Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2474

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

Merck Sharp & Dohme (UK) Limited

09 September 2022

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 lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

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

Pembrolizumab in combination with lenvatinib improved progression-free and overall survival compared with chemotherapy in patients with advanced or recurrent endometrial cancer who had disease progression on or after platinum-based chemotherapy.

This SMC advice takes account of the benefit of Patient Access Schemes (PAS) that improve the cost effectiveness of pembrolizumab and lenvatinib. This advice is contingent upon the continuing availability of these PAS in NHS Scotland or list prices that are equivalent or lower.

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

Chairman, Scottish Medicines Consortium

Published 10 October 2022

Indication

In combination with lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.[1]

Dosing information

Pembrolizumab intravenous (IV) infusion 200mg every 3 weeks or 400 mg every 6 weeks (administered over 30 minutes) in combination with lenvatinib 20mg orally once daily. Treatment should be continued 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. Dose adjustments to manage adverse events are detailed in the summary of product characteristics (SPC).

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.[1,2]

Product availability date

22 November 2021

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

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. It is licensed for use in the treatment of advanced or recurrent endometrial carcinoma in combination with lenvatinib, which is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF).[1,2]

An open-label, phase III study (KEYNOTE-775) recruited women aged at least 18 years with advanced, recurrent or metastatic endometrial cancer (excluding carcinosarcoma or sarcoma) who had disease progression after one platinum-based chemotherapy (or two, if one was adjuvant or neoadjuvant). Patients had at least one measurable lesion on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 or 1. Randomisation was stratified by mismatch repair (MMR) status (deficient [dMMR] or proficient [pMMR]) and within the pMMR population patients were stratified by ECOG performance status score (0 or 1), geographic region (Australia, Canada, Europe, Israel, New Zealand and United States or rest of the world) and history of pelvic radiation (yes or no). Patients were randomised equally to lenvatinib (20mg orally once daily) plus pembrolizumab (200mg IV every 3 weeks) or physician's choice of doxorubicin (60mg/m^2 IV every 3 weeks) or paclitaxel (80mg/m^2 IV weekly for the first 3 weeks of 4-week cycles).[3,4] Treatment continued until disease progression, unacceptable toxicity, 35 cycles of pembrolizumab (with lenvatinib alone beyond this, if clinical benefit present), lifetime exposure of 500mg/m^2 doxorubicin[4,5] The co-primary outcomes

were progression-free survival (PFS) assessed on RECIST version 1.1 by blinded independent central review (BICR) and overall survival (OS). These were primarily assessed in the pMMR population and then in all patients within a hierarchy that included the key secondary outcome, objective response rate (ORR), as listed in Table 1.[3,4]

At the data cut-off 26 October 2020 (primary analysis for PFS), median follow-up was 12.2 months in the pembrolizumab-lenvatinib group and 10.7 months in the chemotherapy group. The primary and key secondary outcomes significantly improved with pembrolizumab-lenvatinib compared with chemotherapy in pMMR and all study patients as detailed in Table 1. Additional secondary outcomes appear to show longer duration of response with pembrolizumab-lenvatinib compared with chemotherapy, with medians of 9.2 versus 5.7 months in the pMMR subgroup and 14.4 versus 5.7 months in all study patients.[3,4]

Table 1: Primary and key secondary outcomes of KEYNOTE-775.[3]

	pMMR subgroup		**All patients**	
	Pembrolizumab	**Chemotherapy**	**Pembrolizumab**	**Chemotherapy**
	N=346	**N=351**	**N=411**	**N=416**
Progression-free survival (PFS)				
Events	247	238	281	286
HR (95% CI)	0.60 (0.50 to 0.72), p<0.001		0.56 (0.47 to 0.66), p<0.001	
Median (months)	6.6	3.8	7.2	3.8
1 year PFS	28%	13%	31%	13%
Overall survival (OS)				
Deaths	165	203	188	245
HR (95% CI)	0.68 (0.56 to 0.84), p<0.001		0.62 (0.51 to 0.75), p<0.001	
Median (months)	17.4	12.0	18.3	11.4
2 year OS	37%	22%	42%	21%
Objective response rate (ORR)				
Rate	30%	15%	32%	15%
Difference (95% CI)	15% (9.1% to 21%), p<0.001		17% (12% to 23%), p<0.001	

CI = confidence interval; HR = hazard ratio; ORR = objective response rate, defined as complete or partial response on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; OS = overall survival; PFS = progression-free survival assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; pMMR = proficient mismatch repair status. Pembrolizumab was administered in combination with lenvatinib.

Health related quality of life was assessed in both the pMMR subgroup and all study patients using the EuroQol 5-dimension 5-level (EQ-5D-5L) visual analogue scale (VAS), European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Endometrial Cancer Module (QLQ-EN24). There were no substantial differences between the treatment groups for these outcomes.[3,4]

In an open-label phase Ib/II study (KEYNOTE-146) there was a subgroup of 108 patients who had endometrial cancer previously treated with platinum-based therapy. In this group, at data cut-off 10 January 2019, median follow-up was 18.7 months. Pembrolizumab-lenvatinib was associated with an ORR of 41% (44/108), with ORR 38% (36/94) in those with pMMR or non-microsatellite instability-high (MSI-H) tumours and 64% (7/11) in those with dMMR or MSI-H tumours. Complete response was achieved by 10%, 11% and 9.1% of patients in the respective populations.[3]

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

Summary of evidence on comparative safety

The European regulatory review noted that pembrolizumab-lenvatinib had a manageable safety profile in the advanced endometrial cancer population that was generally consistent with the established safety profiles of the individual medicines and their combination in other cancers.[3]

In the KEYNOTE-775 study at data cut-off 26 October 2020, median duration of treatment in the pembrolizumab-lenvatinib and chemotherapy groups was 7.59 and 3.43 months, respectively. Adverse events were reported by 99.8% (405/406) and 99.5% (386/388) of patients (232 and 256 events per 100-patient months) in the respective groups and these were considered treatment-related in 97% and 94% of patients (133 and 153 per 100-patient months). Adverse events were of grade 3 of higher severity in 89% and 73% of patients (31 and 49 events per 100-patient months). Serious adverse events were reported by 53% versus 30% of patients (10 events per 100-pateint months in both groups), with these considered treatment-related in 33% and 14% of patients (5.2 and 4.1 events per 100-patient months), respectively. Adverse events led to discontinuation of a study therapy in 33% and 8.0% of patients (5.0 and 2.3 discontinuations per 100-patient years) in the respective groups.[3]

Within the pembrolizumab-lenvatinib group, compared with the chemotherapy group, there were higher rates per 100-patient months of hypertension (11.1 versus 1.6), hypothyroidism (7.0 versus 0.2), diarrhoea (13.2 versus 6.1), weight decrease (4.1 versus 1.3), arthralgia (4.6 versus 1.8), proteinuria (5.1 versus 0.7) and urinary tract infection (3.9 versus 2.8), with smaller differences for decreased appetite (6.0 versus 5.5) and vomiting (7.6 versus 7.1). There were lower rates per 100-patient months for nausea (7.8 versus 16.9), fatigue (4.2 versus 8.3), anaemia (3.8 versus 13.5), neutropenia (1.5 versus 12.2) and alopecia (0.6 versus 6.8).[3]

Adverse events leading to death occurred in 23 and 19 patients in the pembrolizumab-lenvatinib and chemotherapy groups, respectively, and were considered treatment-related in six and eight patients in the respective groups. [3]

Summary of clinical effectiveness issues

Advanced or recurrent endometrial cancer has a poor prognosis with median survival of around 12 months. There is limited clinical evidence and no standard of care for second-line therapy at this stage of the disease, especially when the treatment-free interval following first-line platinum-based chemotherapy is less than 6 months. Doxorubicin and paclitaxel are considered the most active therapies. In patients with a long platinum-free interval, re-challenge with platinum can be considered.[3] Dostarlimab (a PD-1 receptor antagonist) is indicated as monotherapy for treatment of adult patients with dMMR or MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[6] In March 2022, SMC issued advice (SMC2404) that it is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Clinical experts consulted by SMC noted that there is an unmet need for more effective therapies in the treatment of advanced or recurrent endometrial cancer.

Pembrolizumab-lenvatinib is the first combination of PD-1 inhibitor plus VEGF inhibitor licensed for the treatment of advanced or recurrent endometrial cancer after platinum-based therapy. In patients with dMMR disease, it provides an alternative PD-1 inhibitor treatment to dostarlimab (used as monotherapy) and it is the first PD-1 inhibitor therapy for patients with pMMR disease. In this indication, pembrolizumab-lenvatinib meets SMC end-of-life and orphan equivalent criteria.

In KEYNOTE-775, pembrolizumab-lenvatinib compared with chemotherapy (doxorubicin or paclitaxel) significantly improved median PFS by about 3 months and OS by about 5 to 7 months in the pMMR subgroup and overall study population. These outcomes were considered clinically relevant in the European regulatory review. In both groups, ORR were increased by approximately 15% with pembrolizumab-lenvatinib and median duration of response was longer by 3.5 months in the pMMR subgroup and 8.7 months in the total study population.[3,4]

In both the pMMR and total study population the between treatment group comparisons of OS crossed pre-specified boundaries for statistical significance ($p \leq 0.0073$ and $p \leq 0.0064$, respectively) at the interim analysis (26 October 2020).[5] However, more mature and final OS data are expected.[3]

The KEYNOTE-775 study provides direct comparative data versus two chemotherapies (paclitaxel and doxorubicin) commonly used for second-line treatment of advanced or recurrent endometrial cancer. Approximately three-quarters of patients in the chemotherapy group had doxorubicin. The European regulatory review noted that analyses suggested that pembrolizumab-lenvatinib had an advantage versus each chemotherapy drug.[3] The KEYNOTE-775 study does not provide evidence versus re-challenge with platinum-based therapy.

The KEYNOTE-775 study was open-label and this may affect rates of study discontinuation and assessment of subjective outcomes such as quality of life and safety. In the pembrolizumab-lenvatinib group, compared with chemotherapy, there were lower rates of discontinuation prior to study treatment (1.2% versus 6.7%) and lower rates of treatment discontinuation due to patient decision (4.4% versus 7.5%) and physician decision (1.0% versus 5.2%).[3,4]

There was no crossover prior to the data cut-off 26 October 2020 (primary analysis of PFS) in KEYNOTE-775. A lower proportion of patients in the pembrolizumab-lenvatinib group, compared with the chemotherapy group, had subsequent anti-cancer therapy: 32% versus 50% in the pMMR subgroup and 28% versus 48% in the total study population. In the total study population, fewer patients in the pembrolizumab-lenvatinib group had subsequent PD1 or PD-L1 inhibitor (1.0% versus 13%), VEGF or VEGF receptor (VEGFR) inhibitor (2.4% versus 11%), chemotherapy (24% versus 31%), hormonal therapy (6.1% versus 13%) and targeted therapy (1.9% versus 2.9%). Data for the pMMR subgroup were similar.[3] Imbalance in subsequent anti-cancer treatments may confound assessment of OS, but may be representative of practice.

In KEYNOTE-775, within the pMMR and all study patient populations 67% (470/697) and 69% (574/827) of patients had received one prior line of systemic therapy, with 30% and 28% having two prior lines. In the respective populations PFS hazard ratios (HR) were 0.52 and 0.49 in those with one prior line and 0.74 and 0.66 in those with two prior lines; OS HR were 0.61 and 0.57 in those with one prior line and 0.88 and 0.72 in those with two prior lines. About half of the patients in the subgroup that had one prior line (that is, 37% of total study population) had only received

platinum-based therapy in (neo)adjuvant setting and, therefore, had study treatment first-line in the advanced or metastatic setting.[3] There was no efficacy information in this subgroup.

KEYNOTE-775 only recruited patients with good ECOG performance status of 0 or 1, adequate organ function and no conditions that may confound assessment. These resulted in screening failure of about 12% (145/1178) of patients. The study population may not be representative of all patients receiving second-line therapy for endometrial cancer, with less fit patients excluded.[3]

Clinical experts consulted by SMC consider pembrolizumab-lenvatinib a therapeutic advance in the second-line treatment of advanced or recurrent endometrial cancer due to improved efficacy relative to current therapies. They noted that pembrolizumab-lenvatinib would be used in place of current therapies, especially in those patients with good performance status.

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:

- Advanced or relapsed endometrial cancer is often incurable and a devastating diagnosis for patients. It is associated with a high symptom burden that can be multifactorial and difficult to control. Common symptoms include pain, vaginal bleeding, nausea, vomiting, bowel obstruction, shortness of breath and swelling.
- There is a high unmet need for patients with this stage of disease as there is no standard second line treatment. Current options include single agent chemotherapy, which are associated with low response rates and debilitating side effects. Disease that has progressed after first line treatment is often chemotherapy resistant and the prognosis is poor.
- Pembrolizumab and lenvatinib would give patients a treatment option that could provide a meaningful response, improve survival outcomes and reduce the symptom burden of advanced cancer which has a significant impact on quality of life. Patients may be able to return to a normal life and continue to work and spend time with family and friends. PACE participants noted that patients are more likely to be able to live full and active lives which are much harder to maintain on chemotherapy due to side effects and impacts on quality of life.
- The combination treatment is generally well tolerated. PACE participants described how it is associated with fewer debilitating side effects compared with chemotherapy and that the improved safety profile may cause patients to feel less unwell and require fewer unscheduled hospital admissions which are disruptive and affect quality of life. Pembrolizumab is also associated with a shorter duration of infusion and less frequent dosing which is convenient for patients as less time is required in hospital and time efficient for cancer units.
- PACE participants agreed that the place in therapy should be as per the licensed indication.

Additional Patient and Carer Involvement

We received a patient group submission from Peaches Womb Cancer Trust, which is a registered charity. Peaches Womb Cancer Trust has not received any pharmaceutical company funding in the past two years. Representatives from Peaches Womb 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 submitting company presented a cost-utility analysis evaluating pembrolizumab in combination with lenvatinib across the full licenced indication. The model used a partitioned survival structure with patients receiving either pembrolizumab in combination with lenvatinib or chemotherapy. In the chemotherapy arm 25.5% of patients received paclitaxel and 74.5% received doxorubicin, in line with the treatments prescribed in the central study, KEYNOTE-775.[4]

All patients started in the progression-free state and could subsequently transition onwards to progressed disease or death. Occupancy of each state was informed by patient level data from KEYNOTE-775. The model time horizon of 40 years was significantly longer than the observation period of the study. Future state occupancy was estimated using parametric survival curves. Progression-free survival was estimated using the observed study data for the first 10 weeks and then separately fitted log-logistic curves for the remainder of the model. Overall survival was estimated using the observed data up to week 26 after which point an exponential curve was used to project the chemotherapy arm, while a log-logistic curve was used for the pembrolizumab-lenvatinib arm. The company justified the use of alternative survival curves for overall survival based on the differing biological actions of the treatments and an assessment of the underlying hazard profiles' shape.

Health related quality of life was captured using the EQ-5D-5L questionnaire completed by participants of the KEYNOTE-775 study. Scores were converted into EQ-5D-3L equivalents using the van Hout et al (2012) cross walk algorithm.[7] The company used a time-to-death approach for estimating patient utility, with lower values assigned to those patients who had less time before their death. There was an additional disutility applied for those experiencing a grade 3+ adverse event. Utility values were subject to age adjustment in the model.

Medicine costs included in the model covered acquisition costs and administration costs for pembrolizumab, lenvatinib, chemotherapy and subsequent lines of therapy. The model also included costs for the treatment of adverse events. Those in the progression-free state were assumed to incur a wider healthcare cost of £43 per month, built up from outpatient visits, CT scans and blood tests. Those patients in the progressed state were attributed a cost of £50 per month based on outpatient visits and pain medication. End-of-life care was applied as a one-off cost upon transition to death.

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. A confidential PAS is also in place upon lenvatinib.

The results presented do not take account of the PAS for lenvatinib or the PAS for pembrolizumab, but those were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for lenvatinib due to commercial confidentiality and competition law issues.

The company's submitted model estimated that use of pembrolizumab in combination with lenvatinib resulted in an incremental life year gain of 3.42 years over chemotherapy, and incremental quality adjusted life year gain of 1.73. The incremental costs was £113,109 leading to an incremental cost effectiveness ratio of £65,507.

In addition to the base case results, alternative scenarios were projected to help explore areas of uncertainty within the modelling. A selection of these is provided in Table 2 below.

Table 2: Scenario analysis – All medicines at list price

#	Scenario description	Base case description	ICER	% change from base case
Structural assumptions				
1	Time Horizon, 30 years	Time Horizon, 40 years	£65,874	1%
Treatment dose and duration				
2	Pembrolizumab dosing: 400mg Q6W	Pembrolizumab dosing: 200mg Q3W	£66,161	1%
3	Lenvatinib weekly dosing: full 20mg dose	Lenvatinib weekly dosing: RDI based in KEYNOTE-775 study	£69,458	6%
4	ToT cannot exceed PFS (both arms)	ToT as observed in KEYNOTE-775	£59,521	-9%
Efficacy assumptions				
5	PFS (PEM-LEN): 10-week KM + log-normal PFS (Chemo): 10-week KM + log-normal	PFS (PEM-LEN): 10-week KM + log-logistic PFS (Chemo): 10-week KM + log-logistic	£65,448	<1%
6	PFS (PEM-LEN): one-piece log-logistic PFS (chemo): one-piece log-logistic		£65,376	<1%
7	OS (PEM-LEN): 26-week KM + exponential OS (Chemo): 26-week KM + exponential	OS (PEM-LEN): 26-week KM + log-logistic OS (Chemo): 26-week KM + exponential	£215,888	230%
8	OS (PEM-LEN): 26-week KM + Weibull OS (Chemo): 26-week KM + exponential		£135,412	107%
9	Efficacy of PEN+LEN reduced linearly from year 5 to match efficacy of chemo by year 8 (all patients)	No treatment waning effect in PEM-LEN arm	£117,892	80%
10	Efficacy of PEN+LEN reduced linearly from year 8 to match efficacy of chemo by year 10 (70% of patients)		£93,592	43%
Utility inputs				
11	Health state utility values	Time-to-death utility values	£72,049	10%

Cost inputs				
12	Use liposomal/pegylated doxorubicin cost	Use doxorubicin cost	£72,049	10%
13	Vial sharing (no wastage)	No vial sharing	£65,861	1%

Key: ICER, incremental cost-effectiveness ratio; Q6W, 6 weekly dosing; Q3W, 3 weekly dosing; RDI, relative dose intensity; ToT, time on treatment; PFS, progression free survival; OS, overall survival; KM, Kaplan Meier; PEM-LEN, pembrolizumab in combination with lenvatinib.

The strengths of the analysis were identified as being:

- The model structure was typical of oncology appraisals, and felt appropriate to the situation.
- The base case comparator in the model appeared appropriate.
- The main source of clinical evidence came from a randomised control trial comparing pembrolizumab in combination with lenvatinib against a comparator thought reasonably representative of Scottish practice.

The main weaknesses were identified as being:

- The duration of follow-up was relatively short compared to the length of the model, requiring extensive extrapolation. The methods employed to extrapolate the overall survival observed in the KEYNOTE-775 study was a source of uncertainty. The choice of survival function used in the base case for the pembrolizumab-lenvatinib arm was selected based on fit to KEYNOTE-775 data, expert opinion and longer-term survival data collected from a phase II study (KEYNOTE-146[8]). However, long-term projection remained uncertain and alternative curves, while possibly pessimistic, led to large changes in the ICER (see Scenarios 7 and 8 in Table 2).
- Within the base case, it was assumed that the treatment effect of pembrolizumab in combination with lenvatinib was maintained for the duration of a patient's life, despite pembrolizumab being subject to a two-year stopping rule. The company provided some supportive evidence of that assumption through the observed survival data from KEYNOTE-146, which appeared to be plateauing over time. However, this remained uncertain, and treatment waning was explored (see Scenarios 9 and 10 in Table 2). Those scenarios were speculative, but showed if the treatment effect diminished over time the ICER could increase substantially.
- As a result of the assumptions used to project survival curves, a significant population of patients were modelled as living for an extended period in the progressed disease state. The clinical plausibility of that was uncertain.

The Committee considered the benefits of pembrolizumab in combination with lenvatinib 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 met. In addition, as pembrolizumab in combination with lenvatinib is an orphan equivalent medicine pairing, 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 pembrolizumab in combination with lenvatinib for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

In 2021, the British Gynaecological Cancer Society (BGCS) published BGCS Uterine Cancer Guideline: Recommendations for Practice. For the management of relapsed endometrial carcinoma it is recommended that chemotherapy-naïve patients who relapse with systemic disease or those with late relapse after receiving adjuvant chemotherapy, should be considered for doublet chemotherapy with carboplatin and paclitaxel. For patients who relapse more than 6 months after carboplatin and paclitaxel, further platinum-based chemotherapy can be considered. For patients who relapse less than six months after carboplatin and paclitaxel, there is no treatment that could be considered standard of care. Patients requiring second-line systemic therapy should be offered PD-1/PD-L1 inhibitors if the cancer is mismatch repair deficient, or carries a *POLE* mutation, or has a high tumour mutational burden.[9]

In 2016, European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO) and European Society for Radiotherapy and Oncology (ESTRO) published ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. For advanced and recurrent disease this recommends that patients should only be considered for surgery if it is anticipated that cytoreduction with no macroscopic residual disease can be achieved. Radiotherapy may be indicated for primary tumours that are unresectable, or where surgery cannot be performed or is contraindicated for medical reasons. It notes that the majority of patients will be suitable for systemic palliative therapy, with the choice between hormonal treatment and chemotherapy dependent upon several factors, including histopathological and clinical features. Hormone therapy is indicated in advanced or recurrent endometrioid endometrial cancer and is more likely to be effective in grade 1 or 2 endometrioid tumours and in patients with positive progestogen receptor and estrogen receptor status. Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platinum-based drugs and taxanes shown to be the most active agents. For initial chemotherapy, the standard of care is six cycles of 3-weekly carboplatin and paclitaxel. Evidence supporting the use of second-line chemotherapy is less than 6 to 12 months. There is no specific regimen recommended as a standard of care for second-line chemotherapy.[10]

Additional information: comparators

doxorubicin, paclitaxel or re-challenge with platinum-based therapy (in patients with prolonged progression-free interval after initial platinum-based therapy), dostarlimab (patients with dMMR disease)

Additional information: list price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Pembrolizumab Lenvatinib	200mg intravenous infusion every 3 weeks or 400 mg intravenous infusion every 6 weeks 20mg orally once daily	101,596 to 106,856

Costs from BNF online on 30 May 2022. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 71 patients eligible for treatment with pembrolizumab in combination with lenvatinib in year 1 and 77 patients in year 5 to which confidential estimates of treatment uptake 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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

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