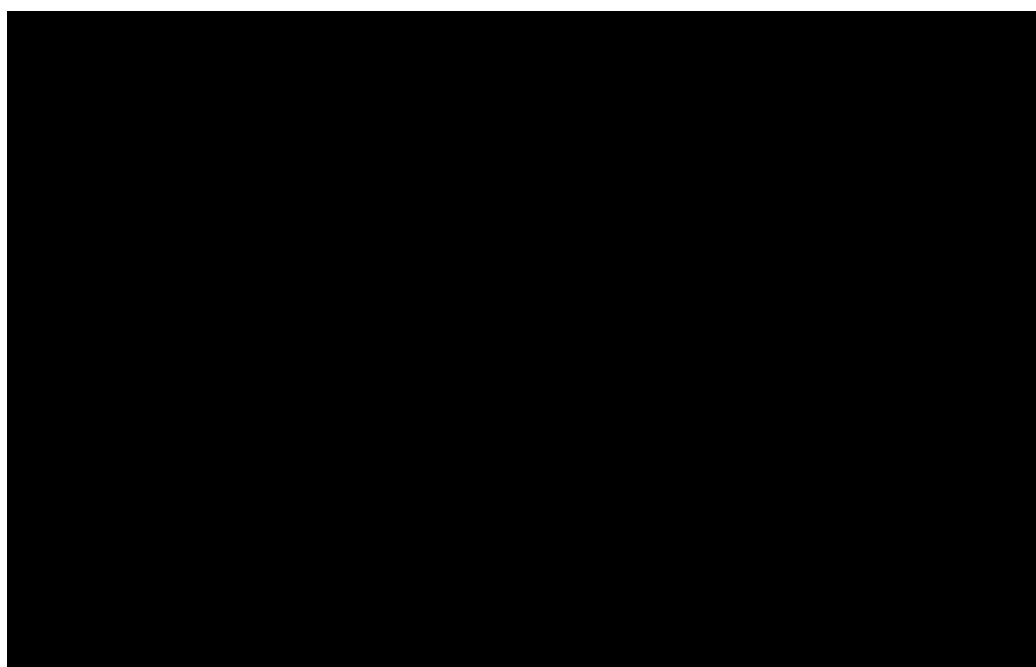
Figure 13: Observed and model-predicted PFS, single-agent chemotherapy (plotted by the EAG)



PFS, progression-free survival; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

Figure 14: Empirical and modelled hazard plots for PFS, cemiplimab and chemotherapy arms (reproduced from clarification Response, Question B6, based on CS Appendix L, Figure 16)



PFS – progression-free survival; ITT – intention to treat; Ind – independently fitted; tx – treatment

Time on treatment

Comparisons of observed and predicted ToT using parametric survival models for cemiplimab and single-agent chemotherapy are presented in Figure 15 and Figure 16, respectively. The AIC and BIC statistics of the fitted parametric survival models for each group are shown in Table 25. Empirical hazard plots and corresponding hazard plots of the parametric models for cemiplimab and single-agent chemotherapy are presented in

Figure 17.

For both the cemiplimab monotherapy and single-agent chemotherapy groups, the generalised gamma fit had the lowest AIC, with the log-normal model associated with the second lowest AIC value. The log-normal model was associated with the lowest BIC value, and the generalised gamma had the second lowest BIC value. For both AIC and BIC, the log-normal and generalised gamma fits were within 5 points of the lowest AIC/BIC value indicating similar statistical fits. The company chose to use the log-normal model for their base case as there was a larger difference in BIC between the log-normal and generalised gamma compared with the AIC values and justified that both models provided good visual fits to the KM curves. The company acknowledged that due to most patients in the EMPOWER Cervical-1 trial stopping treatment with cemiplimab at 96 weeks, there is a large drop in the ToT KM at 96-weeks which the log-normal model does not capture. However, the company highlighted that [REDACTED] of patients were on cemiplimab for 96 weeks or longer due to delays and/or interruptions and therefore the company did not deem it appropriate to censor patients at 96-weeks and use this re-censored data to inform the ToT in the economic model as it would not be reflective of the ToT observed in the trial. The company compared the mean ToT when using the log-normal model versus that observed within the EMPOWER Cervical-1 trial, and these were deemed sufficiently similar ([REDACTED] weeks in the trial vs [REDACTED] weeks in the model). As the generalised gamma was also identified as an appropriate model, this distribution was explored in a scenario analysis.

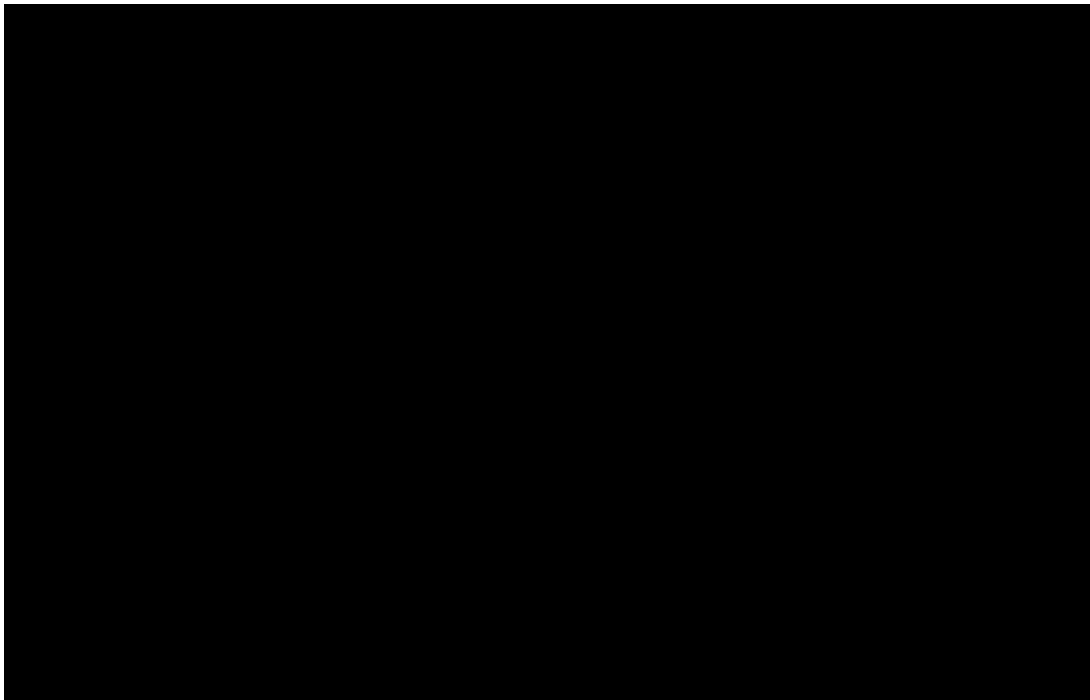
Table 25: AIC and BIC statistics for parametric survival models of ToT (adapted from CS, Table 27)

Distribution	Cemiplimab		Single-agent chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	1339.5 (5)	1343.2 (5)	1763.4 (4)	1767.1 (4)
Weibull	1332.7 (4)	1340.1 (4)	1765.4 (6)	1772.8 (6)
Log-normal	1310.9 (2)	1318.3 (1)	1726.3 (2)	1733.7 (1)
Generalised gamma	1310.4 (1)	1321.5 (2)	1724.9 (1)	1736 (2)
Gompertz	1341.2 (6)	1348.6 (6)	1764.8 (5)	1772.2 (5)
Log-logistic	1317.8 (3)	1325.2 (3)	1748.2 (3)	1755.6 (3)

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

Company's selected base case model highlighted in bold.

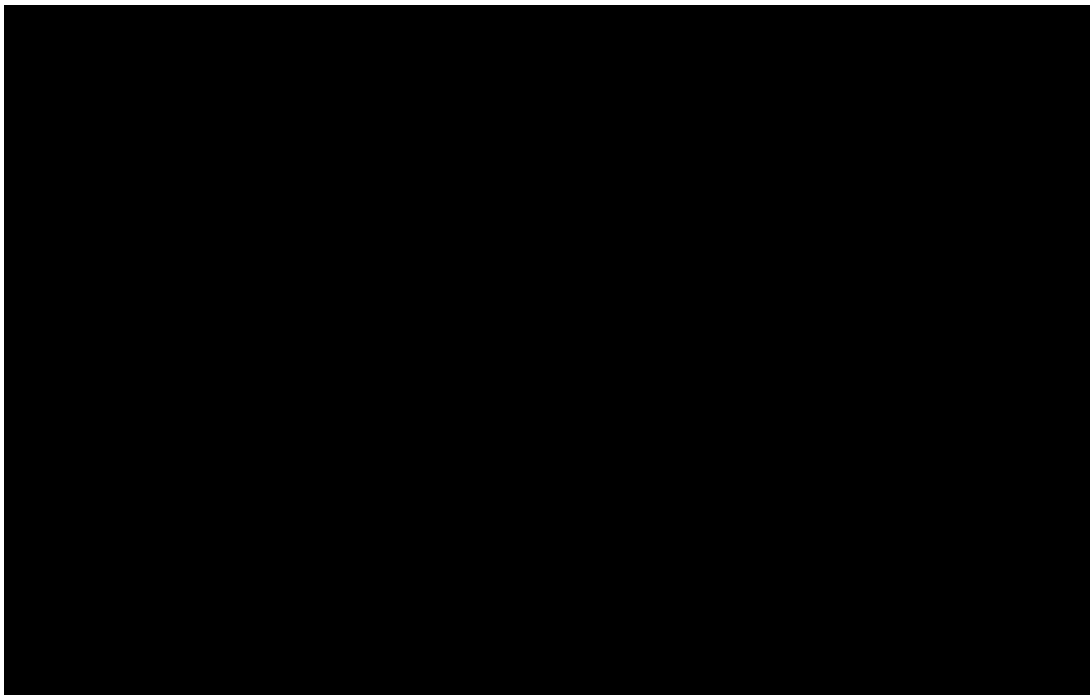
Figure 15: Observed and model-predicted ToT, cemiplimab (plotted by the EAG)



ToT, time on treatment; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

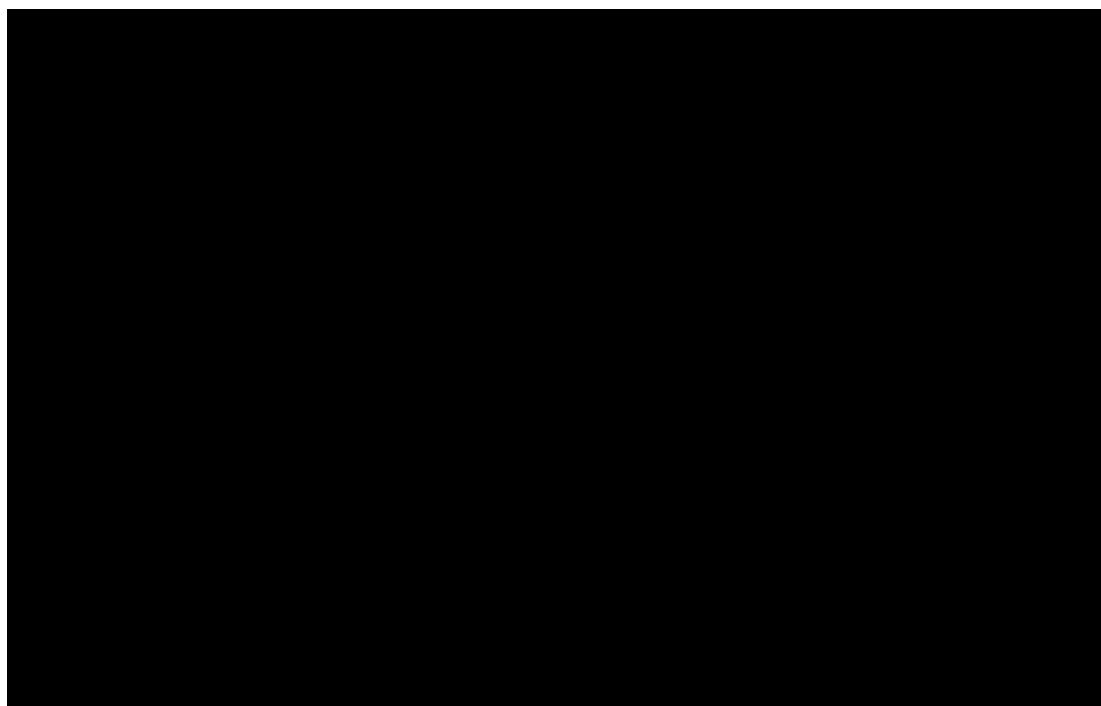
Figure 16: Observed and model-predicted ToT, single-agent chemotherapy (plotted by the EAG)



ToT, time on treatment; KM, Kaplan-Meier

Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

Figure 17: Empirical and modelled hazard plots for ToT, cemiplimab and chemotherapy arms (reproduced from CS Appendix L, Figure 24)



ToT – time on treatment; ITT – intention to treat; Ind – independently fitted; tx – treatment
Gamma model not depicted as this distribution was not included in the updated economic model following the clarification stage.

At the clarification stage the company provided the EAG requested scenarios relating to the modelling of ToT. A scenario was explored (clarification response question B9a) where ToT data for the cemiplimab and chemotherapy arms were censored at 96-weeks (the maximum permitted duration of treatment in the EMPOWER Cervical-1 trial), and standard parametric models were fitted to the re-censored data.¹³ In the chemotherapy arm, all patients had ceased treatment at 96 weeks (clarification response, Appendix 7, Figure 170) and thus it is assumed that no patients were re-censored.¹³ The standard parametric fits for the chemotherapy arm were therefore identical to the original curves in the company base case. Comparisons of the observed and predicted ToT re-censored cemiplimab data are presented in Figure 18. The empirical and model predicted hazards are shown in

Figure 19. As before, the EAG notes that, the formatting of the empirical hazard plots and corresponding model-predicted hazards limits the interpretability of this figure; however, it is included for completeness. The AIC and BIC values are presented in Table 26.

The generalised gamma fit to the cemiplimab ToT re-censored data had the lowest AIC and BIC values, however the company deemed the extrapolation provided by this model to be unrealistic as it resulted in the prediction of patients still being treated at 10 or 20 years following randomisation and fitted better predominantly at the censored end of the KM curve. The company therefore elected to use the second-best fitting model, the log-normal, within this scenario. The company further highlighted that this scenario should be considered a “*worst-case scenario*” as the modelled time on treatment would no longer be considered consistent with the efficacy and safety data from the trial.

The second scenario relating to ToT used the KM curve directly for both the cemiplimab ToT data and ToT for the chemotherapy group.

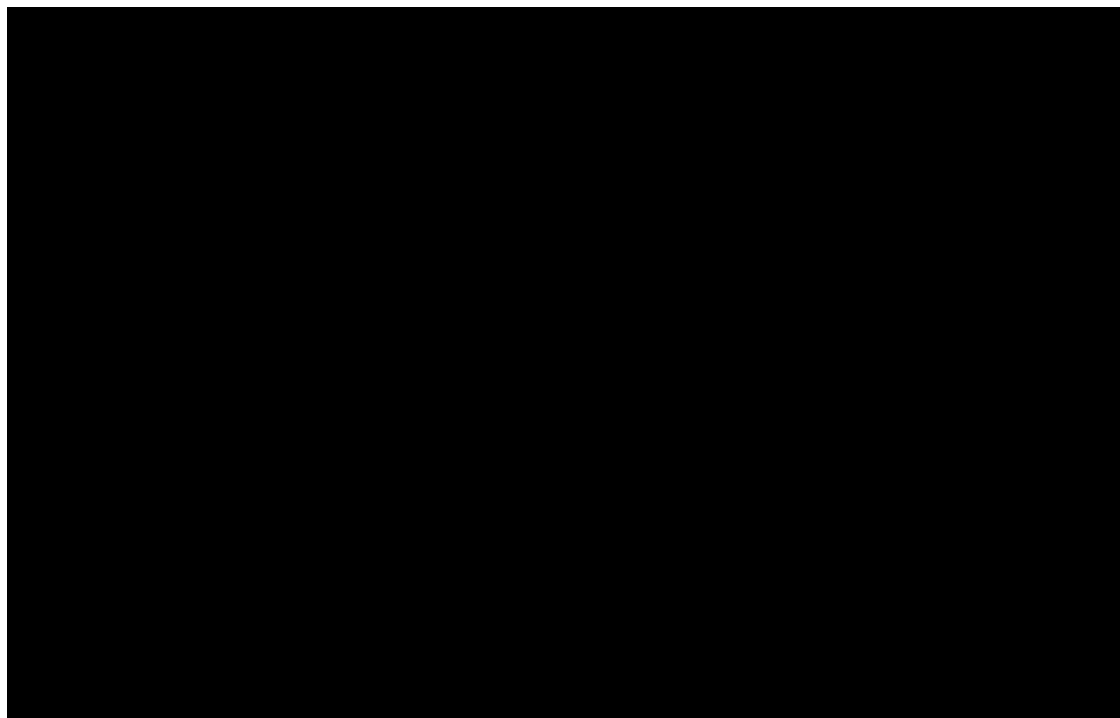
Table 26: AIC and BIC statistics for parametric survival models fits to 96-week censored ToT data (adapted from clarification response, Appendix 7, Table 88)

Distribution	Cemiplimab		Chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	1623.7 (6)	1627.4 (6)	1339.5 (6)	1343.2 (6)
Weibull	1618.3 (5)	1625.7 (5)	1332.7 (5)	1340.1 (5)
Log-normal	1548.6 (2)	1556 (2)	1310.9 (2)	1318.3 (1)
Generalised gamma	1516.5 (1)	1527.6 (1)	1310.4 (1)	1321.5 (2)
Gamma	1624.5 (7)	1631.9 (7)	1325.6 (4)	1333 (4)
Gompertz	1583.9 (4)	1591.3 (4)	1341.2 (7)	1348.6 (7)
Log-logistic	1555.2 (3)	1562.6 (3)	1317.8 (3)	1325.2 (3)

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

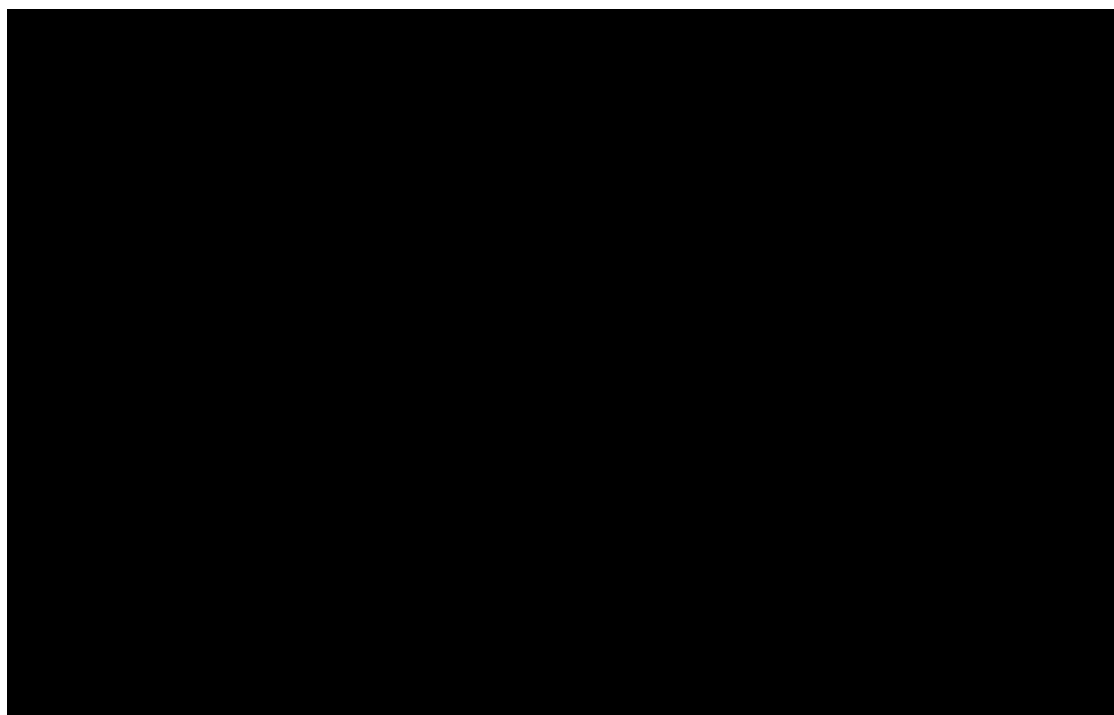
Company's selected model highlighted in bold.

Figure 18: Observed and model-predicted ToT, cemiplimab and chemotherapy arms, re-censored at 96-weeks (reproduced from clarification response B9 Appendix 7, Figure 176)



ToT, time on treatment; KM, Kaplan-Meier

Figure 19: Empirical and modelled hazard plots for ToT, arm, re-censored at 96-weeks (reproduced from, clarification response B9 Appendix 7, Figure 177)



ToT – time on treatment; ITT – intention to treat; Ind – independently fitted; tx – treatment

4.2.6.2 TTE outcomes ($PD-L1 < 1\%$ and $PD-L1 \geq 1\%$ sub-groups)

The company assumed that the models selected for the base-case ITT analysis would be appropriate for the PD-L1 sub-group scenario analysis. For completeness the comparisons of models and the KM curves are presented in the following sections, along with the AIC/BIC values and the comparison of the empirical hazards and model predicted hazards. However, the choice of models for these scenarios were the same as those selected for the ITT analysis. To justify this the company stated that, “*The parametric models used in the base case ITT analysis provide one if [sic] the best fits in this scenario*” and “*the patient numbers are lower in each PD-L1 subgroup, and therefore the results of the survival analysis are more uncertain*” (clarification response, A21).

Overall survival

Comparisons of observed and predicted OS using parametric survival models for the cemiplimab and single-agent chemotherapy arms in the $PD-L1 < 1\%$ and $PD-L1 \geq 1\%$ sub-groups are presented in Figure 20. The AIC and BIC statistics of the fitted parametric survival models for each group are shown in Table 27 and Table 28. Empirical hazard plots and corresponding hazard plots of the parametric models fit to the PD-L1 status subgroups for the cemiplimab and chemotherapy arms are presented in Figure 21. The interpretation of the empirical hazard plots and corresponding model-predicted hazards

for these analyses is again restricted due to the number of analyses presented within a single figure; however, this figure is included for completeness.

Table 27: AIC and BIC statistics for parametric survival models of OS, PD-L1 < 1% sub-group (adapted from clarification response, Appendix 1, Table 4)

Distribution	Cemiplimab (PD-L1 < 1%)		Single-agent chemotherapy (PD-L1 <1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	421.1 (5)	423.3 (4)	429.3 (4)	431.5 (4)
Weibull	422.8 (6)	427.2 (6)	431.2 (7)	435.6 (7)
Log-normal	414.1 (2)	418.5 (1)	420.3 (2)	424.7 (2)
Generalised gamma	412.7 (1)	419.3 (2)	422 (3)	428.7 (3)
Gompertz	423.1 (7)	427.5 (7)	430.2 (6)	434.6 (6)
Log-logistic	420.9 (4)	425.3 (5)	429.5 (5)	433.9 (5)
Gamma	417.3 (3)	421.7 (3)	420.1 (1)	424.5 (1)

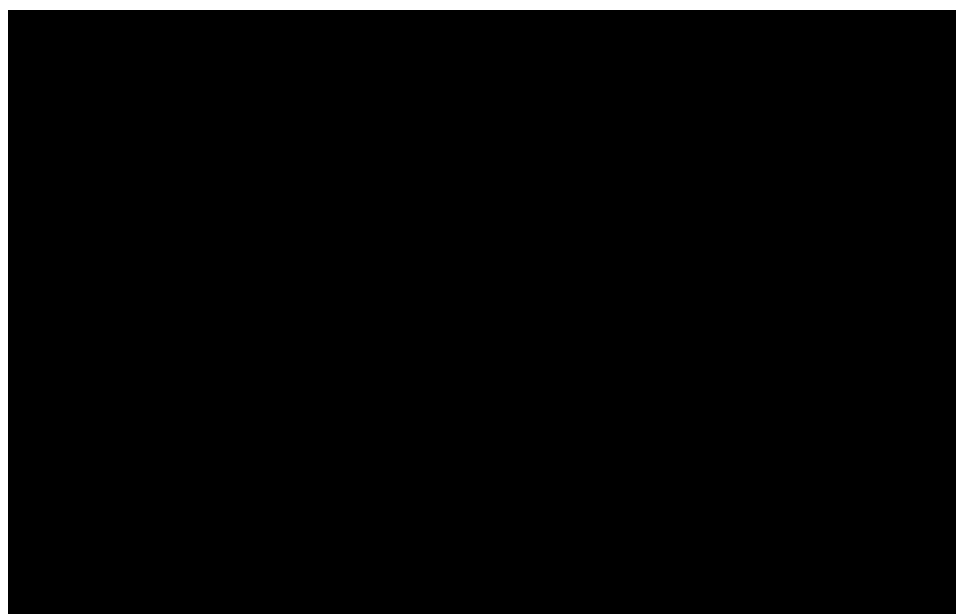
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Table 28: AIC and BIC statistics for parametric survival models of OS, PD-L1 ≥ 1% sub-group (adapted from clarification response, Appendix 1, Table 4)

Distribution	Cemiplimab (PD-L1 ≥ 1%)		Single-agent chemotherapy (PD-L1 ≥ 1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	719.6 (5)	722.4 (5)	748.3 (5)	751.1 (4)
Weibull	720.6 (6)	726.1 (6)	748.7 (6)	754.3 (6)
Log-normal	707.1 (1)	712.6 (1)	739.3 (2)	744.9 (2)
Generalised gamma	707.9 (2)	716.2 (3)	740.6 (3)	749 (3)
Gompertz	721.5 (7)	727 (7)	746.5 (4)	752.1 (5)
Log-logistic	714.7 (4)	720.2 (4)	749.8 (7)	755.4 (7)
Gamma	709.2 (3)	714.7 (2)	736.7 (1)	742.3 (1)

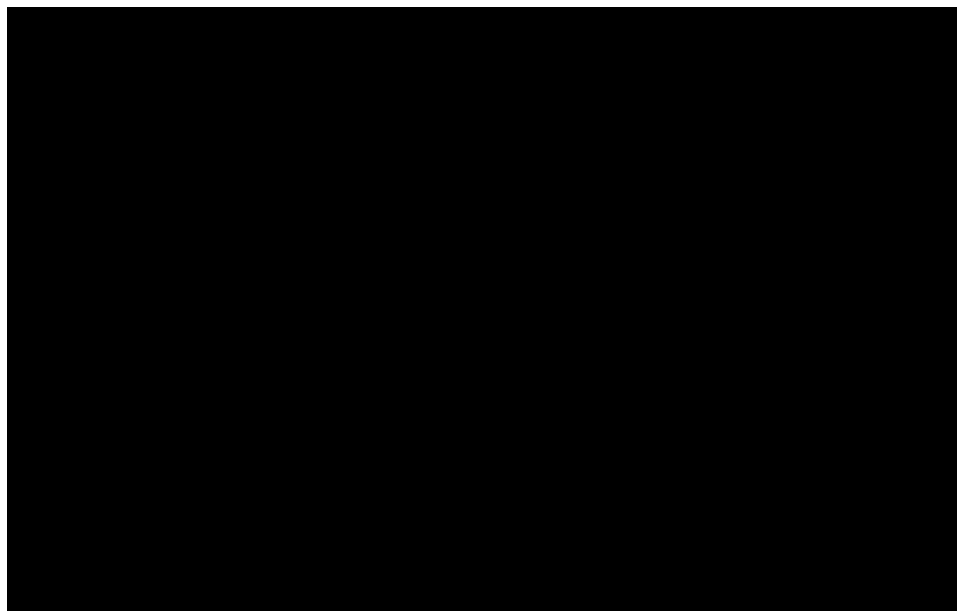
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Figure 20: Observed and model-predicted OS in PD-L1 < 1% and PD-L1 ≥ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 1, Figure 32)



OS, overall survival; KM, Kaplan-Meier

Figure 21: Empirical and modelled hazard plots for OS in PD-L1 < 1% and PD-L1 ≥ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 7, Figure 33)



OS – overall survival; ITT – intention to treat; Ind – independently fitted; tx – treatment

Progression-free survival

Comparisons of observed and predicted PFS using parametric survival models for the cemiplimab and single-agent chemotherapy arms in the PD-L1 < 1% and PD-L1 ≥ 1% sub-groups are presented in Figure 22. The AIC and BIC statistics of the fitted parametric survival models for each group are shown in Table 29 and Table 30. Empirical hazard plots and corresponding hazard plots of the parametric models for the PD-L1 subgroups for the cemiplimab and chemotherapy arms are presented in Figure 23. The interpretation of the empirical hazard plots and corresponding model-predicted hazards for these analyses is again restricted due to the number of analyses presented within a single figure; however, this figure is included for completeness.

Table 29: AIC and BIC statistics for parametric survival models of PFS, PD-L1 < 1% sub-group (adapted from clarification response, Appendix 1, Table 32)

Distribution	Cemiplimab (PD-L1<1%)		Single-agent chemotherapy (PD-L1<1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	361.9 (5)	364.1 (5)	344.1 (5)	346.3 (4)
Weibull	362.4 (6)	366.8 (6)	344.4 (6)	348.9 (6)
Log-normal	340.6 (2)	345 (2)	333 (1)	337.4 (1)
Generalised gamma	314.9 (1)	321.4 (1)	334.5 (2)	341.2 (3)
Gompertz	363.8 (7)	368.2 (7)	342.3 (4)	346.8 (5)
Log-logistic	354.4 (4)	358.8 (4)	346.1 (7)	350.5 (7)
Gamma	342.3 (3)	346.6 (3)	335.1 (3)	339.5 (2)

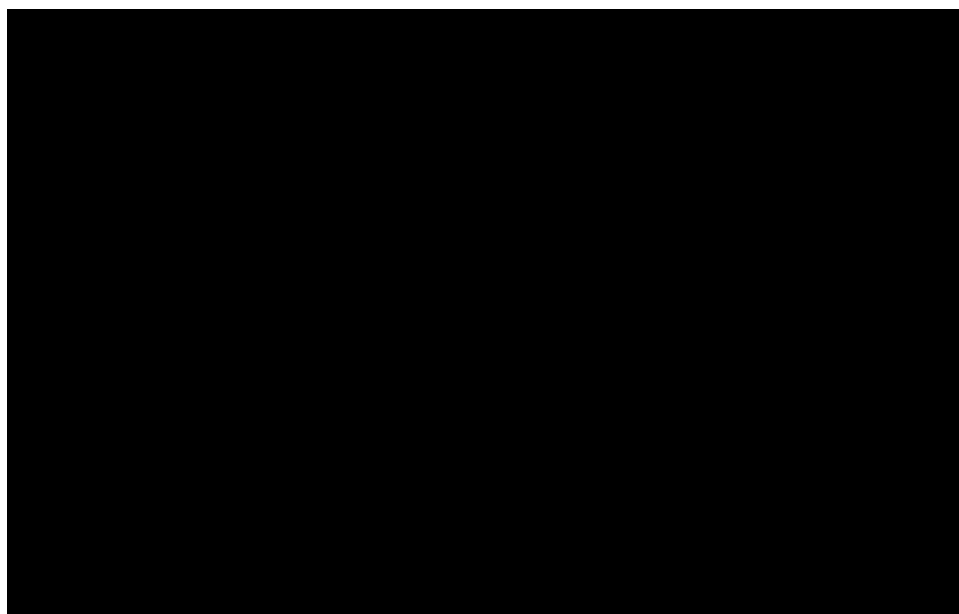
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Table 30: AIC and BIC statistics for parametric survival models of PFS, PD-L1 ≥ 1% sub-group (adapted from clarification response, Appendix 1, Table 32)

Distribution	Cemiplimab (PD-L1 ≥ 1%)		Single-agent chemotherapy (PD-L1 ≥ 1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	652.7 (7)	655.5 (7)	577.6 (6)	580.4 (6)
Weibull	641.9 (5)	647.4 (5)	574.4 (5)	580 (5)
Log-normal	608.2 (2)	613.7 (2)	553.6 (1)	559.2 (1)
Generalised gamma	585.6 (1)	593.8 (1)	553.9 (2)	562.3 (2)
Gompertz	649.1 (6)	654.6 (6)	569.7 (4)	575.3 (4)
Log-logistic	619.7 (4)	625.2 (4)	579.5 (7)	585.1 (7)
Gamma	610.3 (3)	615.8 (3)	558.9 (3)	564.5 (3)

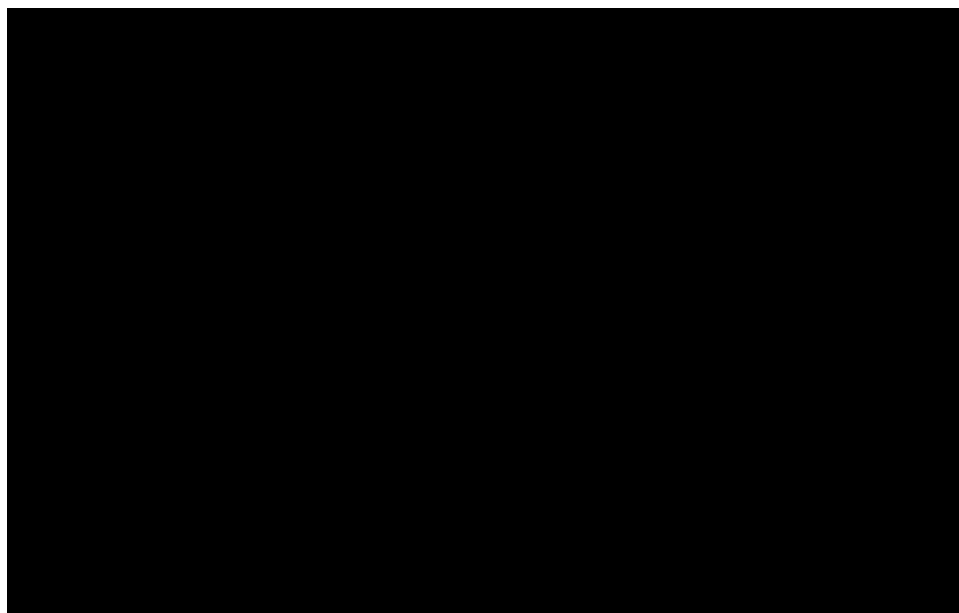
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Figure 22: Observed and model-predicted PFS in PD-L1 < 1% and PD-L1 ≥ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 7, Figure 88)



PFS, progression-free survival; KM, Kaplan-Meier

Figure 23: Empirical and modelled hazard plots for PFS in PD-L1 < 1% and PD-L1 ≥ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 7, Figure 89)



PFS – progression-free survival; ITT – intention to treat; Ind – independently fitted; tx – treatment

Time on treatment

Comparisons of observed and predicted ToT using parametric survival models for the cemiplimab and single-agent chemotherapy arms in the $\text{PD-L1} < 1\%$ and $\text{PD-L1} \geq 1\%$ sub-groups are presented in Figure 24. The AIC and BIC statistics of the fitted parametric survival models for each group are shown in Table 31 and Table 32. Empirical hazard plots and corresponding hazard plots of the parametric models are presented in Figure 25. The interpretation of the empirical hazard plots and corresponding model-predicted hazards for these analyses is even more restricted due to the number of analyses presented within a single figure; however, this figure is included for completeness.

Table 31: AIC and BIC statistics for parametric survival models of ToT, PD-L1 < 1% sub-group (adapted from clarification response, Appendix 1, Table 60)

Distribution	Cemiplimab (PD-L1<1%)		Single-agent chemotherapy (PD-L1<1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	384 (4)	386.2 (4)	308.2 (4)	310.4 (4)
Weibull	386 (7)	390.4 (7)	309.7 (6)	314.1 (6)
Log-normal	374.6 (2)	379 (2)	301.8 (1)	306.2 (1)
Generalised gamma	371.7 (1)	378.3 (1)	303.7 (2)	310.4 (3)
Gompertz	385.7 (5)	390.1 (5)	308.7 (5)	313.1 (5)
Log-logistic	385.8 (6)	390.2 (6)	310 (7)	314.4 (7)
Gamma	380.3 (3)	384.7 (3)	305.1 (3)	309.6 (2)

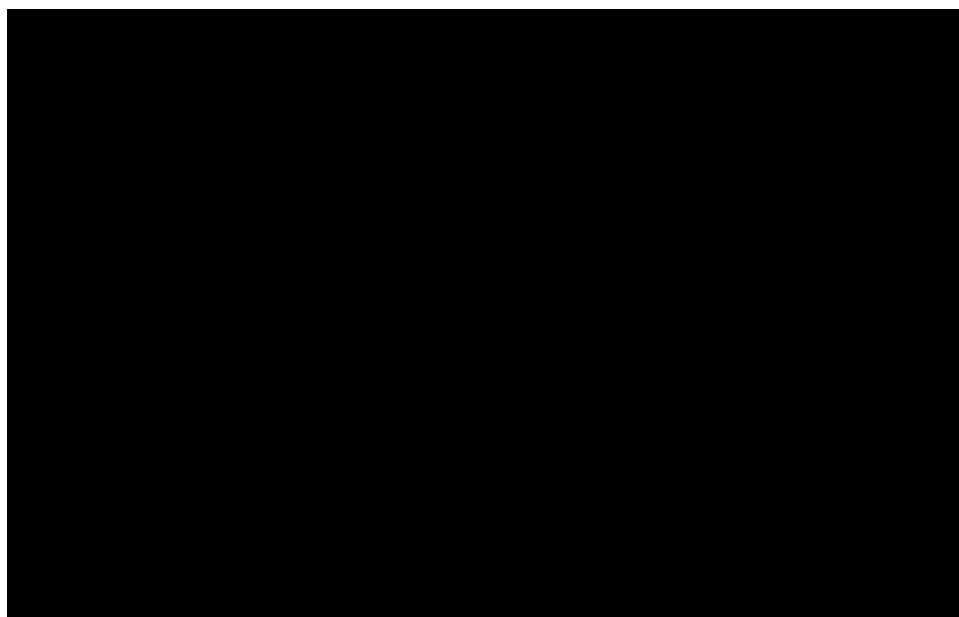
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Table 32: AIC and BIC statistics for parametric survival models of ToT, PD-L1 ≥ 1% sub-group (adapted from clarification response, Appendix 1, Table 60)

Distribution	Cemiplimab (PD-L1 ≥ 1%)		Single-agent chemotherapy (PD-L1 ≥ 1%)	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	685.6 (4)	688.4 (4)	537.3 (6)	540.1 (6)
Weibull	687.6 (7)	693.1 (7)	531.9 (5)	537.4 (5)
Log-normal	674.7 (1)	680.2 (1)	525 (1)	530.6 (1)
Generalised gamma	676.3 (2)	684.6 (2)	525.4 (2)	533.7 (3)
Gompertz	687.3 (5)	692.7 (5)	528.3 (4)	533.9 (4)
Log-logistic	687.5 (6)	693 (6)	538.1 (7)	543.6 (7)
Gamma	682.6 (3)	688.1 (3)	527.4 (3)	532.9 (2)

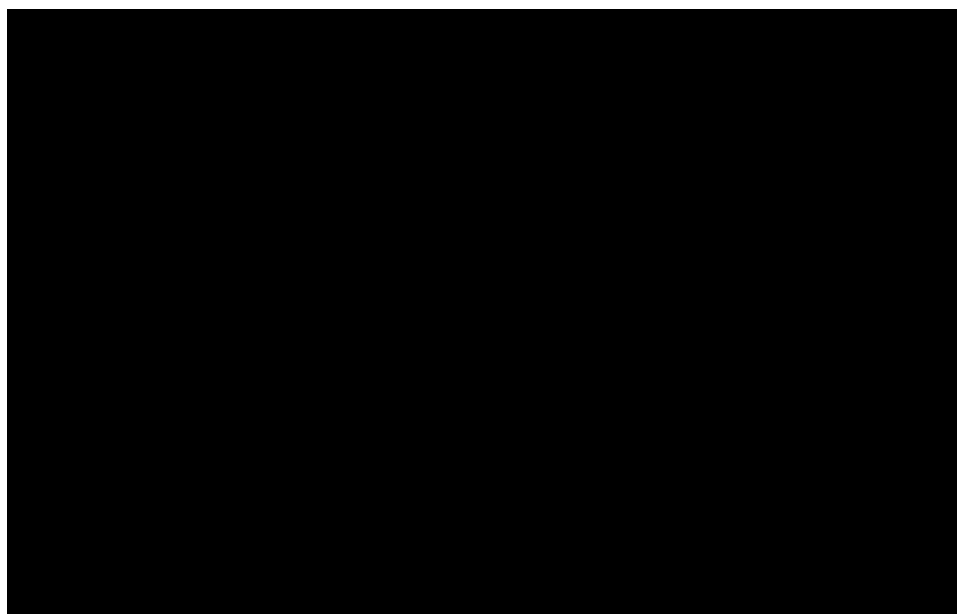
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Company's selected model highlighted in bold.

Figure 24: Observed and model-predicted ToT in PD-L1 < 1% and PD-L1 $\geq$ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 7, Figure 120)



ToT, time on treatment; KM, Kaplan-Meier

Figure 25: Empirical and modelled hazard plots for ToT in PD-L1 < 1% and PD-L1 ≥ 1% sub-groups, cemiplimab and chemotherapy arms (reproduced from clarification response, Appendix 7, Figure 121)



ToT – time on treatment; ITT – intention to treat; Ind – independently fitted; tx – treatment

4.2.6.3 TTE outcomes (PD-L1 < 1% ECOG-adjusted population)

The Scottish Medicines Consortium (SMC) advisory document on cemiplimab for this indication describes an economic scenario analysis conducted whereby efficacy within the model was informed solely by the PD-L1 < 1% sub-group. The EAG requested more details of this scenario analysis in clarification question A21. In the original scenario analysis conducted for the SMC submission, only patients with samples tested within 6 months were included in the PD-L1 < 1% scenario analysis. It was noted that when using this more restricted set of samples there was an imbalance in ECOG PS between the groups with [REDACTED] versus [REDACTED] having ECOG PS equal to 1 in the cemiplimab and chemotherapy arms respectively. Due to this imbalance the company therefore adjusted for ECOG PS within the SMC scenario analyses of TTE outcomes.

However, the company provided the EAG with an updated scenario analysis using all patients with a recorded PD-L1 status (irrespective of when the samples were tested). In this updated scenario analysis, the imbalance in ECOG PS was no longer evident with [REDACTED] and [REDACTED] of patients in the cemiplimab and chemotherapy arms having an ECOG PS equal to 1 respectively. The company provided the updated scenario analysis, and included all updated plots for the PD-L1 < 1% ECOG=0 and ECOG=1 sub-groups in Appendix 7 of the clarification response (Sections 6-8).¹³

Through additional comparisons of the ECOG-adjusted curves and PD-L1 < 1% (non-adjusted) curves, (see Section 4.2.6.5) the EAG found they were sufficiently similar which further supported the conclusion that the imbalance in ECOG status was no longer evident. Given that the imbalance in ECOG PS is no longer evident in the PD-L1 < 1% sub-group when all samples irrespective of the time to testing is considered, the EAG does not present the ECOG-adjusted OS, PFS and ToT curves here, nor is this scenario analysis considered further by the EAG.

4.2.6.4 EAG critique of treatment effectiveness evidence

The EAG believes that the overall approach to the selection of models was generally appropriate, and the company's selected base case and scenarios captured a plausible range of ICERs. The EAG also notes the maturity of the data from the EMPOWER Cervical-1 trial which helps to reduce uncertainty when extrapolating to the lifetime horizon. This being said, the EAG has some points of concern relating to the analysis of the TTE outcomes which are outlined below. These issues inform the EAG base case and are additionally explored within EAG scenario analyses which are summarised in Section 4.2.6.5.

When choosing the most appropriate model for OS, PFS and ToT, AIC/BIC values, visual inspection of goodness of fit and clinical plausibility were considered. Though the hazard plots were provided by the company, to what degree the hazards were considered during the curve selection process is unclear to the EAG. Additionally, some of the hazard plots comparing the empirical hazards and the model predicted hazards were not fit for purpose due to too many subgroups being presented within the same figure, thus the interpretation of these comparisons was limited. However, given that the chosen models typically had hazard functions somewhat similar to the observed empirical hazard functions, where this could be assessed, the EAG believes it is likely that the consideration of the hazard functions would not have changed the company model choices. The EAG therefore considers this issue to have minimal impact on the cost-effectiveness assessment but highlights that the explicit consideration of the hazard trend would have strengthened the curve selection approach.

Further to this, although the empirical hazard plots were presented within CS Appendix L, the method of producing the empirical hazard plots was initially not outlined by the company. In clarification question B4, the company confirmed that b-splines via the bshazard function in R, were used to plot the smoothed empirical hazard.¹³ Parameters were left as default values except the "err" parameter which was set to 0.01. However, differences were observed between the smoothed hazard functions shown across the plots in CS Appendix L, and therefore it is unclear whether b-splines were indeed used for *all* smoothed hazard plots presented or whether there were alternative configurations used between plots. Additionally, the EAG re-constructed the trial IPD using the Guyot algorithm⁷⁰ and plotted the smoothed hazards using the b-spline approach (in accordance with the company's approach) and

differences were evident in this comparison also. As the hazards did not appear to have been explicitly used during curve selection, it is unlikely that this issue would impact the selection of curves, however the EAG believes this discrepancy should have been addressed to make the comparison of hazard functions more transparent.

The company provided several scenarios in which alternative models were chosen for OS given that generally these model fits were poorer than those observed for PFS. Separate scenarios using the log-normal and log-logistic models for cemiplimab OS and the log-logistic model for chemotherapy OS were conducted. The EAG believes that further exploration of these alternative models should be considered when all alternative models for OS are considered.

The company did not explore more complex models when modelling TTE outcome data, as it was believed by the company that the use of complex models was not necessary due to the adequate fits to the KMs in the observed period and the potential for overfitting if using flexible spline-based approaches. For PFS the EAG agrees that the chosen standard parametric curves are appropriate and sufficient for including PFS within the economic model. However, the EAG believes that the OS data from the EMPOWER Cervical-1 trial was not necessarily best captured by the standard parametric models. For instance, the OS (ITT population) extrapolations shown in Figure 9 and Figure 10 for the cemiplimab and chemotherapy arms respectively, both show that there are periods where the company base case choice of the generalised gamma model over and underestimates the OS KM estimates. The smoothed empirical hazards in Figure 11 also shows hazard shapes which could potentially be better fit by more flexible approaches such as spline models. The EAG therefore believe that spline models should have been considered and have explored this further using reconstructed IPD, see Section 4.2.6.5.

Due to the majority of patients stopping treatment at 96-weeks and a small subset of patients, who experienced delays or interruptions, the ToT KM curve for cemiplimab had an abrupt decrease at 96-weeks. When fitting standard parametric models, this resulted in model fits that provided a generally poor fit to the ToT data. The company explored this in two scenario analyses, as explained in Section 4.2.6.1. The EAG believes that given the maturity of the ToT for both arms, the use of a parametric model for ToT is unnecessary and likely introduces additional uncertainty and inaccuracy in the cost-effectiveness analysis. Therefore, the EAG considers that the direct use of the KM to model ToT is the most appropriate approach for its base case analysis. The company did not update their base case at the clarification stage, however the EAG believes the company should have considered this given the improved reflection of the EMPOWER Cervical-1 ToT data when using the KM approach.

Whilst the choice of the approach to incorporate ToT within the economic model is important, the EAG acknowledges that ToT is constrained by PFS in the company base case model. In the CS it is stated that patients in the EMPOWER Cervical-1 trial with unconventional response consistent with pseudo-progression could be treated beyond progression provided they met certain criteria. The company further clarified the conditions that needed to be met in the clarification response question A15 and confirmed that this was not considered in the chemotherapy arm.¹³ In Table 48 of the EPAR³⁹, it is stated that 70 patients in the cemiplimab arm received treatment beyond documented progressive disease. Given that some patients received treatment beyond progression in the trial, the EAG does not believe that it is necessarily appropriate to cap ToT by PFS as this may underestimate the time on treatment for this subgroup of patients who received treatment beyond their initial progression event.

The EAG also notes some concerns with the approaches employed for the company scenario analyses. In the scenario analysis explicitly exploring the PD-L1 < 1% and PD-L1 ≥ 1% populations, the company chose to use the same parametric models as selected for the ITT population to model OS, PFS and ToT in the subgroups. The only discussion provided on the parametric fits to the subgroup specific data was the statement in response to clarification question A21 that, “*The parametric models used in the base case ITT analysis provide one if [sic] the best fits in this scenario.*” Although the company later clarified during the FAC check that they had considered the fits of different parametric models in both the ITT population and the relevant subgroup, no further discussion of the goodness of fit or the AIC/BIC values was provided and the EAG remains unclear how this combined assessment was made. Given the comparisons of model fit to the KM curves for the respective sub-groups (see Figure 20, Figure 22 and Figure 24) it was difficult for the EAG to fully assess the goodness of fit due to the limited size/resolution of the figures. The EAG therefore further explored the choice of curves, see Section 4.6.2.5 through the use of re-constructed IPD and explored alternative model choices in scenario analyses.

4.2.6.5 Additional work conducted by the EAG

Fitting of flexible parametric models to OS ITT data

The company did not provide any exploration of more flexible models such as spline models as requested by the EAG in clarification question B7.¹³ Given the poorer fit of the standard parametric models to OS for both arms, the EAG explored the fitting of spline models. The EAG digitised the OS KM curves for the cemiplimab and chemotherapy arms and generated pseudo-IPD using the Guyot algorithm.⁷⁰ The EAG then fit spline models with one to three knots, on the normal, odds and hazards scales using the flexsurv package in R. Comparisons of observed and predicted OS using spline models for cemiplimab and single-agent chemotherapy are presented in Figure 26 and Figure 27, respectively. The AIC and BIC statistics corresponding to the spline models for each group are shown in Table 33.

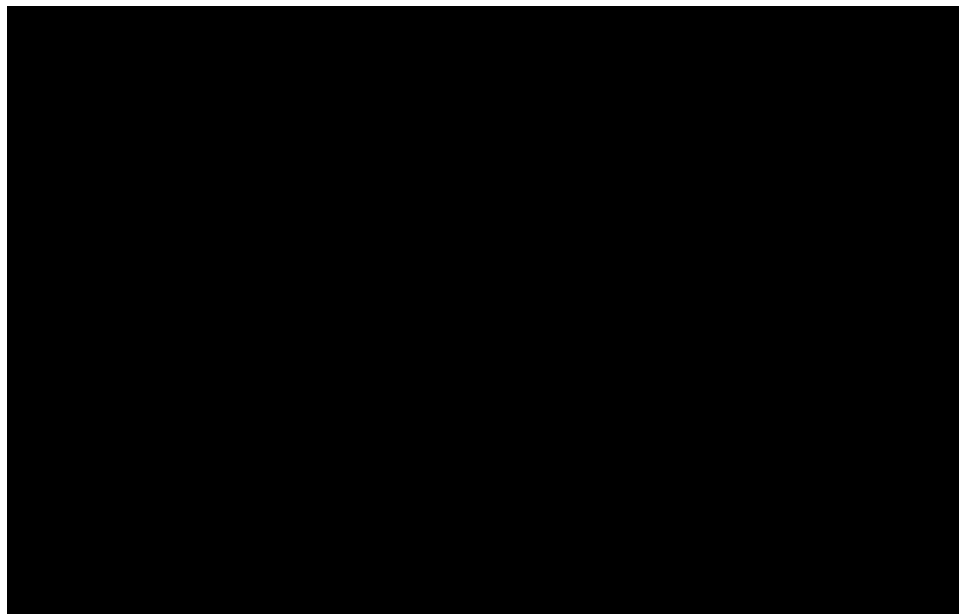
All of the spline models fitted provided good visual fit to the KM curve estimated from the reconstructed IPD. A two-knot model was chosen as all models appeared to show good visual fit, but the two-knot models provided good AIC/BIC rankings with a reduced likelihood of overfitting. The two-knot spline model on the hazards model was within 5 points of the lowest AIC for both the cemiplimab and chemotherapy arm and was within 5 points of the lowest BIC for the chemotherapy arm. The model on the hazards scale was chosen to impose that the log cumulative hazard is a smooth function of log time. Given the similarity of the spline model fits and extrapolations, the EAG explored this single spline model for OS in both arms and believes it to be sufficient to explore the use of more flexible models for OS.

Table 33: AIC and BIC statistics for spline models fitted to OS, reconstructed by the EAG

Distribution	Cemiplimab		Single-agent chemotherapy	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
scale-hazard,nknot-1	1880.346014	1891.497097	1787.749534	1798.900617
scale-hazard,nknot-2	1881.994057	1896.862167	1786.290946	1801.159056
scale-hazard,nknot-3	1883.205868	1901.791007	1787.104576	1805.689714
scale-odds,nknot-1	1879.857775	1891.008858	1784.987712	1796.138795
scale-odds,nknot-2	1881.691443	1896.559553	1786.748428	1801.616539
scale-odds,nknot-3	1883.263387	1901.848525	1787.623554	1806.208693
scale-normal,nknot-1	1882.751905	1893.902988	1790.177592	1801.328675
scale-normal,nknot-2	1882.790143	1897.658254	1787.024116	1801.892227
scale-normal,nknot-3	1884.384291	1902.96943	1787.516667	1806.101806

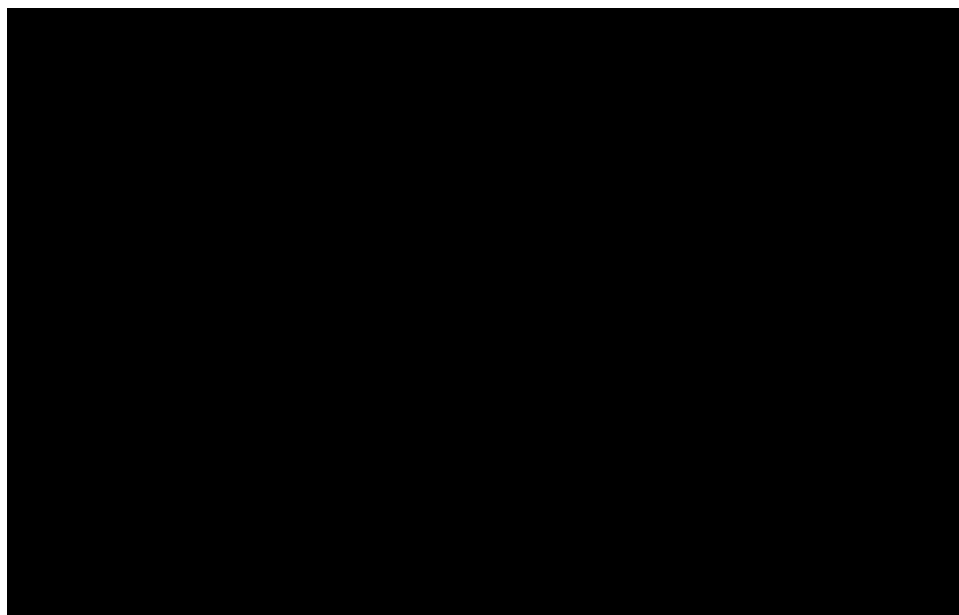
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
EAG selected scenario in bold.

Figure 26: Observed and model-predicted OS, cemiplimab (using reconstructed IPD and plotted by the EAG)



OS, overall survival; KM, Kaplan-Meier

Figure 27: Observed and model-predicted OS, chemotherapy (using reconstructed IPD and plotted by the EAG)



OS, overall survival; KM, Kaplan-Meier

Assessment of model fits for the PD-L1 < 1% and PD-L1 ≥ 1% sub-group OS and PFS

The EAG used the company analyses of the PD-L1 < 1% and PD-L1 ≥ 1% subgroups, presented in Section 4.2.6.2 supplemented with EAG analyses using re-constructed IPD. The EAG explored the model fits further as the presentation of the model fits by the company was not adequate to enable external assessment of goodness of fit.

The EAG model fits based on the re-constructed IPD are not presented here as they largely re-produce what was initially provided by the company. The EAG agrees that the company selected models were appropriate for the majority of cases but believes that alternative models for: OS cemiplimab (PD-L1 < 1% subgroup) and PFS chemotherapy (PD-L1 < 1% and PD-L1 ≥ 1% subgroups) could have been selected. Given the AIC/BIC and visual fits, the EAG believes that log-normal models (as opposed to generalised gamma models) would be more appropriate fits for these subgroups/outcomes. For these three curve choices, the generalised gamma distribution presented the most optimistic projections, and thus the EAG explored the choice of the log-normal model, which provided good visual and statistical fits to the data but with lower projected OS and PFS. Additionally, following the previous discussion of ToT, the EAG did not believe the models chosen for ToT in the PD-L1 < 1% or PD-L1 ≥ 1% subgroups, to be adequate and that the KM should be used for both arms across both subgroups.

Comparison of PD-L1 < 1% and ECOG-adjusted PD-L1 < 1% TTE outcomes

As highlighted in Section 4.2.6.3, the EAG believes the adjustment of the PD-L1 < 1% TTE outcomes by ECOG PS to be unnecessary due to the minimisation of group imbalance when using the larger sample of PD-L1 tested patients (no longer limited to patients with PD-L1 tests within 6 months of collection). To ensure that it was indeed the case that the un-adjusted PD-L1 < 1% curves were similar to the ECOG-adjusted PD-L1 < 1% TTE curves, the EAG first re-assessed the model choices for the PD-L1 < 1% ECOG sub-groups for each arm and then compared the ECOG-adjusted and unadjusted curves.

The PD-L1 < 1% ECOG subgroups had low numbers of individuals resulting in increased uncertainty when model fitting. This also resulted in potentially unexpected observations, such as the PFS KM in the chemotherapy arm ECOG=1 PD-L1 < 1% subgroup appearing to be greater than the ECOG=0 PD-L1 < 1% subgroup. This highlights the potential uncertainty in these subgroups and therefore the full model selection process is not included within the EAG report. The generalised gamma model was chosen by the EAG to model PFS in all ECOG subgroups for all arms, and the log-normal for OS in all ECOG subgroups for all arms. The comparisons of the ECOG-adjusted and unadjusted PD-L1 < 1% curves are shown in Figure 28 and Figure 29. It is clear there is minimal difference between these curves and thus the EAG is content that the scenario with adjustment for ECOG is not required.

Figure 28: Comparison of unadjusted PD-L1 < 1% OS with ECOG-adjusted PD-L1 < 1% OS, cemiplimab and chemotherapy (plotted by the EAG)

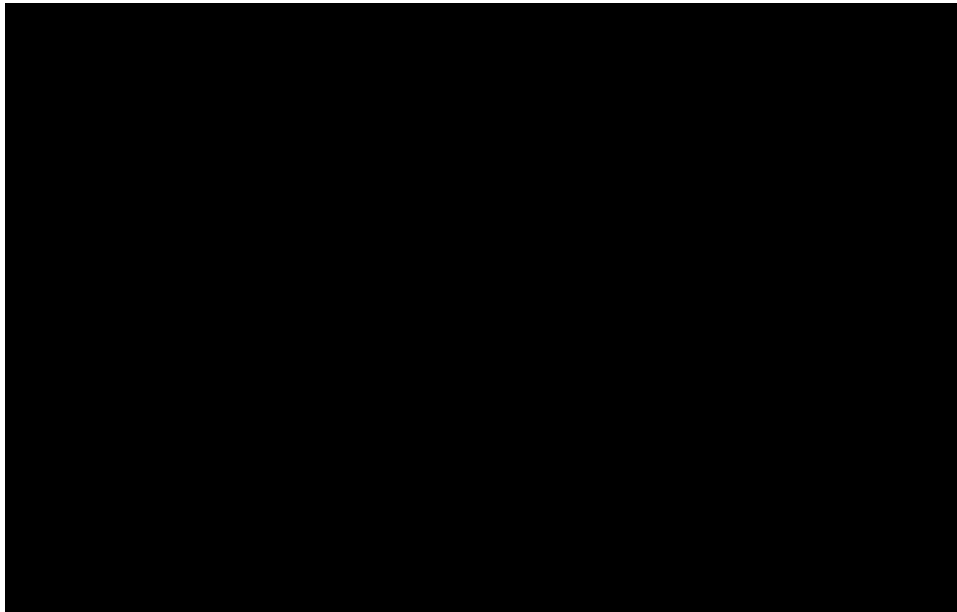
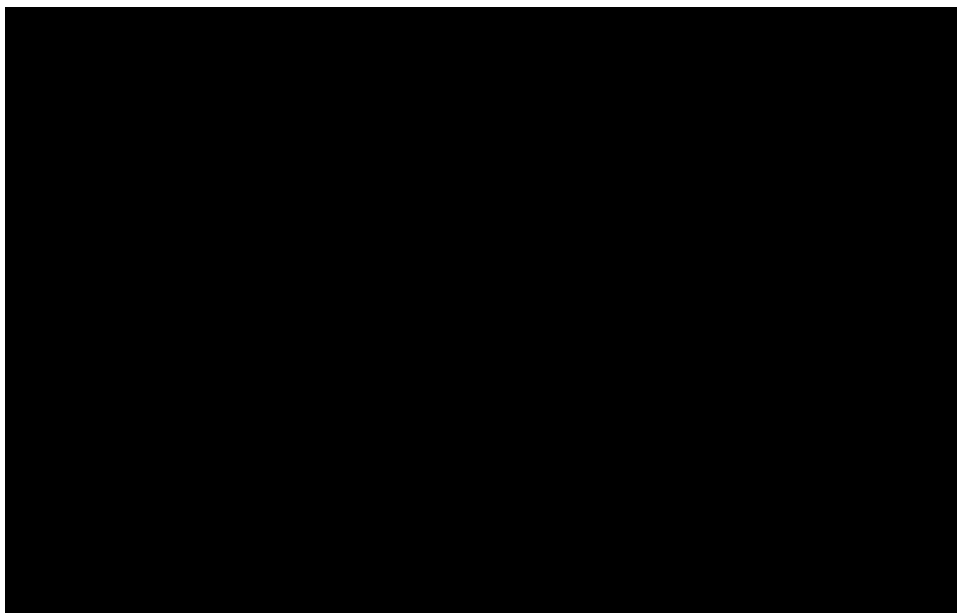


Figure 29: Comparison of unadjusted PD-L1 < 1% PFS with ECOG-adjusted PD-L1 < 1% PFS, cemiplimab and chemotherapy (plotted by the EAG)



EAG base case and scenario analyses relating to TTE outcomes

Given the above and the points highlighted in Section 4.2.6.4, the EAG has chosen to use the ITT population for its base case, using the generalised gamma model for OS and PFS (both arms), the KM curves directly for ToT (both arms) without constraining ToT by PFS. To include the explicit consideration of uncertainty of ToT within the probabilistic sensitivity analysis (PSA), the EAG

bootstrapped the re-constructed IPD and estimated the KM for each IPD sample, these estimations of the KM were then used within the PSA.

Scenario analyses explored by the EAG include:

- Re-introduction of capping ToT by PFS for both arms
- Use of the log-normal/log-logistic model for cemiplimab OS and log-logistic model for chemotherapy OS
- Use of the two-knot spline on the hazards scale for OS in both arms.
- Exploration of the weighted scenario analysis of PD-L1 < 1% and PD-L1 ≥ 1% sub-groups (not adjusted for ECOG PS), using the EAG selected models (as opposed to the models used for the ITT analysis). The weighting of QALYs and costs is according to an assumed 96% of patients being PD-L1 < 1% .
- Exploration of assuming all TTE outcomes are informed by the PD-L1 < 1% subgroup by assuming that 100% of patients are PD-L1 < 1%
- Exploration of the impact of allowing treatment to continue beyond 96 weeks using the log-normal curves fitted to the KM ToT data censored at 96 weeks, whilst recognising that this is a pessimistic scenario as OS and PFS are not adjusted.

4.2.7 Adverse events

The company's model incorporates TEAEs of Grade ≥3 that were reported by at least 2% of patients, as well as Grade ≥3 TEAEs experienced in less than 2% of patients where the incidence of that TEAE of any grade was greater than 5% in either arm of EMPOWER Cervical-1²³ (see Table 28 of CS). Methods for estimating QALY losses and management costs associated with TEAEs are described in detail in Sections 4.2.8.3 and 4.2.9.4, respectively.

The company's original model did not include immune-related AEs. The EAG's clinical experts stated that immune-related AEs could be associated with substantial resource use and a negative impact on the HRQoL. The CS states that immune-related AEs of Grade ≥3 occurred in ■■■% of patients in the cemiplimab arm in EMPOWER Cervical-1. In response to clarification question B11, the company states that hepatobiliary disorders were the only category of immune-related AE that met the above-mentioned criteria for inclusion in the economic model (■■■% Grade ≥3).¹³ A scenario analysis was

conducted by the company to explore the impact of including this AE, which showed a minimal effect on the ICER.

4.2.8 Health-related quality of life

The company used the data from EMPOWER Cervical-1²³ in its base case (see Section 4.2.8.1) and conducted a SLR to identify external studies which reported health state utilities relevant for patients with r/m CC who have progressed on or after platinum-based chemotherapy. The SLR is described in CS Appendix N. The identified studies are discussed in Section 4.2.8.2.

4.2.8.1 HRQoL data from EMPOWER Cervical-1

The EQ-5D quality of life measure was not administered in EMPOWER Cervical-1.²³ The EORTC QLQ-C30 was administered at baseline, before each six-week treatment cycle for patients remaining on treatment and twice in the post-treatment follow-up period, however, scores for patient on treatment were only evaluable up to cycle 8. Scores obtained on the EORTC QLQ-C30 were mapped to EQ-5D-3L values using the mapping algorithm reported by Longworth *et al.*⁷¹ The Longworth mapping algorithm has been externally validated for multiple myeloma, breast and lung cancer, and has been used in a recent SMC appraisal of cemiplimab for the treatment of cervical cancer.⁷² To account for the multiple data points for the same patient collected in EMPOWER Cervical-1, a linear mixed-effect repeated measures model (MMRM) was used for the post-baseline mapped EQ-5D-3L score, fitting the following covariates as fixed effects: treatment arm, visit number, baseline EQ-5D score, geographical region, histology, treatment-by-visit interaction, baseline EQ-5D score by-visit interaction. These covariates were chosen as they were the covariates originally used in the assessment of GHS from EORTC-QLQ-C30 collected in the EMPOWER Cervical-1 trial. Patient identification number was fitted as a random intercept to allow for correlation between repeated visits. Fewer PROs were recorded at later visits and therefore the Kenward-Roger degrees of freedom method was used to provide more precise small-sample estimators of the covariance matrix of the fixed-effects covariates.⁷³ Restricted maximum-likelihood estimation was used to account for the degrees of freedom used when estimating the variance components of the fixed-effects parameters. The overall mean treatment effect and pre- and post-progression treatment effects were estimated (see Table 34).

Table 34: MMRM analysis: pre- and post-progression EQ-5D-3L score (reproduced from CS, Appendix N, Table 2)

	Cemiplimab (n=215)			Chemotherapy (n=181)			Treatment arms combined		
	Mean	SE	95% CI	Mean	SE	95% CI	n	Mean	SE

Pre- progression	0.735	0.017	(0.702 to 0.768)	0.622	0.020	(0.583 to 0.661)	396		
Post- progression	-	-	-	-	-	-		0.613	

Abbreviations: CI, confidence interval; SE, standard error

The company highlighted that there were fewer PROs recorded for patients who has progressed which could lead to greater uncertainty when estimating utilities for this population. In Oaknin *et al.* 2022²², it was explored whether relaxing the assumption of missing at random would impact the analysis of PROs. A pattern mixture-model with multiple delta values was employed and demonstrated that across multiple scenarios, differences in PROs still favoured cemiplimab even when data for progressed patients was assumed to be not-missing-at-random.

4.2.8.2 HRQoL data from external sources

The company's SLR identified three cost-effectiveness analysis studies in which utility values for pre-progression and post-progression health states were used.^{41, 44, 74} In both Liu *et al.*⁴¹ and Shi *et al.*,⁴⁴ health state utility values were sourced from KEYNOTE-158,^{75, 76} which collected EQ-5D scores in US patients with unresectable or metastatic endometrial cancer and deficient mismatch repair or high microsatellite instability (dMMR/MSI-H). However, it is unclear whether the EQ-5D-3L or EQ-5D-5L was used. In Zhu *et al.*,⁷⁴ the utility data were informed by a study evaluating human papillomavirus vaccination in a Chinese population:^{77, 78} the value for cured cancer was used to reflect pre-progression state, and the value for distant cancer was used for the post-progression state.

Additionally, the company identified two technology appraisals: (i) the SMC appraisal of bevacizumab in combination with paclitaxel and cisplatin/topotecan in patients who cannot receive platinum-based chemotherapy for the treatment of persistent, recurrent or metastatic cervical cancer,⁷⁹ and (ii) the NICE TA939 evaluating pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer.¹⁰ In the SMC appraisal, the pre-progression utility value was estimated by mapping Functional Assessment of Cancer Therapy – General (FACT-G) data from GOG 240 Study⁸⁰ to EQ-5D values using the mapping algorithm reported by Teckle *et al.*,⁸¹ a Canadian study including patients with breast, lung and colorectal cancers. It is not reported whether EQ-5D-3L or EQ-5D-5L was used. The post-progression utility value was based on an assumed 20% decrement applied to pre-progression utility value. Utility values used in TA939 are redacted. Table 35 summarises health states utility values identified in the above-mentioned studies.

The EAG was unclear how the company selected the four studies included in Table 35, for discussion in CS, Section 3.4.3, from those identified in the full review of HRQoL studies presented in CS, Appendix F. Although this was not a major concern given the availability of utility data derived from the EMPOWER Cervical-1 trial.

Table 35: Summary of health state utility values identified in SLR

	Pre-progression, mean (95% CI)	Post-progression, mean (95% CI)	Source of utility values
Liu <i>et al.</i> , Shi <i>et al.</i>	0.817 (0.797 - 0.836)	0.779 (0.699 - 0.859)	KEYNOTE-158, ^{75, 76} (EQ-5D scores collected in patients with unresectable or metastatic endometrial cancer and dMMR/MSI-H)
Zhu <i>et al.</i>	0.87 (0.783 - 0.957)*	0.60 (0.54 - 0.66)*	Zou <i>et al.</i> ⁷⁷ and Zhao <i>et al.</i> ⁷⁸
SMC appraisal of bevacizumab	0.79 (NR)	0.63 (NR)	Pre-progression utility was estimated by mapping FACT-G data from GOG 240 Study ⁸⁰ to EQ-5D values using the mapping algorithm reported by Teckle <i>et al.</i> ⁸¹ Post-progression utility was estimated by applying a 20% decrement to the pre-progression utility.

Abbreviations: CI, confidence interval; dMMR/MSI-H, deficient mismatch repair or high microsatellite instability; SMC, Scottish Medicines Consortium; FACT-G, Functional Assessment of Cancer Therapy - General; EQ-5D, EuroQoL 5-Dimension; NR, not reported

*low and high range used in the economic analysis (95% CI or SE were not reported)

4.2.8.3 HRQoL data applied in the model

As the utility values identified in SLR studies were sourced from different populations or indications, the company did not consider them appropriate for inclusion in the base case analysis. Therefore, the EQ-5D-3L utility values mapped from the EORTC QLQ-C30 collected in EMPOWER Cervical-1²³ (4 Jan 2021 data cut) were used in the base case model. All utility values within the economic model are adjusted for increasing age based on the EQ-5D-3L estimates for the UK general population reported by Hernández Alava *et al.*⁵⁶

(i) Health state utility value – pre-progression health state

In the overall analysis where HRQoL data were not separated by progression status, cemiplimab showed statistically significant higher utility values than chemotherapy group at all follow-up visits except the 6th visit. When restricted to the pre-progression state, utility values became statistically significant at all

visits, with a slightly larger mean difference (■■■■, 95% CI: ■■■■ to ■■■■). As a result, the company applied the treatment-specific utility value for each arm in the base case: 0.735 (95% CI: 0.702 to 0.768) for cemiplimab and 0.622 (95% CI: 0.583 to 0.661) for chemotherapy. The CS states that the lower utility value of chemotherapy group was supported by the company's clinical experts, with two clinicians expecting a utility value of 0.5 for this group in the pre-progression health state, which was explored in the company's scenario analyses.

(ii) Health state utility value – post-progression health state

Unlike for the pre-progression health state, the company states that the treatment-specific utility values for the post-progression health state could not be estimated based on EMPOWER Cervical-1 for the following reasons: (i) fewer data to model arm-specific values since only ■■ (■■■■%) out of the 396 patients completed the questionnaire, (ii) ■■ out of ■■ (■■■■%) were from the cemiplimab arm and ■■ out of ■■ (■■■■%) from the chemotherapy arm, and (iii) the number of patients completing the questionnaire in the chemotherapy arm was only ■■ in the second visit and less than ■■ beyond the fourth visit. Instead, the company estimated the post-progression mean score using data combined across both arms, which was 0.613 (95% CI: 0.570 to 0.656). This is similar to the pre-progression utility value in the chemotherapy group (0.622), and the company states that if this combined score were applied in the chemotherapy group, it would assume that disease progression does not affect HRQoL in the chemotherapy group, which contradicts clinical experience. Therefore, the combined score of 0.613 was used for post-progression utility for the cemiplimab group, while a decrement approach was used to estimate the post-progression utility for the chemotherapy group. The relative disutility (■■■■ reduction) from pre- to post-progression health state observed in the cemiplimab arm was used to estimate the post-progression utility for the chemotherapy group, resulting in a value of 0.519 (■■■■). The company's clinical experts stated that a difference in utility post-progression for patients who had previously received chemotherapy versus those who had previously received immunotherapy may be expected due to chemotherapy being associated with persistent AEs. Different utility values and assumptions were explored in the company's scenario analyses including utilities in the chemotherapy arm based on clinical expert advice and utilities across both arms based on estimates from the SMC appraisal of bevacizumab (see CS, Table 30 and Section 5.1.2.3).¹

(iii) Health state utility value – end-of-life (EOL) state

The company's model also incorporated a reduction in utility value for the last 30 days of life, applying a value of 0.092 to patients during this period. This value was sourced from Chevalier *et al.*⁵⁵ who reported the utility value for disease progression with palliative treatment for the r/m CC elicited from the French general population using the time trade-off methods.

Table 36: Summary of utility values for cost-effectiveness analysis (adapted from CS, Table 29)

Health state	Utility, mean	SE	Source and justification
Pre-progression - cemiplimab	0.74	0.02	EMPOWER Cervical-1 ²³ (cemiplimab arm)
Pre-progression - chemotherapy	0.62	0.02	EMPOWER Cervical-1 (chemotherapy arm)
Post-progression - cemiplimab	0.61	0.02	EMPOWER Cervical-1 (combined scores across treatment arms)
Post-progression - chemotherapy	0.52	0.05*	Assumed the same relative utility reduction (■%) from pre- to post-progression state, as observed in the cemiplimab arm of EMPOWER Cervical-1
EOL (for last 30 days)	0.09	0.01	Chevalier <i>et al.</i> ⁵⁵

Abbreviations: EOL, end-of-life; SE, standard error

*SE based on 10% mean estimates.

(iv) Disutility associated with TEAEs

The CS states that QALY losses due to TEAEs were not included in the base case model, based on the assumption that these are captured through treatment-specific health state utility values; however, they were explored in the scenario analysis. In the scenario analysis, the model incorporates the expected QALY losses by multiplying the disutility of each TEAE by its respective duration and the probability of experiencing each TEAE. Each TEAE is assumed to have a duration of 28 days based on the clinical input, and disutility values were sourced from the published literature, previous TAs and clinical assumptions. The incidence of each AE was informed by EMPOWER Cervical-1. The QALY losses for each TEAE are summed to estimate a one-off QALY loss and applied in the first model cycle. AE frequencies, utility decrements and the expected QALY losses are summarised in Table 37.

Table 37: Summary of TEAE frequencies and their utility decrements used in the scenario analysis (adapted from CS, Table 28)

TEAEs	Frequency of TEAEs		Disutility	Source of disutility
	Cemiplimab	Single-agent chemotherapy		
Abdominal pain			0.0468	Similar to diarrhoea
Alanine aminotransferase increased			0.0567	Other liver disorders in Sullivan <i>et al.</i> ⁸²
Anaemia			0.0810	NICE TA581. ⁸³ Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma.
Arthralgia			0.0844	Similar to pain in extremity
Aspartate aminotransferase increase			0.0567	Other liver disorders in Sullivan <i>et al.</i>
Asthenia			0.0980	Similar to fatigue
Back pain			0.0844	Similar to pain in extremity
Blood creatinine increased			0.0567	Other liver disorders in Sullivan <i>et al.</i>
Constipation			0.0468	Similar to diarrhoea
Cough			0.0277	Other respiratory system diseases in Sullivan <i>et al.</i>
Decreased appetite			0.0480	Similar to vomiting
Diarrhoea			0.0468	Nafees <i>et al.</i> ⁸⁴
Dyspnoea			0.0277	Other respiratory system diseases in Sullivan <i>et al.</i>
Fatigue			0.0980	Chevalier <i>et al.</i> ⁵⁵
Headache			0.0844	Similar to pain in extremity
Hydronephrosis			0.0567	Other liver disorders in Sullivan <i>et al.</i>
Hyperglycaemia			0.0351	Diabetes in Sullivan <i>et al.</i>
Hypoalbuminaemia			0.0810	Similar to anaemia
Hypokalaemia			0.0810	Similar to anaemia
Hypothyroidism			0.0005	Sullivan <i>et al.</i>
Insomnia			0.0980	Similar to fatigue
Leukopenia			0.0897	Similar to neutropenia
Nausea			0.0480	Nafees <i>et al.</i>
Neutropenia			0.0897	Nafees <i>et al.</i>
Neutrophil count decreased			0.0897	Similar to neutropenia and febrile neutropenia
Oedema peripheral			0.0844	Assumed pain in extremity
Pain in extremity			0.0844	Sullivan <i>et al.</i>

Pelvic Pain				0.0844	Similar to pain in extremity
Pruritus				0.0325	Similar to rash
Pyrexia				0.1100	Beusterien <i>et al.</i>
Rash				0.0325	Nafees <i>et al.</i>
Stomatitis				0.0400	NICE TA581. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma.
Thrombocytopenia				0.0897	Similar to neutropenia and febrile neutropenia
Urinary tract infection				0.0093	Other urinary tract infection in Sullivan <i>et al.</i>
Vomiting				0.0480	Nafees <i>et al.</i>
White blood cell count decreased				0.0897	Similar to neutropenia and febrile neutropenia
Hepatobiliary disorders				NR	
Expected QALY loss (one-off) *	0.0021	0.0042			

TEAE, treatment-emergent adverse event; QALY, quality-adjusted life-year; NR – not reported

*based on 28-day duration and exclude hepatobiliary disorders

4.2.8.4 EAG's critique of approaches used to estimate utilities within the model

The EAG notes that the utility values used in the economic model were derived from the primary analysis of the study (Jan 2021).²² Based on the company's clarification response (A28)¹³ and the final CSR,⁴⁰ the EAG is generally satisfied that the results are comparable between the two data cuts.

When discussing the clinical face validity of assuming that utility may vary by treatment arm in the pre-progression health state, the company's clinical experts stated that *"chemotherapy has important [sic] side effects, immunotherapies are very well tolerated, and patients on immunotherapies tend to have good quality of life, that you don't see on chemotherapy"*. Furthermore, the company's clinical experts noted the potential for utility differences post-progression due to the impact of persistent AEs. Given the emphasis on utility differences being driven by TEAE profiles both pre- and post-progression, the EAG requested the company conduct a regression analysis for utility including terms for TEAEs of grade ≥ 3 in addition to terms for progression status. In the clarification response (B12), the company states that they could not conduct the requested analysis due to a lack of IPD on TEAEs.¹³

The EAG also considers that the post-progression utility values derived from EMPOWER Cervical-1 (the combined score of 0.613 and the [REDACTED] relative reduction from pre- to post-progression) remain uncertain due to low post-progression completion rates ([REDACTED]%) of the HRQoL questionnaire in the study. The company's clarification response to question A31 states that *"lower completion rates in patients who have progressed are to be expected, as some of these patients will be in a poor clinical state (both physically and emotionally) and completing questionnaires will not be a priority for such patients or their medical professionals"* and *"further information on the specific reasons for the difference in PRO collection after progression is not available"*.¹³ Additionally, the company cited the authors' discussion from Oaknin *et al.*,²² stating that *"there was a higher dropout rate in the chemotherapy arm due to differences in progression and survival in favour of cemiplimab"* and *"PROs collected after the discontinuation of study treatment (which was most commonly due to progression) would be confounded by the effects of subsequent treatments on QoL and symptoms."*

The EAG agrees with the use of the MMRM approach to account for repeated measures and believes it to be generally appropriate. The EAG does note that the covariates and interaction terms should have had additional justification, beyond that they were the covariates used in the trial analysis of GHS from EORTC QLQ-C30. Given that the MMRM in this submission is for the purpose of informing the utility estimates being used within the economic model, the model definition (covariate list and interaction terms) should have been re-assessed in the context of this submission. Additionally, clinical justification for the inclusion of the covariates would have further strengthened the approach. As IPD was not

available to the EAG, the EAG was unable to explore the impact of the choice of model and thus the potential impact on the utilities used within the economic model is uncertain.

One of the EAG's clinical advisors was generally satisfied with the assumption that health state utility could vary according to the treatment received, while the other commented that utility values could be the same across treatment arms following disease progression. The EAG notes that the company did not present arm specific estimates of post-progression utility values using data available across all visits, as was presented for the pre-progression utility values. Although the company noted at the FAC check that data had been presented in CS, Appendix N, Table 6, on arm-specific estimates of utility at different time-points, summary values across all post-progression visits appear to have been reported only for the cemiplimab arm. It is stated in Appendix N that, *"there were no patients in the chemotherapy arm for visits 7 and 8, hence an overall treatment difference could not be calculated using this model."* However, the EAG is unclear why the analysis could not be conducted by restricting the analysis to fewer visits. The company also did not conduct a regression analysis including covariates for treatment arm, progression and presence of TEAEs. It is therefore difficult to determine whether the model should include differential estimates of post-progression utility. The EAG considers that it may be incorrect to assume the same proportionate decrement (■%) associated with progression in both arms. It notes in particular that if the lower pre-progression utility for chemotherapy observed in the EMPOWER Cervical-1 trial is being driven by AEs associated with the chemotherapy treatment itself, then this AE related utility decrement may be reversed when patients stop chemotherapy treatment. This would mean that patients who have stopped chemotherapy due to disease progression may have a similar quality of life to patients who have stopped cemiplimab due to disease progression, and their post-progression utilities would then be likely to be similar. Although the EAG acknowledges the point made by the company's clinical experts that some specific chemotherapy-related AEs may not be reversible, e.g., peripheral neuropathy, this was infrequently reported in the trial (■% in both arms for pain in extremity of grade ≥ 3 , and for any grade ■% for cemiplimab and ■% for chemotherapy), and many of the most common treatment-related AEs reported in EMPOWER Cervical-1 chemotherapy arm (anaemia, nausea, fatigue, vomiting, constipation, decreased appetite) are likely to be reversible. The EAG has therefore conducted an exploratory analysis (EA3) in which the pre-progression utilities are informed by the treatment arm specific estimates from EMPOWER Cervical-1, but the post-progression utility values in both arms are informed by the pooled post progression utility from EMPOWER cervical-1. This assumption was also incorporated into the EAG's preferred base case.

However, the EAG also recognises that there is uncertainty regarding whether the application of treatment-dependent utilities is appropriate. It has therefore explored two alternative assumptions in its additional sensitivity analyses. In the first scenario (ASA4a) it explored the impact of applying the same

utility values in both treatment groups: [REDACTED] for the pre-progression state and 0.613 for the post-progression state, estimated based on pooled data across treatment arms in EMPOWER Cervical-1. In this EAG scenario, the QALY losses related to TEAEs were applied as a one-off value in the first model cycle. However, the EAG notes that this scenario may be pessimistic given the difference in pre-progression utilities observed in the EMPOWER Cervical-1 trial. In the second scenario (ASA4b), it applies the company's preferred approach in which treatment dependent utilities are applied both pre-progression and post-progression without further adjustment for TEAEs. The purpose of this analysis is to demonstrate the impact of assuming differential post-progression utilities within the context of the other assumptions included in the preferred EAG's base case scenario.

4.2.9 Resources and costs

The company performed a SLR to identify healthcare resource use and costs for patients with r/m CC who have progressed on or after platinum-based therapy, and details are provided in CS Appendix G. No studies relevant to UK resource use or costs were identified.

The company's model includes costs associated with: (i) drug acquisition and administration (first-and subsequent-line treatments); (ii) management of TEAEs and (iii) disease management including EOL care (terminal care). Table 38 summarises the costs applied within the model; further details are provided in the subsequent sections. It should be noted that the original version of the company's executable model includes several programming errors related to costs. Following the clarification round, the company submitted an updated version of its economic model that included correction to some programming errors.¹³ The text in the subsequent sections relates to the cost assumptions in the updated version of the company's economic model, unless otherwise stated. There are no relevant confidential prices for comparator and subsequent treatments.

Table 38: Summary of costs applied in the company's base case model

Cost component	Cemiplimab	Chemotherapy
Acquisition costs (second-line treatment) - per treatment cycle (including PAS discount of cemiplimab) *	[REDACTED]	Pemetrexed: £ [REDACTED] Gemcitabine: £ [REDACTED] Topotecan: £ [REDACTED] Irinotecan: £ [REDACTED] Vinorelbine: £ [REDACTED]
Administration costs (second-line treatment) - per treatment cycle	£387	£387 (for pemetrexed, gemcitabine, topotecan and vinorelbine) £476 (for irinotecan) [§]
Acquisition and administration costs (subsequent-line treatments) - once-only costs**	£2,615	£1,299
AE management costs - once-only costs [†]	£891	£1,468

Disease management costs – per weekly model cycle	Pre-progression - on treatment: £118 Pre-progression - off treatment: £102 Post-progression: £202	Pre-progression - on treatment: £137 Pre-progression - off treatment: £122 Post-progression: £217
EOL care costs – once-only costs [‡]	£709	£709

Abbreviations: EOL, end-of-life; PAS, Patient Access Scheme; AE, adverse events

*excluding RDI

**including RDI

†excluding hepatobiliary disorders

‡ Weely costs. The company's model erroneously applies this cost as a 30-day cost. See details in Section 4.2.9.8.

§ for a 6-weekly treatment cycle

4.2.9.1 Drug acquisition costs

Table 37 summarises the total drug acquisition costs of cemiplimab and single-agent chemotherapies given in patients with r/m CC who have progressed on or after platinum-based chemotherapy. All drug costs were applied as costs per treatment cycle in the model. For the comparator group, the costs per treatment cycle reflects the weighted average of five different single-agent chemotherapies, including pemetrexed, gemcitabine, topotecan, irinotecan and vinorelbine, based on their distribution in the comparator treatment mix (see Table 20). The company also conducted two additional scenarios: one assessing the distribution of treatment mix based on the clinical input (5.96% gemcitabine, 8.93% topotecan, 5.96% irinotecan, 5.96% vinorelbine, 46.40% weekly paclitaxel, 7.44% carboplatin plus doxorubicin pegylated liposomal, 7.44% carboplatin plus gemcitabine and 11.91% carboplatin) and one assuming 100% weekly paclitaxel. The latter was requested by the EAG at clarification (question B1),¹³ as the company's description of the current treatment pathway (CS, Section 1.3.3.1)¹ described weekly paclitaxel as being commonly used but it made up less than 50% of the treatment offered in the company's scenario analysis that intended to reflect the distribution of treatments in UK clinical practice.

The list price per pack of 350 mg cemiplimab was taken from the British National Formulary (BNF)⁴⁹ as £4,650. The company has an agreed PAS for cemiplimab of [REDACTED]%, and the cost per 350 mg vial including PAS discount is [REDACTED]. Unit costs of single-agent chemotherapies were taken from the Electronic Market Information Tool (eMIT) (see Table 39).⁵⁰ The dosing schedules for both cemiplimab and comparator chemotherapies were sourced from the study protocol of EMPOWER Cervical-1.³⁸ Within the economic model, the expected acquisition costs were calculated by multiplying patients on treatment at the start of the model cycle (using the log-normal parametric survival model fitted to the treatment-arm specific ToT data from EMPOWER Cervical-1),²³ the RDI and the acquisition costs per treatment cycle. Of note, the model applied a constraint so that the cumulative probability of ToT cannot be higher than the cumulative probability of PFS at any timepoint. The mean duration of treatment exposure were 15.2 weeks for cemiplimab and 10.1 weeks for chemotherapy. The EAG notes that the ToT data in the chemotherapy arm reflects the overall group rather than each individual single-agent

chemotherapy. The RDIs for cemiplimab and comparator chemotherapies were taken from the final analysis of EMPOWER Cervical-1.

The base case model assumes that vial sharing is available for all administrations, applying the minimum price per mg. Drug wastage due to variability in BSA and the use of non-divisible vial sizes was not included in the base case but was explored in the scenario analysis, in which BSA-dependent dosing was calculated using the method of moments.

Table 39: Drug acquisition costs per treatment cycle, second-line setting

Treatment	Administration route	Dosing schedule (weeks)	Total dose per treatment cycle (mg)	Cost per mg	Costs per treatment cycle	RDI	Expected costs per treatment cycle	Source
Cemiplimab	IV	350 mg, Q3W	350	N/a	■■■■	■	■■■■	EMPOWER Cervical-1, ³⁸ BNF ⁴⁹
<i>Single-agent chemotherapy</i>								
Pemetrexed	IV	Day 1, Q3W	■	£0.05	■	■	■	EMPOWER Cervical-1, eMIT ⁵⁰
Gemcitabine	IV	Days 1 and 8, Q3W	■■■	£0.01	■	■	■	
Topotecan	IV	Days 1-5, Q3W	■	£10.41	■■■	■	■■■	
Irinotecan	IV	Days 1, 8, 15, and 22, Q6W	■	£0.03	■	■	■	
Vinorelbine	IV	Days 1 and 8, Q3W	■	£0.35	■■■	■	■	
Weighted average cost of single-agent chemotherapy group (37% for pemetrexed, 40% for gemcitabine, 7% for topotecan, 6% for irinotecan and 11% for vinorelbine)							■	

Abbreviations: RDI, relative dose intensity; IV, intravenous; mg, milligrams; m2, square meter; Q3W, every 3 weeks; Q6W, every 6 weeks; BNF, British National Formulary; eMIT, electronic market information tool, N/a, not applicable

4.2.9.2 Drug administration costs

The company's model assumes that cemiplimab and all comparator chemotherapies are administered in either an outpatient or day-case setting. The unit costs per administration were calculated as a weighted average of outpatient and day-case costs, taken from the NHS Reference Costs 2024/25.⁵¹ The cost of simple parenteral chemotherapy delivery (SB12Z) was applied to the administration of cemiplimab and all chemotherapies, except irinotecan, for which the cost of complex parenteral chemotherapy delivery (SB13Z) was applied. In the scenario analysis, the cost of complex chemotherapy delivery (SB13Z) was applied to the administration of irinotecan, paclitaxel, carboplatin plus doxorubicin pegylated liposomal and carboplatin plus gemcitabine, which requires an infusion duration of more than 60 minutes, and the cost of simple parenteral chemotherapy (SB12Z) was applied to the rest chemotherapy options. Additionally, pemetrexed treatment incurred additional administration costs for pre-medication, including oral folic acid and intramuscular B12 injections (less than £1 per treatment cycle). The administration costs were applied as one-off costs in each treatment cycle, conditional on the probability of being alive and remaining on treatment (based on ToT function).

4.2.9.4 Management costs of TEAEs

The base case model includes the costs of managing TEAEs based on the frequencies from EMPOWER-Cervical-1²³ (see details in Table 37). Unit costs were estimated as weighted non-elective inpatient costs, taken from NHS Reference Costs 2024/25,⁵¹ and assumptions.

Table 40 summarises the unit costs for managing TEAE used in the economic model. The expected TEAE management costs are estimated to be £891 for cemiplimab and £1,468 for single-agent chemotherapy and are applied as one-off costs to all patients in the first model cycle. Base case model excludes the cost of hepatobiliary disorders (immune-related TEAE). TEAEs associated with subsequent treatments are not included in the model. The EAG considers that these are unlikely to have a significant impact on the cost-effectiveness results, however, it has included hepatobiliary TEAEs in its preferred base case (see EA6 in Section 5.2.2).

Table 40: Management costs of TEAEs

TEAEs	Unit costs	Source of unit costs (NHS Reference Costs 2024/25, ⁵¹ unless otherwise stated)
Abdominal pain	£755	Weighted average costs for health care resource group (HRG) code FD05A and FD05B: Abdominal Pain w/wo Interventions
Alanine aminotransferase increased	£2,526	Weighted average costs for HRG code GC17: Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions
Anaemia	£1,664	Weighted average costs for HRG code SA04G, SA04H, SA04J, SA04K & SA04L: Iron Deficiency Anaemia
Arthralgia	£1,471	Weighted average costs for HRG code HD26: Musculoskeletal Signs or Symptoms
Aspartate aminotransferase increase	£2,526	Assumes same as alanine aminotransferase increased
Asthenia	£1,398	Assumed same as pyrexia
Back pain	£1,311	Weighted average costs for HRG code HC32G, HC32H, HC32J and HC32K: Low back pain w/wo Interventions
Blood creatinine increased	£2,526	Assumes same as alanine aminotransferase increased
Constipation	£2,166	Weighted average costs for HRG code FD10A:FD10M: Non-Malignant Gastrointestinal Tract Disorders w/wo Interventions
Cough	£879	Weighted average costs for HRG code DZ19H:DZ19N: Other Respiratory Disorders w/wo Interventions
Decreased appetite	£2,166	Assumed same as constipation
Diarrhoea	£2,166	Assumed same as constipation
Dyspnoea	£879	Assumed same as cough
Fatigue	£1,398	Assumed same as pyrexia
Headache	£877	Weighted average costs for HRG code AA31C-AA31E: Headache, Migraine or Cerebrospinal Fluid Leak
Hydronephrosis	£6,161	Weighted average costs for HRG code LA09J-LA09L: General Renal Disorders with Interventions
Hyperglycaemia	£679	Weighted average costs for HRG code WH13A:WH13C: Abnormal Findings without Diagnosis, w/wo interventions
Hypoalbuminaemia	£2,133	Same as leukopenia
Hypokalaemia	£2,133	Same as leukopenia
Hypothyroidism	£1,663	Weighted average costs for HRG code KA07: Non-Surgical Thyroid Disorders
Insomnia	£1,450	Weighted average costs for HRG code AA43: Sleep Disorders, excluding Sleep Apnoea
Leukopenia	£2,133	Weighted average costs for HRG code SA08: Other Haematological or Splenic Disorders
Nausea	£2,166	Assumed same as constipation

Neutropenia	£2,575	Weighted average costs for HRG code SA35A:SA35E: Agranulocytosis
Neutrophil count decreased	£2,575	Assumed same as neutropenia
Oedema peripheral	£873	Weighted average costs for HRG code WH10: Unspecified Oedema
Pain in extremity	£1,471	Assumed same as back pain
Pelvic Pain	£1,518	Weighted average costs for HRG code MB09A: Non-Malignant Gynaecological Disorders w/wo Interventions
Pruritus	£654	Assumed same as rash
Pyrexia	£1,398	Weighted average costs for HRG code WJ07A:WJ07D: Fever of Unknown Origin w/wo Interventions
Rash	£654	Weighted average costs for HRG code JD07K: Skin Disorders without Interventions
Stomatitis	£1,423	Weighted average costs for HRG code CB02A: Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, w/wo Interventions
Thrombocytopenia	£2,564	Weighted average costs for HRG code SA012: Thrombocytopenia
Urinary tract infection	£2,555	Weighted average costs for HRG code LA04: Kidney or Urinary Tract Infections, w/wo Interventions
Vomiting	£2,166	Weighted average costs for HRG code FD10A:FD10M: Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions
White blood cell count decreased	£2,133	Assumed same as leukopenia
Hepatobiliary disorders	£2,550	Weighted average costs for HRG code GC17A:GC17K: Non-Malignant, Hepatobiliary or Pancreatic Disorders
Abdominal pain	£755	Weighted average costs for HRG code FD05A and FD05B: Abdominal Pain w/wo Interventions
Alanine aminotransferase increased	£2,526	Weighted average costs for HRG code GC17: Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions
Anaemia	£1,664	Weighted average costs for HRG code SA04G, SA04H, SA04J, SA04K & SA04L: Iron Deficiency Anaemia
Arthralgia	£1,471	Weighted average costs for HRG code HD26: Musculoskeletal Signs or Symptoms
Aspartate aminotransferase increase	£2,526	Assumes same as alanine aminotransferase increased
Asthenia	£1,398	Assumed same as pyrexia
Back pain	£1,311	Weighted average costs for HRG code HC32G, HC32H, HC32J and HC32K: Low back pain w/wo Interventions
Blood creatinine increased	£2,526	Assumes same as alanine aminotransferase increased
Constipation	£2,166	Weighted average costs for HRG code FD10A:FD10M: Non-Malignant Gastrointestinal Tract Disorders w/wo Interventions
Cough	£879	Weighted average costs for HRG code DZ19H:DZ19N: Other Respiratory Disorders w/wo Interventions
Decreased appetite	£2,166	Assumed same as constipation

Diarrhoea	£2,166	Assumed same as constipation
Dyspnoea	£879	Assumed same as cough
Fatigue	£1,398	Assumed same as pyrexia
Headache	£877	Weighted average costs for HRG code AA31C-AA31E: Headache, Migraine or Cerebrospinal Fluid Leak
Hydronephrosis	£6,161	Weighted average costs for HRG code LA09J-LA09L: General Renal Disorders with Interventions
Hyperglycaemia	£679	Weighted average costs for HRG code WH13A:WH13C: Abnormal Findings without Diagnosis, w/wo interventions
Hypoalbuminaemia	£2,133	Same as leukopenia
Hypokalaemia	£2,133	Same as leukopenia
Hypothyroidism	£1,663	Weighted average costs for HRG code KA07: Non-Surgical Thyroid Disorders
Insomnia	£1,450	Weighted average costs for HRG code AA43: Sleep Disorders, excluding Sleep Apnoea
Leukopenia	£2,133	Weighted average costs for HRG code SA08: Other Haematological or Splenic Disorders
Nausea	£2,166	Assumed same as constipation
Neutropenia	£2,575	Weighted average costs for HRG code SA35A:SA35E: Agranulocytosis
Neutrophil count decreased	£2,575	Assumed same as neutropenia
Oedema peripheral	£873	Weighted average costs for HRG code WH10: Unspecified Oedema
Pain in extremity	£1,471	Assumed same as back pain
Pelvic Pain	£1,518	Weighted average costs for HRG code MB09A: Non-Malignant Gynaecological Disorders w/wo Interventions
Pruritus	£654	Assumed same as rash
Pyrexia	£1,398	Weighted average costs for HRG code WJ07A:WJ07D: Fever of Unknown Origin w/wo Interventions
Rash	£654	Weighted average costs for HRG code JD07K: Skin Disorders without Interventions
Stomatitis	£1,423	Weighted average costs for HRG code CB02A: Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, w/wo Interventions
Thrombocytopenia	£2,564	Weighted average costs for HRG code SA012: Thrombocytopenia
Urinary tract infection	£2,555	Weighted average costs for HRG code LA04: Kidney or Urinary Tract Infections, w/wo Interventions
Vomiting	£2,166	Weighted average costs for HRG code FD10A:FD10M: Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions
White blood cell count decreased	£2,133	Assumed same as leukopenia
Hepatobiliary disorders	£2,550	Weighted average costs for HRG code GC17A:GC17K: Non-Malignant, Hepatobiliary or Pancreatic Disorders

4.2.9.5 Subsequent treatment costs following disease progression (third-line setting)

Following disease progression, patients are assumed to receive active subsequent chemotherapy or BSC. Chemotherapy options include carboplatin in combination with paclitaxel/gemcitabine, as well as single-agent carboplatin, paclitaxel and topotecan.

As ToT estimates for each subsequent treatment were unavailable, expected costs were estimated as the product of drug acquisition cost per treatment cycle, total number of treatment cycles, RDI and proportion of patients receiving each treatment. Dosing schedules and total treatment cycles were based on NHS protocols⁶¹⁻⁶⁴ and clinical expert inputs. Unit costs were obtained from eMIT 2025.⁵⁰ The RDIs for gemcitabine and topotecan were taken from EMPOWER Cervical-1,²³ whereas the RDIs for the remaining chemotherapies were assumed to be ■■■, corresponding to the average RDI for chemotherapies observed in EMPOWER Cervical-1. The proportion of patients receiving subsequent-line treatments in both cemiplimab and chemotherapy groups was informed by clinical input and is summarised in Table 41.

As shown in Table 42 and Table 43, expected drug acquisition and administration costs for subsequent treatments are estimated to be £2,615 for cemiplimab group and £1,299 for chemotherapy group and are applied as one-off costs to all patients at the point of disease progression.

Table 41: Distribution of subsequent treatments applied in the company's model following disease progression (adapted from CS, Table 38)

Component	Cemiplimab	Chemotherapy	Source
Carboplatin in combination with paclitaxel	13.75%	12.50%	Clinical input ⁸⁵⁻⁸⁸
Carboplatin in combination with gemcitabine	7.50%	6.25%	
Carboplatin	1.88%	1.88%	
Paclitaxel	21.25%	6.25%	
Topotecan	5.00%	5.00%	
BSC	50.63%	68.13%	

Abbreviations: BSC, best supportive care

Table 42: Drug acquisition costs of active subsequent-line treatments

Treatment	Administration route	Dosing schedule (weeks)	Total dose per treatment cycle (mg)	Cost per mg	Costs per treatment cycle	RDI	Mean treatment duration (treatment cycles)	Total expected costs	Source
Carboplatin in combination with paclitaxel									
Carboplatin	IV	750 mg, week 1, Q3W	750	£0.04	■	■	6	■	NHS chemotherapy protocol ⁶⁴
Paclitaxel	IV	175 mg/m ² , week 1, Q3W	290	£0.08	■	■	6	■	
Carboplatin in combination with gemcitabine									
Carboplatin	IV	600 mg, week 1, Q3W	600	£0.04	■	■	6	■	NHS chemotherapy protocol ⁶²
Gemcitabine	IV	1000 mg/m ² , days 1 and 8, Q3W	3,316	£0.01	■	■	6	■	
Single-agent treatments									
Carboplatin	IV	750 mg, week 1, Q3W	750	£0.04	■	■	6	■	NHS chemotherapy protocol ⁶³
Paclitaxel	IV	80 mg/m ² , days 1, 8 and 15, Q3W	398	£0.08	■	■	6	■	NHS chemotherapy protocol ⁶¹
Topotecan	IV	1.5 mg/m ² , days 1 to 5, Q3W	12	£22.87	■	■	6	■	NR
Weighted average acquisition cost of active subsequent treatments - cemiplimab group*								■	
Weighted average acquisition cost of active subsequent treatments – chemotherapy group*								■	

Abbreviations: RDI, relative dose intensity; IV, intravenous; mg, milligrams; m², square meter; Q3W, every 3 weeks; N/a, not applicable; NR, not reported

* based on the distribution of each subsequent treatment

Table 43: Drug administration costs of active subsequent-line treatments

Treatment	Dosing schedule (weeks)	Mean treatment duration (treatment cycles)	Number of administrations per treatment cycle	Cost per administration	Total expected costs	Source
<i>Carboplatin in combination with paclitaxel</i>						
Carboplatin	750 mg, week 1, Q3W	6	1	£529	£0 [‡] (EAG correction = £3,176)	NHS Reference Costs 2023/24 ⁵¹
Paclitaxel	175 mg/m ² , week 1, Q3W	6	1			
<i>Carboplatin in combination with gemcitabine</i>						
Carboplatin	600 mg, week 1, Q3W	6	1	£862 [†]	£0 [‡] (EAG correction = £5,172)	NHS Reference Costs 2023/24
Gemcitabine	1000 mg/m ² , days 1 and 8, Q3W	6	2			
<i>Single-agent treatments</i>						
Carboplatin	750 mg, week 1, Q3W	6	1	£387	£2,319	NHS Reference Costs 2023/24
Paclitaxel	80 mg/m ² , days 1, 8 and 15, Q3W	6	3	£476	£8,559	
Topotecan	1.5 mg/m ² , days 1 to 5, Q3W	6	5	£387	£11,596	
Weighted average administration cost of active subsequent treatments - cemiplimab group*					£2,442	
Weighted average administration cost of active subsequent treatments - chemotherapy group*					£1,158	

Abbreviations: mg, milligrams; m², square meter; Q3W, every 3 weeks

* based on the distribution of each subsequent treatment

[†] The model assumed a combined cost for simple and complex chemotherapy delivery.

[‡] The company's base case model includes programming error

4.2.9.6 Health state management and terminal care costs

The company's model includes the per-model cycle disease management costs related to the following health states: pre-progression (on treatment), pre-progression (off-treatment), post-progression and dead (terminal care). The expected costs were estimated by multiplying the unit cost by frequency of resource use and the proportion of patients requiring each resource. Unit costs for each resource use component were taken from NHS Reference Costs 2024/25⁵¹ and PSSRU 2024⁵² (see Table 44). The company sought clinical advice to inform resource use estimates due to a lack of the resource use data in this setting. Apart from terminal care costs, the model assumes treatment-dependent health state management costs in the model, whereby the chemotherapy group requires more resources and therefore incurs higher disease management costs than the cemiplimab group. In response to clarification question B34, a scenario was explored in which the resource use in post-progression state is the same across treatment groups.¹³ The company's estimates of frequency of resource use and the proportion of patients requiring each resource are provided in Tables 34 and 35 of the CS.¹ Table 45 summarises the per-model cycle (weekly) costs applied in the economic model.

Table 44: Summary of unit costs applied in disease management and terminal care costs (adapted from the company's economic model)

Activity	Cost per visit	Reference (NHS Reference Costs 2023/24, ⁵¹ unless otherwise stated)
Hospital based visits		
Gynaecologist	£199.00	Weighted average of consultant and non-consultant led non-admitted face-to-face attendance, follow up. Service code 502 (code WF01A)
Oncologist (face-to-face visit)	£184.30	Weighted average of consultant and non-consultant led non-admitted face-to-face attendance, follow-up. Service code 503 (code WF01A)
Oncologist (non-face to face visit)	£150.42	Weighted average of consultant and non-consultant led non-admitted face-to-face attendance follow-up. Service code 503 (code WF01C)
Specialist nurse	£132.24	Specialist Nursing, cancer-related, adult, face-to-face. Service code 03 (code N10AF)
Community based care		
GP	£45.00	PSSRU 23/24. Unit cost per surgery consultation lasting 10 minutes, including direct care staff costs and with qualification costs
Nurse	£49.00	PSSRU 23/24. Cost per working hour including qualifications average of band 4 & 5
Pain specialist	£170.52	Weighted average of other specialist nursing, adult, face-to-face. Service code 25 (code N29AF)
Specialist nurse	£72.79	Weighted average of specialist nursing, Palliative/Respite Care, adult, face-to-face and non-face-to-face. Service code 03 (codes N21AN and N21AF)

Palliative care team	£104.69	Specialist Nursing, Palliative/Respite Care, Adult, Face to face. Service code 0315 (code N21AF)
Imaging		
CT scan	£133.23	Weighted average of outpatient computerized tomography scans with and without contrast (code RD20A, RD21A, RD22Z to RD27Z)
ECG	£80.16	Directly Accessed Diagnostic Services, Diagnostic Imaging Service (code EY51Z)
Lab tests		
Complete blood count	£2.78	Directly accessed pathology service; haematology. Service code 822 and 999 (code PATH05)
Hepatic function	£1.54	Directly accessed pathology service; clinical biochemistry. Service codes 822 and 999 (code PATH04)
Renal function	£1.54	Assumed same as hepatic function
Cortisol	£1.54	Directly accessed pathology service. Service codes 822 and 999 (code PATH04)
Glucose, HbA1c	£1.54	Assumed same as magnesium
Thyroid	£2.78	Assumed same as complete blood count
Magnesium	£1.54	Directly accessed pathology service; clinical biochemistry. Service codes 822 and 999 (code PATH04)

Abbreviations: CT, Computed tomography; ECG, electrocardiogram; GP, General Practitioner. HbA1c, glycated hemoglobin

Table 45: Disease management and terminal care costs per weekly model cycle

	Cemiplimab	Chemotherapy
Pre-progression - on treatment	£118	£137
Pre-progression - off treatment	£102	£122
Post-progression	£202	£217
Terminal care	£709	

4.2.9.8 EAG critique of resource use and costs

(i) Drug acquisition and administration costs (second-line treatments)

In the calculation of drug acquisition costs, the company's model assumes that all chemotherapy treatments start in model cycle 1, whereas cemiplimab treatment starts in model cycle 0. The company's clarification response (B32) states that "*the first week in the patient's journey is cycle 1*".¹³ The EAG considers that this inconsistent approach results in a slight underestimation of the drug acquisition costs in the chemotherapy arm. This error was corrected in the EAG's preferred analysis (see EA1a, Section 5.2.2). However, given the weekly cycle length of the model, the impact on the ICER was minimal.

In the company's model, the ToT is capped by the PFS so that the cumulative probability of ToT does not exceed that of PFS at any timepoint assuming that cemiplimab or chemotherapy treatment is stopped at the time of disease progression. As discussed in Sections 3.2.1.3 and 4.2.6.4, this approach does not fully reflect EMPOWER Cervical-1, in which 23% of patients continued treatment with cemiplimab

following disease progression (patients with pseudo-progression). As a result, the company's base case model is likely to underestimate the treatment costs in the cemiplimab group while capturing the survival benefits from continued treatment with cemiplimab.

Additionally, the ToT data for chemotherapy group was based on the overall group rather than individual components, which may have different discontinuation rates. However, the EAG clinical advisors did not think that these rates should differ, given the similar efficacy and safety profile across chemotherapies. Additionally, as the costs per treatment cycle for most chemotherapy options are similar except for topotecan, the EAG considers that the company's approach would likely to introduce minimal bias into the cost-effectiveness results.

The EAG notes that EMPOWER Cervical-1 Study protocol allows patients to continue chemotherapy treatments until disease progression or intolerable side-effects. However, some NHS protocols for single-agent chemotherapies,^{61, 89-92} recommended treatment is provided for a maximum of 6 treatment cycles. The company's additional scenario exploring the assumption of 100% weekly paclitaxel for the comparator also incorporates the stopping rule at 18 weeks (6 treatment cycles), but the impact of restricting treatment to 18 weeks for the chemotherapies included in the company's base case was not explored by the company. Therefore, the EAG conducted a scenario, ASA8, in which all chemotherapy treatments are stopped at 18 weeks in order to reflect the NHS treatment protocols. The EAG clinical expert whose preferred second-line treatment was weekly paclitaxel stated that they would offer weekly paclitaxel beyond 18 weeks in some patients and would potentially continue treatment for 8 to 12 months in patients who continued to respond to weekly paclitaxel. This was motivated by a lack of effective third-line options. Therefore, the EAG adapted the company's 100% weekly paclitaxel scenario to remove the 18-week restriction on treatment duration to explore the potential for longer durations of use in clinical practice (see Section 5.2.4, ASA7).

(ii) Subsequent-line treatments

The CS states that the dosing schedules for active subsequent treatments were sourced from NHS protocols. However, the EAG was unable to validate the dose of topotecan and notes that the model applies 1.5 mg/m² on days 1 to 5 Q3W, which is slightly higher than that specified in the EMPOWER Cervical-1 study protocol (1.0 mg/m² on days 1 to 5 Q3W), which is the source cited by the company. Nevertheless, the EAG considers this discrepancy to have a minimal impact on the ICER.

In response to clarification question B31, the company model incorporates the drug administration costs associated with subsequent-line treatments.¹³ However, the company introduced new programming errors when incorporating the administration costs of: (i) carboplatin plus paclitaxel and (ii) carboplatin

plus gemcitabine, which were erroneously set to zero. The EAG has included a correction of this error in its preferred analysis (see EA1c, Section 5.2.2).

The company's model applies the cost of subsequent-line treatment as a once-only cost to all patients at the time of disease progression based on the function of PFS. As PFS counts both progression and death as events, the EAG believes that the company's approach may overestimate the costs because patients who die before disease progression were assumed to incur the costs of subsequent-line treatments. The company's response to clarification questions B24 and B27 state that "*it is not possible to distinguish the proportion of patients dying pre- and post-progression*" and a potential solution is "*assuming that all patients live at least a week after progression (i.e. one cycle), which is the current approach*".¹³ However, the EAG notes that information is provided in the CSR on the proportion of PFS events that are deaths versus progressions making it possible to adjust the subsequent costs accordingly.⁴⁰ In order to adjust for PFS events which were deaths, the EAG's preferred analysis multiplied the drug acquisition and administration costs of subsequent treatments (see EA4, Section 5.2.2) by one minus the proportion of PFS events that were fatal. The method assumes that the proportion of PFS events that are deaths does not vary over time. The rates were taken from EMPOWER Cervical-1 and estimated to be [REDACTED] in the cemiplimab group and [REDACTED] in the chemotherapy group.

The proportion of patients receiving subsequent-line treatments was based on the average input from four clinical experts, and the EAG considers these estimates still remain uncertain. The company's clarification response to question B36 states that post-progression treatments in EMPOWER Cervical-1 were recorded as broad categories rather than as specific treatments, and therefore the study data were not suitable for modelling purposes.¹³ The proportion of patients receiving active subsequent treatment in EMPOWER Cervical-1 was [REDACTED] and [REDACTED] in the cemiplimab and chemotherapy groups, respectively. Compared with the base case model inputs, the observed values are similar in the cemiplimab ([REDACTED] versus 49.4%) group but higher in the chemotherapy group ([REDACTED] versus 31.9%). However, the EAG considers this unlikely to substantially affect the ICER and only explored this in the EAG's scenario analyses (Section 5.2.4).

(iii) Health state management and terminal care costs

The company's model assumes that resource use in both pre- and post-progression health states are treatment-dependent, with the chemotherapy group requiring more resources. The EAG's clinical advisors commented that monitoring requirements following disease progression should not be different across treatment groups; therefore, the EAG has conducted an exploratory analysis in which it assumes the same post-progression health state management costs in both treatment groups (EA5). The EAG

also incorporated this assumption in its preferred base case scenario. Additionally, the EAG's clinical advisors consider that resource use in the post-progression health state depends on the type of subsequent treatment received: patients who received active subsequent treatments require more frequent monitoring than those who receive BSC. Therefore, the EAG conducted a scenario (ASA5) in which only patients receiving active subsequent treatments were assumed to incur health state management costs similar to pre-progression state, while patients with BSC were assumed to incur only palliative care costs. It should be noted that this scenario did not account for the duration of subsequent treatment received as the company's model did not allow this, although in the last 30 days of life the costs are already adjusted to reflect the EOL costs. The ICERs did not change substantially in either of the analyses exploring alternative resource use assumptions (EA5 or ASA5).

The company's model erroneously applies EOL cost of £708.55 as a 30-day cost rather than £3,080.91. Based on the resource use data summarised in Table 36 of the CS and the executable model (worksheet "Detailed routine care costs", cells AG37:AG38 and AG65:AG66), the EAG believes that the 30-day cost of EOL should be £3,080.91. The EAG corrected this error in the EAG's preferred analysis (see EA1b, Section 5.2.2). As all patients in the model ultimately enter the dead state in both treatment groups, this correction was not associated with a substantial change in the ICER.

4.2.10 Model evaluation and validation steps taken by the company

Model evaluation

The ICERs for cemiplimab versus single-agent chemotherapy are presented using both deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,500 Monte Carlo samples. The results of the PSA are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). All model results include the PAS-discounted price for cemiplimab and the list prices for single-agent chemotherapies. All ICERs are presented using decision modifiers of both 1.0 and 1.7. Application of a 1.7 severity modifier is consistent with estimates of the proportionate QALY shortfall obtained using the Decision Support Unit (DSU) severity shortfall calculator,⁹³ in line with NICE TSD23,⁹⁴ and the comparator QALY estimates from the company's base case model (see Section 5.3.1). Several scenario analyses were explored to assess the impact of alternative modelling assumptions, particularly: time horizon; discount rates; treatment mix in the comparator arm; chemotherapy unit costs; the inclusion of TEAE disutilities; drug wastage; health state utility values; and the choice of standard parametric models for survival extrapolation.

For many parameters that are calculated as a function of several inputs including cost parameters related to TEAE management, subsequent treatment, routine care and drug acquisition, the company's PSA takes quite a simplistic approach and applies a standard error (SE) of 10% to the total calculated value.

This may under or overestimate the variance expected if the uncertainty in individual parameters were required to be captured using different distributions. The company's clarification response to question B37 states that *"this is a reasonable simplification used for most cancer models, where the AEs or subsequent treatments are not driving the results"*, and *"any change would be negligible, since subsequent treatments constitute only 4.64% of incremental costs and AEs constitute only 2.17% of incremental costs"*.¹³ The EAG is not satisfied with the company's response as this issue also applies to the estimation of uncertainty associated with drug acquisition costs and routine care costs which are more significant drivers of cost-effectiveness (■% and ■% of incremental costs respectively in the company's base case). For example, a 10% SE is assumed for the acquisition cost of cemiplimab, but the only uncertain variable incorporated into this calculation is the RDI for cemiplimab. The SE around this RDI estimate should be obtainable from the EMPOWER Cervical-1 trial, and it would be much better to include the actual uncertainty associated with the RDI (including the requirement for RDI to be bound between 0 and 1) than to presume a 10% SE for cemiplimab drug acquisition costs. For routine care costs, which are dependent on multiple estimates obtained from clinical experts, the EAG accepts that using a simple 10% SE may be a pragmatic approach. However, it notes that this simplistic approach reduces the validity of the PSA as a means of determining uncertainty around the ICER.

Model validation

The CS states that the company conducted three types of validation for their economic analysis: conceptual, clinical/biological and technical. For conceptual validation, the key assumptions and model inputs were validated by five clinical experts (four from England and Wales and one from Scotland). For clinical/biological validation, the survival predications from the economic model were compared with median PFS, OS and ToT values from EMPOWER Cervical-1, as well as PFS and OS from a published real-world study²⁷ and were also presented to clinical experts. For technical validation, economic model programming was conducted by two modellers, one responsible for the original programming and the other for checking calculations and reference formulas. An additional team member also checked the model inputs.

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions, Section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity, Section 5.4 describes confidential comparator and subsequent treatment prices and Section 5 presents conclusions. All results presented in Section 5 are based on the updated version of the company's model submitted in response to the clarification process.¹³

5.1 Company's cost-effectiveness results

5.1.1 Company's base case

Table 46 presents the central cost-effectiveness estimates from the probabilistic and deterministic models, comparing cemiplimab with chemotherapy. All ICERs include PAS discount for cemiplimab and are presented using severity modifiers of both 1.0 and 1.7. The probabilistic version of the model suggests that cemiplimab is associated with an incremental gain of 0.80 QALYs and an incremental cost of ████████, leading to an expected ICER of ████████ per QALY gained (without severity modifier) and ████████ per QALY gained (with a severity modifier of 1.7). The deterministic model suggests similar findings with a slightly higher ICER of ████████ per QALY gained (without severity modifier) and ████████ per QALY gained (with a severity modifier of 1.7). A detailed breakdown of costs and QALYs is summarised in Table 47.

Table 46: Company's discounted base case cost-effectiveness results, cemiplimab versus chemotherapy, includes cemiplimab PAS, with and without severity weighting

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Probabilistic model[‡]								
Cemiplimab	2.52	1.37	■	1.38	0.80	■	■	■
Chemotherapy	1.14	0.57	£17,091					
Deterministic model								
Cemiplimab	2.45	1.35	■	1.32	0.78	■	■	■
Chemotherapy	1.13	0.57	£16,936					

Abbreviations: LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

*undiscounted

‡re-run by the EAG for 1,500 iterations

Table 47: Base case disaggregated outcomes for the post-clarification company's deterministic model (extracted from the company model by the EAG)

	Cemiplimab	Chemotherapy	Increment (cemiplimab versus chemotherapy)
Disaggregated costs (discounted)			
Drug acquisition costs	██████████	£220	██████████
Drug administration costs	£3,853	£3,746	£107
Subsequent treatment costs	£2,517	£1,282	£1,235
Disease management costs	£16,953	£10,220	£6,733
TEAE management costs	£891	£1,468	-£578
Total costs	██████████	£16,936	██████████
Disaggregated QALYs without severity weighting (discounted)			
Pre-progression (On treatment)	0.41	0.19	0.25
Pre-progression (Off treatment)	0.34	0.06	0.38
Post-progression	0.60	0.31	0.38
Total QALYs	1.35	0.57	1.02

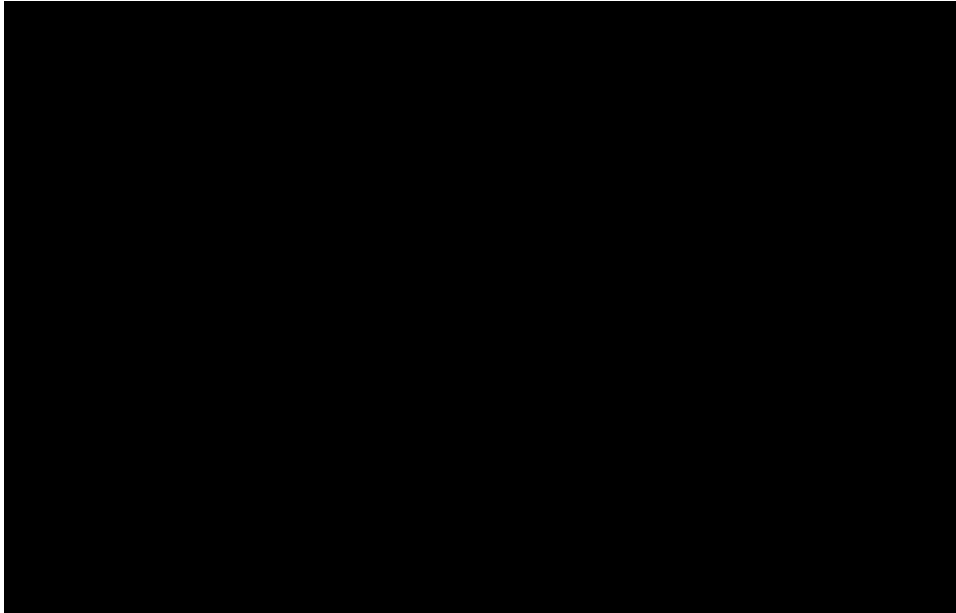
Abbreviations: *QALY* - quality-adjusted life year; *TEAE* - treatment-emergent adverse event

5.1.2 Company's sensitivity and scenario analyses

5.1.2.1 Probabilistic sensitivity analysis

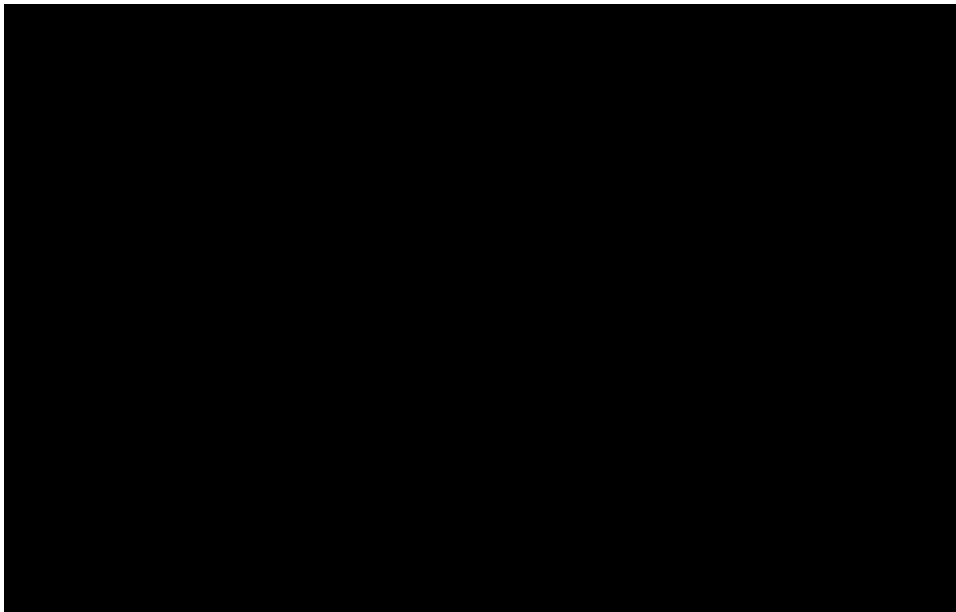
The PSA scatterplots are presented in Figure 30 and Figure 31 and CEACs are presented in Figure 32. The CEACs indicate that the probabilities of cemiplimab generating more net benefit than chemotherapy when assuming a disease severity modifier of 1, are ██████% at a willingness-to-pay (WTP) threshold of £25,000 per QALY gained and ██████% at a WTP threshold of £35,000 per QALY gained. When applying a disease severity modifier of 1.7, the probabilities become ██████% at the £25,000 per QALY gained threshold and ██████% at £35,000 per QALY gained threshold.

Figure 30: Cost-effectiveness plane, cemiplimab versus chemotherapy, includes cemiplimab PAS, without severity weighting (reproduced from Figure 14 of clarification response)



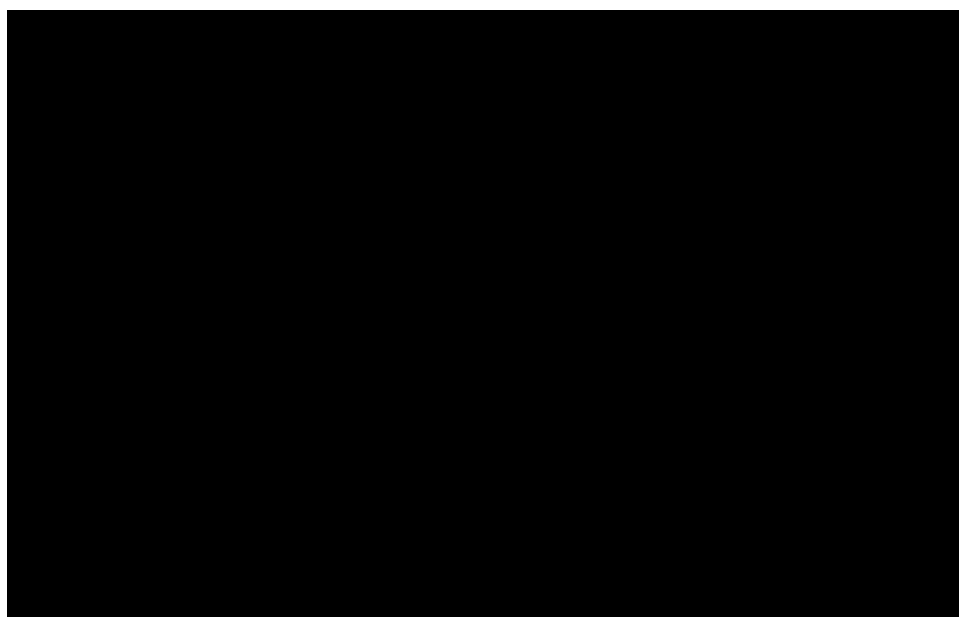
Abbreviations: QALY - quality-adjusted life year

Figure 31: Cost-effectiveness plane, cemiplimab versus chemotherapy, includes cemiplimab PAS, with a 1.7 severity modifier (reproduced from Figure 16 of clarification response)



Abbreviations: QALY - quality-adjusted life year

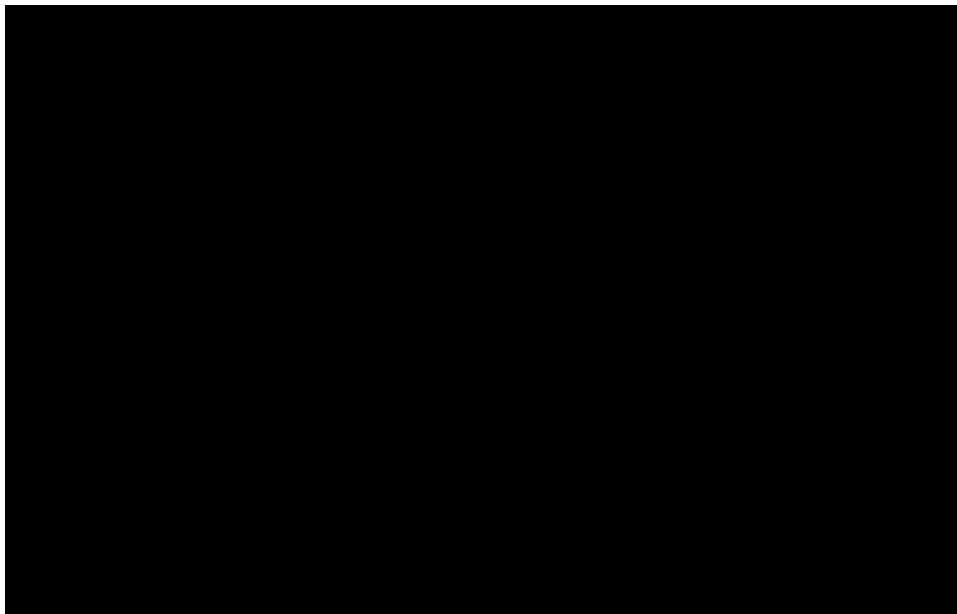
Figure 32: Cost-effectiveness acceptability curves, cemiplimab versus chemotherapy, includes cemiplimab PAS, with a severity modifier of 1.0 and 1.7 (regenerated by the EAG)



5.1.2.2 Deterministic sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact, on the ICER of varying specific parameters in isolation and to identify the main model drivers. Parameters were varied according to its 95% CI, SE or a 10% variation of the mean estimates if those parameters were unavailable. The results are illustrated using the tornado diagram in Figure 33. The ICER was most sensitive to the shape and scale parameters of the log-normal parametric model for ToT, followed by the post-progression health state utility value in the chemotherapy group and management costs of post-progression state in the cemiplimab group. Across all the OWSAs, the ICER ranges from [REDACTED] to [REDACTED] per QALY gained (without severity modifier) and from [REDACTED] to [REDACTED] per QALY gained (with a 1.7 severity modifier).

Figure 33: Tornado plot presenting results of OWSA using 10 most sensitive parameters, cemiplimab versus chemotherapy, includes cemiplimab PAS, without severity weighting (reproduced from Figure 18 of clarification response)



Abbreviations: ToT –

time on treatment; PFS - progression-free survival, IV - intravenous

5.1.2.3 Scenario analysis

Table 48 presents the results of the company's scenario analyses. Across all of the scenario analyses tested, without a severity modifier, the ICER for cemiplimab versus chemotherapy ranges from [REDACTED] per QALY gained (ECOG adjusted PD-L1 < 1% population) to [REDACTED] per QALY gained (ToT for both arms fitted to censored data at 96 weeks using a generalised gamma distribution). When applying a severity modifier of 1.7, the corresponding ICERs range from [REDACTED] per QALY gained to [REDACTED] per QALY gained.

Table 48: Company's scenario analyses on the primary base case (generated by the EAG using the company's updated model)

Scenario description	Incremental QALYs	Incremental Costs	ICER without severity modifier	ICER with severity modifier of 1.7
Base case - deterministic	0.78			
Time horizon = 10 years	0.64			
Time horizon = 20 years	0.75			
Discount rate = 0.0%	0.99			
Discount rate = 6.0%	0.69			
Treatment mix in the comparator arm based on the clinical input	0.78			
Comparator arm based on 100% weekly paclitaxel	0.78			
Weighted average of PD-L1 < 1% & PD-L1 ≥ 1% patients*	0.96			
ECOG adjusted PD-L1 < 1% population	0.75			
OS - chemotherapy = log-normal distribution	0.78			
OS - chemotherapy = log-logistic distribution	0.76			
OS - cemiplimab = log-normal distribution	0.70			
ToT - both arms = generalised gamma distribution	0.78			
PFS - both arms = log-normal distribution	0.75			
Chemotherapy unit cost based on average cost per mg instead of minimum cost per mg across available formulations	0.78			
Chemotherapy unit cost based on maximum cost per mg instead of minimum cost per mg across available formulations	0.78			
Inclusion of TEAE disutilities	0.79			
Exclusion of age adjustment to utilities	0.80			

Scenario description	Incremental QALYs	Incremental Costs	ICER without severity modifier	ICER with severity modifier of 1.7
Health state utility values based on SMC bevacizumab appraisal ⁷⁹ (pre-progression both arms: 0.79 and post-progression both arms:0.63)	0.72			
Health state utility values based on clinical input (post-progression cemiplimab: 0.50, post-progression chemotherapy: 0.42)	0.89			
Exclusion of RDI	0.78			
Inclusion of drug wastage	0.78			
Removal of capping ToT by PFS	0.78			
Exclusion of EOL utilities	0.79			
ToT for both arms: fitted to censored data at 96 weeks, log-normal distribution	0.78			
ToT for both arms: fitted to censored data at 96 weeks, generalised gamma distribution	0.78			
ToT for both arms based on KM curves	0.78			
Assuming no specialist nurse visit in post-progression state in both arms	0.78			
Assuming same specialist nurse visit in post-progression state in both arms	0.78			
Addition of hepatobiliary disorders in TEAE management costs	0.78			

Abbreviations: ECOG – Eastern Cooperative Oncology Group; EOL - end-of-life; ICER - incremental cost-effectiveness ratio; KM - Kaplan-Meier; OS - overall survival; PD-L1 – Programmed Cell Death-Ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; RDI, relative dose intensity; SMC, Scottish Medicines Consortium; TEAE - treatment-emergent adverse event; ToT – time on treatment;

*a detailed breakdown of each component of this scenario is provided in Appendix 2

5.2 EAG's additional analyses

5.2.1 Model validation and face validity checks conducted by the EAG

The EAG performed cell checks and conducted face validity checks on the impact of cost effectiveness outcomes when inputs were varied. The EAG could not detect any logical inconsistencies or suspicious model behaviour, and it believes that the company's model is reliable for decision-making. The EAG also checked the correspondence between model inputs and original source data. A few minor discrepancies were identified in unit costs related to ECG, management of headache and management of elevated alanine aminotransferase. The magnitude of these differences is minimal (less than £7), and the EAG considers they are unlikely to have a significant impact on the cost-effectiveness results; therefore they are not corrected in the EAG's preferred analysis.

5.2.2 EAG's exploratory analyses using company's base case

The EAG's exploratory analyses (EA) were undertaken using the updated model which was provided as part of the company's clarification response.¹³ All analyses were undertaken using the deterministic version of the model. The results of the EAG's preferred analysis are presented using both deterministic and probabilistic versions of the model. All results include PAS discount of cemiplimab and are presented using decision modifiers of both 1.0 and 1.7. Table 49 summaries the EAG's EAs and Table 50 reports the results for each individual EA. Across all EAs, the ICER only varied between [REDACTED] and [REDACTED] per QALY gained.

EA1: Correction of minor programming errors

The following corrections were applied to the company's updated model within a single combined analysis:

- (a) The programming error related to starting treatment in the chemotherapy group, as detailed in Section 4.2.9.8, was corrected. All patients now initiate chemotherapy at cycle 0, rather than cycle 1, to align with cemiplimab group.
- (b) The EOL care cost was amended to reflect a 30-day costs of £3,081 (Section 4.2.9.8).
- (c) The drug administration costs of (i) carboplatin plus paclitaxel and (ii) carboplatin plus gemcitabine were included in the calculation of expected subsequent treatment costs (Section 4.2.9.8). The drug administration costs were estimated to be £3,176 for carboplatin plus paclitaxel, and £5,172 for carboplatin plus gemcitabine.

EA2: Using the KM data to inform ToT with removal PFS capping

As discussed in Section 4.2.6.4, the EAG prefers to use KM ToT data for both cemiplimab and chemotherapy groups. Additionally, the PFS capping on the ToT was removed to reflect a proportion of patients receiving cemiplimab following disease progression (pseudo-progression) in EMPOWER

Cervical-1. The analysis was implemented using additional functionalities included in the company's updated model provided in response to the clarification request. The EAG acknowledges that whilst this analysis captures the additional time on treatment for patients remaining on cemiplimab treatment following pseudo-progression, which is important to accurately capture the cemiplimab treatment costs, it does not adjust the timing of progression within the model for these patients who are assumed to move to the post-progression health state at the time the pseudo-progression event occurred.

EA3: Assuming same post-progression utility in both arms

As discussed in Section 4.2.8.4, the AE related utility decrement may be reversed following discontinuation of chemotherapy due to disease progression; therefore, patients may have a similar quality of life to those who have stopped cemiplimab due to disease progression. In this analysis, the pre-progression utilities are informed by the treatment arm specific estimates from EMPOWER Cervical-1, but the post-progression utility values in both arms are informed by the pooled post progression utility from EMPOWER cervical-1 (0.613).

EA4: Adjustment of PFS to account for fatal events

As discussed in Section 4.2.9.8, the subsequent treatment costs could be overestimated as the company's approach did not differentiate between disease progression and death events before progression. Within this analysis, an adjustment was applied to account for the proportion of PFS events which were deaths when calculating subsequent treatment costs. The EAG estimated the fatal progression rate by dividing the number of PFS death events by the total number of PFS events per treatment arm, ■■■ in the cemiplimab group and ■■■ in the chemotherapy group, based on EMPOWER Cervical-1 (Table 29 of the final CSR).⁴⁰ Subsequent-line treatment costs were then applied only to non-fatal events.

EA5: Assuming same resource use in post-progression health state in both arms

Based on the EAG's clinical input, this analysis assumes that resource use requirements are the same in both treatment groups following disease progression. When setting these equal, the resource use estimates for cemiplimab were applied to the chemotherapy comparator arm.

EA6: Inclusion of immune-related TEAE

As discussed in Section 4.2.7.1, the immune-related TEAE (hepatobiliary disorders) are incorporated in the model using the functionality provided in the company's updated model.

Table 49: Summary of EAG's exploratory analyses using company's base case

EA number	Company's base case assumption	EAG scenario	Section in EAG report
EA1	Programming errors related to treatment starting cycles, EOL care costs and drug administration of subsequent treatments	Correction of programming errors	4.2.9.8
EA2	Using the log-normal standard parametric model fitted to ToT data from EMPOWER Cervical-1. Capping cumulative probability of ToT by that of PFS.	Using the KM ToT data with no PFS capping for ToT.	4.2.6.4
EA3	Assuming treatment-dependent health state utility values based on EMPOWER Cervical-1, pre-progression utility: 0.735 for cemiplimab, 0.613 for chemotherapy post-progression utility: 0.622 for cemiplimab, 0.519 for chemotherapy	Assuming same post-progression utility value across treatment groups based on EMPOWER Cervical-1, pre-progression utility: 0.735 for cemiplimab, 0.613 for chemotherapy, post-progression utility: 0.613 for both arms	4.2.8.4
EA4	Using PFS events which were not adjusted for fatal events in the calculation of subsequent treatment costs	Adjusting PFS to account for fatal events in the calculation of subsequent treatment costs	4.2.9.8
EA5	Assuming treatment-dependent resource use for post-progression health state	Assuming same resource use for post-progression health state in both groups	4.2.9.8
EA6	Exclusion immune-mediated TEAEs	Inclusion of immune-mediated TEAEs	4.2.7.1

Abbreviations: EOL, end-of-life; PFS, progression-free survival; KM, Kaplan-Meier; TEAE, treatment emergent adverse events; ToT, time on treatment

Table 50: Results of EAG’s exploratory analyses using company’s base case

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Company’s base case: deterministic model								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,936					
EA1: Correction of minor programming errors								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£20,185					
EA2: Using the KM data to inform ToT with no PFS capping on ToT in the cemiplimab group								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,682					
EA3: Assuming same post-progression utility value across treatment groups based on EMPOWER Cervical-1 (0.613)								
Cemiplimab	2.45	1.35	█	1.32	0.73	█	█	█
Chemotherapy	1.13	0.62	£16,936					
EA4: Adjustment of PFS to account for fatal events								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,664					
EA5: Assuming same resource use in post-progression health state in both arms								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,481					
EA6: Inclusion of immune-related TEAE								
Cemiplimab	2.45	1.35	█	1.32	0.78	█	█	█
Chemotherapy	1.13	0.57	£16,936					

Abbreviations: ICER - incremental cost-effectiveness ratio; KM – Kaplan-Meier; LYG - life year gained; PFS – progression-free survival; QALY - quality-adjusted life year; TEAE – treatment emergent adverse events; ToT – time on treatment

*undiscounted

5.2.3 EAG's preferred analysis

The EAG's base case combines all EAs (EAs 1-6) listed in Table 49. The deterministic and probabilistic results for the EAG's base case are presented in Table 51. It can be seen that the ICER in the EAG's preferred base case is higher than the ICER in the company's base case; £[REDACTED] versus £[REDACTED] for the deterministic analysis (when applying a severity modifier of 1.7). The probabilistic ICER for the EAG's preferred base case is similar at £[REDACTED]. The probabilities of cemiplimab generating more net benefit than chemotherapy when assuming a disease severity modifier of 1, are [REDACTED]% at a WTP threshold of £25,000 per QALY gained and [REDACTED]% at a WTP threshold of £35,000 per QALY gained. When applying a disease severity modifier of 1.7, the probabilities become [REDACTED]% at the £25,000 per QALY gained threshold and [REDACTED]% at £35,000 per QALY gained threshold.

Table 51: Results using EAG's preferred model assumptions, cemiplimab versus chemotherapy, includes cemiplimab PAS, with and without severity weighting

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Company's base case (probabilistic model)								
Cemiplimab	2.52	1.37	■	1.38	0.80	■	■	■
Chemotherapy	1.14	0.57	£17,091					
Company's base case (deterministic model)								
Cemiplimab	2.45	1.35	■	1.32	0.78	■	■	■
Chemotherapy	1.13	0.57	£16,936					
EAG's base case (probabilistic model)								
Cemiplimab	2.51	1.37	■	1.42	0.74	■	■	■
Chemotherapy	1.09	0.63	£19,172					
EAG's base case (deterministic model)								
Cemiplimab	2.45	1.35	■	1.32	0.73	■	■	■
Chemotherapy	1.13	0.62	£19,043					

Abbreviations: LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

*undiscounted

5.2.4 Scenario analyses using EAG's preferred assumptions

The EAG conducted several additional sensitivity analyses (ASAs) using its deterministic base case as the starting point. The analyses are summarised in Table 52, with results presented in Table 53. All scenarios generated ICERs in the range between [REDACTED] and [REDACTED] (with a severity modifier of 1.0) and between [REDACTED] and [REDACTED] (with a severity modifier of 1.7).

Table 52: Summary of EAG's scenario analyses using EAG's preferred assumptions

ASA number	EAG's base case assumption	EAG's scenario
ASA1a	OS for both arms: generalised gamma	OS cemiplimab: log-normal, OS chemotherapy: log-logistic
ASA1b		OS cemiplimab: log-logistic, OS chemotherapy: log-logistic
ASA1c		OS cemiplimab: 2-knot hazard RCS model, OS chemotherapy: 2-knot hazard RCS model
ASA2	Population: ITT, OS and PFS for both arms: generalised gamma ToT for both arms: KM ToT	Population: PD-L1-weighted (PD-L1 < 1% = 96%), PD-L1 < 1% group; OS cemiplimab arm and PFS chemotherapy arm: log-normal, other curve choice as per company model PD-L1 ≥ 1% group; PFS chemotherapy arm: log-normal, other curve choice as per company model ToT for both arms in both subgroups: KM ToT estimated by the EAG
ASA3		Population: PD-L1-weighted (PD-L1 < 1% = 100%) PD-L1 < 1% group; OS cemiplimab arm and PFS chemotherapy arm: log-normal, other curve choice as per company model ToT for both arms: KM ToT estimated by the EAG
ASA4a	Assuming same post-progression utility value across treatment groups based on EMPOWER Cervical-1, pre-progression utility: 0.735 for cemiplimab, 0.613 for chemotherapy, post-progression utility: 0.613 for both arms	Assuming treatment-independent health state utility values based on the pooled data across arms from EMPOWER Cervical-1, pre-progression utility: [REDACTED], post-progression utility: 0.613 QALY losses related to TEAEs were applied as a one-off value in the first model cycle (see Table 37)
ASA4b		As in the company's base case, assuming treatment-dependent health state utility values based on EMPOWER Cervical-1, pre-progression utility: 0.735 for cemiplimab, 0.613 for chemotherapy post-progression utility: 0.622 for cemiplimab, 0.519 for chemotherapy

ASA5	Post-progression health state management costs applied to all patients following disease progression, regardless of type of subsequent treatment received	Post-progression health state management costs applied only to patients receiving active subsequent treatment and assumed same resource use as in pre-progression health state (on treatment). Patients receiving BSC were assumed to incur only palliative care costs.
ASA6	Proportion of patients receiving subsequent treatment based on the company's clinical input (49.38% for cemiplimab and 31.88% for chemotherapy)	Proportion of patients receiving active subsequent treatment based on EMPOWER Cervical-1 (██████% for cemiplimab and ██████% for chemotherapy)
ASA7	Assuming 37% pemetrexed, 40% gemcitabine, 7% topotecan, 6% irinotecan and 11% vinorelbine for comparator group (based on EMPOWER Cervical-1)	Assuming 100% paclitaxel for comparator group (based on clinical input), with removal of treatment stopping rule at 18 weeks
ASA8	Assuming all chemotherapy treatments follow ToT, based on EMPOWER Cervical-1	Assuming all chemotherapy treatments followed ToT and discontinued at 18 weeks
ASA9	Using KM ToT for both groups without capping of cemiplimab ToT by PFS	Using KM ToT for both groups with cemiplimab ToT capped by PFS
ASA10		Using log-normal curve fitted to the ToT data censored data at 96 weeks, removal of PFS capping before 96 weeks

ASA, additional sensitivity analysis; OS, overall survival, PFS, progression-free survival, ToT, time on treatment; ITT, intention-to-treat; KM, Kaplan-Meier; RCS, restricted cubic splines

Table 53: Results of EAG's scenario analyses using EAG's preferred assumptions

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
EAG's base case: deterministic								
Cemiplimab	2.45	1.35	██████	1.32	0.73	██████	██████	██████
Chemotherapy	1.13	0.62	£19,043					
ASA1a: OS cemiplimab = log-normal, OS chemotherapy = log-logistic, Population = ITT								
Cemiplimab	2.21	1.26	██████	1.00	0.61	██████	██████	██████
Chemotherapy	1.21	0.65	£19,566					
ASA1b: OS cemiplimab = log-logistic, OS chemotherapy = log-logistic, Population = ITT								
Cemiplimab	2.35	1.30	██████	1.15	0.65	██████	██████	██████
Chemotherapy	1.21	0.65	£19,566					
ASA1c: OS cemiplimab = 2-knot hazard RCS model, OS chemotherapy = 2-knot hazard RCS model, Population = ITT								
Cemiplimab	2.41	1.34	██████	1.18	0.68	██████	██████	██████
Chemotherapy	1.23	0.67	£19,826					
ASA2: OS cemiplimab and PFS chemo arms in PD-L1 < 1% group = log-normal, PFS chemo arm in PD-L1 ≥ 1% group = log-normal, Population = PD-L1-weighted (PD-L1 < 1% = 96% of the population) [†]								
Cemiplimab	1.97	1.12	██████	0.85	0.51	██████	██████	██████
Chemotherapy	1.12	0.61	£19,041					
ASA3: OS cemiplimab and PFS chemo arms in PD-L1 < 1% group = log-normal, Population = PD-L1-weighted (PD-L1 < 1% = 100% of the population)								
Cemiplimab	1.93	1.10	██████	0.81	0.49	██████	██████	██████
Chemotherapy	1.12	0.61	£19,040					
ASA4a: Assuming treatment-independent health state utility values (pre-progression utility = █████, post-progression utility = 0.613)								
Cemiplimab	2.45	1.29	██████	1.32	0.65	██████	██████	██████
Chemotherapy	1.13	0.64	£19,043					
ASA4b: Assuming treatment-dependent health state utility values in both pre- and post-progression health states								

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Cemiplimab	2.45	1.35	████████	1.32	0.78	████████	████████	████████
Chemotherapy	1.13	0.57	£19,043					
ASA5: Post-progression resource use costs applied only to patients receiving active subsequent treatment, assumed same resource use as in pre-progression health state - on treatment, patients with BSC incur only palliative treatment costs								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£17,597					
ASA6: Proportion of patients receiving active subsequent treatment based on EMPOWER Cervical-1								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£19,901					
ASA7: Assuming 100% paclitaxel for comparator group, with removal of treatment stopping rule at 18 weeks								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£22,262					
ASA8: Assuming all chemotherapy treatments stopped at 18 weeks								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£17,974					
ASA9: Using KM ToT for both groups with cemiplimab ToT capped by PFS								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£19,043					
ASA10: Using ToT data fitted to censored data at 96 weeks, removal of PFS capping before 96 weeks								
Cemiplimab	2.45	1.35	████████	1.32	0.73	████████	████████	████████
Chemotherapy	1.13	0.62	£19,306					

Abbreviations: ASA, additional sensitivity analysis; BSC – best supportive care; ICER - incremental cost-effectiveness ratio; ITT; intention-to-treat; KM – Kaplan-Meier; LYG - life year gained; OS - overall survival; PD-L1 – Programmed cell death-Ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; RCS – restricted cubic splines; ToT – time on treatment

*undiscounted

†a detail breakdown of each component of this scenario is provided in Appendix 2.

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company states that cemiplimab meets the criteria for a severity weight of 1.7, with an absolute shortfall of 15.21 QALYs and a proportional shortfall of 0.96 QALY. The severity shortfall estimates were derived using the methods outlined in NICE DSU TSD23⁹⁴ and the DSU severity shortfall calculator.⁹³ The company applied the assumptions summarised in Table 54 within the QALY shortfall calculator to generate QALYs for the general population (people without the condition). The EAG considers it appropriate to assume a severity modifier of 1.7 for this decision problem because the proportional shortfall was estimated to be 0.96. The company's and EAG's preferred assumptions for estimating QALY shortfall estimates are summarised in Table 54 for the general population. The results of QALY shortfall analyses and preferred QALY weightings for the company's and EAG's base cases are presented in Abbreviations: QALY, quality-adjusted life-year

Table 55.

Table 54: Summary of company's and EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value	Reference to section in submission or source
Sex distribution	100%	CS Section 2.6.1
Starting age (year)	51.14	CS Section 3.3.1, Table 20
Expected years of life (undiscounted)	34.00	Office for National Statistics lifetables for England and Wales (2022-2024)
Expected QALYs (discounted)	15.78	Executable model
Discount rate	3.50%	CS Section 3.2.6

Abbreviations: QALY, quality-adjusted life-year

Table 55: Results of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

-	Expected total QALYs for the general population (discounted)	Expected total QALYs for people living with a condition on current treatment (discounted)	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	15.78	0.57	15.21	0.96	1.7
EAG's base case	15.78	0.62	15.15	0.96	1.7

Abbreviations: QALY, quality-adjusted life-year

5.3.2 Uncaptured benefits

CS, Section 3.11 describes how a more efficacious treatment that is better tolerated would allow the person with r/m CC to continue to participate in employment or to continue to provide care for other young or elderly family members.¹ The EAG considers that these types of benefits would be classified as productivity benefits, which fall outside of the NICE reference case. Although the CS states that, “*benefit for carers and also family members could be considerable*,” there is no specific description of how the treatment would provide QALY gains in people who care for women with r/m CC. Instead the discussion of uncaptured benefits focuses mainly on benefits to people who are cared for by the person with r/m CC. In order to justify uncaptured benefits for carers, the EAG would have preferred to have seen a more explicit description of the impact of the condition and the impact of different treatments on people caring for the person with r/m CC. The CS also describes how the process of care is less burdensome for patients having cemiplimab versus those having weekly paclitaxel, owing to the 3-weekly dosing of cemiplimab and the shorter infusion time (30 minutes versus 3 hours). The CS also states that the 3-weekly dosing for cemiplimab will free up capacity in chemotherapy infusion suites if it replaces weekly paclitaxel. However, the EAG notes that weekly paclitaxel is not one of the comparator regimens included in the company’s base case and even in the company’s scenario analysis implementing a mix of comparator regimens based on clinical advice, weekly paclitaxel is assumed to be used only 46% of the time, with only topotecan having a more intensive treatment regimen than paclitaxel. The EAG considers that the company’s description of uncaptured benefits places too much emphasis on a comparison with weekly paclitaxel which is not justified given its absence from the company’s base case mix of comparator treatments.

5.3.3 Health inequalities

Section 1.4 of the CS states that people in more deprived socioeconomic groups are disproportionately affected by the cervical cancer, with incidence rates 65% higher in the most deprived socioeconomic group than in the least deprived group. People in the most deprived group are more likely to have a delayed diagnosis and therefore present with advanced cervical cancer. The company states that patients in the most deprived group are disproportionately affected by treatment decision-making and the lack of an effective and well-tolerated second-line treatment for recurrent, persistent and/or metastatic cervical cancer. However, the company has not provided a specific analysis, such as a distributional cost-effectiveness analysis, demonstrating that recommending cemiplimab has the potential to reduce health inequalities. The EAG considers that these disparities are unlikely to be impacted by whether this technology is reimbursed for this indication as they are mostly associated with disease incidence or delayed diagnosis.

5.4 Confidential comparator and subsequent treatment prices

The PAS discount is applied to cemiplimab within the model. As there are no confidential prices for the chemotherapies included in the comparator group, a confidential appendix is not provided.

5.5 Conclusions of the cost-effectiveness section

The EAG was satisfied that the company's model was generally well programmed and suitable for decision making, although it notes three minor programming errors which it corrected in its EAG exploratory analyses. The probabilistic version of the company's base case model provides an expected ICER of [REDACTED] (with a severity modifier of 1.0) and [REDACTED] (with a severity modifier of 1.7). The deterministic ICERs are similar at [REDACTED] and [REDACTED], respectively. The company's scenario analyses provided ICERs ranging from [REDACTED] to [REDACTED] when the severity modifier is 1.0, and from [REDACTED] to [REDACTED] when the severity modifier is 1.7. The ICER is highest when ToT is modelled using the generalised gamma survival model fitted to censored data at 96 weeks in both arms, but this scenario should be considered to be pessimistic as further discussed below.

All of the EAG's exploratory analyses had a minimal impact on the ICER except EA3 and the ICER for the EAG's preferred analysis is moderately increased from the company's base case. The probabilistic ICERs for the EAG's preferred base case are [REDACTED] (with a severity modifier of 1.0) and [REDACTED] (with a severity modifier of 1.7). Deterministic ICERs are similar at [REDACTED] and [REDACTED], respectively. However, the EAG identified several key areas of uncertainties, some of which could not be fully addressed within the EAG's exploratory analyses.

The first key uncertainty relates to the distribution of patients by PD-L1 status within the population likely to receive cemiplimab in clinical practice. The licensed indication for cemiplimab is not restricted by PD-L1 status, and the EMPOWER Cervical-1 trial recruited patients irrespective of PD-L1 status, with PD-L1 status unavailable for 39% of the enrolled cohort. In the cohort with known PD-L1 status, 36% in both arms had PD-L1 < 1%. The EAG notes that the expected mix of PD-L1 status in the target population remains uncertain, but the EAG agrees with the company that a very high proportion is likely to be PD-L1 negative. Although both the company's and the EAG's base cases use the ITT data unweighted by PD-L1 status, different subgroup analyses by PD-L1 status were explored in scenario analyses. For a hypothetical cohort that is 96% PD-L1 negative, the ICERs (with a severity modifier of 1.7) range from £[REDACTED] using the company's preferred base case assumptions to [REDACTED] when using the EAG's preferred base case assumptions. The difference in these ICERs is largely due to the EAG having different preferred extrapolations for OS and PFS within the PD-L1 subgroups. Assuming a 100% PD-L1 negative subgroup, the ICER (with a severity modifier of 1.7) becomes [REDACTED] with the EAG's preferred assumptions. The EAG's scenario analyses demonstrate that the ICER has the

potential to be higher in a cohort dominated by PD-L1 negative patients. However, the EAG does not present the result adjusted for the mix of PD-L1 status as its preferred base case as it considers that the estimates of OS and PFS stratified by PD-L1 status that inform this analysis should be interpreted with caution. This is because the subgroup analyses for PD-L1 status were not pre-specified and were conducted on a subset of the trial population due to some patients having unknown PD-L1 status.

Secondly, there is uncertainty about ToT for cemiplimab in clinical practice. Although the SmPC does not specify a stopping rule, the trial protocol restricted cemiplimab treatment to 96 weeks. Both the company's and the EAG's scenario analyses indicate that cost-effectiveness estimates are sensitive to the choice of survival curves used to extrapolate ToT from the 96-week censored ToT KM data. However, these scenarios are based on the pessimistic assumption that any use beyond 96 weeks would not improve PFS or OS outcomes. The EAG therefore concludes that the expected cost of treatment over the patient's lifetime and the impact of extended treatment on OS and PFS outcomes remains uncertain.

Patients in the cemiplimab arm of EMPOWER Cervical-1 were allowed to continue treatment beyond progression if the progression was considered to be a pseudo-progression by the investigator. These patients were still recorded as progressed for the purpose of PFS assessment, meaning that ToT could be longer than PFS for these individuals. However, the company's base case model applies a cap to ensure that the proportion of patients remaining on treatment does not exceed the proportion remaining progression-free at any timepoint. The EAG's clinical experts confirmed that they would continue treatment in clinical practice if pseudo-progression was suspected and further progression was not observed. The EAG therefore prefers to remove the PFS capping on ToT and use the KM ToT estimates directly in order to better reflect both the outcomes measured in the trial and the expected use of cemiplimab in clinical practice. The EAG incorporated these changes in its preferred analysis and also explored the impact of reintroducing capping in the scenario analysis. The impact on the ICER of applying the capping of ToT by PFS to the EAG base case or removing it from the company's base case is estimated to be small.

Without further information on arm-specific post-progression utility values observed in EMPOWER Cervical-1 and in the absence of a regression analysis including covariates for treatment arm, progression and presence of adverse events, the EAG considers the assumption of different post-progression utility values across arms (based on the same proportionate decrement [■%] associated with progression) remains uncertain. The EAG's clinical experts suggested that post-progression utility should be the same across treatment arms. Therefore, the EAG prefers to assume the same post-progression utility in both arms in its base case analysis. It also explored the impact of assuming

treatment-independent utility in both pre- and post-progression health states in the scenario analysis. Whilst the uncertainty around whether treatment-dependent utilities are appropriate in the post-progression state only has a moderate impact on the ICER, this single factor accounts for the majority of the difference between the EAG and the company's base case ICERs.

Despite tisotumab vedotin being listed as a comparator in the final NICE scope, the company does not consider it to be a relevant comparator as it does not believe that it is currently part of established clinical practice in the NHS. No evidence on the clinical and cost-effectiveness of cemiplimab relative to tisotumab vedotin was provided by the company. Tisotumab vedotin received a UK marketing authorisation from the MHRA in December 2025. The EAG considers that due to overlapping TA timeframes, there is uncertainty regarding whether tisotumab vedotin will form part of established clinical practice by the time the committee makes its final decision on cemiplimab. The EAG would have therefore preferred the company to have provided a comparison against tisotumab vedotin for the committee to consider. In the absence of this evidence, the impact on the ICER of including tisotumab vedotin as a comparator is unknown.

In the comparison of cemiplimab with single-agent chemotherapy, the EAG's base case ICER is not substantially different from the ICER provided by the company's base case. The EAG has identified a number of uncertainties that have the potential to increase the ICER, although the impact of these uncertainties on the ICER remained moderate with none of the EAG's scenario analyses providing an ICER over £[REDACTED] per QALY (when applying a severity modifier of 1.7).

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Appendix 1: Cochrane Risk of Bias (RoB2) assessment of the EMPOWER-Cervical-1 trial (modified from CS, company’s clarification response to question A11)

Domain	Signalling Question	CS Assessment	EAG Assessment
Randomisation process	1.1. Was the allocation sequence random?	Y - "Patients were randomly assigned in a 1:1 ratio to receive either cemiplimab or the investigator’s choice of chemotherapy as the control therapy".	Yes- “Patients were randomly assigned in a 1:1 ratio to receive either cemiplimab or the investigator’s choice of chemotherapy as the control therapy”
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned?	Y - "Randomization was stratified according to histologic type (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]), geographic region (North America, Asia, or rest of the world), previous bevacizumab exposure (yes or no), and ECOG performance-status score (0 or 1)".	Yes – Regeneron Pharmaceuticals ³⁸ explicitly states in the protocol “..according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee)”, suggesting that the allocation sequence was concealed
	1.3 Did baseline differences suggest a problem with randomisation?	N - “The demographic and disease characteristics of the patients at baseline were balanced between the treatment groups (Table 1).”	No – “The demographic and disease characteristics of the patients at baseline were balanced between the treatment groups.”
	Risk of bias judgement (randomisation)	Low	Low - randomisation and concealment of allocation sequence, and no baseline imbalances of key prognostic factors.
Deviations from intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Y - “We conducted EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9, an open-label, multicenter, phase 3 trial...”	Yes – ““an open-label, multicenter, phase 3 trial”
	2.2. Were carers and people delivering interventions aware of assignments?		Yes- As stated above

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations arising from trial context?	N- "Control therapy was discontinued at the onset of disease progression or development of unacceptable toxic effects, with stopping rules for adverse events outlined in the protocol and no crossover allowed."	No - Both groups adhered to the protocol-mandated rules for treatment continuation and discontinuation, and no crossover occurred. However, there was one non-adherent participant (reason unknown) in the control group, but this was very small in proportion and isolated to plausibly affect outcomes.
	2.4. If Y/PY to 2.3: Could deviations have affected outcome?	NA	NA
	2.5. If Y/PY/NI to 2.4: Were deviations balanced between groups?	NA	NA
	2.6. Was an appropriate analysis used to estimate effect of assignment?	Y - "The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle, with patients grouped according to randomized treatment assignment, regardless of adherence."	Yes - "The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle, with patients grouped according to randomized treatment assignment, regardless of adherence." Yes - "Secondary end points of progression-free survival, objective response, response duration, and quality of life were similarly analyzed with the use of the intention-to-treat principle."
	2.7. If N/PN/NI to 2.6: Potential substantial impact of misanalysis?	NA	NA
	Risk-of-bias judgement (effect of assignment)	Low	Low - Awareness of the assignment did not cause bias in the effect estimate, adherence was high, and an

			intention-to-treat (ITT) analysis was conducted.
Missing outcome data	3.1 Were data available for nearly all participants?	Y- "304 were assigned to receive cemiplimab and were included in the efficacy analysis."	Yes - "304 were assigned to receive cemiplimab and were included in the efficacy analysis"
	3.2. If N/PN/Ni to 3.1: Evidence result not biased by missing data?	NA	NA
	3.3. If N/PN to 3.2: Could missingness depend on true value?	NA	NA
	3.4. If Y/PY/Ni to 3.3: Likely missingness depended on true value?	NA	NA
	Risk-of-bias judgement (missing data)	Low	Low - All randomised participants had complete data.
Measurement of outcome (primary endpoint)	4.1 Was measurement method inappropriate?	N - "The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle".	No – standardised and valid tools including RECIST 1.1 and QLQ-C30.
	4.2. Could measurement differ between groups?	N - "The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle".	No – Consistent measurement across groups.
	4.3 Were outcome assessors aware?	Y - "an open-label, multicenter, phase 3 trial"	Yes - "an open-label, multicenter, phase 3 trial"
	4.4. Could assessment be influenced by knowledge?	N - Death and date of death are objective and unlikely to be influenced by assessor	OS: No – objective outcomes, unlikely to be influenced by knowledge of intervention. PFS, ORR, DOR: Yes – No blinded central review; subjective outcomes QoL: Yes – participant-reported outcomes in an open-label are influenced by knowledge of assigned intervention

	4.5. Likely assessment influenced by knowledge?	NA - Death and date of death are objective and unlikely to be influenced by assessor	OS: NA – unlikely to be influenced by assessor’s knowledge PFS, ORR, DOR, QoL: Yes – subjective; likely to be influenced by assessor’s knowledge
	Risk-of-bias judgement (measurement)	Low	Some concerns – although the primary outcome was objective, the secondary outcomes were susceptible to detection bias.
Selection of reported result	5.1. Analysed according to pre-specified plan?	Y - “The statistical analysis plan is available with the protocol at NEJM.org.”	Yes - “The statistical analysis plan is available with the protocol at NEJM.org.”
	5.2. Multiple eligible outcome measurements?	N - “The primary end point, overall survival”	No - Measurement of outcomes utilised single and standardised definitions
	5.3. Multiple eligible analyses?	N - “Differences in overall and progression-free survival were assessed with the log-rank test with the use of geographic region and tumor histologic type as stratification factors, as prespecified in the statistical analysis plan.”	No - “Differences in overall and progression-free survival were assessed with the log-rank test with the use of geographic region and tumor histologic type as stratification factors, as prespecified in the statistical analysis plan.1”
	Risk-of-bias judgement (selection)	Low	Low – pre-specified analysis plan and single outcome measurement and analysis applied
Overall risk of bias	-	Low	Some concern – Most domains were judged at low risk of bias, but overall, there were some concerns primarily due to potential bias in measuring secondary outcomes.

Appendix 2: A detailed breakdown of PD-L1-weighted scenario for both the company's and the EAG's base cases

Option	LYGs*	QALYs	Costs	Incremental LYGs*	Incremental QALYs	Incremental costs	ICER without severity modifier	ICER with severity modifier of 1.7
Company's model for PD-L1 < 1% patients: OS and PFS in both arms= generalised gamma, ToT in both arms = log-normal								
Cemiplimab	3.15	1.51	████████	2.03	0.96	████████	████████	████████
Chemotherapy	1.12	0.56	£16,760					
Company's model for PD-L1 ≥ 1% patients: OS and PFS in both arms= generalised gamma, ToT in both arms = log-normal								
Cemiplimab	2.86	1.53	████████	1.75	0.97	████████	████████	████████
Chemotherapy	1.11	0.56	16,835					
Company's scenario exploring a weighted average of PD-L1 < 1% & PD-L1 ≥ 1% patients (PD-L1 < 1% = 96% of the population)								
Cemiplimab	3.14	1.51	████████	2.02	0.96	████████	████████	████████
Chemotherapy	1.12	0.56	16,763					
EAG's model for PD-L1 < 1% patients: OS in cemiplimab and PFS in chemotherapy arms = log-normal, ToT in both arms = KM ToT								
Cemiplimab	1.93	1.10	████████	0.81	0.49	████████	████████	████████
Chemotherapy	1.12	0.61	£19,040					
EAG's model for PD-L1 ≥ 1% patients: PFS in chemotherapy arm = log-normal, ToT in both arms = KM ToT								
Cemiplimab	2.86	1.53	████████	1.75	0.92	████████	████████	████████
Chemotherapy	1.11	0.61	£19,070					
EAG's ASA2: a weighted average of PD-L1 < 1% & PD-L1 ≥ 1% patients (PD-L1 < 1% = 96% of the population)								
Cemiplimab	1.97	1.12	████████	0.85	0.51	████████	████████	████████
Chemotherapy	1.12	0.61	£19,041					

Abbreviations: LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ASA, additional sensitivity analysis; PD-L1 – Programmed cell death-Ligand 1; OS - overall survival; PFS - progression-free survival; ToT – time on treatment; BSC – best supportive care

*undiscounted

Single Technology Appraisal

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy (review of TA901) [ID6610]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 26 February** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

General comment: We thank the EAG for their thorough work and consider that the EAG report, with few exceptions, represents a balanced critique of the evidence. We have identified a number of areas of the report that would benefit from correction and clarification, as outlined in the tables below. However, we note that none of these, nor the key issues identified in the EAG report, would change the reasonable conclusions that can be drawn from the entirety of the evidence. Cemiplimab is highly clinically effective, provides a much-needed step change in therapy for a small patient population with high unmet need, and with the ICERs at its current PAS price well below £30,000/QALY in all plausible scenarios conducted by the company and by the EAG using its preferred model, cemiplimab is highly likely to represent a cost-effective use of NHS resources in this underserved cervical cancer population.

Issue 1 Tisotumab vedotin as comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 17 and 39-40. In describing the Company's arguments as to why tisotumab vedotin (TV) is not a relevant comparator, the report omits some key points of argument made at CQ stage.	Please include the following in the summary of the Company's arguments. "The Company also notes that the ongoing appraisal of TV does not include cemiplimab as a comparator, and pointed out that NICE Manual section 2.6 notes: 'The chosen comparator must be established in practice and have substantial use in the NHS in England for the same indication'."	This is an important point, raised by the EAG as a key issue, and in the interests of full transparency, these points should be noted in the report.	This is not a matter of factual accuracy. The EAG's report summarises the points the EAG considers most relevant. The committee has access to the company's full submission and its clarification response, and the committee will be aware of the wording of the NICE manual.
p. 17. The report states that "The cost-effectiveness of	Please amend to "due to the lack of evidence provided by the company,	This is an important point, raised by the EAG as a key	This is not a matter of factual accuracy. Further

cemiplimab versus tisotumab vedotin is unknown due to the lack of evidence provided by the company.”	the lack of publicly available price for tisotumab vedotin, and because the cost-effectiveness of TV vs cemiplimab is not explored in the ongoing appraisal of TV”.	issue, and in the interests of full transparency, these points should be noted in the report.	information on the evidence available to the company to provide a comparison against tisotumab vedotin is provided in the following row and a fuller discussion is provided in Section 2.3.3. (p37-38)

Issue 2 Distribution of patients by PD-L1 tumour expression status within the population expected to receive cemiplimab in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
p. 19, p. 90, p. 101 and p. 113 the report states: “the EAG notes that this is due to the company selecting curves to extrapolate OS and PFS in the PD-L1 negative and positive subgroups, based on the best fitting curves in the ITT population” “The company chose to use the same parametric models used in the base case (using the ITT population) for OS,	Please revise as follows: “the EAG notes that this is due to the company selecting curves to extrapolate OS and PFS in the PD-L1 negative and positive subgroups, based on the best fitting curves in both the relevant subgroup and the ITT population” “The company justified this approach based on the best fitting curves in both the relevant subgroup and the ITT population.”	This is an important point, raised by the EAG as a key issue. The quoted sentences suggest that no update of the analysis was conducted, or that the additional analyses were not taken into account. This is incorrect and is important to clarify as the alternative selection of parametric models by the EAG drives the increase in the ICER for this EAG scenario.	This is not a matter of factual inaccuracy. The EAG report does not suggest that the company has not made an assessment of the relevant curves in the PD-L1 subgroup. The process is described over 10 pages in Section 4.2.6.2 and is further critiqued in Section 4.2.6.5.

PFS and ToT. The company justified this approach by stating that in these scenario analyses the number of patients is reduced and there is potentially an increased uncertainty when selecting the most appropriate model.” “However, the choice of model for this scenario was not updated from those selected for the ITT analysis.” “the choice of models for OS, PFS and ToT was not updated”	“However, the choice of model for this scenario was the same as those selected for the ITT analysis.” “the choice of models for OS, PFS and ToT was the same as those selected for the ITT analysis”	The company had assessed the fit of the parametric curves for the specific subgroups, and had provided the results in Appendix 1 of the Response to clarification questions. The response to Question A21 summarised that “The parametric models used in the base case ITT analysis provide one of the best fits in this scenario. As the patient numbers are low in each ECOG subgroup, and therefore the results of the survival analysis are uncertain, the same parametric models were used as in the ITT population.” The curves therefore were selected based on both the assessment of the fit in the given population and the selection in the ITT population given the low patient numbers in the post-hoc subgroup (e.g. the PD-L1<1% population consist of only 22% of the ITT population [134 out of 608]).	Although Appendix 1 of the company’s clarification response provides a description of the method to be used to select the appropriate survival distribution and all of the information required to make that assessment, it does not in fact provide any discussion of the most appropriate curves. Whereas a discussion of the best fitting distributions was provided in Appendix L for the curves fitted to the ITT population. The only information the EAG had on the company’s choice of curves for the PD-L1 subgroups was in the company’s response to A21 which stated “<i>The parametric models used in the base case</i>

			<i>ITT analysis provide one of the best fits in this scenario,” with no further discussion regarding why this model was chosen over others.</i> However, given that the company has now clarified that it took the fits in both populations into account when making its decision, the EAG has amended the report to reflect this (edits on pages 17,18, 88, 89, 99, 112)
p. 116 the report states: “The EAG agrees that the company selected models were appropriate for the majority of cases but believes that alternative models for: OS cemiplimab (PD-L1 < 1% subgroup) and PFS cemiplimab (PD-L1 < 1% and PD-L1 ≥ 1% subgroups) should have been selected.	Please consider providing detailed explanation of why the EAG believes the log-normal model is more appropriate.	The currently given explanation appears to contradict the data. This is important, as the alternative selection of parametric models by the EAG drives the increase in the ICER for this EAG scenario. For OS cemiplimab PD-L1 < 1% subgroup (please see	We thank the company for highlighting this. In the quoted text, the subgroups and outcomes where the EAG suggested an alternative model choice should have been the following: OS cemiplimab (PD-L1<1%) and PFS

Given the AIC/BIC and visual fits, the EAG believes that log-normal models (as opposed to generalised gamma models) would be more appropriate fits for these subgroups/outcomes.”		appendix 1 of response to clarification questions): • AIC was lower for the generalised gamma model than for the log-normal, though the difference was minimal (1.4), below the threshold of 5, which represents meaningful difference as described by the EAG. Therefore, according to AIC, there was no difference between the two models. • While BIC was lower for the log-normal model than for the generalised gamma model, this difference was minimal (0.8), well below the threshold of 5 quoted by the EAG. Therefore, according to BIC, there was no difference between the two models.	chemotherapy_(PD-L1<1% and PD-L1≥ 1%). This has been amended in the text. The EAG noted in these cases that the generalised gamma extrapolation provided the most optimistic projections of OS and PFS. Whilst this model did provide good visual and statistical fit, the log-normal distribution provided similar visual and statistical fits (as noted by the company) but with lower projected OS and PFS estimates. The EAG therefore deemed it appropriate to select these curves within their scenario analysis to further assess the impact of this model choice. Appropriate amendments outlining

		- Based on visual fit, there is no visible difference between the models. - No explanation was provided why the EAG considers a different model should be used for chemotherapy vs cemiplimab. For PFS cemiplimab PD-L1 < 1%, both AIC and BIC were much lower for the generalised gamma model (difference for AIC and BIC respectively: 25.7 and 23.6). For chemotherapy there were no important differences between the two models (difference for AIC and BIC respectively: 1.5 and 3.8). No explanation was provided why the EAG considers that a different model should be used for chemotherapy vs cemiplimab. For PFS cemiplimab and chemotherapy PD-L1 $\geq 1\%$ the same pattern can be seen. It is	this have been made on page 115

		therefore not clear why the EAG categorically prefers its chosen models.	
The description of EAG's ASA2 scenario does not match between tables and body text: p. 116 the report describes the use of "alternative model [lognormal] for OS cemiplimab (PD-L1 < 1% subgroup) and PFS cemiplimab (PD-L1 < 1% and PD-L1 ≥ 1% subgroups)" Table 3 and 52: "PD-L1 < 1% group; OS both arms: log-normal, other curve choice as per company model ; PD-L1 ≥ 1% group; PFS chemo arm: log-normal, other curve choice as per company model"	Please clarify if the description in the tables or in the body text is correct.	The description of the scenario analyses provided in the tables and the text does not correspond. This is important, as the alternative selection of parametric models by the EAG drives the increase in the ICER for this scenario of the EAG.	We thank the company for highlighting the discrepancy between the text on page 115 and the EAG's description of ASA2 and ASA3. We have now updated the descriptions of ASA2 and ASA3 (p158) to align with the amended text (see the above response). Results have been updated in Table 3, Table 53 and Appendix 2 and in relevant sections of the text of pages 18, 26, 158 and 164.

Issue 3 Application of treatment dependent utilities particularly for the post-progression state

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
p. 22 The report states regarding the company's approach for estimating post-progression utility for the chemotherapy arm: "The company considered this approach to be necessary because the pre-progression utility for chemotherapy was very similar to the pooled post-progression utility value and the company considered that this lacked clinical face validity."	Please add the following: "The company considered this approach to be necessary because of the lack of data for the chemotherapy arm post-progression, and because the pooled post-progression utility (representing mainly the cemiplimab arm) meant that the pre-progression utility for chemotherapy was very similar to the pooled post-progression utility value, and the company considered that this lacked clinical face validity."	This was raised by the EAG as a key issue, and is the biggest driver of the difference between the Company's and EAG's base case ICER estimates (albeit that the absolute impact on the ICER as actually small). The report provides only part of the justification submitted by the company. The approach was selected mainly because the very limited data for the chemotherapy arm post-progression (described in detail in both the main text of the CS and in Appendix N) meant that a reliable estimate could not be calculated for the chemotherapy arm post-progression, and the pooled data was driven mainly by data from the cemiplimab	This is not a matter of factual inaccuracy. The EAG is trying to provide a succinct summary of the issue for the purposes of the executive summary with a fuller discussion provided in Section 4.2.8. However, the EAG has added a sentence in section 4.2.8.3 to make it clear that the company's clinical experts supported a difference in utility post-progression due to persistent AEs from chemotherapy (p121). This is then referenced again in the EAG's critique in Section 4.2.8.4 (p125). The EAG had already made reference to the possibility of different post-progression utilities being

		arm and so most closely represented the post progression utility for cemiplimab, rather than both trial arms.	possible due to persistent AEs following chemotherapy in the executive summary on page 22, but additional text has been added on page 21 to make it clear that the company's clinical experts supported this position. The text in section 4.2.8.3 already makes reference to the post-progression data being informed predominantly by cemiplimab patients. However, this fact in itself does not support a difference between arms in post-progression utility. Hence this rationale is not mentioned in the executive summary.
p. 22 The report states regarding the company's approach for estimating post-progression utility for the chemotherapy arm: "The company also stated	Please amend to the following: "The company also stated that different pre- and post -progression utility values were consistent with clinical expectations of poorer quality of life for patients receiving chemotherapy	The current description is not an accurate description of the clinical expectations described in the CS (this	See response to previous comment.

that different pre-progression utility values were consistent with clinical expectations of poorer quality of life for patients receiving chemotherapy versus immunotherapy due to immunotherapy being better tolerated with a lower rate of adverse events (AEs)."	versus immunotherapy due to immunotherapy being better tolerated with a lower rate of adverse events (AEs)."	might be just an inadvertent omission?). The clinical experts' expectations were that quality of life was not only poorer pre-progression for chemotherapy, but also for post-progression, due to the lingering AEs, that are also acknowledged by the EAG on page 127. This was in line with comments by one of the two clinical advisors of the EAG also.	
p. 22 The report states: "The EAG notes that the company did not present arm specific estimates of post-progression utility values."	Please clarify.	While a single utility value for the chemotherapy arm for the post-progression period was not presented due to extremely limited data, values were provided for the post-progression visits where at least 1 patient had data (please see Table 6 and Figure 4 of Appendix N of the CS).	The EAG is correct that the company has not provided an estimate of post-progression utility using all data points available, equivalent to that provided for the progression-free state. The fact that the company provides estimates for individual visits that are based on a smaller sample size than that would be achieved when averaging across all

			visits and then cites 'extremely limited data' as the rationale for not providing the latter does not appear to be consistent, especially when Table 6 does provide an overall arm specific estimate for cemiplimab only. Appendix N implies that the lack of data for later visits in the chemotherapy arm prohibits this analysis from being conducted but it is unclear why the analysis could not be conducted using data up to visit 6. The EAG acknowledges that any analysis of the data in the chemotherapy arm would likely be associated with considerable uncertainty due to the limited data, but still considers that the company has not provided an adequate exploration of

			post-progression utility values. It has made an edit on page 126 to discuss the additional data available in Appendix N and clarify the lack of a single estimate equivalent to that provided for pre-progression utility.
p.22 The report states: “This would mean that patients who have stopped chemotherapy due to disease progression may have a similar quality of life to patients who have stopped cemiplimab due to disease progression, and their post-progression utilities would then be likely to be similar.” Similarly on p. 127 the report states “This would mean that patients who have stopped chemotherapy due to	Please add the following: “It would also mean that progression has no or extremely limited effect on patients who had chemotherapy, which lacks face validity and is not in line with the views of clinical experts.”	The report does not mention that it would also mean that progression has no or extremely limited effect on patients who had chemotherapy (utility changing from 0.62 to 0.61). This lacks face validity and is not in line with the views of clinical experts consulted by the company, nor is it in line with the suggestion of lingering side effects based on the views of the EAG’s clinical expert. This was explained in the CS in section 3.4.5 on page 112 and in section 3.7.2 Table 44, and in the Responses to	This is not a matter of factual accuracy. The EAG does not agree with the company’s interpretation that assuming the same post-progression utility value across arms results in progression having a limited impact in the chemotherapy arm. If the low pre-progression utility value for chemotherapy is being driven by AEs then the gain in utility from coming off treatment and having the AEs reversed may be offset by the loss of utility associated with

disease progression may have a similar quality of life to patients who have stopped cemiplimab due to disease progression, and their post-progression utilities would then be likely to be similar.”		clarification questions for question B13.	progression to give a small net change. This is not the same as saying that progression has no impact. The EAG has noted that AEs such as grade 3+ peripheral neuropathy appear to occur infrequently and in a  so it is not convinced that this can be used as a rationale for lower post-progression utility, see page 126.
p. 126, the report states: “The CS states that treatment-dependent health state utility values were applied in both pre-progression and post-progression health states because of the statistically significant difference in pre-	Please consider revising the sentence to reflect the CS: “The CS states that treatment-dependent health state utility values were applied in both pre-progression and post-progression health states because of the statistically significant difference in utility values between the cemiplimab and chemotherapy	The CS describes the significant difference between the overall utility values between treatment arms without separating them according to progression status. Additionally on page 112 the CS states, that “The	The EAG has re-written this paragraph (p125) so it now focuses on describing AEs as a possible explanation for differences in utilities between arms and then discusses the lack of a regression analysis including AEs to

progression utility values between the cemiplimab and chemotherapy groups in EMPOWER Cervical-1.”	groups in EMPOWER Cervical-1, to include progression disutility in both treatment arms, and in line with clinical expert input.”	combined post-progression mean score was 0.613 (95% CI: 0.570 to 0.656), which represents almost the same value as the pre-progression utility for chemotherapy (0.622). Using this utility for both treatment arms would assume that patients’ HRQoL is not affected by progression if they were taking chemotherapy but is affected by progression if they were taking cemiplimab. This is counterintuitive and contradicts the experience reported by the clinical experts. Additionally, all clinical experts agreed that utilities post-progression would differ between patients who have progressed on 2L cemiplimab vs those who have progressed on 2L chemotherapy, due to persistent AEs with chemotherapy.”	explore this potential driver of utility. Please see the EAG’s response in the previous row on whether the small difference in utilities between the chemotherapy arm pre-progression and the pooled post-progression utility value lacks clinical face validity.

Issue 4 Treatment duration, including treatment beyond progression

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
p. 58 (1 st paragraph) the report states that: "treatment beyond progression occurred in a sizable minority (23%) and therefore has a greater potential to impact the OS and PFS estimates".	Please add the following: "However, the Company noted that PFS in the trial was defined by first reported progression - including pseudo-progression in the cemiplimab arm - which may have underestimated actual PFS in patients on cemiplimab."	This is an important point, raised by the EAG as a key issue. This clarification would provide a balanced discussion of the issue and avoid misinterpretation of the current statement.	The EAG has added a statement similar to that suggested by the company to highlight the potential direction of bias for PFS in patients having pseudo-progression (p56).
Page 20 The report states: "The company's scenario analysis using a log-normal curve to extrapolate from the 96-week censored ToT KM increased the ICER from [REDACTED] to [REDACTED], whereas the ICER increased to £[REDACTED] when using the generalised gamma curve. The EAG notes that the company describes the generalised gamma both as better fitting to the KM	Please revise the second sentence on page 20 as follows: "The EAG notes that the company describes the generalised gamma and log-normal as the best fits according to statistical criteria, however, the company noted that the generalised gamma model has a highly unrealistic long tail and fits	This is an important point, as this relates to a clinically implausible scenario, which is the only scenario that leads to an ICER >£30,000/QALY. The company, in response to clarification question B9, does not describe the generalised gamma as "better fitting to the KM data". Rather, it notes that according to AIC it is the best fitting model, while according to BIC the log-normal model fits the chemotherapy arm better. The generalised gamma model only fits better at the censored end of the	This is not a matter of factual accuracy. The EAG is merely reporting a scenario analysis presented by the company. Whilst the company's clarification response to B9 does describe the best fitting curves according to both AIC and BIC and it does note that the log-normal had a lower BIC

data and as having a highly unrealistic long tail.” Page 98, the report states: “The generalised gamma fit to the cemiplimab ToT re-censored data had the lowest AIC and BIC values, however the company deemed the extrapolation provided by this model to be unrealistic as it resulted in the prediction of patients still being treated at 10 or 20 years following randomisation.”	better only at the censored end of the KM curve.” Please revise the second sentence on page 98 similarly as follows: “The generalised gamma fit to the cemiplimab ToT re-censored data had the lowest AIC and BIC values, however the company deemed the extrapolation provided by this model to be unrealistic as it resulted in the prediction of patients still being treated at 10 or 20 years following randomisation and fitted better only at the censored end of the KM curve.”	KM curve (not the main part of the KM curve), where there are few patients and high uncertainty: “According to AIC, the best fitting model is generalised gamma, followed by the log-normal model, while according to BIC it is either generalised gamma or log-normal depending on the treatment arm (for chemotherapy the log-normal model fits better). Based on the comparison to the observed data, in the cemiplimab arm, the generalised model fits better the artificial, censored end of the observed data.” The current representation of our submission on this point is therefore incorrect in the EAG report, and open to misinterpretation. Additionally, the EAG report describes only one of the reasons why the generalised gamma model is unrealistic. Our response to clarification question B9 also stated: “The use of generalised gamma relies heavily on the fit to the censored, artificial end of the	for the chemotherapy arm, it later describes the log-normal as the “<i>second-best fitting</i>” model, hence the EAG’s interpretation that the company considered the generalised gamma to be the best fitting model. Furthermore, the text in executive summary cannot reproduce the discussion regarding the company’s consideration of the best fitting model in full as it is a summary of the issue. Although the company makes the point that the generalised gamma only fits better at the censored end of the KM curve, this scenario aimed to capture the potential impact of continued treatment

		curve (Figure 9). As it relies on an artificial set of data, its extrapolation is unrealistic. As seen in Figure 9, the generalised gamma model predicts patients to be on cemiplimab treatment even at 10 or 20 years. In the short term, ToT consistently runs above the PFS curve (Figure 10) and in the long-term ToT is very similar to PFS (Figure 11)."	(ignoring the trial imposed 96-week stopping rule). The EAG therefore believes that the end of the KM curve, although artificially censored is a good predictor of the ongoing usage beyond 96 weeks in this scenario compared to the early part of the ToT KM curve that is more likely to reflect early discontinuations due to AEs associated with starting treatment. However, the EAG has amended the text (p19 and p96/97) to better reflect the nuances given the company's concern that the current text may be misinterpreted.
p21. The report states: "Based on this the EAG believes that the ToT in	Please consider deleting this sentence.	The scenario suggested by the EAG is outside the licenced use of cemiplimab in cervical cancer	This is not a matter of factual accuracy.

the model should reflect the actual use of cemiplimab within the clinical trial including any treatment beyond progression.”		(which stipulates treatment may be continued only until disease progression or unacceptable toxicity), and according to the Manual (section 2.2.6) NICE will not develop technology appraisal guidance outside the licence of the technology.	Whilst the SmPC states that treatment can be continued until ‘disease progression,’ it does not provide strict criteria to define disease progression, leaving the treating clinician to distinguish between events that are considered to be a true disease progression and those considered to be a pseudo-progression. The EAG’s clinical advisors stated that they would continue to treat with cemiplimab if the progression observed was considered to be a pseudo-progression as they do already for other immunotherapies. Therefore, the EAG believes that the usage beyond progression observed in the trial,

			which was limited to progression events consistent with pseudo-progression, would occur in clinical practice and would not be considered to fall outside the licensed indication. Furthermore, if the ToT estimates are capped by PFS within the model, they will no longer reflect what occurred in the trial and there will be a discontinuity between the modelled treatment costs and the trial-based estimates of OS and PFS.
p. 19 The report states: “The EMPOWER Cervical-1 trial restricted patients to 16 six-week cycles of cemiplimab (equivalent to 96 weeks of treatment	Please consider revising the statement to reflect the trial.	While the EMPOWER Cervical-1 trial does recommend cemiplimab treatment for up to 96 weeks, it also allows for a longer treatment duration based on eligibility.¹ As a result, in the trial, ■ patients (■%) used cemiplimab ≥96 weeks.	This is not a matter of factual inaccuracy. Patients were restricted in the trial to 16 six-week cycles for the initial treatment course which would be

without delays or interruptions)."			equivalent to 96 weeks when excluding delays or interruptions. Some patients will have had longer than 96 weeks treatment due to dose interruptions or delays but here we are merely stating that 16 cycles is equivalent to 96 weeks when given without delays or interruptions. We have edited the text in the Issue 3 box (p18) to make it clear that treating clinicians would be reluctant to stop at "96 weeks (or 16 six-week cycles)."
p. 19 The report states: "The EAG is therefore concerned that the cost of treatment over the lifetime of a patient could be substantially higher in clinical practice."	Please consider revising the statement by deleting "substantially": "The EAG is therefore concerned that the cost of treatment over the lifetime of a patient could be higher in clinical practice".	In all plausible scenarios the mean time on treatment (ToT) is very stable, increasing by █% (1.6 days) or decreasing by █% (-7 days) with no plausible scenario suggesting any substantial change.	The EAG believes that the quoted statement is reasonable based on the difference in costs between the EAG base-case and the scenario (ASA10) exploring the log-

		EAG is concerned with two issues: 1. Continuing cemiplimab treatment beyond progression, which, in some cases, is allowed in the trial, but not in clinical practice based on the license. 2. Continuing cemiplimab treatment beyond 96 weeks, which is allowed in clinical practice, but, according to EAG's interpretation, not in the trial (this interpretation is not in line with the trial). For the first issue, the scenario analysis submitted by the company uses the KM curve from the trial and after the KM, the extrapolation. Without the cap for progression, while not in line with the license, it represents treatment duration in the trial, using the trial data without any modifications. In the company's base case it increases the ICER marginally, from £[REDACTED]/QALY to £[REDACTED]/QALY. Using the KM is already part of the	normal model fitted to the 96 week censored ToT KM data, which included capping for PFS after 96 weeks to reflect the fact that progression events occurring after 96 weeks are unlikely to be considered pseudo-progressions. The EAG notes that ASA10 does not use the generalised gamma model for ToT, which would result in a mean ToT of [REDACTED] months compared to the [REDACTED] months mean ToT for the log-normal model which was used in ASA10. Whilst there is only a [REDACTED] month increase from the mean ToT in the EAG's base case to the mean ToT used in ASA10, this increases the incremental costs by

		EAG's base case, so it does not change the results. These scenarios include all treatment administrations in the trial, including those beyond progression. With regard to increasing ToT, the mean extrapolated ToT in the company's base case model is █ months for cemiplimab. Using the Kaplan-Meier curve from the trial as it is and not capping it by progression (a scenario which is inconsistent with the licence), increases the mean ToT to █ months (a █% or a 1.6-day increase). In the EAG model, using the EAG base case, the mean ToT also increases to █). Using the method recommended by the EAG but in line with the licence (capping it by progression) decreases the ToT to █ months (a █% or 7-day decrease). For the second issue, EAG is concerned about the 96 weeks treatment limit for cemiplimab in the trial, which might not be used in	~£█. Additionally, █% of patients have stopped treatment at 3 years when using the log-normal model to extrapolate ToT. Whilst this scenario may not accurately reflect the impact of extended treatment on OS and PFS outcomes it does explore the potential impact on costs of use beyond 96 weeks in clinical practice. The small proportion of patients continuing on treatment beyond 96 weeks in the EMPOWER Cervical-1 trial (█%) represent those who had yet to complete the 16 six-week cycles specified as the maximum treatment in the study protocol due to dose delays or interruptions,

		clinical practice. However, the EMPOWER Cervical-1 trial does allow for patients to go beyond 96 weeks using the extension phase based on eligibility.¹ As a result, in the trial, █ patients (█%) used cemiplimab ≥96 weeks. The EAG recommended censoring the KM at 96 weeks and fitting the parametric model on the censored curves. Using the KM and the extrapolated curve based on this, did not change the ICER or the ToT results compared to using the KM and the extrapolation without censoring. The only scenarios where ToT can be higher includes those, where instead of using the available KM curve, a fitted parametric curve is used without a cap for progression. The use of parametric models instead of the KM curve was deemed by the EAG “unnecessary and likely introduces additional uncertainty and inaccuracy in the cost-effectiveness analysis” (p. 112). Additionally, the removal of the cap for progression uses cemiplimab outside its licenced	and the █% who received retreatment following disease progression. Therefore these data cannot be used to predict the proportion continuing beyond 96 weeks in clinical practice where the only restrictions to continued treatment are disease progression or unacceptable toxicity and retreatment after progression is not part of the licensed indication.

		indication (after progression). Even this only leads to a ■ month increase in the ToT (■ months). The only way to achieve a “substantial” increase in the ToT, is by using the above ‘inaccurate and uncertain’ method and assuming unrealistic extrapolation (with the generalised gamma model), that leads to patients taking cemiplimab for up to 20 years after treatment initiation.	
p. 164 (2nd paragraph). The report states that: “The ICER is highest when ToT is modelled using the generalised gamma survival model fitted to censored data at 96 weeks in both arms, but this scenario should be considered to be pessimistic as further discussed below.”	Please amend to “... in both arms, but this scenario is clinically implausible because it models cemiplimab treatment to extend for up to 20 years and beyond in some patients.”	“Pessimistic” is an inappropriate term because it implies that the scenario is within the bounds of possibility, which is clearly not the case. To reiterate, this implausible scenario is the only scenario that leads to an ICER exceeding £30,000/QALY - amongst the company’s and the EAG’s analyses.	This is not factually inaccurate. It is a summary statement in the conclusion section highlighting the highest ICER provided in the company’s scenario analyses. Further discussion on why it is considered pessimistic is provided in later paragraphs of Section 5.5. Furthermore, the committee should note that scenario analysis

			ASA10 which used survival models fitted to the 96 week censored ToT KM, did not use the generalised gamma model to extrapolate ToT and used the log-normal preferred by the company. It also included capping for PFS beyond 96 weeks. It should also be noted that the log-normal model predicts that █% of patients will have stopped treatment at 3 years.

Issue 5: Generalisability of the trial to NHS practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
P. 76 (final paragraph). The report states that the trial has "limited applicability and	Please consider amending in light of the points below.		The EAG does not consider this statement to be factually

generalisability to current UK practice”.			inaccurate as the following paragraph justifies the statement.
p. 58 (3 rd paragraph) and 76 (final paragraph). The report states that: “In the EMPOWER Cervical-1 trial, most patients had experienced disease progression within 6 months of prior platinum-based therapy, leaving uncertainty about the applicability of the evidence to patients relapsing more than 6 months after prior platinum treatment.”	Please add: “However, as a short interval to progression after platinum-based chemotherapy is an adverse prognostic factor associated with poorer survival in r/mCC, there is no reason to suppose that the treatment effect of cemiplimab would be smaller in patients who had a longer PFS with platinum-based therapy”.	If anything, patients with a longer time to relapse would be expected to do better than those with a shorter interval, as the 2020 study in 668 patients by de Foucher et al. ² showed that platinum sensitivity status was a strong prognostic factor for OS after recurrence in advanced CC.	This is not a matter of factual inaccuracy. The EAG has commented on the small proportion of patients enrolled who had progressed more than 6 months after platinum-based therapy as this pertains to the generalisability of the EMPOWER Cervical-1 trial to this subgroup of patients presenting in clinical practice. Information of whether platinum-sensitivity predicts better or worse outcomes in general in patients with r/m CC does not address the issue of these patients being under-represented in the EMPOWER Cervical-1 trial.

p. 77 The report states that: “the EMPOWER-Cervical-1 trial evidence may not fully reflect anticipated routine practice, as the trial excluded patients previously treated with anti-PD-L1 agents”. However, In the 1st line of p.77, the report states that: “cemiplimab is expected to be used as a second-line treatment in patients who have not received prior immunotherapy”. The fact that the trial excluded patients with prior immunotherapy actually supports the generalisability of the trial to clinical practice.	Please reword in light of the contradictory nature of the observations and incorrect interpretation on p.77 about the effect on generalisability of excluding patients with prior immunotherapy.	The fact that the trial excluded patients with prior immunotherapy actually supports the generalisability of the trial to clinical practice. However, the current wording implies that it limits the generalisability rather than supports it.	The quote had been taken out of context. The full sentence is “Finally, cemiplimab is expected to be used as a second-line treatment in patients who have not received prior immunotherapy, representing a narrower subset of the full licensed population.” Whilst we accept that the exclusion of patients with prior immunotherapy from the trial may align the expectation that it would be used in those without prior immunotherapy treatment in clinical practice, it is still true that the license is not restricted to immunotherapy naïve patients. The EAG considers that this is a point the committee should be

			aware of when making recommendations.
p. 56 The report states that: "However, the small number of UK sites (n=2) and patients (not explicitly reported in the CS or Tewari <i>et al.</i> ,) may limit direct applicability to the NHS setting".	Please amend to "... may limit direct applicability to the NHS setting, although UK clinical experts consulted by the company considered that the trial was generalisable to the NHS."	For balance, and to avoid misleading the committee, it is important to acknowledge the clinical expert input on this topic, which confirmed that the trial was generalisable.	The statement made by the EAG is factually accurate, however, we have added the suggested text for additional context (p54).

Other issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
p. 14 lines 2-3. The EAG report states: "The company submission (CS) states that cemiplimab would be given as monotherapy." This is the licensed indication for cemiplimab.	Add "in line with its licensed indication".	Current wording is potentially misleading as it could be read as implying a difference from the licensed indication.	The EAG has amended the first sentence to say "This External Assessment Group (EAG) report assesses cemiplimab as monotherapy for treating recurrent or metastatic cervical cancer (r/m CC) that has progressed on or

			after platinum-based chemotherapy,” to match the sentence at the start of the background section. It has removed the following standalone statement regarding its usage as a monotherapy (p13).
p. 163 (5.3.3) The report states that “The EAG considers that these disparities are unlikely to be impacted by whether this technology is reimbursed for this indication as they are mostly associated with disease incidence or delayed diagnosis.”	Suggest remove this sentence.	The fact patients from deprived socioeconomic groups have a higher incidence and receive a delayed diagnosis means they are at higher risk for having recurrent/metastatic cervical cancer. The decision on whether to reimburse cemiplimab will therefore impact on socioeconomically deprived groups to a greater extent than those in less deprived groups. A DCEA is not required for the committee to recognise this in its decision-making.	This is not a matter of factual inaccuracy. The quoted statement is about whether access to treatment will alter incidence rates or diagnostic delay, and the EAG does not consider that it will. Whilst a DCEA is not required for the committee to consider the potential impact of treatment access on existing inequalities, the option to submit such evidence is now

			part of the NICE manual and the EAG is simply reporting that this has not been done.
p. 49. (Section 3.1.4) In relation to quality assessment in the SLR, the report states: "Due to the lack of detail in the CS (including the company's clarification response to question A10), ³ it is unclear how the quality assessment process was undertaken."	Please add: "However, the assessments by the company and the EAG reached the same conclusion, that the trial was at low risk of bias".	A balanced discussion of this point would include the EAG's risk of bias assessment and would confirm that they reached the same conclusion that trial was at low risk of bias.	Not a matter of factual inaccuracy. The quoted text appears in the EAG's critique of the company's SLR (Section 3.1.4) and is therefore concerned with the methods used by the company and how well these were reported and not whether the EAG agreed with the risk of bias assessment. It is already stated in Section 3.2.1.3 that "that the primary outcome of OS is at low risk of bias " and again in Section 3.7

			that the “The EMPOWER-Cervical-1 trial was generally well conducted and was judged by both the company and the EAG to be at low risk of bias for the primary outcome of OS”
p. 49 (section 3.2) The report states that: “Furthermore, the CS (Section 2.13) does not cite any ongoing studies that will provide additional evidence for cemiplimab in the indication being appraised within the next 12 months.”	Please amend to “the CS reports there are no ongoing RCTs of cemiplimab in r/m CC”.	The amended wording accurately reflects the statement made in the CS.	Amended as suggested (p47).
p. 81 (section 4.1.3). The Company considers that the EAG’s description of our approach to the literature in CS Section 3.1 is	Please amend to acknowledge that the CS does set out the rationale for a de novo economic evaluation using a partitioned survival analysis, with reference to	The following discussion points were listed in the CS Section 3.1 and support the rationale for a de novo economic evaluation using a partitioned survival analysis: At the time of the development of the model structure (2022), only Phippen 20134 was	This is not a matter of factual inaccuracy. The EAG has critiqued the company’s review of published economic

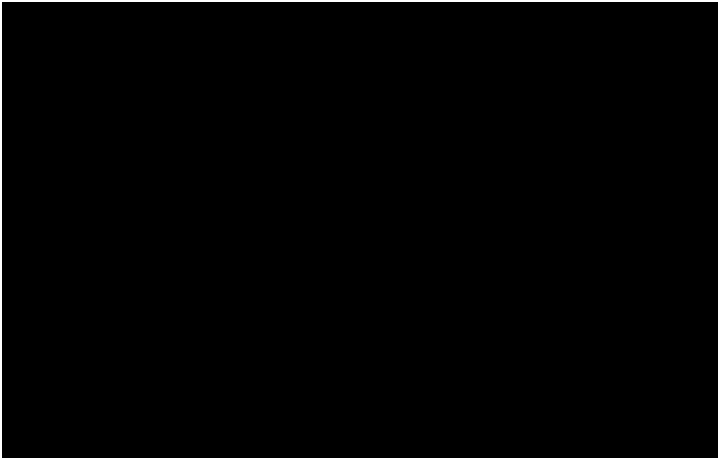
incomplete, and creates an impression that we have not given due regard to literature.	the literature and to prior NICE appraisals.	available, which used a simple decision-tree structure with median survivals assigned for each treatment strategy. This model was not appropriate for the scope of the current model • The two more recent 2L models, and the Shi 2022 1L model, all used progression and death to determine health states, via partitioned survival analysis (PartSA), which is the approach adopted for the de novo model developed for this submission. These structures are based on the implicit assumption that progression and mortality drive costs and health outcomes. The US-based cost inputs from these models were not relevant for decision making. Section 3.1 also includes a discussion of the two prior NICE TAs in this disease area, and why the PartSA approach adopted in our model is suitable vs the STM used in TA939.	evaluations reported in CS, Section 3.1 in EAG report, Section 4.1. The company later makes reference to these studies and some more recent TAs when justifying its choice of model structure in CS, Section 3.2. However, the EAG has not made any criticism of the company's choice to use a partitioned survival model. Therefore repeating the company's justification for its chosen model structure in relation to those used in the published literature is not necessary within the EAG report.

p. 163 (5.3.2). The report states that: “The EAG considers that the company’s description of uncaptured benefits places too much emphasis on a comparison with weekly paclitaxel which is not justified given its absence from the company’s base case mix of comparator treatments.”	Please consider removing this statement.	The EAG accepts that outcomes with different 2L chemotherapies are likely to be similar and the trial outcomes in the comparator arm are sufficiently representative. The fact that the trial did not include paclitaxel is therefore irrelevant to whether paclitaxel is used in UK clinical practice and the outcomes we would expect to see with its use. In the scenario based on clinical advice, 46% receive weekly paclitaxel. Therefore, almost half of patients in clinical practice will accrue the uncaptured benefits relative to weekly paclitaxel. We also note that one of the EAG’s clinical experts reports that they would not only use paclitaxel, but would continue it beyond 18 weeks in patients who continue to respond to it. Furthermore, the EAG included 100% paclitaxel use without an 18-week stopping rule as a scenario analysis (ASA7), which suggest that weekly paclitaxel is highly relevant. In light of all of these points, we consider that the uncaptured benefits vs weekly paclitaxel are highly relevant to patients and service providers in NHS practice and should be taken into account in decision-making.	This is not a matter of factual inaccuracy. Whilst the EAG has stated that OS and PFS outcomes may be similar across the different single-agent chemotherapies used in the clinical trial and those used in clinical practice, issues related to the burden of treatment will vary by regimen and the EAG considers that it is unrepresentative to focus solely on weekly paclitaxel when discussing uncaptured benefits versus current clinical practice when it is not included in the company’s base case scenario.

p. 24 and 140: The report cites NHS protocols that specify that for comparator treatments from the EMPOWER Cervical-1 trial have a maximum duration of 6 cycles contrasting it with the trial. E.g. “Furthermore, in EMPOWER Cervical-1, patients randomised to the chemotherapy arm could receive treatment for up to 96 weeks. The EAG is concerned that this does not reflect clinical practice as NHS treatment protocols for many of the second-line chemotherapies included in the comparator arm specify a maximum duration of 6 cycles,	Please consider removing this statement.	The report does not provide the full citation for these protocols, so it is difficult to verify the specific protocols (1 colorectal cancer, 1 lung cancer, 1 breast cancer, 1 ovarian cancer and 1 gynecological cancer protocols). However, the published protocols do not always align with this statement. For example, one of the irinotecan colorectal protocols (in the indication used in the EAG report), suggests treatment up to 8 cycles⁴ and another one does not provide a maximum duration.⁵ For pemetrexed, one protocol does not set a maximum, only mentions that 6 cycles are set in the Aria system,⁶ another mentions that it is taken until progression.⁷ While the EMPOWER Cervical-1 trial does allow for longer treatment duration, the median duration of chemotherapy treatment was 10.05 weeks, and the mean duration was 14.68 weeks (CSR Table 25), well within the 6 cycles.	As the company has noted, there is variation in the number of treatment cycles recommended in different NHS treatment protocols for these single-agent chemotherapy regimens. The EAG has included a restriction for 18 weeks only as a scenario analysis (ASA8) to explore the potential impact of restricting treatment to 18 weeks. However, in response to the company’s concern, the EAG has amended the text (p140) to make the variation in NHS protocols clearer in the text. It has also amended the references for the NHS protocol the

equivalent to 18 weeks of treatment.”			EAG has cited to link these clearly to the online documents it refers to.
p.29 and other pages mentioning ASA5: EAG’s additional sensitivity analysis (ASA5) to explore the impact of assuming that post-progression resource use for patients having active treatment post-progression is the same as pre-progression resource use.	Please revise the implementation of this scenario and the reporting of its results.	The EAG’s implementation is overestimating the per cycle post-progression health state costs and therefore overestimating total cost and ICER for the treatment with the longer post-progression period, i.e., cemiplimab. This results in a biased estimate. This is due to the assumption used in the EAG’s implementation, that patients who receive active treatment post-progression will incur the higher health state costs associated with the active treatment not just for the duration of the active treatment, but until death.	Unfortunately the company’s model does not distinguish between time on subsequent treatment in the post-progression state and time spent on best supportive care. Therefore, the EAG is not able to adjust this scenario to address the inaccuracy the company has raised. However, the EAG still considers that this scenario is worth reporting as a means of exploring the impact of uncertainty in post-progression costs and it notes that the ICER for ASA5 is

			lower than the EAG base case. The EAG has amended text on page 142 to make this limitation clearer.
p. 91: The report states, that “The clinical experts suggested that the generalised gamma model or the log-normal would be a more appropriate and representative choice. Therefore, the generalised gamma was chosen for the company base case [...]”	Please consider revising the sentence: “All clinical experts suggested that the generalised gamma model would an appropriate and representative choice, and some of the experts also suggested the use of the log-normal distribution. Therefore, the generalised gamma was chosen for the company base case [...]”	The current sentence does not reflect the CS, which states in section 3.3.2: “However, UK clinical experts, who were consulted independently, stated that predictions with the log-logistic and Gompertz models (which only provided the fourth best fit in terms of statistical criteria) are too optimistic for chemotherapies, and the predictions with the generalised gamma model reflect best the survival with chemotherapies in current clinical practice for this patient population.^{6-8,51,52} Some of the experts also recommended predictions with the log-normal distribution as representative of current UK clinical practice.^{6-8,51} As a result, the generalised gamma model was selected in the base case”	This is not a matter of factual inaccuracy. However, the EAG has amended the text to reflect the company’s suggestion (p89).
p. 112 the report states: “However, the EAG believes that the OS data from the EMPOWER Cervical-1 trial was not	Please consider revising the sentences quoted.	The graphs show a good visual fit of the predicted curves to the observed curves in both treatment arms using the generalised gamma model used in the base case. Please see below the graph from the cost-effectiveness model Survival curves sheet, which allows showing only the selected	This is not a matter of factual inaccuracy. The EAG has re-considered the visual fits and it is still of the opinion that the

necessarily best captured by the standard parametric models. For instance, the OS (ITT population) extrapolations shown in Figure 9 and Figure 10 for the cemiplimab and chemotherapy arms respectively, both show that there are periods where the company base case choice of the generalised gamma model over and underestimates the OS KM estimates. The smoothed empirical hazards in Figure 11 also shows hazard shapes which could potentially be better fit by more flexible approaches such as spline models.”		curves for clearer visualisation. The hazard curves only show some deviation at the end of the curves where there are few patients, and the confidence interval is large as can be seen in the CS Appendix L Figure 8. The selected generalised gamma curve is within the confidence interval of the observed curve. This is supported by the results of the EAG’s more flexible curves which modified the ICER by only 4%. 	generalized gamma is over predicting around 20 months for both arms and then underpredicting around 35 months for cemiplimab and 40 months for chemotherapy. The EAG therefore considered it prudent to explore more flexible models which may avoid this over and under estimation of the KM. Though the company is correct that the 95% confidence intervals of the hazard plots (Appendix L, Figure 8) are wide at later time points, the EAG highlights that it was unclear what methods used to generate

On p. 113 similarly the report states.” Given the poorer fit of the standard parametric models to OS for both arms, the EAG explored the fitting of spline models.”			these smoothed hazard plots.
p. 121 the report states: “The EAG was unclear how the company selected the four studies included in Table 35, for discussion in CS, Section 3.4.2, from those identified in the full review of HRQoL studies presented in CS, Appendix F.”	Please consider deleting this sentence.	The CS describes the selection process stating that “Three studies were identified that included utility values for Pre-progression and Post-progression health states”. Additionally, as described in the CS, two HTA assessments were also considered, and one of them with relevant data was included in addition to the published studies.	The EAG has tried to keep Section 4.2.8.2 brief as the CS presents utility data based on the EMPOWER Cervical-1 trial that is more relevant than the estimates from the literature. However, it can elaborate here on why it made that statement. There were some studies included in Appendix F which were not included in CS, Section 3.4.3, and which the EAG could not understand

			why they were not relevant from the information presented. One example is Gupta 2022 for which data on utility is presented in Appendix F, Table 24, covering states such as stable disease, partial response, complete response and progressive disease. It is unclear to the EAG why these data were not presented in the main CS given the availability of utility data for progressed disease. The reverse is also true with utilities included in CS, Table 30, from the SMC appraisal of bevacizumab which were not identified in the SLR reported in

			Appendix F, despite it stating that grey literature, including the SMC website, were searched. The EAG is simply making the point that there is not a clear relationship between the studies reported in Appendix F and those presented in the main CS.
Table 38 reports the 2 nd and subsequent line of treatments inconsistently.	Please consider either revising or adding explanation.	2 nd line treatment costs reported without RDI, while subsequent treatment acquisition costs are reported with the RDI included. Please also note that there is a typo: the cost of vinorelbine should be £31, not £33.	The EAG does not agree that the costs for vinorelbine have been reported incorrectly. (30mg/m ² x ■■■ m ² x £0.33/mg x 2 admin per cycle=£■■■) We have added a footnote to say that subsequent treatment costs include RDI. We have also updated CIC marking in Table 38 and 39 so that the

			body surface area was not back-calculable.
p. 141 the report states: “The company’s response to clarification questions B24 and B27 state that “it is not possible to distinguish the proportion of patients dying pre- and post-progression” [...]However, the EAG notes that information is provided in the CSR on the proportion of PFS events that are deaths versus progressions making it possible to adjust the subsequent costs accordingly.”	Please consider revising as follows: “The company’s response to clarification questions B24 and B27 state that within the partitioned survival model approach “it is not possible to distinguish the proportion of patients dying pre- and post-progression” [...]However, the EAG notes that information is provided in the CSR on the proportion of PFS events that are deaths versus progressions and assuming that the distribution of deaths and progressions in PFS stays constant through the time horizon it would be possible to adjust the subsequent costs accordingly.”	The response in the clarification questions states that within the partitioned survival model approach it is not possible to distinguish the proportion of patients dying pre- and post-progression. This is illustrated by the EAG’s approach, which, as described in the response, substitutes one assumption with another, i.e., it assumes that the distribution of deaths and progressions in PFS stays constant through the time horizon, instead of assuming that patients progress for a week before death. As also described in the response and demonstrated by the EAGs changes, the assumption used has negligible effect on the ICER.	The EAG has added a statement to make it explicit that its approach assumes that the proportion does not vary over time (p141).

Marking check

Location of incorrect marking	Description of incorrect marking	Amended marking				EAG response
EAG Report p. 67-68	Values should be marked CIC, as per the CS (p. 60-61), as the PFS subgroup analysis is unpublished.		Cemiplimab (Events/Total)	Chemo (Events/Total)	HR (95% CI)	Apologies, amended as requested
		All patients				
		Age group 1				
		<65				
		>=65				
		Age group 2				
		<65				
		>=65 and <75				
		>=75				
		Race				
		White				
		Non-white				
		#lines of prior systemic therapy for r/m disease				
		1 line				
		>1 line				
		Disease status				
		Metastatic				
		Recurrent/persistent				
		Time of progression after prior platinum therapy				
		<=6 months				
		> 6 months				

		Investigator choice chemo prior to randomisation			
	Pemetrexed				
	Topotecan				
	Irinotecan				
	Gemcitabine				
	Vinorelbine				
		Histology per IWRS			
	SCC				
	Non-SCC				
		Histology per EDC			
	SCC				
	Non-SCC				
		Geographic region group 1			
	North America				
	Asia				
	Rest of world				
		Geographic region group 2			
	Japan				
	Outside of Japan				
		ECOG status per IWRS			
	0				
	1				
		ECOG status per EDC			
	0				
	1				
		Prior bevacizumab use per IWRS			
	Yes				
	No				

EAG report p. 124-125 (Table 37)	Values should be marked CIC in line with CS Table 28	Prior bevacizumab use per EDC				Apologies, amended as requested
		Yes	████	████	████████████	
		No	████	████	████████████	
		TEAEs	Frequency of TEAEs		Disutility	Source of disutility
			Cemiplimab	Single-agent chemotherapy		
		Abdominal pain	████	████	0.0468	Similar to diarrhoea
		Alanine aminotransferase increased	████	████	0.0567	Other liver disorders in Sullivan <i>et al.</i> ⁸
		Anaemia	████	████	0.0810	NICE TA581. ⁹ Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma.
		Arthralgia	████	████	0.0844	Similar to pain in extremity
		Aspartate aminotransferase increase	████	████	0.0567	Other liver disorders in Sullivan <i>et al.</i>
		Asthenia	████	████	0.0980	Similar to fatigue

		Back pain	■	■	0.0844	Similar to pain in extremity	
		Blood creatinine increased	■	■	0.0567	Other liver disorders in Sullivan <i>et al.</i>	
		Constipation	■	■	0.0468	Similar to diarrhoea	
		Cough	■	■	0.0277	Other respiratory system diseases in Sullivan <i>et al.</i>	
		Decreased appetite	■	■	0.0480	Similar to vomiting	
		Diarrhoea	■	■	0.0468	Nafees <i>et al.</i> ¹⁰	
		Dyspnoea	■	■	0.0277	Other respiratory system diseases in Sullivan <i>et al.</i>	
		Fatigue	■	■	0.0980	Chevalier <i>et al.</i> ¹¹	
		Headache	■	■	0.0844	Similar to pain in extremity	
		Hydronephrosis	■	■	0.0567	Other liver disorders in	

					Sullivan <i>et al.</i>	
		Hyperglycaemia	■	■	0.0351	Diabetes in Sullivan <i>et al.</i>
		Hypoalbuminaemia	■	■	0.0810	Similar to anaemia
		Hypokalaemia	■	■	0.0810	Similar to anaemia
		Hypothyroidism	■	■	0.0005	Sullivan <i>et al.</i>
		Insomnia	■	■	0.0980	Similar to fatigue
		Leukopenia	■	■	0.0897	Similar to neutropenia
		Nausea	■	■	0.0480	Nafees <i>et al.</i>
		Neutropenia	■	■	0.0897	Nafees <i>et al.</i>
		Neutrophil count decreased	■	■	0.0897	Similar to neutropenia and febrile neutropenia
		Oedema peripheral	■	■	0.0844	Assumed pain in extremity
		Pain in extremity	■	■	0.0844	Sullivan <i>et al.</i>
		Pelvic Pain	■	■	0.0844	Similar to pain in extremity

		Pruritus	■	■	0.0325	Similar to rash	
		Pyrexia	■	■	0.1100	Beusterien <i>et al.</i>	
		Rash	■	■	0.0325	Nafees <i>et al.</i>	
		Stomatitis	■	■	0.0400	NICE TA581. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma.	
		Thrombocytopenia	■	■	0.0897	Similar to neutropenia and febrile neutropenia	
		Urinary tract infection	■	■	0.0093	Other urinary tract infection in Sullivan <i>et al.</i>	
		Vomiting	■	■	0.0480	Nafees <i>et al.</i>	
		White blood cell count decreased	■	■	0.0897	Similar to neutropenia and febrile neutropenia	

		Hepatobiliary disorders	■	■	NR		
		Expected QALY loss (one-off) *	0.0021	0.0042			
EAG Report p. 141, 3 rd paragraph	Marking has been omitted from one value, please mark it as shown.	The proportion of patients receiving active subsequent treatment in EMPOWER Cervical-1 was ■ and ■ in the cemiplimab and chemotherapy groups, respectively. Compared with the base case model inputs, the observed values are similar in the cemiplimab (■ versus ■) group but higher in the chemotherapy group (■ versus 31.88%).					The values of 49.4% and 31.9% are the proportion not receiving active subsequent treatment as per CS, Table 38. They have been calculated as one minus the proportion receiving clinical trial or BSC (50.6% and 68.1%). These values were not redacted in CS, Table 38. However, the EAG has amended the report such that they are now reported to the same number of decimal places as

			in CS Table 38, to avoid confusion.

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