Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2719

cemiplimab concentrate for solution for infusion (Libtayo®)

Regeneron UK Ltd

10 January 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process.

cemiplimab (Libtayo®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

In a phase III study, cemiplimab monotherapy resulted in a significant improvement in overall survival, compared with investigator's choice of chemotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Cemiplimab is a fully humanised immunoglobulin G4 (IgG4) monoclonal antibody that increases T cell responses including anti-tumour responses by binding to the programmed cell death-1 (PD-1) receptor and blocking its interaction with its ligands PD-L1 and PD-L2.[1, 2] The recommended dose of cemiplimab is 350 mg every 3 weeks, administered as an intravenous (IV) infusion over 30 minutes; treatment may be continued until disease progression or unacceptable toxicity.[1]

1.2. Disease background

Cervical cancer is a condition whose prevalence in Scotland has largely fallen because of well-established cervical screening and human papilloma virus (HPV) vaccination programmes (started in 2008).[3] However, there are still approximately 340 new cases of cervical cancer diagnosed in Scotland each year; with more diagnoses occurring in areas of high deprivation.[4] The peak incidence of cervical cancer in the UK is in the 30 to 34 years age group.[5] There are two main histologic subtypes of cervical cancer: squamous cell carcinoma (SCC), which accounts for approximately 80% of cases; and adenocarcinoma, which accounts for approximately 20% of cases.[2, 6, 7] Several retrospective studies showed that patients with adenocarcinoma have a higher risk of developing metastases, resulting in a poorer prognosis.[2, 8]

Following treatment of early-stage cervical cancer, distant metastases or multiple recurrence sites develop in up to 61% of patients, usually within the first two years of completing treatment. Recurrent cervical cancer presents as disease isolated to the pelvis (locoregional recurrence), where morbidity can be severely debilitating, or with disease involving other organs or outside the pelvis.[2, 9] Metastatic cervical cancer is normally incurable with 5-year survival rates as low as 15% previously reported.[2] PD-L1 expression is frequently expressed in cervical carcinomas particularly in locally advanced and HPV independent tumours.[7] A study reported a 70% rate of positive PD-L1 expression in patients with cervical cancer, and this was more commonly observed in those with advanced-stage carcinoma, lymph node metastasis, vascular invasion, HPV infection, or previous history of neoadjuvant chemotherapy.[10]

1.3. Treatment pathway and relevant comparators

Preferred first-line treatment for distant recurrent and/or metastatic cervical cancer (chemotherapy naïve) is platinum-based doublet chemotherapy (cisplatin or carboplatin in combination with paclitaxel) with or without bevacizumab.[7, 9] The addition of bevacizumab is associated with improved survival but also increased toxicity, therefore not all patients are suitable for triplet therapy.[7] The addition of pembrolizumab to platinum-based chemotherapy with or without bevacizumab is recommended in patients with PD-L1 positive tumours, assessed as a combined positive score (CPS) ≥ 1; pembrolizumab was accepted for restricted use within NHSScotland for this indication (SMC2501).

There is no standard second-line treatment following progression after first-line therapy. Suitable patients may be rechallenged with platinum-based chemotherapy. Vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel are alternative options, but response outcomes are poor, with overall survival (OS) ranging from 5.0 to 12.7 months.[9] A UK-based

retrospective review (2004 to 2014) of 75 patients with recurrent or metastatic cervical cancer showed that approximately 70% received second-line treatment, with around 39% receiving third-line therapy.[11] The submitting company considered a basket of chemotherapies (based on those used in the EMPIRICAL CERVICAL-1 study) to be the relevant comparator. The latest European guidelines advise that cemiplimab should be offered as a second-line treatment to patients with distant recurrent or metastatic disease regardless of PD-L1 status, provided they have not received immunotherapy first-line.[7]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Cemiplimab meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The main evidence to support the use of cemiplimab for this indication comes from the EMPOWER CERVICAL-1 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	EMPOWER CERVICAL-1[2, 12]
Study design	International, randomised, open-label, phase III study.
Eligible patients	• Adults (≥ 18 years) with recurrent, persistent, and/or metastatic cervical cancer, for which there is not a curative-intent option (surgery or radiation therapy with or without chemotherapy). • Tumour progression or recurrence after treatment with platinum therapy for metastatic, persistent, or recurrent cervical cancer. • Measurable disease as defined by RECIST version 1.1. • ECOG PS 0 or 1. • Anticipated life expectancy >12 weeks. • Previously treated with bevacizumab and paclitaxel (unless they had declined this treatment, it was deemed unsuitable, or bevacizumab was unavailable). • Previous bevacizumab treatment must have been discontinued due to progression or toxicity before enrolment to this study. • No prior anti-PD-1 or anti-PD-L1 therapy. • No patients with ongoing or recent (within 5 years) autoimmune disease that required systemic therapy with immunosuppressant agents.
Treatments & randomisation	Patients were randomised equally to receive cemiplimab 350 mg IV every 21 days (n=304) or IC chemotherapy (n=304). IC chemotherapy, determined before randomisation from protocol-specified options reflecting local treatment availability, were: • pemetrexed (500 mg/m^2 BSA IV every 21 days) • topotecan (1 mg/m^2 IV daily for 5 days, as part of a 3-week cycle) • irinotecan (100 mg/m^2 IV once weekly for 4 weeks, as part of a 6-week cycle) • gemcitabine (1000 mg m^2 IV on days 1 and 8, as part of a 3-week cycle) • vinorelbine (30 mg/m^2 IV on days 1 and 8, as part of a 3-week cycle) Treatment continued up to 96 weeks or until disease progression or unacceptable toxicity.[a] Crossover was not permitted.

	Randomisation was stratified by histology (squamous cell carcinoma or adenocarcinoma), geographic region (North America, Asia, or rest of the world), previous bevacizumab exposure (yes or no), and ECOG performance-status (0 or 1). The stratification factors of prior bevacizumab use and ECOG performance status were used for balancing treatment assignment only and were not included in the statistical model for analysis of the primary endpoint.
Primary outcome	Overall survival, defined as the time from randomisation to the date of death, in the SCC population, then the total population.
Secondary outcomes	<u>Secondary outcomes in pre-specified hierarchical order</u> • PFS in the SCC patients. • Overall LS mean change from baseline in the GHS/QoL scale[b] in SCC patients. • Overall LS mean change from baseline in the physical functioning scale[b] in SCC patients. • ORR in SCC patients. • PFS in total population. • ORR in total population. • LS mean change from baseline to cycle 2 in GHS/QoL scale[b] in SCC patients. Tumour assessments were performed every 6 weeks for the first 24 weeks and every 12 weeks thereafter.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy.

[a] Patients had the option of repeat treatment if they had completed 96 weeks of treatment and then experienced progressive disease in the post-treatment follow-up period.

[b]From the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (QLQ-C30)

Abbreviations: BSA = body surface area; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GHS/QoL = global health status/quality of life; IC = investigator's choice; IV = intravenous; LS = least-squares; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SCC = squamous cell carcinoma.

At the primary analysis (data cut off 04 January 2021), after a median follow-up of 18.2 months, treatment with cemiplimab resulted in statistically significant improvements in overall survival (OS), compared with investigator's choice (IC) of chemotherapy, in both the squamous cell carcinoma (SCC) population (n=477/608) and total population (n=608). There were also statistically significant improvements with cemiplimab compared with IC chemotherapy, in several secondary outcomes, including progression-free survival (PFS) and objective response rate (ORR).[2, 12]

Table 2.2: Primary and selected secondary outcomes from EMPOWER CERVICAL-1 study in the SCC populations and total populations at the primary analysis (data cut-off 04 January 2021).[2, 12]

	SCC population (n=477)		**Total population (n=608)**	
	Cemiplimab (n=239)	**IC chemotherapy (n=238)**	**Cemiplimab (n=304)**	**IC chemotherapy (n=304)**
Median follow-up	16.8 months	16.8 months	17.9 months	18.3 months
Primary outcome: overall survival				
Deaths, n	143	161	184	211
Median OS	11.1 months	8.8 months	12.0 months	8.5 months
HR (95% CI), p-value	0.73 (0.58 to 0.91), p=0.00306		0.69 (0.56 to 0.84), p=0.00011	
KM estimated OS at 12 months	48%	35%	50%	33%
KM estimated OS at 24 months	25%	24%	24%	13%

Secondary outcome: progression-free survival (as per RECIST 1.1 assessed by investigator)				
PFS events, n	197	214	253	269
Median PFS	2.8 months	2.9 months	2.8 months	2.9 months
HR (95% CI), p-value	0.71 (0.58 to 0.86), p=0.00026		0.75 (0.62 to 0.89), p=0.00048	
KM estimated PFS at 12 months	19%	7.3%	11%	8.2%
KM estimated PFS at 24 months	9.7%	Not estimable	8.5%	Not estimable
Secondary outcome: objective response rate (as per RECIST 1.1 assessed by investigator)				
ORR, % (95% CI)	18% (13.0 to 23.0)	6.7% (3.9 to 10.7)	16% (12.5 to 21.1)	6.3% (3.8 to 9.6)
Odds ratio (95% CI), p-value	3.0 (1.63 to 5.53), p=0.00014		2.98 (1.71 to 5.22), p=0.00004	
CR, %	2.9%	0.8%	3.3%	1.0%
PR, %	15%	5.9%	13%	5.3%

Abbreviations: CI = confidence interval; CR = complete response; HR=hazard ratio; IC = investigator's choice; IV = intravenous; KM=Kaplan-Meier;ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SCC = squamous cell carcinoma.

The submitting company also provided results from a final OS analysis (data cut-off 03 October 2023), with a median follow-up of at least 42 months.[13] The OS and PFS results at this cut-off were used to inform the economic analyses; the median OS and PFS (in the cemiplimab and IC chemotherapy groups) were consistent with the earlier data cut-offs.[13]

The proportions of chemotherapy chosen by the investigator in the IC chemotherapy group (n=304) were: gemcitabine (n=121, 40%), pemetrexed (n=111, 37%), vinorelbine (n=32, 11%), topotecan (n=21, 6.9%), and irinotecan (n=19, 6.3%).[2, 12] Subgroup analysis (data cut-off 04 January 2021) according to the type of chemotherapy chosen by the investigator showed median overall survival in the IC chemotherapy group (for the overall population) was: 6.5 months (95% CI: 4.4 to 8.8) for topotecan; 7.6 months (95% CI: 5.2 to 13.2) for vinorelbine; 7.7 months (95% CI: 6.4 to 9.8) for pemetrexed; 9.0 months (95% CI: 7.0 to 10.6) for gemcitabine; and 11.8 months (95% CI: 6.9 to 14.9) for irinotecan.[12]

An exploratory subgroup analysis was conducted on survival by tumour PD-L1 Tumour Cell expression status. Of the total population, 42% (254/608) had samples that were tested for PD-L1; among these samples, 64% (162/254) were PD-L1 ≥ 1% and 36% (92/254) were PD-L1 < 1%. At an updated exploratory OS analysis (data cut-off 04 Jan 2022), with median duration of follow-up of 30.2 months, the HR for the PD-L1 ≥ 1% group was 0.70 (95% CI: 0.48 to 1.01) and the HR for the PD-L1 < 1% group was 0.85 (95% CI: 0.53 to 1.36).[2]

*Other data were also assessed but remain confidential.**

2.2. Quality of life (QoL) outcomes

QoL was measured using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30); this includes five function scales, nine symptom scales, and a global health status (GHS) and quality-of-life (QoL) scale. At the primary analysis (data cut off 04 January 2021), the overall least squares difference between the treatment groups for both of these scales were statistically significant (for the SCC population) and numerically in favour (for the total population) of cemiplimab.[14]

3. Summary of Safety Evidence

In the EMPOWER-Cervical 1 study at data cut-off 04 January 2021, the median duration of treatment was longer in the cemiplimab group (15.2 weeks) than in the chemotherapy group (10 weeks). [2]

The safety analysis set (SAF) included all randomised patients who received any study drug and is based on the treatment received (as treated). In the cemiplimab (n=300) and IC chemotherapy (n=290) groups respectively, the proportions of patients reporting serious treatment emergent adverse events (30% versus 27%), and treatment emergent adverse events (TEAEs) resulting in treatment discontinuation (8.7% versus 5.2%), were slightly higher in the cemiplimab group.[2, 12] Regarding immune-mediated AEs: any (16% versus 0.7%), grade ≥3 (5.3% versus 0.7%), serious (5.0% versus 0.7%), and those resulting in discontinuation (5.0% versus 0.7%), were all higher in the cemiplimab group. However, these were mostly low-grade and deemed to be manageable.[2]

The proportion of patients with any treatment-related AEs (57% versus 81%), grade ≥3 treatment-related AEs (15% versus 40%), treatment-related TEAEs leading to a drug interruption/delay (11% versus 28%), and treatment-related TEAEs leading to a dose reduction (0.0% versus 19%) were all lower in the cemiplimab group compared to the IC chemotherapy group.[12]

The most common grade 3 or higher TEAEs (experienced by ≥2% of patients in either treatment group) were: anaemia (12% versus 27%), urinary tract infection (5.0% versus 2.8%), hypokalaemia (2.7% versus 2.4%), asthenia (2.3% versus 1.0%), hydronephrosis (2.3% versus 0.7), neutropenia (1.0% versus 9.0%), vomiting (1.0% versus 2.4%), leukopenia (0.3% versus 2.4%), nausea (0.3% versus 2.1%), neutrophil count decreased (0.3% versus 4.1%), thrombocytopenia (0.3% versus 3.1%), and white blood cell count decreased (0.0% versus 2.1%).[2, 12] Grade 3 or higher TEAEs from the final analysis (data cut-off 03 October 2023) were included in the cost-effectiveness analysis; the rates of these were very similar to those from the earlier (04 January 2021) data cut-off.

The European regulator concluded that the safety profile demonstrated in the EMPOWER CERVICAL-1 study is consistent with cemiplimab's mode of action and established safety profile in other conditions.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the EMPOWER CERVICAL-1 study, cemiplimab treatment resulted in a statistically significant improvement in overall survival compared with IC chemotherapy[2, 12]; a median survival gain of approximately 3 months is considered clinically relevant for this patient population.[2] Cemiplimab treatment also resulted in statistically significant improvement in several secondary outcomes, including PFS and ORR.[2, 12]
- The study population reflects the proportion of patients expected to have squamous and non-squamous cervical cancer subtypes in clinical practice.[2, 6, 7] The survival benefit of cemiplimab was evident across both squamous and non-squamous subtypes.[2]

- The inclusion criteria of the study are consistent with the anticipated patient population since all patients in the study had prior platinum therapy, and no patients had received prior immunotherapy. Additionally, all patients had received at least one prior line of systemic therapy for recurrent or metastatic disease.[2, 12]

4.2. Key uncertainties

- The licensed indication is irrespective of PD-L1 status. Patients with PD-L1 CPS ≥ 1 are eligible to receive pembrolizumab at the first-line stage, although a small proportion will be ineligible (due to, for example, contraindications such as autoimmune conditions or active infection) but still be eligible for second-line cemiplimab. The EMPOWER-Cervical-1 study did not permit prior anti-PD-L1 or anti PD1 therapy, and cemiplimab is anticipated to be used in patients who have not received prior immunotherapy (that is pembrolizumab). Therefore it is likely to be used for patients with a PD-L1 combined positive score (CPS) < 1. An exploratory subgroup analysis based on PD-L1 status suggested that efficacy improved with increasing PD-L1 expression and there was uncertainty regarding the benefit in PD-L1 <1% subpopulation given this represented only 15% (92/608) of patients in the total population. However, the regulatory authority considered there to be clinical benefit in this underpowered subgroup.[1]

- There is uncertainty whether the proportions of the five chemotherapy agents used in the IC chemotherapy comparator group match those used in Scottish clinical practice for this indication. Based on the responses of clinical experts contacted by SMC, the use of topotecan would perhaps be greater than in the study (6.9%). However, there is no recognised standard of care and the chemotherapy agents used in the IC chemotherapy comparator group of the study are potential treatment options for second-line (and beyond) recurrent or metastatic cervical cancer.[6] There is no evidence versus retreatment with platinum-based chemotherapy.

- No patients had an ECOG PS ≥ 2 in the EMPOWER CERVICAL-1 study.[2, 12] It is likely that there would be some patients with an ECOG PS ≥2, especially at the second-line and beyond stage, who would be eligible for treatment in Scottish clinical practice.

- Cemiplimab showed statistically significant benefit against IC chemotherapy in the SCC population in quality of life scores.[14] However, the clinical significance is uncertain given the open-label design may have biased these patient reported outcomes.[2] Additionally, the differences between the treatment groups for the patient reported outcomes assessing GHS/QoL and physical functioning (in the SCC and total populations) were below the pre-specified 10-point threshold for a clinically meaningful difference.[14]

4.3. Clinical expert input

Clinical experts consulted by SMC considered 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.

4.4. Service implications

Clinical experts consulted by SMC considered that the place in therapy of cemiplimab is as second-line treatment to patients with distant recurrent or metastatic disease regardless of PD-L1 status,

provided they have not received immunotherapy first-line. They considered that the introduction of this medicine would not significantly impact on patients and/or service delivery compared with currently used chemotherapy treatments.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of cemiplimab (Libtayo®), as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced or relapsed cervical cancer is generally an incurable and devastating diagnosis with a short life expectancy. Peak incidence is in young woman aged between 30 to 34 years often with caring and financial responsibility for young families and/or elderly family members. Advanced / relapsed disease carries a huge symptom burden for patients with impairment on activities of daily living, self-care and quality of life. Patients have a high and complex symptom burden. Common symptoms include pain, vaginal bleeding, bowel obstruction, vescio or rectal vaginal fistula formation, shortness of breath, fatigue, and fluid retention. Patients may have had surgery as part of their treatment plan in the earlier stages of cervical cancer which can have longstanding complications. Some may not be able to have children as a result of cervical cancer. 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. Advanced or relapsed cervical cancer is also associated with poor mental health, with anxiety and depression commonly reported. Patients worry about the return of the cancer and in the future more generally for themselves and for their loved ones.
- There is currently no second-line standard of care option for patients with advanced cervical cancer. In the first-line, patients can receive platinum-based doublet chemotherapy with or without bevacizumab. However, second-line treatment options are very limited, and the focus is often on supportive care only. Further chemotherapy options vary by treatment centre, but all are associated with poor response rates and high rates of toxicity. Immunotherapy (pembrolizumab) has been recently made available in this setting for patients in the first-line if they have high PDL1 expression. This leaves a significant gap and a high unmet need for those patients ineligible for currently available immunotherapy (i.e. patients with tumours that do not express PD-L1 and those whose tumours do express PD-L1 but who for a variety of reasons did not receive earlier treatment with pembrolizumab). For example, patients may have had neoadjuvant chemotherapy treatment and would therefore not be eligible for pembrolizumab.
- Cemiplimab is an immunotherapy treatment that would enable patients to continue experiencing good quality of life without heavy symptomatic burden from rapidly progressing cancer, and to ultimately live longer. Cemiplimab could allow young women to continue in employment or education or provide ongoing care of young dependants and elderly family members. The ability to continue with day-to-day life as quickly as possible is very important for both patients and their families. In addition, cemiplimab treatment can be delivered in a

chemotherapy day unit, and the infusions are quick to deliver and are less frequent than chemotherapy. This is convenient for patients and allows them to maintain quality of life with less frequent hospital visits and increased time at home with less disruption. PACE participants also considered that the toxicity profile of cemiplimab is preferable to second line chemotherapy agents in carefully selected patients. Cemiplimab is available to patients irrespective of PDL1 status. Cemiplimab offers hope for patients at a durable response and will help to alleviate anxiety.

- Cemiplimab provides a much more effective treatment option which can improve the lives of patients and family members/carers. It would allow patients to maintain independence and quality of life for longer durations, which has benefits for family members and carers. Given the high incidence of cervical cancer in young women the ability to continue caring for their families is of the upmost importance to this patient group and minimising time in hospital whilst providing meaningful clinical benefit cannot be underestimated. Patients in this setting can be carers themselves, for both young children and older family members. 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. The safety profile of cemiplimab is also felt to be better than conventional chemotherapy, which has the added benefit of patients requiring less support from family members or carers. Fewer hospital visits for administration also has benefits for family members and carers, who often accompany patients to these visits. Altogether, the benefits for family members and carers are considerable.

- Immunotherapies such as cemiplimab are used widely within Scottish Cancer Centres who have well equipped clinical pathways in place to deliver and monitor treatment. Chair time in chemotherapy units and outpatient visits are generally less than with conventional chemotherapy, which is an important consideration and benefit to the service. Treatment and monitoring protocols outlined in the clinical studies should be adopted, which will allow for early detection of toxicity as well as clinical effectiveness, including timely cessation of medications should it not prove effective. The introduction of cemiplimab would help address a large gap in current practice, allowing patients to receive an effective immunotherapy who would otherwise at present not receive one. PACE participants highlighted the potential equality issues related to cervical cancer and women's health, and noted that cemiplimab would be a positive step in addressing these.

Additional Patient and Carer Involvement

We did not receive any Patient Group Submissions for this medicine. However, SMC's public involvement team worked closely with Patient Group Partner, the Scottish Cancer Coalition, to support the participation of a patient with lived experience of cervical cancer in the assessment of this medicine. The Scottish Cancer Coalition has not received any pharmaceutical company funding in the past two years. We received a PACE statement from the patient expert supported by the Scottish Cancer Coalition. The patient expert also participated in the PACE meeting. The key points of their statement have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis is presented in Table 6.1.

Table 6.1 Description of economic analysis

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Time horizon</td><td>Lifetime horizon, translating to 33 years.</td></tr>
<tr><td>Population</td><td>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.</td></tr>
<tr><td>Comparators</td><td>A basket of chemotherapy based on those used in EMPOWER-Cervical 1[12] was used as the comparator. They were distributed as below:
<table>
<tr><th>Chemotherapies included</th><th>Percentage of patients receiving</th></tr>
<tr><td>Pemetrexed</td><td>36.5%</td></tr>
<tr><td>Gemcitabine</td><td>39.8%</td></tr>
<tr><td>Topotecan</td><td>6.9%</td></tr>
<tr><td>Irinotecan</td><td>6.3%</td></tr>
<tr><td>Vinorelbine</td><td>10.5%</td></tr>
</table></td></tr>
<tr><td>Model description</td><td>The submitting company submitted a partitioned survival analysis. The model defined health states based on survival curves and included three health states: pre-progression, post-progression, and death. The distribution of patients between these states was estimated using the area under the survival curves. All patients started in the pre-progression state and the cycle length in the model was 7 days.</td></tr>
<tr><td>Clinical data</td><td>The source of the clinical evidence was the EMPOWER Cervical-1 trial as described above.[12] Treatment continued up to 96 weeks or until disease progression or unacceptable toxicity.</td></tr>
<tr><td>Extrapolation</td><td>The model extrapolated the overall survival (OS), progression-free survival (PFS) and time on treatment (ToT) outcomes. The company followed appropriate steps to determine the approach to extrapolation with the resulting base case distributions being applied as presented below:
Parametric models used in the base case are presented below:
<table>
<tr><th>Treatment</th><th>Base case distributions used for cemiplimab</th><th>Base case distributions used for chemotherapy</th></tr>
<tr><td>Overall survival</td><td>Log-normal</td><td>Generalised gamma</td></tr>
<tr><td>Progression-free survival</td><td>Generalised gamma</td><td>Generalised gamma</td></tr>
<tr><td>Tim-on-treatment</td><td>Log-normal</td><td>Log-normal</td></tr>
</table></td></tr>
<tr><td>Quality of life</td><td>In the EMPOWER-Cervical 1 trial, health-related quality of life (HRQoL) was measured using the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire, administered at baseline and across eight visits up to 96 weeks. 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. A linear mixed-effect repeated measures model (MMRM) of the post EQ-5D-3L score was then performed. On the basis of the results obtained, treatment-specific utility values were applied in the model.</td></tr>
<tr><td>Costs and resource use</td><td>Medicine costs included were acquisition and administration costs, subsequent treatment costs and adverse event costs. No wastage costs were included in either treatment arm. Other costs included were disease management costs, estimated by expert opinion. This resource use was assumed to be</td></tr>
</table>

	the same for patients on cemiplimab and for patients on chemotherapy, except for additional endocrinologist visits once every 3-4 months, for a small proportion of patients on cemiplimab.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

The main driver of results was the acquisition cost of cemiplimab and the increased pre-progression period due to the better PFS results with cemiplimab. The quality adjusted life year (QALY) gain over chemotherapy was 0.70.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Tables 6.1 and 6.2.

Table 6.1 Scenario Analysis Results

	Parameter	Base case	Scenario	Incremental QALYs
	Base case			0.70
1	Time horizon	Lifetime	10 years	0.61
2	Comparator	Mono chemotherapies	Combination chemotherapies	0.70
3	Parametric curve for OS chemotherapy	Generalised gamma	Log-normal	0.70
4			Log-logistic	0.68
5	Parametric curve for OS cemiplimab	Log-normal	Generalised gamma	0.79
6	Parametric curve for ToT for both arms	Log-normal	Generalised gamma	0.70
7	Parametric curve for PFS for both arms	Generalised gamma	Log-normal	0.67
8	Chemotherapy costs	Mean costs per mg	Minimum cost per mg	0.70
9			Maximum cost per mg	0.70
10	TEAE disutilities	Excluded	Included	0.71
11	Health state utilities	EMPOWER-Cervical 1 trial utilities: treatment specific	Shi et al. 2022	0.70
12			SMC bevacizumab utilities	0.64

13			Clinical expert input	0.81
14	RDI	Included	Excluded	0.70

Abbreviations: BSC = best supportive care; QALYs =quality-adjusted life years; RCT = Randomized controlled clinical trials; OS = Overall survival; ToT = Time on treatment; PFS = Progression free survival; TEAE = Treatment-emergent adverse event

Additional scenario analyses provided are presented in Table 6.2.

Table 6.2 Additional Scenario Analysis Results

	Parameter	**Base case**	**Scenario**	**Incr. QALYs**
	Base case			0.70
1	Time horizon	Lifetime	5 years	0.46
2	Health state utilities	EMPOWER-Cervical 1 trial utilities: treatment specific	Equal post- progression utilities	0.65
3	Combined scenario		Equal post- progression utilities & AE disutilities & 5-year time horizon	0.41
4	PD-L1 status	ITT	PD-L1 <1% adjusted for ECOG PS	0.33
5		ITT	Population reweighted for PD-L1 status	0.46
6	Combined scenario		- PD-L1 <1% within stability window adjusted for ECOG PS - 10 year time horizon - Equal post progression utilities and AE disutilities	0.29

7	Combined scenario		- Population reweighted for PD-L1 status - 10 year time horizon - Equal post progression utilities and AE disutilities	0.37

Abbreviations: AE= adverse events; BSC = best supportive care; QALYs =quality-adjusted life years; RCT = Randomized controlled clinical trials; OS = Overall survival; ToT = Time on treatment; PFS = Progression free survival; TEAE = Treatment-emergent adverse event; ITT = intention to treat; PD-L1 = Programmed cell death-ligand 1

6.4. Key strengths

- The model type was appropriate.

6.5. Key uncertainties

- There is uncertainty whether the proportions of the five chemotherapy agents used in the IC chemotherapy comparator group match those used in Scottish clinical practice for this indication.
- The Longworth algorithm used for the mapping of utility values has not been validated for cervical cancer and is a cause of uncertainty. The company did provide scenario analyses using alternative sources for the utility values as shown in Tables 6.1 and 6.2. These had varying degrees of effects on the cost-effectiveness ratio.
- Treatment-specific utilities for the post-progression health state were used in the base case. A scenario with equal post-progression values was provided which had an upward effect on the ICER. SMC clinical experts however provided some reassurance that better quality of life for cemiplimab-treated patients in the post-progression state could be plausible at least in the initial post-progression period.
- Resource use was obtained through expert interviews, which is a source of uncertainty.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee also considered the benefits of cemiplimab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as cemiplimab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted cemiplimab for use in NHSScotland.

8. Guidelines and Protocols

The European Society of Gynaecological Oncology (ESGO) jointly with the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP) published evidence-based guidelines for the management of patients with cervical cancer. Published in 2017; updated in 2023.[7]

The European Society for Medical Oncology (ESMO) - Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Published in 2008; updated in 2017.[6]

The British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: Recommendations for practice. Published in 2020.[9]

9. Additional Information

9.1. Product availability date

02 February 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Cemiplimab concentrate for solution for infusion	**350 mg every 3 weeks until disease progression**	**80,600**

Costs from BNF online on 26 September 2024. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.