pembrolizumab concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme (UK) Limited

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

ADVICE: following a full submission

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

Indication under review:
As monotherapy for adults with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in the following settings:

- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

As monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, 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;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

In two phase II, single-arm studies, pembrolizumab demonstrated objective response rates from 34% to 56% in patients with MSI-H or dMMR tumours.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Pembrolizumab is a humanised monoclonal antibody that blocks the interaction between programmed cell death-1 (PD-1) receptor and its ligands, PD-L1 and PD-L2. This potentiates T-cell responses, including anti-tumour responses of antigen presenting cells and tumours or other cells in the tumour microenvironment.[1]

The recommended dose of pembrolizumab in adults is either 200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes. For the indications under review, treatment should be continued for up to 35 cycles (approximately 2 years) or until disease progression or unacceptable toxicity.[1]

1.2. Disease background

There are five advanced solid tumours' sites covered by the licensed indication: colorectal, endometrial, gastric, small intestine, and biliary, all with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). The prevalence of MSI-H varies widely across tumour types; endometrial, colorectal, and gastric cancers have reportedly the highest prevalence (generally >10%), with other cancers having a MSI-H prevalence <5%. MSI-H cancers are typically characterised by a high mutational burden and tumour-specific neoantigen load, and can be associated with highly upregulated expression of PD-1 and PD-L1, as well as other immune checkpoints. The prognostic effect of MSI-H/dMMR status varies by tumour type and by stage. In patients with early stage colorectal cancer (CRC), MSI-H/dMMR may be associated with a survival advantage, and in contrast, patients with MSI-H/dMMR metastatic CRC may have a worse prognosis; however, the literature on this is not conclusive. Similar observations have also been made regarding endometrial tumours, and early stage gastric tumours, albeit the evidence is limited.[2]

1.3. Treatment pathway and relevant comparators

In MSI-H/dMMR unresectable/metastatic CRC, pembrolizumab is the first-line treatment option (SMC2375) for the majority of patients. In patients who receive fluoropyrimidine-based combination chemotherapy first-line, nivolumab plus ipilimumab is likely to continue to be the second-line treatment option. Based on this, use of pembrolizumab for CRC in the indication under review is expected to be very limited. Dostarlimab is accepted for use within NHSScotland on an interim basis (SMC2404) as monotherapy for the treatment of adult patients with MSI-H/dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. In addition, pembrolizumab in combination with lenvatinib (SMC2474) is a treatment option for 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. Patients with unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy would usually receive treatment with further chemotherapy.

Table 1 presents details of the relevant comparators for each tumour type.

Table 1.1. Relevant comparators.

Indication by tumour site	Comparator
Colorectal cancer (unresectable or metastatic, previously treated with fluoropyrimidine-based combination therapy) Likely limited unmet need in this patient group.	nivolumab plus ipilimumab (SMC2394)
	trifluridine plus tipiracil (SMC 1221/17)
	FOLFIRI/FOLFOX/FOLFOX4/mFOLFOX6
Endometrial cancer (advanced or recurrent, 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)	dostarlimab (SMC2404)
	pembrolizumab with lenvatinib (SMC2474)
	chemotherapy (doxorubicin, paclitaxel)
	paclitaxel plus carboplatin
Gastric cancer (unresectable or metastatic previously treated with at least one prior therapy)	FOLFIRI
	taxanes (docetaxel, paclitaxel)
	trifluridine plus tipiracil (SMC2329, for use as third line treatment)
Small intestine cancer (unresectable or metastatic previously treated with at least one prior therapy)	FOLFOX/FOLFIRI
Biliary cancer (unresectable or metastatic previously treated with at least one prior therapy)	mFOLFOX/mFOLFIRI
Abbreviations: FOLFIRI = folinic acid, fluorouracil and irinotecan; (m)FOLFOX = (modified) folinic acid, fluorouracil and oxaliplatin.	

1.4. Category for decision-making process

Eligibility for a PACE meeting
Pembrolizumab meets SMC end of life criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of pembrolizumab for the treatment of patients with select MSI-H/dMMR tumours comes from KEYNOTE-158 and KEYNOTE-164. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies [2-4]

Criteria	KEYNOTE-164	KEYNOTE-158
Study design	Open-label, single-arm, international, phase II study	Open-label, single-arm, international, phase II study
Eligible patients	• ≥18 years of age • Locally confirmed dMMR or MSI-H CRC • A histologically proven locally advanced unresectable or metastatic (Stage IV) CRC • Previous treatment with standard of care therapies: at least two lines of fluoropyrimidine, oxaliplatin, and irinotecan (cohort A) and at least one line of systemic fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAb (cohort B)	• ≥18 years of age • Histologically or cytologically-documented, advanced (metastatic and/or unresectable) solid tumour that was incurable and for which prior standard first-line treatment had failed. • Any advanced solid tumour (except CRC), which was MSI-H positive (cohort K). • Evaluable tissue sample for biomarker analysis from a tumour lesion not previously irradiated.

	• ECOG performance status of 0 or 1 • Life expectancy of greater than 3 months • At least one measurable lesion by RECIST v1.1 as determined by central review for response assessment.	• A tumour that was positive for one or more of the pre-specified primary biomarker(s), as assessed by the central laboratory. • Radiologically measurable disease based on RECIST version 1.1 confirmed by independent central radiologic review. • ECOG performance status of 0 or 1. • Life expectancy of at least 3 months.
Treatments	Patients received intravenous pembrolizumab 200mg every 3 weeks for up to a maximum of 35 cycles (approximately 2 years). Treatment was continued until confirmed radiographic disease progression. Discontinuation could be considered in patients who attained a confirmed CR, provided that they had received at least eight cycles of pembrolizumab and had at least two cycles of pembrolizumab after the date that CR was declared. These patients could restart treatment for up to 17 additional cycles (approximately one year) if radiographic disease progression occurred at the discretion of the investigator.	Pembrolizumab 200mg every 3 weeks for up to a maximum of 35 cycles (approximately 2 years). Treatment was continued until confirmed radiographic disease progression. For patients who had initial radiological evidence of radiological disease progression (as per RECIST v1.1), the investigator was able to continue a patient on study treatment until repeat imaging was obtained, provided the patient was clinically stable. Discontinuation of treatment may be considered for patients who attained a confirmed CR and have been treated for at least 24 weeks, receiving at least two doses of pembrolizumab and at least 80% of the planned dose beyond the date when the initial CR was declared. These patients could restart treatment for up to 17 additional cycles (approximately one year) if radiographic disease progression occurred at the discretion of the investigator.
Randomisation	Not applicable.	Not applicable.
Primary outcome	ORR (proportion of patients with CR or PR) as assessed by independent central radiology review per RECIST v1.1.	ORR, defined as the proportion of patients with a CR or PR as per RECIST v1.1 as assessed by independent central radiologic review.
Secondary outcomes	DOR, PFS, OS.	DOR, PFS, OS.
Statistical analysis	No adjustments for multiplicity.	No adjustments for multiplicity.
Abbreviations: CR = complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours.		

The ORR of pembrolizumab ranged from 34% in colorectal cancer to 56% in small intestine cancer.
See Table 2.2 for details on the key results of KEYNOTE-158 and KEYNOTE-164.

Table 2.2. Key efficacy results from KEYNOTE-164 (data cut February 2021) (ASaT population) and KEYNOTE-158 (data cut October 2021).[2, 5, 6]

	KEYNOTE-164	KEYNOTE-158			
	Colorectal cancer (n=124)	**Endometrial (n=83)**	**Gastric (n=51)**	**Small intestine (n=27)**	**Cholangiocarcinoma (n=22)**
	Primary outcome: ORR (RECIST 1.1, independent central radiologic review)				
ORR (CR+PR)	34%	51%	37%	56%	41%
CR	9.7%	16%	14%	15%	14%
PR	24%	35%	24%	41%	27%
SD	19%	19%	14%	22%	14%
	Secondary outcome: DOR (RECIST 1.1, independent central radiologic review)				
Responders (CR+PR)	42	42	19	15	9
Median DOR	NR	NR	NR	NR	30.6 months
Response duration ≥18 months	92%	65%	90%	84%	78%
	Secondary outcome: PFS (RECIST 1.1, independent central radiologic review)				
Events	84	51	33	14	18
Median PFS	4.0 months	13.1 months	4.1 months	23.4 months	4.2 months
PFS rate at 24 months	34%	39%	38%	50%	32%
	Secondary outcome: OS (RECIST 1.1, independent central radiologic review)				
Events	69	32	29	10	16
Median OS	36.1 months	NR	26.9 months	NR	19.4 months
OS rate at 24 months	59%	67%	50%	63%	50%

Abbreviations: ASaT = all subjects as treated population, defined as all patients who received ≥1 dose of pembrolizumab (KEYNOTE-164) and had ≥6 months of follow-up (KEYNOTE-158); CR = complete response; DOR = duration of response; NR= Not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease.

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed in KEYNOTE-158 using two questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EQ-5D-3L. These instruments were administered at baseline, at regular intervals throughout treatment, and 30 days after treatment discontinuation. At data cut October 2020, pembrolizumab generally improved HRQoL from baseline to week 9, and then it remained stable or improved by week 111. Patients who achieved an objective radiologic response during treatment in particular tended to experience clinically meaningful benefits in HRQoL.[7]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing pembrolizumab with relevant comparators in Scottish clinical practice, the submitting company presented ten naïve unadjusted indirect treatment

comparisons (ITCs) and three unanchored matching-adjusted indirect comparisons (MAICs). Only results from the MAICs were used to inform the economic base case for the pembrolizumab, lenvatinib and dostarlimab comparators in endometrial cancer.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Ten naïve unadjusted indirect treatment comparisons (ITCs) and three unanchored matching-adjusted indirect comparisons (MAICs).
Population	Patients with histologically proven locally advanced unresectable or metastatic (unresectable stage III or stage IV) colorectal cancer irrespective of MSI-high or dMMR status; patients with advanced (metastatic and/or unresectable) endometrial carcinoma, gastric carcinoma, biliary adenocarcinoma and small intestine carcinoma by histology irrespective of MSI-high or dMMR status with recurrent disease when stage is not specified.
Comparators	**CRC:** pooled FOLFOX/FOLFIRI; and trifluridine/tipiracil **Endometrial carcinoma:** physician's choice of paclitaxel and doxorubicin; pembrolizumab plus lenvatinib; and dostarlimab **Gastric carcinoma:** FOLFIRI; and paclitaxel **Small intestine carcinoma**: nab-paclitaxel (company maintain there was a lack of evidence to compare with FOLFOX/FOLFIRI) **Biliary carcinoma:** mFOLFOX; and mFOLFIRI
Studies included	**CRC:** pooled efficacy data from Li et al 2018;[8] ECOG3200;[9] Cao et al 2015;[10] Moore et al 2016[11] and Xie et al 2014[12] (FOLFOX/FOLFIRI); pooled data from Yoshino et al 2012[13]; Recourse[14] and Terra[15] studies [trifluridine/tipiracil] **Endometrial carcinoma:** KEYNOTE-775[16, 17] (physician's choice of paclitaxel and doxorubicin and pembrolizumab plus lenvatinib); Garnet study[18] (dostarlimab) **Gastric carcinoma:** pooled efficacy data from SUN-CASE [19]and Sym et al 2013[20] studies (FOLFIRI); and Chao et al 2021[21] (paclitaxel). **Small intestine carcinoma**: Overman et al 2018[22] (nab-paclitaxel) **Biliary carcinoma:** pooled data from Choi et al 2021[23], Hwang et al 2015[24] and Kim et al 2019[25] (FOLFOX); and Choi et al 2021[23] (FOLFIRI)
Outcomes	Overall survival and progression-free survival.
Results	The results suggest that: **In CRC:** Pembrolizumab was superior to FOLFOX/FOLFIRI (OS HR = 0.30 [95% confidence interval [CI] 0.23 to 0.39]; PFS HR = 0.54 [95% CI 0.43 to 0.69]) and trifluridine/tipiracil (OS HR = 0.26 [95% CI: 0.18 to 0.38]; PFS HR 0.34 [95% CI: 0.25 to 0.46]) (naïve unadjusted analyses). **In endometrial carcinoma:** Pembrolizumab was superior to physician's choice of paclitaxel or doxorubicin (OS HR = 0.26 [95% CI: 0.13 to 0.51]); PFS HR = 0.37 [95% CI: 0.22 to 0.61]). However, there was no evidence of a difference between pembrolizumab and pembrolizumab plus lenvatinib (OS HR = 0.58 [95% CI: 0.31 to 1.10]; PFS HR = 0.97 [95% CI 0.61 to 1.55]) or dostarlimab (OS HR = 1.01 [95% CI: 0.55 to 1.87]; PFS HR = 0.89 [95% CI: 0.58 to 1.37]) (unanchored MAIC analyses). **In gastric carcinoma:** Pembrolizumab was superior to FOLFIRI (OS HR = 0.40 [95% CI: 0.23 to 0.71]; PFS HR = 0.41 [95% CI: 0.24 to 0.70]). However, there was no evidence of a difference between pembrolizumab and paclitaxel (OS HR = 0.52 [95% CI 0.25 to 1.09; PFS HR = 0.73 [95% CI: 0.36 to 1.51]) (naïve unadjusted analyses). **In small intestine carcinoma:** Pembrolizumab was superior to nab-paclitaxel (OS HR = 0.18 [95% CI: 0.07 to 0.45]; PFS HR = 0.22 [95% CI: 0.09 to 0.52]) (naïve unadjusted analyses). **In biliary carcinoma:** Pembrolizumab was superior to mFOLFOX (OS HR = 0.30 [95% CI: 0.16 to 0.58]; PFS HR = 0.50 [95% CI: 0.27 to 0.92]) and mFOLFIRI (OS HR = 0.27 [95% CI: 0.14 to 0.54]; PFS HR = 0.36 [95% CI: 0.18 to 0.71]) (naïve unadjusted analyses).

3. Summary of Safety Evidence

No comparative safety data are available. Refer to the summary of product characteristics for details.[1]

In the KEYNOTE-158 study at data cut-off October 2020, in patients who received at least one dose of pembrolizumab (n=351, Cohort K [any advanced solid tumour except CRC, which was MSI-H positive]), any treatment-related adverse event (AE) was reported by 65% (227/351) of patients; 12% experienced a grade 3 to 5 treatment-related AE; 6.6% discontinued treatment owing to a treatment-related AE. In KEYNOTE-164 at data-cut off February 2021, treatment-related AEs were reported by 64% of patients in cohort A (n=61, ≥2 prior treatment lines) and 71% of patients in cohort B (n=62, ≥1 prior treatment line); grade 3 or 4 treatment-related AEs were reported by 16% of patients in cohort A and 13% of patients in cohort B; discontinuation due to treatment-related AEs was 3.3% in cohort A and 3.2% in cohort B. .[6, 31]

The most frequently reported treatment-related AEs of any grade with an incidence >5% in patients that received at least one dose of pembrolizumab (KEYNOTE-158 [data cut October 2020]/KEYNOTE-164 cohort A/cohort B [data cut September 2018]) were: pruritus (15%/13%/7.9%), fatigue (12%/10%/17%), diarrhoea (12%/13%/11%), arthralgia (9.4%/16%/11%), asthenia (9.1%/13%/3.2%), hypothyroidism (8.8%/4.9%/17%), rash (7.1%/not reported/not reported), nausea (6.3%/16%/7.9%).[3, 4]

Immune-mediated AEs, regardless of attribution to study treatment or immune relatedness by the investigator, occurred in 20% of patients (KEYNOTE-158); 4.8% experienced grade 3-5 immune-mediated AEs. In KEYNOTE-164 (data cut September 2018), immune-mediated AEs or infusion reactions occurred in 29% of patients; 4.8% had a grade 3-4 immune-mediated AE.[3, 4]

The safety profile in patients with metastatic MSI-H/dMMR solid tumours is comparable to the well-known safety profile of pembrolizumab monotherapy. No new safety concerns were identified from KEYNOTE-164 or KEYNOTE-158.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Positive ORR results from studies KEYNOTE-158 and KEYNOTE-164 demonstrate anti-tumour activity in this group of less common cancers, most with limited effective treatment options.
- DOR had not been reached for the majority of tumour groups (excluding cholangiocarcinoma where DOR was 30.6 months) demonstrating a sustained response.

4.2. Key uncertainties

- There were several limitations in the study design and methodology of KEYNOTE-158 and KEYNOTE-164. As single-arm, open-label, phase II studies, these are associated with various biases. Both studies were largely exploratory in nature; only cohort A (≥2 prior lines of therapy) in KEYNOTE-164 had a statistical hypothesis. No adjustments for multiplicity were made, which increases the risk of type 1 statistical error. Sample sizes were small, especially for the gastric (n=51), small intestine (n=27), and biliary cancer (n=22) subgroups. Subgroups were analysed

in a post-hoc, data-driven fashion, meaning results are at a high risk of bias.[2]

- In the absence of direct evidence versus relevant comparators, several ITCs were conducted, which had the following limitations:
    - Some relevant comparators in Scottish clinical practice were not included in the analyses. The submitting company considered that there was little unmet need in patients with CRC since the majority of patients would receive pembrolizumab in the first-line setting and in those who received chemotherapy first-line, nivolumab plus ipilimumab would remain the preferred second-line treatment option. It is anticipated that pembrolizumab would only be considered in patients unsuitable for nivolumab plus ipilimumab and therefore the company did not provide a comparison versus nivolumab plus ipilimumab.
    - The magnitude of benefit of pembrolizumab over comparators is highly uncertain due to the small sample sizes used and the resulting wide 95% confidence intervals.
    - Unanchored and unadjusted comparisons are inherently at high risk of bias. The unanchored MAICs adjust for a very small number of prognostic factors, which may reduce bias, but the results are nevertheless uncertain.
    - There was considerable heterogeneity across studies included in each ITC/MAIC and there were significant missing data for most patient baseline characteristics. The majority of comparator populations, apart from those with endometrial cancer, did not specifically include patients with MSI-H/dMMR disease.
    - No HRQoL or safety outcomes were assessed.

    In conclusion, due to the aforementioned limitations, there is a high degree of uncertainty and likely bias in the results versus all comparators. However, given the large differences reported between pembrolizumab and chemotherapy regimens, it would seem reasonable to suggest a PFS and OS benefit with pembrolizumab versus chemotherapy regimens.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that pembrolizumab fills an unmet need in this therapeutic area, as treatment options for patients with MSI-H/dMMR tumours are limited. They consider pembrolizumab to be a therapeutic advancement in these settings since it is an effective and well-tolerated treatment.

4.4. Service implications

Service implications are expected to be limited due to small patient numbers, although management of patients with immunotherapy-related side effects may add clinical burden to the system.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from: Bowel Cancer UK, Guts UK and AMMF – The cholangiocarcinoma charity. Bowel Cancer UK and Guts UK are registered charities and AMMF is a charitable incorporated organisation.

- Bowel Cancer UK has received 2% pharmaceutical company funding in the past two years, including from the submitting company. Guts UK has received 1.1% pharmaceutical company funding in the past two years, including from the submitting company. AMMF has received 32.5% pharmaceutical company funding in the past two years, with none from the submitting company.

- A diagnosis of bowel cancer can be life changing for those diagnosed, as well as their friends and family, and is even more acute for those at the metastatic stage of the disease when it is harder to treat and there is a low chance of survival. The other advanced cancers covered by this indication are often known as the less survivable cancers, they tend to be diagnosed late, when the treatment options are limited. The physical and mental effects of these conditions have a devastating impact on patients and their families.

- This treatment works by a different mechanism to chemotherapy and offers an option for treatment where there are currently few options available, with some patients unable to access a treatment that could prolong their life.

- With a life limiting condition, it is extremely important that people living with these cancers enjoy time with their family. Patients felt that this treatment offers them greater hope, potentially added months or years of life, additional treatment choice and fewer side effects than chemotherapy. This could give them a better quality of life and allow them to participate in family activities.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company presented the following case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (40 years) –tested in scenario analysis
Population	Adults who have MSI-H or dMMR tumours in: - unresectable or metastatic colorectal cancer (mCRC) after previous fluoropyrimidine-based combination therapy - advanced or recurrent endometrial carcinoma, 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 - unresectable or metastatic gastric cancer, small intestine cancer or biliary cancer, who have disease progression on or following at least one prior therapy
Comparators	The comparators of interest were weighted as estimated for their 'market share' in clinical practice: Colorectal cancer: trifluridine plus tipiracil (30%), pooled FOLFIRI/FOLFOX regimens (70%) Endometrial cancer: chemotherapy (physician's choice of paclitaxel: 5% or doxorubicin: 5%) pembrolizumab and lenvatinib 80%, dostarlimab 10% Gastric cancer: FOLFIRI (30%) or paclitaxel (70%) Small intestine cancer: nab-paclitaxel (100%)

	Biliary cancer: mFOLFOX (90%), mFOLFIRI (10%)
Model description	The model is a multi-cohort partitioned survival model based on the proportion of patients expected for each tumour site in the clinical trials data from KEYNOTE-158 and KEYNOTE-164 (colorectal 40.39%, endometrial 27.04%, gastric 16.7%, small intestine 8.79% and biliary cancer 7.17%), but this was tested in scenario analysis whereby the proportions seen in clinical practice were applied instead (colorectal 29.5%, endometrial 26.3%, gastric 30.9%, small intestine 8.5% and biliary cancer 4.8%). The model cycle length is 1 week and patients start off in a progression free state (on or off treatment) and can remain there, move to the progressive disease state or the death state. If they enter the progressive disease state (on or off treatment) they can either remain there or move to the absorbing death state.
Clinical data	Clinical data were taken from the KEYNOTE-158 and KEYNOTE-164 studies for pembrolizumab. However, as these were single arm studies, comparator data were sourced from the same studies that had been used to inform the ITC. The number of available studies to compare with the pembrolizumab data varied depending on tumour site. Various ITC methods were considered in order to determine the relative efficacy of pembrolizumab to standard of care treatments as described in the clinical sections above. These results from these methods were used to populate the comparator arms of the economic model. Time to treatment discontinuation was also considered (primarily based on either published literature reported median time on treatment or an assumption that patients discontinue upon progression). Treatment waning effects were based on previous NICE appraisal external assessment group critiques of treatment waning effects for other submissions. A treatment waning effect is applied in the base case.
Extrapolation	For overall and progression free survival, data from the KEYNOTE-158 and KEYNOTE-164 studies were extrapolated using Bayesian hierarchical modelling for the pembrolizumab arm (base case which used the log-normal distribution). This was tested in scenario using in terms of the choice of distribution applied to all pembrolizumab arms (Weibull) and fitting standard parametric distribution to each tumour site instead of using Bayesian hierarchical modelling. For comparator arms, tumour specific distributions were chosen from the methods available in the ITC (namely the MAIC which was used for the comparators of pembrolizumab plus lenvatinib, and dostarlimab, both in the endometrial tumour site, or parametric distributions in all other cases). For the parametric distributions, the statistical best fit using, for example, Akaike's Information Criterion (AIC), was most often chosen but this was tested in scenario analysis.
Quality of life	No colorectal cancer EQ-5D data were collected in KEYNOTE-164 so utility values were tumour- specific and taken from a study by Grothey et al 2013. For the other four cancers in KEYNOTE-158, the mean utility values used in the base case were taken from this study's EQ-5D data but were dependent on time to death. The base case values were tested in scenario analysis where tumour site specific health state utilities were used instead, except in the case of colorectal cancer because the values in the Grothey et al 2013 study were health state specific. Utility values were assumed not to vary by treatment in and of itself. Adverse event disutilities were included in a scenario analysis but assumed to be incorporated within EQ-5D scores used to derive the base case data.
Costs and resource use	Costs included the costs of medicines (pembrolizumab and comparators), adjusted for relative dose intensity, administration costs, the cost of subsequent therapies, the cost of healthcare resource use and adverse event costs. A one-off end of life cost was also applied.

	Routine data sources including the BNF, MIMS, NHS Reference Costs, PSSRU and previous NICE Technology Appraisals were used to estimate costs (either taken from or inflated to a price year of 2020-21). Adverse event unit costs were not reported.
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. PAS discounts are in place for trifluridine plus tipiracil, lenvatinib and dostarlimab and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The overall, and histology specific base case results are shown in Table 6.21 and 6.22 below. The results presented do not take account of the PASs for trifluridine plus tiperacil, lenvatinib and dostarlimab and the PAS for pembrolizumab, but these 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 trifluridine plus tiperacil, lenvatinib and dostarlimab for due to commercial confidentiality and competition law issues.

Table 6.21 – Overall base case results (list prices for all medicines)

Technologies	**ICER (£/QALY)**	**NHB**
Pembrolizumab versus SoC	£26,187	0.25
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.		

Table 6.22 – Histology-specific base case results (list price for all medicines)

Tumour site	**ICER (£)**	**NHB**
CRC	£39,372	0.71
Endometrial	Pembrolizumab dominates	1.53
Gastric	£25,469	0.26
Small intestine	£25,523	0.44
Cholangiocarcinoma	£20,961	0.61

6.3. Sensitivity analyses

Deterministic, probabilistic and scenario analyses were all performed. Probabilistic sensitivity analysis ICER results were lower or identical to the base case for the overall and at each tumour site.

For the deterministic sensitivity analysis, the model results overall were most sensitive to the PFS and OS hazard ratios for the pembrolizumab and lenvatinib comparator at the endometrial tumour site, as well as the hazard ratio for the dostarlimab comparator PFS hazard ratio also at the endometrial tumour site. Additional scenario analysis showed that the ICERs for each of the different histology-specific indications were sensitive to different parameters but it was common for the variation of the ICER with changes to the treatment waning assumption, the use of standard parametric models for pembrolizumab data (rather than Bayesian hierarchical modelling), and assumptions around the distribution used for Bayesian hierarchical model (e.g. using the Weibull distribution rather than the base case log normal distribution for the pembrolizumab arms).

For the scenario analysis, only the overall ICER results are presented. Testing of the time horizon was more extensive but the most extreme values have been included in the Table below to show that the impact on the ICER for these changes individually is anticipated to be low.

Table 6.33 – Overall Scenario Analysis Results (list price for all medicines)

Rank	Scenario	ICER
Base case		£26,187
1	Pembrolizumab OS, PFS - Standard PSMs	£50,079
2	No treatment waning	£22,627
3	QALYs and costs undiscounted	£27,181
4	Pembrolizumab PFS - 2-piece BHMs	£28,456
5	QALYs and costs discount rate - 1.5%	£29,434
6	Pembrolizumab OS, PFS - BHM, Weibull	£32,229
7	Utilities: progression-based health state utility values by tumour site	£34,424
8	End of Life costs not applied	£32,761
9	Remove pembrolizumab limit of 35 cycles of therapy	£33,191
10	Pembrolizumab RDI = 100%	£33,193
11	Include testing costs	£32,671
12	No subsequent therapy costs	£32,400
13	AE disutilities applied	£32,363
14	Using UK epidemiological data for tumour distributions	£33,835
15	QALYs and costs discount rate 6%	£35,919
16	Time horizon 10 years	£37,692

6.4. Key strengths

- The model has used standard methods to identify and estimate the parameters needed for the model and the processes undertaken are generally well reported. Median survival was reached for most trial outcomes and the model includes a treatment waning effect.

6.5. Key uncertainties

- The model suffers from the inherent uncertainty created by the fact that the main clinical data (KEYNOTE-158 and KEYNOTE-164) are single arm studies. This creates uncertainty in the differences between the comparative data and pembrolizumab data not only during study follow up timeframes but also in the extrapolation of the resulting hazard ratios over the longer term, because they are drawn from different sources.
- For the pembrolizumab intervention methods the submitting company provided additional data for standard parametric modelling scenarios with different distributions but the impact on the ICER (compared with the best fitting standard parametric distribution choice used in scenario analysis 1) is minimal, even though the use of standard parametric modelling rather than Bayesian hierarchical modelling (scenario analysis 1) itself has a large impact.
- In addition, for comparators, the choice of MAIC/ITC method to be extrapolated was specific to the outcome (PFS or OS), tumour site (endometrial cancer) and comparator (pembrolizumab plus lenvatinib and dostarlimab) under consideration and this was not fully tested in scenario analysis. Given the uncertainties, the Committee considered it

would be preferrable to have an analysis with the same consistent method used for all distributions (standard parametric modelling).

- It was felt that although the submitting company has provided results on the effect of altering each distribution choice for the individual PFS and OS parameters by tumour site, results for standard parametric models used throughout would be desirable. Nevertheless, the Committee did not think, given the available results so far, that further analysis would likely increase the ICER beyond a level where it could still be considered cost-effective.
- The submitting company had also, in response to queries, provided results relating to the time horizon (as a lifetime horizon of 40 years may not fully reflect the age or life expectancy of the patient population), justification for their choice of utility values (compared with available literature values presented in the submission), treatment waning assumptions (start time for treatment waning and duration of waning effect) and the and proportions of patients receiving care for each tumour type expected to form the overall population in clinical practice (compared to the clinical trial proportions). Again, ICER results were stable when these values were tested and it is notable that treatment waning was included in the base case analysis which results in conservative estimates of the value of pembrolizumab.

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

7. Conclusion

After considering all the available evidence, the Committee accepted pembrolizumab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 126 on diagnosis and management of colorectal cancer was published in December 2011 and updated in August 2016.[26]

The National Institute for Health and Care Excellence (NICE) published clinical guideline number NG83: oesophago-gastric cancer: assessment and management in adults in January 2018, which was last updated in July 2023; and clinical guideline number 151: colorectal cancer in January 2020, which was last updated in December 2021.[27]

The European Society for Medical Oncology (ESMO) published guidelines on the diagnosis, treatment and follow-up of endometrial cancer in 2022, gastric cancer in 2022 and biliary tract cancer in 2023, respectively.[28-30]

9. Additional Information

9.1. Date of licensing

16 May 2022.

9.2. Product availability date

Available.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
pembrolizumab	**200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes.**	**3 week cycle: 5,260** **6 week cycle: 10,520**

Costs from BNF online on 05 October 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 37 patients eligible for treatment with pembrolizumab in year 1, with 38 patients in year 5. The estimate uptake rate was 100% for both years, resulting in 37 patients estimated to receive treatment in year 1 and 38 patients in year 5.

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.

*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 09 November 2023.

**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.