Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2501

pembrolizumab 25mg/mL concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme (UK) Limited

13 January 2023

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

pembrolizumab (Keytruda®) is accepted for restricted use within NHSScotland.

Indication under review: in combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express programmed death ligand 1 (PD-L1) with a combined positive score (CPS)≥1.

SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule.

In a phase III study, the addition of pembrolizumab to chemotherapy with or without bevacizumab was associated with a significant improvement in progression-free survival and overall survival in patients with persistent, recurrent or metastatic cervical cancer with PD-L1 CPS≥1.

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

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

Chair
Scottish Medicines Consortium

Indication

In combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS≥1.[1]

Dosing Information

The recommended dose of pembrolizumab is either 200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (that is, an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Patient selection for treatment with pembrolizumab based on the tumour expression of PD-L1 should be confirmed by a validated test.

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. Please refer to the summary of product characteristics (SPC) for further details.[1]

Product availability date

15 May 2022

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

Summary of evidence on comparative efficacy

Pembrolizumab is a monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. This blockade potentiates T-cell responses, which stimulates immune-mediated antitumour activity.[1]

Evidence to support the efficacy and safety of pembrolizumab for the indication under review is from KEYNOTE-826, a randomised, double-blind, phase III study. KEYNOTE-826 recruited adult patients with persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix that had not been treated with systemic chemotherapy and was not amenable to curative treatment (such as with surgery and/or radiation). Previous radiotherapy, including chemoradiotherapy, was permitted if it was completed at least 2 weeks before randomisation and all associated toxic effects had resolved. Patients had measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 and tumour

sample available for determination of PD-L1 status. Patients were randomised equally to receive pembrolizumab 200mg (n=308) or placebo (n=309) every 3 weeks for up to 35 cycles. Both treatment groups also received investigator's choice of cisplatin (50mg/m^2) or carboplatin (area under the concentration-time curve [AUC] 5mg/mL/minute) in combination with paclitaxel (175mg/m^2) with or without bevacizumab (15mg/kg) every 3 weeks. Duration of chemotherapy was limited to 6 cycles (patients with ongoing clinical benefit could continue chemotherapy beyond 6 cycles after consultation with the study sponsor). All treatments were administered intravenously. Randomisation was stratified according to metastatic disease at diagnosis (yes or no), planned bevacizumab use (yes or no) and PD-L1 CPS (<1 or 1 to <10 or ≥10).[2, 3]

KEYNOTE-826 had co-primary outcomes: overall survival and progression-free survival (PFS) assessed according to RECIST version 1.1 by investigator review. Overall survival was defined as the time between date of randomisation and death due to any cause. PFS was defined as the time between date of randomisation to the date of first progression or death due to any cause, whichever occurred first. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. A hierarchical statistical testing strategy was applied to the primary outcomes for different study populations within the ITT based on PD-L1 CPS status. Overall survival and PFS were each tested sequentially in patients with a PD-L1 CPS≥1, in the full ITT population, and in patients with PD-L1 CPS≥10. The marketing authorisation has been granted for patients with a PD-L1 CPS≥1 therefore other patient populations will not be discussed in detail.[2, 3]

At an interim analysis (data cut-off 3 May 2021) with a median follow-up of approximately 17 months, the addition of pembrolizumab to chemotherapy with or without bevacizumab resulted in a statistically significant improvement in PFS and overall survival in patients with a PD-L1 CPS≥1. Secondary outcomes including objective response rate (ORR) and duration of response (DOR) were also supportive and favoured the pembrolizumab group. Results are presented in Table 1.[2, 3]

Table 1: Primary and selected secondary outcomes from KEYNOTE-826 in the PD-L1 CPS≥1 ITT population (data cut-off 3 May 2021).[2, 3]

	Pembrolizumab plus standard of care (n=273)	**Placebo plus standard of care (n=275)**
Median follow-up	18.3 months	16.3 months
Primary outcome: PFS assessed by investigator per RECIST v1.1		
PFS events	157	198
Median PFS	10.4 months	8.2 months
HR (95% CI)	0.62 (0.50 to 0.77), p<0.001	
KM estimated PFS at 24 months	33%	14%
Primary outcome: overall survival		
Deaths	118	154
Median overall survival	NR	16.3 months
HR (95% CI)	0.64 (0.50 to 0.81), p<0.001	
KM estimated overall survival at 24 months	53%	42%
Secondary outcomes: ORR and DOR assessed by investigator per RECIST v1.1		
ORR, %	68%	50%

Complete response	23%	13%
Partial response	45%	37%
Median DOR	18.0 months	10.4 months
CI=confidence interval; CPS=combined positive score; DOR=duration of response; HR=hazard ratio; KM=Kaplan–Meier; ITT=intention-to-treat, NR=not reached; ORR=objective response rate; PFS=progression-free survival; PD-L1=programmed death ligand 1; RECIST v1.1= Response Evaluation Criteria In Solid Tumours version 1.1; Standard of care = investigator's choice of cisplatin or carboplatin in combination with paclitaxel with or without bevacizumab		

Subgroup analyses for the primary outcomes in the PD-L1 CPS≥1 population were generally consistent with the PD-L1 CPS≥1 ITT. However, the absolute difference varied across some subgroups with a smaller difference in the groups with metastatic disease and those who did not receive bevacizumab.[2, 3]

Health Related Quality of Life was assessed using EuroQoL 5-dimension 5-level (EQ-5D-5L) and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires. At the 3 May 2021 data cut-off, a higher proportion of patients in the pembrolizumab group had improved or stable EQ-5D-5L visual analogue scale scores compared with placebo (78% compared with 72% in the full population). The mean change in EORTC QLQ-C30 global health status score was similar between groups.[3-5]

Summary of evidence on comparative safety

The regulatory assessment report noted that the addition of pembrolizumab to chemotherapy with or without bevacizumab increased overall toxicity. Adverse events were more frequently reported than has been observed for other licensed indications of pembrolizumab and chemotherapy and tolerability worsened with age. However, the general safety profiles of the treatment combinations were reflective of the known toxicities of individual therapies and no new safety signals were identified.[2]

In KEYNOTE-826 at the 3 May 2021 data cut-off, the median duration of treatment in the pembrolizumab group was 10.0 months and in the placebo group was 7.7 months in the total study population. In analyses by treatment received, a treatment-emergent adverse event (AE) was reported by 99% (305/307) of patients in the pembrolizumab group and 99% (307/309) in the placebo group and these were considered treatment-related in 97% of patients in both groups. In the pembrolizumab and placebo groups respectively, patients reporting a grade 3 or higher AE were 82% versus 75%, patients with a reported serious AE were 50% versus 42%, patients discontinuing any therapy due to an AE were 38% versus 26% and patients discontinuing all therapies due to an AE were 5.9% and 4.9%.[2, 3]

The most frequently reported treatment-emergent AEs of grade 3 to 5 with an incidence >5% in the pembrolizumab group versus the placebo group were: anaemia (30% versus 27%), neutrophil count decreased (13.0% versus 8.4%), neutropenia (12% versus 9.7%), hypertension (9.4% versus 11%), urinary tract infection (8.8% versus 8.1%), thrombocytopenia (7.5% versus 4.5%), febrile neutropenia (7.2% versus 4.5%), platelet count decreased (6.8% versus 4.5%) and white blood cell

count decreased (6.8% versus 4.2%). Potential immune-related adverse events occurred in 34% of patients in the pembrolizumab group and 15% in the placebo group; these were grade 3 to 5 in 11% and 2.9% of patients in each group respectively. One patient in the pembrolizumab group died from an immune-related AE (encephalitis). In both groups, infusion reactions occurred in 13% of patients and were of grade 3 to 5 severity in 2.3% of patients.[2, 3]

Summary of clinical effectiveness issues

The most significant cause of cervical cancer is persistent papillomavirus infection; human papilloma virus (HPV) is detected in 99% of cases. Although there is now a HPV vaccination programme and a well established cervical screening programme, there were 266 people diagnosed with cervical cancer in 2020 in Scotland (this number was lower than expected due to a pause in the screening programme) and incidence is not expected to decrease in the next few years. In Scotland, there are more diagnoses in areas of high deprivation and over half of those affected are aged between 20 and 54 years. Metastatic or recurrent cervical cancer is often symptomatic and associated with significant morbidity; the median overall survival with current first-line therapies is between 13 and 17 months. Selected patients with a good performance status are offered palliative chemotherapy with the aim to reduce symptom burden and improve quality of life. The preferred first-line treatment is platinum doublet chemotherapy with cisplatin or carboplatin in combination with paclitaxel with or without bevacizumab. The addition of bevacizumab is associated with improved survival but also increased toxicity therefore not all patients are suitable for triplet therapy. Cisplatin in combination with topotecan may provide an alternative option for some patients. 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.[6-9] Pembrolizumab meets SMC end of life and orphan equivalent criteria for this indication and clinical experts consulted by SMC considered that this treatment regimen fills an unmet need in this hard to treat population with poor prognosis.

In KEYNOTE-826, the addition of pembrolizumab to standard first-line treatment for persistent, recurrent, or metastatic cervical cancer demonstrated a 2.2 month improvement in median PFS in patients with PD-L1 CPS≥1; overall survival was also improved though median survival time had not been reached at data cut-off 03 May 2021. These results were statistically significant and considered clinically relevant by the regulator. Secondary outcomes were supportive including an 18% improvement in ORR and 7.6 month improvement in DOR. A lack of benefit was observed in the small PD-L1 CPS<1 subgroup and taken with results from other studies, the regulator restricted the indication to the PD-L1 CPS≥1 population.[2]

There were some limitations associated with KEYNOTE-826. Despite the study having a double-blind design, the primary outcome, PFS and secondary outcome, ORR were assessed by the investigator, which could potentially bias results. Results from PFS and ORR assessed by blinded independent central review (BICR) indicated a consistent benefit with the addition of

pembrolizumab to standard first-line treatment.[2, 3] At the data cut-off (May 2021), follow-up was 17 months and approximately 50% of study participants had died, a final overall survival analysis is planned which will provide more mature data, though results may be confounded by subsequent treatments. In KEYNOTE-826, pembrolizumab was continued for up to 2 years; evidence of efficacy beyond this treatment period is limited.

The KEYNOTE-826 study was not designed or powered to evaluate the addition of bevacizumab to pembrolizumab plus chemotherapy in patients eligible for treatment with bevacizumab and subgroup analyses should be interpreted with caution. In this study, suitability to receive bevacizumab may reflect differing patient characteristics across the subgroups. In both the subgroups with and without bevacizumab, the benefits of pembrolizumab versus placebo were consistent with the primary analysis. However, median PFS and overall survival were generally lower for both treatment groups (pembrolizumab and placebo) in the subgroup of patients who did not receive bevacizumab. Subgroup analysis of patients with metastatic disease at diagnosis indicate less benefit than in the full CPS≥1 population. However, a regulatory review noted that newly diagnosed metastatic disease is an independent poor prognostic factor and additional analyses did not justify exclusion of difficult to treat patients with newly diagnosed metastatic disease from the indication.[2]

Patients in KEYNOTE-826 had persistent, recurrent, or metastatic carcinoma of the cervix that had not been treated with systemic chemotherapy, that is, they were receiving first-line systemic anticancer therapy for this stage of the disease. The study does not provide data on the efficacy of pembrolizumab at later lines of treatment. KEYNOTE-826 assessed pembrolizumab in combination with cisplatin or carboplatin plus paclitaxel with or without bevacizumab; experts in Scotland have confirmed that this is the predominant treatment used in clinical practice. There is limited evidence for pembrolizumab in combination with other chemotherapy regimens that may be used for the treatment of persistent, recurrent, or metastatic cervical cancer.

Clinical experts consulted by SMC considered the introduction of pembrolizumab for the indication under review to be a therapeutic advance and that its place in therapy would be in addition to current first-line treatment with cisplatin or carboplatin in combination with paclitaxel with or without bevacizumab. There may be some service implications, namely an increase in clinic visits and capacity requirements to administer an additional treatment, and laboratory resource use to conduct PD-L1 CPS testing to select eligible patients. Additional monitoring and treatment may be required to manage immune-related adverse events.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

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 **pembrolizumab**, as an **orphan-equivalent and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Persistent, recurrent or metastatic cervical cancer is an incurable disease with a poor prognosis. The progression of both distant metastatic and locoregional disease and associated symptoms can have a profound effect on quality of life.
- Many patients affected by the condition are young, in the prime of their lives, are still working and are valuable contributors to society. The diagnosis has a devastating impact on their lives and can lead to feelings of worry, fear and utter despair.
- PACE participants agreed that there was a high unmet need in this area because of a lack of effective treatment options. Standard first line treatment is platinum plus paclitaxel chemotherapy with or without bevacizumab, however many patients are not eligible to receive bevacizumab. Therefore, identifying new first-line treatment options in this disease area is critical.
- Pembrolizumab is the first immunotherapy licensed for this indication and represents a step change in clinical practice for the treatment of patients with persistent, recurrent or metastatic cervical cancer. The results of the KEYNOTE-826 study demonstrated that a significant minority of patients can achieve a prolonged durable response. PACE participants agreed that the significance of this type of response cannot be underestimated. Patients could reclaim a normal life, return to work, maintain caring responsibilities and continue to make a valuable contribution to society.
- Pembrolizumab is associated with immune-related toxicities, however oncology teams are familiar with appropriate monitoring and management of these and have established protocols in place.
- PACE clinicians agreed that pembrolizumab will be used as per the licensed indication and that in clinical practice it is more likely to be used in the first-line setting in addition to standard chemotherapy.

Additional Patient and Carer Involvement

We received a patient group submission from Jo's Cervical Cancer Trust, which is a registered charity. Jo's Cervical Cancer Trust received 2% pharmaceutical company funding in the past two years, including from the submitting company Representatives from Jo's Cervical Cancer Trust participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company presented a cost-utility analysis that evaluated pembrolizumab in combination with standard of care (PEM+SoC) for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS≥1. The comparator was standard of care (SoC) consisting of platinum chemotherapy (cisplatin or carboplatin) in combination with paclitaxel, with or without bevacizumab. This aligned with SMC clinical expert feedback on current treatment.

A state transition model was developed using the individual patient data for the CPS≥1 population of KEYNOTE-826 for clinical effectiveness data for intervention and comparator. The model health states were progression-free, progressed disease and death. The time horizon was lifetime (50 years in the base case), the model cycle length was 1 week and both costs and QALYs were discounted at a rate of 3.5% per annum, in line with SMC guidance. Progression-free survival (PFS) and time-to-progression (TTP) were based directly on the KEYNOTE-826 Kaplan–Meier (KM) estimates for each treatment arm up to a cut-off point at week 37, with log-logistic distributions fitted to the KM estimates from week 37 onward. The proportion of patients remaining in the progression-free health state was based on PFS (capped by TTP and general population overall survival [OS]), while TTP informed transitions to the progressed disease health state. Generalized gamma distributions were fitted for extrapolation of post-progression survival (PPS) in each treatment arm and was capped by general population OS. PFS and PPS were used to estimate the proportion in the death health state.

Time-to-death utility values were calculated using regression models based on the EQ-5D-5L measurements collected from patients in KEYNOTE-826, which were mapped to EQ-5D-3L using the van Hout et al. 2012[10] algorithm. A utility decrement was applied for Grade 3+ AEs.

Drug acquisition costs in the model were based on the actual received dose in KEYNOTE-826. Pembrolizumab was given up to 35 treatment cycles (~2 years) and other treatments used with pembrolizumab and SoC were administered for a maximum of 6 treatment cycles. Treatments were administered intravenously and administration costs were accrued for the duration of treatment. Time on treatment was based directly on the KEYNOTE-826 KM estimates for the entire duration. Costs due to Grade 3+ adverse events (AEs) occurring in more than 5% of patients in KEYNOTE-826 were included in the model. A one-off cost due to subsequent treatment was applied at progression, based on the proportion of patients receiving paclitaxel, doxorubicin, fluorouracil or cisplatin plus gemcitabine in KEYNOTE-826 and the average observed duration of each. Monitoring costs for consultant outpatient appointments and computerised tomography (CT) scans were estimated, as well as costs of diagnostic PD-L1 testing and end-of-life costs, with monthly resource usage estimates based on clinician opinion from an advisory board[11].

A Patient Access Scheme (PAS) proposed by the submitting company was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price.

The base case analysis suggested that pembrolizumab would lead to an increase in the number quality adjusted life years (QALYs) over SoC alone, mostly due to more time spent in the pre-progression state. At the same time, pembrolizumab use was predicted to increase costs, primarily through additional drug acquisition cost. Inclusive of the PAS discount on pembrolizumab, the incremental cost-effectiveness ratio (ICER) was £33,690.

Deterministic sensitivity analysis focused on treatment cycle/ duration and resource use estimates and demonstrated some sensitivity in the ICER related to varying the proportion incurring pembrolizumab treatment cost in the PEM+SoC arm (scenario 9 in Table 2), but there was little sensitivity in the ICER associated with any other parameters included in the one-way sensitivity analysis. Several scenario analyses were performed (Table 2), with the greatest uncertainty associated with the extrapolation approach: the lowest ICER was associated with applying generalised gamma functions fitted to the KM data beyond week 46 for PFS & TTP and from week 0 for PPS (£26,459/QALY), with the highest ICER associated with applying fully-fitted log-logistic functions for PFS, TTP and PFS (£84,566/QALY).

Table 2: Key scenario and sensitivity analysis

	Scenario	**ICER (with PAS)**
	Base case	£33,690
1.	Expected treatment dose	£37,054
2.	TTP & PFS: Fully fitted Log-Logistic	£70,981
3.	TTP & PFS: 37-wk KM + Mean of Log-logistic & Weibull	£39,569
4.	TTP & PFS: 46-wk KM + Generalised gamma	£26,459
5.	PPS: Fully fitted Lognormal	£35,936
6.	PPS: Fully fitted Log-Logistic	£36,367
7.	Assume equivalent PPS across arms based on pooled estimates from KEYNOTE-826	£35,889
8.	Alternative utility values based on bevacizumab SMC DAD (2016)[12]	£32,578
9.	Subsequent treatment costs excluded	£33,833
10.	PFS based on BICR	£29,902
11.	Time horizon of 20 years	£39,558
12.	Sensitivity analysis: proportion receiving pembrolizumab varied	£33,102 to £34,278
	Combined scenarios	
13.	(**1.**) Expected treatment dose, (**2.**) TTP & PFS: Fully-fitted Log-Logistic	£78,106
14.	(**2.**) TTP & PFS: Fully-fitted Log-Logistic, (**5.**) PPS: Fully-fitted Lognormal	£82,478
15.	(**2.**,**6.**) TTP, PFS, PPS: Fully-fitted Log-Logistic	£84,566
Abbreviations: AE, adverse events; BICR, blinded independent central review; PF, progression free; PFS, progression free survival; PD, progressed disease; PPS, post-progression survival; TTP, time-to-progression		

The economic analysis was associated with a significant number of weaknesses/ uncertainties:

- The OS data for the CPS≥1 population were less mature than PFS and it is uncertain to what extent short-term PFS gains (as observed in KEYNOTE-826) would translate into long-term OS benefits. Longer follow-up would be needed to confirm that OS in the PEM+SoC arm would plateau to a similar extent as PFS. Indirectly modelled OS for the intervention

appears to plateau between approximately 20 to 30 years in the base case, with high life year gains generated for the intervention (+2.76 LYs).

- While justification was provided for the model structure, it would be useful to assess the impact that this had on the model results. A partitioned survival model (PSM) - a simpler structure that is commonly used for modelling outcomes in cancer - was requested but was not provided due to time limitations. In response to this request, the company provided an alternative model structure using a response based model which resulted in an increase in the ICER to £49k. However, this method is not commonly used as it is associated with uncertainty. The relative reduction in extrapolated OS compared with extrapolated (unadjusted) PFS over time appeared to be greater for the intervention than for the comparator, so it is possible that the ICER would have been much higher had a PSM been used. The Committee noted the concerns raised with the use of the state transition model structure preferred by the company, but also acknowledged the company had provided evidence to show that the estimates derived from the model were broadly consistent with the clinical study estimates and also supported by wider published evidence.
- A piecewise model was used for PFS and TTP, rather than smoother, fully-fitted parametric distributions. The justification for this was that the KM estimates were stepped due to the timing of the tumour imaging assessments in the KEYNOTE-826, although it is unclear why using the KM estimates directly until week 37 would therefore be preferable to a smoother function. There were options in the economic model to use fully-fitted parametric distributions, which use more of the trial data to inform long-term modelled outcomes and potentially make the short-term outcomes more generalisable to the patient population by smoothing out steps in the KM curve due to the timing of observations. Using fully-fitted parametric distributions for PFS and TTP resulted in a substantially higher ICER (scenario 2 in Table 2).
- Fully-fitted generalized gamma distributions were used to model PPS in the base case, though lognormal and log-logistic distributions provided a better statistical fit to the KM data and resulted in modelled 2- and 3-year PPS in the SoC arm closer to that reported in the GOG 240 trial[13], a phase III trial used for external validation. Using the fully-fitted distributions for PFS also resulted in modelled 2-,3- and 4-year PFS closer to that reported in the GOG 240 trial, and combining the two fulfilled the company's criteria for modelled OS but resulted in substantially higher ICERs (scenarios 14 and 15 in Table 2).
- The modelling approach for PFS, TTP and PPS did not account for interval censoring due to the timing of the observations. Results using a method accounting for interval censoring between tumour assessment dates were not provided but the company noted this was unlikely to have a large impact on the results.
- The treatment costs were adjusted because the number of administered doses in KEYNOTE-826 differed from those in the trial protocol (i.e. the 'actual vs. expected cycles'). The treatment costs were reduced for pembrolizumab, while those for the chemotherapies were increased more greatly in the SoC arm than the PEM+SoC arm. The costs of bevacizumab were reduced in both arms, but relatively more for the intervention. The model should be as generalisable as possible to clinical practice and, while doses may be missed in practice, the expected number is likely to give a better estimate of the treatment

costs incurred (scenarios 1 and 13 in Table 2). However, it should be noted that this analysis only adjusts the costs and does not account for any potential increase in efficacy.

- Subgroup analysis could have been provided for patients receiving treatment with and without bevacizumab; the proportion of patients receiving bevacizumab in the model only affects the treatment costs and these were not varied in either the scenario or sensitivity analyses. However, KEYNOTE-826 was not designed or powered for a formal assessment by bevacizumab use.

The Committee considered the benefits of pembrolizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as pembrolizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted pembrolizumab for restricted use in NHSScotland.

Additional information: guidelines and protocols

The British Gynaecological Cancer Society (BGCS) produced the BGCS Cervical Cancer Guidelines: Recommendations for Practice in 2021.[7] This guideline makes the following recommendations for chemotherapy in metastatic or advanced cervical cancer:

- All patients with newly diagnosed stage 4 or relapsed cervical cancer should be treated as part of a multidisciplinary team, due to the complexity of disease relapse, especially when in the pelvis, where morbidity can be severely debilitating.
- Patients with a WHO performance status (WHO PS) 0 or 1 should be considered for systemic treatment, whereas those with lower performance status should be carefully risk assessed as to their suitability and likely benefit from treatment, with the patient fully informed of expectations and limitations of chemotherapy. Best supportive care or palliative radiotherapy may be a more preferable option for these patients.
- For those patients who are chemotherapy naive with stage 4 disease, first-line treatment would be systemic chemotherapy with cisplatin and paclitaxel or carboplatin and paclitaxel doublets with or without bevacizumab depending on any patient risk factors. However, bevacizumab may lead to prolonged benefit and should be offered if not contraindicated.
- When bevacizumab was given alongside the chemotherapy, there was an overall survival advantage of 3 months and median PFS advantage of 2 months, with a higher response rate when compared to platinum and paclitaxel or platinum and topotecan alone, as shown in the GOG 240 trial[13].
- Second-line treatment and beyond is dependent on the interval of progression since first-line treatment; in those patients with a good partial response with first-line treatment and are more than 6 months out, rechallenging with platinum and paclitaxel could be considered. Mitomycin and 5-fluorouracil, vinorelbine, docetaxel, gemcitabine, weekly paclitaxel and topotecan have some activity but there is no standard of care. Response

rates are universally poor and entry into clinical trials where possible to assess novel and immunotherapeutic agents should be strongly considered depending on patient's fitness and desires.

The European Society for Medical Oncology (ESMO) published Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2008 which were updated in 2017.[6] These guidelines make the following recommendations for the management of advanced or metastatic disease:

- Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is indicated if the patient has a PS < 2 and no formal contraindications.
- Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS.
- Paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile.
- The combination of paclitaxel and carboplatin could be considered an alternative for patients that are not candidates for cisplatin.
- 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.

These guidelines both predate the availability of pembrolizumab for the indication under review.

Additional information: comparators

Carboplatin or cisplatin in combination with paclitaxel with or without bevacizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 3 week cycle (£)
Pembrolizumab	200mg intravenously every 3 weeks.	5,260

Costs from BNF online on 21/09/22. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 33 patients eligible for treatment with pembrolizumab in year 1 and 31 patients in year 5, to which confidential uptake rates were applied.

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 11 November 2022.

**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.