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SMC2644

pembrolizumab concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme Ltd.

07 June 2024

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 medicine process

pembrolizumab (Keytruda®) is not recommended for use within NHSScotland.

Indication under review: in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

In a phase III study, the addition of pembrolizumab to trastuzumab plus doublet chemotherapy (using a fluoropyrimidine and platinum-containing regimen) was associated with a significant improvement in progression-free survival and overall survival in adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in whose tumours express PD-L1 with a CPS ≥ 1.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Chair
Scottish Medicines Consortium

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1. Clinical Context

1.1. Medicine background

Pembrolizumab is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor, blocking its interaction with 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 is 200 mg of pembrolizumab every 3 weeks or 400 mg every 6 weeks administered via intravenous infusion over 30 minutes and patients should be treated until disease progression or unacceptable toxicity. [1]

1.2. Disease background

Gastric cancer and gastro-oesophageal junction cancer rank as the fourth and sixth leading causes of cancer-related deaths. [2] In the UK, gastric cancer accounts for 2% of all new cancer cases. It is estimated that approximately 50% of gastric cancers in the UK occurred in people aged 75 years and older and occur twice as frequently in men compared to women. [3]

These cancers are often diagnosed at an advanced stage, possibly owing to non-specific symptoms. Unfortunately, curative treatments are not appropriate for an estimated 60% of gastric and gastro-oesophageal junction cancers [4] and survival rates at 12 months from diagnosis with metastatic gastric and gastro-oesophageal junction cancer are low at approximately 20%. [3]

About 30% of tumours at gastroesophageal junction and 15% of gastric cancers show human epidermal growth factor receptor 2 (HER2) positivity. [5] The overexpression of HER-2 serves as a market for identifying patients who may benefit from a HER2-targeted therapeutic approach alongside chemotherapy. [6]

1.3. Treatment pathway and relevant comparators

The anti-HER2 antibody trastuzumab in combination with platinum (cisplatin or oxaliplatin) and fluoropyrimidine (capecitabine, 5-fluorouracil) doublet chemotherapy is recommended as a treatment option for people with HER2 positive locally advanced and metastatic gastric or gastroesophageal junction adenocarcinoma. [7,8]

In 2015, SMC issued advice that trastuzumab is accepted for used in combination with cisplatin and capecitabine or 5-fluorouracil in untreated patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. This was restricted for use in patients whose tumours have HER2 overexpression defined by immunohistochemistry (IHC) 3+ (“HER2 high expresser”).

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 for pembrolizumab in the indication under review comes from the ongoing KEYNOTE-811 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study [1, 9, 10]

Criteria	KEYNOTE-811
Study design	Phase III, randomised, placebo-controlled, double-blind, multi-site trial.
Eligible patients	• Aged 18 years and over • Previously untreated locally advanced or metastatic HER2 positive gastric or gastroesophageal adenocarcinoma • HER2-positivity defined as either IHC 3+ or IHC 2+ in combination with ISH+ or FISH • Life expectancy >6 months • Eastern Cooperative Oncology Group Performance status of 0 or 1
Treatments	Either pembrolizumab plus standard care or placebo plus standard care. Prior to randomisation, investigators decided on standard care treatment with trastuzumab plus platinum/fluoropyrimidine doublet regimens with capecitabine and oxaliplatin or cisplatin and 5 fluorouracil. Treatments were used as follows: • Cisplatin: 80 mg/m^2, IV infusion, day 1 of each Q3W cycle for up to 6 cycles (or beyond at the discretion of the investigator) • 5 fluorouracil: 800 mg/m^2, IV infusion, continuous on days 1 to 5 of each Q3W cycle for up to 1 additional year beyond 35 administrations of pembrolizumab or placebo • Oxaliplatin: 130 mg/m^2, IV infusion, day 1 of each Q3W cycle over 2 hours (which could be capped at 6 or 8 cycles as per local country guidelines) • Capecitabine: 1000 mg/m^2, orally twice per day on day 1 to 14 of each Q3W cycle for up to 1 additional year beyond 35 administrations of pembrolizumab or placebo • Trastuzumab: loading dose of 8 mg/kg body weight, and then 6 mg/kg body weight thereafter, IV infusion, day 1 of each Q3W cycle for up to 1 year beyond 35 administrations of pembrolizumab or placebo • Pembrolizumab: 200 mg, IV infusion, day 1 of each Q3W for up to 35 cycles • Placebo: IV infusion, day 1 of each Q3W for up to 35 cycles An additional Japan-specific cohort with different standard of care treatment was included in the study and analysed separately. However, only data from the main cohort of patients, referred to as Global cohort, were considered relevant for licensing, therefore this Japan-specific cohort is not further discussed in this document.
Randomisation	Equal randomisation and stratification by geographic region (Europe/Israel/North America/Australia or Asia or the Rest of the World), PD-L1 (positive or negative based on CPS ≥1), chemotherapy regimen (cisplatin and 5 fluorouracil or capecitabine and oxaliplatin).
Primary outcomes	• PFS per RECIST 1.1 assessed by BICR between treatment groups, defined as the time from randomisation to the first documented disease progression per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first • OS defined as the time from randomisation to death due to any cause.
Secondary outcomes	• ORR per RECIST 1.1 by BICR, defined as the proportion of participants who had a complete or partial response. • Duration of response, per RECIST 1.1 as assessed by BICR, defined as the time from first complete or partial response to subsequent disease progression or death from any cause, whichever occurs first.

Statistical analysis	An intent to treat analysis was performed for efficacy outcomes. The primary outcomes were measured using Cox proportion hazards and event rates over time were estimated using the Kaplan-Meier method. Adjustment for multiple testing was based on Maurer and Bretz [11] graphical approach.

Abbreviations: BICR, blinded independent central review; CPS, combined positive score; FISH, fluorescent in-situ hybridisation; IHC, immunohistochemistry; ISH+, in-situ hybridisation positive; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, 3 weekly; RECIST, Response Evaluation Criteria in Solid Tumours.

The regulator has restricted the indication to patients with CPS ≥1. Therefore, the submission presented data for the subgroup of patients with CPS ≥1 (86% [594/692] of the Global cohort), herein referred to as the Global cohort CPS ≥1.[1] Additionally, the submitting company have provided evidence from a post-hoc subgroup analysis on participants from non-Asia geographic regions who had a CPS ≥1, which were used in the economic base case. This subgroup accounted for 58% (402/692) of the Global cohort, herein referred to as non-Asia region CPS ≥1.

At the interim analysis three (data cut-off date: 29 March 2023; final analysis of progression-free [PFS] by blinded independent central review [BICR] and interim analysis of overall survival [OS]), the study showed improvements in PFS and OS with pembrolizumab plus standard care when compared with placebo plus standard care. In the non-Asia region CPS ≥1 subgroup, results are broadly consistent, though the magnitude of effect appears greater. [9]

Table 2.2 Results of primary and secondary outcomes – interim analysis three (data cut-off date: 29 March 2023) [9, 15-16]

	Global cohort CPS ≥1		**Non-Asia region CPS ≥1**	
	Pembrolizumab plus standard care	Placebo plus standard care	Pembrolizumab plus standard care	Placebo plus standard care
	(N=298)	(N=296)	(N=202)	(N=200)
Median duration of follow up	20 months [c]	18.2 months [c]	NR	NR
Progression-free survival (primary outcome)				
Number of PFS events (%)	217 (73)	225 (76)	155 (77)	161 (80)
Kaplan-Meier Estimates (months)[a]				
Median (95% CI)	10.9 (8.5 to 12.5)	7.3 (6.8 to 8.5)	9.9 (8.3 to 11.4)	6.4 (5.6 to 7.4)
Hazard Ratio (95% CI)[b]	0.71 (0.59 to 0.86)		0.64 (0.51 to 0.80) [c]	
PFS rate at 12 months based on KM estimate, % (95% CI)	46 (40 to 52)	33 (27 to 39)	42 (35 to 49) [c]	24 (18 to 31) [c]
Overall survival (primary outcome)				
Number of Deaths (%)	204 (68)	218 (74)	149 (74)	165 (82)
Kaplan-Meier Estimates (months)[a]				
Median (95% CI)	20.0 (17.9 to 22.7)	15.7 (13.5 to 18.5)	18.6 (15.5 to 21.2)	12.6 (11.1 to 14.9)
Hazard Ratio (95% CI)[b]	0.81 (0.67 to 0.98)		0.70 (0.56 to 0.87) [c]	
OS rate at 12 months based on KM estimate, % (95% CI)	70 (64 to 74)	61 (55 to 66)	66 (59 to 72) [c]	53 (46 to 60) [c]

Secondary outcomes			
ORR, %	73	58	NR
Difference in ORR, % (95% CI)	15 (7 to 22)		NR
Duration of response (months [range])	11 (1 to 50)	10 (1 to 49)	NR

Abbreviations: BICR, Blinded Independent Central Review; KM, Kaplan-Meier; CI; confidence intervals; CPS, combined positive score; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
No hypotheses were tested and 95% CI are presented for reference only.
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox proportional hazards model with Efron's method of tie handling with treatment as a covariate.
[c] These values are from the company's submission and could not be verified from the references provided by the submitting company.

2.2. Health-related quality of life outcomes

Health-related quality of life questionnaires were distributed to participants throughout the study duration. These were: Eastern Cooperative Oncology Group (EORTC) core quality of Life questionnaire-C30 (EORTC QLQ-C30), EORTC quality of Life questionnaire – Gastric Cancer Module (EORTC QLQ-STO-22) that looks specifically at the quality of life of patients with gastric cancer, and the European Quality of Life Five Dimension Five Level (EQ-5D-5L) that looks at the general health status of a patient. Results suggest no differences in health-related quality of life between the two treatment groups. [6]

3. Summary of Safety Evidence

No new safety concerns were identified and the safety profile of this combination reflects the established safety profile of pembrolizumab and of the chemotherapy regimens administered. Caution is advised in patients aged over 75 years when pembrolizumab is combined with chemotherapy and risks versus benefits should be assessed on an individual basis. [1, 6]

At the study interim analysis three (data cut-off date: 29 March 2023) in the Global cohort CPS ≥1 patients, nearly all participants experienced one or more adverse events (AEs) in the pembrolizumab plus standard care group (99% [296/298]) and placebo plus standard care (100% [295/295]); almost all were treatment related AEs (97% versus 96%). Patients reporting a treatment related serious AEs were 28% versus 24%. AEs of grade 3 to 5 were experienced more frequently in the pembrolizumab plus standard care group compared to placebo plus standard care (74% versus 66%). In the non-Asia region CPS ≥1, AEs of grade 3 or higher were experienced by 80% (162/202) versus 72% (143/199) of patients. [17]

The company provided safety information for the Global cohort CPS ≥1 patients, including the most frequently reported treatment related grade 3 or higher AEs with an incidence >5% in the pembrolizumab plus standard care group versus the placebo plus standard care. These results were considered confidential by the company. [17]

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

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- KEYNOTE-811 provided evidence to suggest the addition of pembrolizumab to standard of care improved PFS (with a gain of nearly 4 months) and OS (with a gain of approximately 4 months) in untreated adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥1.
- Considering the current life expectancy in this patient population is poor, the improvements in PFS and OS were considered clinically relevant by regulators. [6]
- The secondary outcomes, objective response rate and duration of response, were supportive of a benefit with the addition of pembrolizumab to standard of care.

4.2. Key uncertainties

- The submission is based on subgroup analyses. However, KEYNOTE-811 was not powered to detect differences between subgroups and there was no adjustment for multiple testing, precluding formal hypothesis testing. Randomisation was stratified by PD-L1 positivity based on CPS ≥1; and in patients with CPS <1, a detrimental effect of adding pembrolizumab to standard of care emerged, leading to a restriction of indication to the CPS ≥1 group, in which data suggested clinically relevant benefits when adding pembrolizumab to standard of care. [6] The use of data from patients with CPS ≥1 is therefore considered adequate. Randomisation was also stratified by geographic region; and subgroup analysis results by geographic region suggested pembrolizumab plus standard care compared to placebo plus standard care was not effective in patients from Asia regions but were effective in patients from non-Asia regions. The submitting company argue non-Asia region CPS ≥1 population (combining data from the Western Europe/Israel/North America/Australia and the Rest of the World cohorts) is more generalisable to clinical practice in NHS Scotland given patient characteristics, clinical pathway differences between regions and results from KEYNOTE-811 and previous studies suggesting a regional effect modifier in this population. However, the reliability of using clinical effectiveness data from the non-Asia region CPS ≥1 subgroup is uncertain due to the post-hoc nature of the analysis conducted in these patients.
- The chemotherapy regimen options used in combination with trastuzumab in KEYNOTE-811 did not included cisplatin plus capecitabine (oxaliplatin plus capecitabine was permitted), which is a recommended treatment option. [7] However, the European Society for Medical Oncology guidelines suggest that the platinum-based chemotherapy options, cisplatin and oxaliplatin are equally effective; and the fluoropyrimidines, 5-fluorouracil and capecitabine, are deemed clinically equivalent, which is consistent with the wider literature. [12, 13, 14]
- There is some uncertainty about the generalisability of KEYNOTE-811 data due to the clinical trial population being generally younger and having a higher proportion of males compared with the likely eligible population in Scottish practice. Also, only relatively fit patients (with ECOG performance status of 0-1) and without significant cardiac conditions (due to the use in combination with trastuzumab, associated with cardiotoxicity) were recruited in this study.[6]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that, despite the availability of current treatments, there is an unmet need and the addition of pembrolizumab to standard of care is a therapeutic advancement thanks to improvements in PFS and OS in a patient population with poor prognosis.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the service delivery, as it might increase clinic loads and slightly increase chair time.

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

5. Patient and clinician engagement PACE

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

The key points expressed by the group were:

- Due to their incurable nature, poor prognosis, limited treatment options and debilitating symptoms, gastric and gastro-oesophageal junction adenocarcinomas significantly affect patients' physical, emotional and psychological wellbeing. The emotional impact on carers and families is also profound.
- Trastuzumab with chemotherapy, the standard treatment, may offer limited benefits and can cause severe side effects, contributing to physical and psychological suffering.
- For tolerable increases in toxicity, the addition of this immunotherapy to standard treatment could lead to long-lasting durable responses, even with metastatic disease and extend survival, which would be transformative and positively impact patients' overall wellbeing.
- With potentially prolonged responses and survivals, patients may maintain independence for longer periods, which would help alleviate the burden on their families and carers. Families may experience reduced stress and renewed hope for their loved one's wellbeing treated with this new combination.
- It is expected that this well-known immunotherapy would lead to very limited additional burden on services with minimal increase in chair time (but no additional visits) given that patients are already receiving the chemotherapy and trastuzumab backbone.

Additional Patient and Carer Involvement

We received a patient group submission from OCHRE: the oesophageal cancer charity, which is a registered charity. OCHRE has not received any pharmaceutical company funding in the past two years. A representative from OCHRE participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company presented the following economic case as summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime (40 years). This was varied in scenario analysis to a minimum of 8 years (based on the time horizon used when trastuzumab was accepted for use by SMC) which may be extreme. However, a shorter time horizon than 40 years may be more reflective of the population of interest given the staging of their disease and because the average age of new patients in this indication is typically 75 years old and older.
Population	The population of interest is patients receiving first line treatment of locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma, whose tumours express PD-L1 with a CPS ≥ 1.
Comparators	Comparators are the current standard of care which the submitting company defines as trastuzumab plus chemotherapy with capecitabine and oxaliplatin or cisplatin plus 5 fluorouracil. The model assumes around 78% patients receive capecitabine and oxaliplatin and 22% receive cisplatin plus 5 fluorouracil based on clinical data from the KEYNOTE-811 study. It has been noted by some clinical experts consulted by SMC that oxaliplatin may be more commonly used than cisplatin in clinical practice in Scotland, owing to a more favourable toxicity profile.
Model description	A partitioned survival analysis was provided which included three health states: progression-free, progressed disease and death. This aligned with the modelling approach used in previous technology appraisals in this disease area and was considered an appropriate model structure.
Clinical data	Clinical data came from the KEYNOTE-811 study. The clinical effectiveness evidence for the relevant subgroup (the non-Asia study population with a CPS of greater than or equal to 1) suggested a median PFS of 9.9 months in the pembrolizumab group compared with 6.4 months in the standard of care arm, with a hazard ratio of 0.64 (95% CI: 0.51 to 0.80) and OS of 18.6 months in the pembrolizumab group compared with 12.06 months in the standard of care arm, a hazard ratio of 0.7 (95% CI: 0.56 to 0.87). Time to treatment discontinuation used Kaplan-Meier data and did not require extrapolation owing to the available data from the study.
Extrapolation	Proportional hazard assumptions were assumed not to be met, so independent distributions were fitted to each arm of the Kaplan-Meier data for extrapolation. For OS these were the Weibull distribution and a spline 2 knot odds distribution for the standard of care and pembrolizumab respectively. For PFS, the log normal distribution was used for both the standard of care and pembrolizumab arms. A treatment waning assumption was applied in scenario analysis.
Quality of life	Utilities used in the model were grouped by time to death in the base case, but sensitivity analysis used health state utilities. Quality of life data had been collected using the EQ-5D-5L as part of the KEYNOTE-811 study and were mapped to the 3L data set for use in the economic model.
Costs and resource use	Medicines acquisition costs, administration costs, disease monitoring costs, subsequent treatment costs, adverse event costs and end of life costs were included. Medicines costs were adjusted to account for relative dose intensity and treatment durations for each of the medicines. Diagnostic testing costs were not included in the base case but were in scenario analyses.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case results are shown in Table 6.2 below.

Table 6.2 Base case results (list prices)

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Trastuzumab plus chemotherapy	-	-	-
Pembrolizumab with trastuzumab plus chemotherapy	93,294	0.973	95,870

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.3. Sensitivity analyses

Selected scenario analyses are shown in Table 6.3 below.

Table 6.3 – Scenario analyses (list prices)

	Scenario Name	Base case	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
	Base case		93,294	0.973	95,870
1	Time horizon = 8 years	40 years	91,888	0.613	149,802
2	Time horizon = 20 years	40 years	93,008	0.902	103,075
3	OS – gradual treatment waning between 7 & 9 years	No treatment waning effect	92,863	0.658	141,032
4	Progression-based utility approach with PFS value = base case and PD value based on TA208 method	Time to death utilities	93,294	0.866	107,689
5	Progression-based utilities from KEYNOTE-811 study	Time to death utilities	93,294	0.909	102,662
6	Overall survival choice of distribution – comparator arm (log logistic)	Weibull	92,987	0.731	127,262
7	Overall survival choice of distribution – pembrolizumab arm (log logistic)	2 knot odds spline model	92,996	0.727	127,951
8	Exclude RDI for 1L drugs	Include RDI for first line drugs	97,326	0.973	100,013
9	Include PD-L1 diagnostic testing costs	Exclude PD-L1 diagnostic testing costs	93,294	0.973	95,870
10	Baseline age increased to 75 years old plus time horizon of 25 years	60.2 years and time horizon of 40 years	93,180	0.880	105,877
11	Baseline age raised to 75 years old plus time horizon of 8 years	60.2 years and time horizon of 40 years	91,888	0.611	150,423
12	Time horizon of 8 years and use of health state utilities	40 years and time to death utilities	91,888	0.583	157,705

13	Time horizon of 8 years and health state utility for progression-free patients from KEYNOTE-811 study, 0.577 for patients with progressed disease	40 years and time to death utilities	91,888	0.543	169,363

Abbreviations: ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressed disease; PFS = progression-free survival; QALYs = quality-adjusted life years; RDI = relative dose intensity;

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

6.4. Key strengths

The partitioned survival model structure is commonly used for such indications and the comparators of interest do seem to reflect standard practice. The availability of clinical study data that directly compares the new treatment in addition to standard of care, versus standard of care plus placebo is helpful in reducing the need for indirect comparisons.

6.5. Key uncertainties

- Varying the choice of distribution used to inform overall survival had a large impact on the ICER. The Committee considered the log-logistic distribution (scenarios 6 and 7) potentially provided a more realistic estimate of cost-effectiveness given the clinical data uncertainties, in particular the use of the more favourable non-Asia subgroup data and other generalisability concerns described above.
- The results were sensitive to assumptions about treatment waning. While it was useful to include these results as a scenario analysis, it is unclear clinically when this should commence and how long a waning effect could last given the end of life indication.
- Off-label use of subcutaneous trastuzumab is potentially more relevant to current clinical practice in Scotland. Further confirmation of the effect of the price of subcutaneous trastuzumab on the economic analysis was provided showing minimal impact on the results.
- The long time horizon raises concerns about potentially unrealistic survival estimates as the model baseline population age (60.20 years) is likely younger than the expected baseline age of patients in clinical practice in Scotland (75 years and older) and given that this is an end of life medicine. Nevertheless, the 8 year time horizon tested in scenario analysis may also be extreme, as it reflected clinical practice prior to the introduction of trastuzumab to the standard of care. A 20 year or 25 year time horizon (scenarios 2 and 10) was considered more appropriate.
- While the non-Asia region cohort clinical data used in the model data was considered by the submitting company be more generalisable to a Scottish population, the sample sizes are smaller which may introduce uncertainties that have not been fully tested in scenario analyses. A scenario analysis that uses either the intention to treat (ITT) population or a suitable proxy for their results in terms of expected PFS and OS would have been helpful.
- The use of time to death utilities based on pre-defined cut-offs may underestimate the time that patients spend experiencing poorer health utilities. Although a range of relevant combinations of alternative health state utility values were tested in scenario analysis, these

did show an impact on the ICER. It is unclear that the scenarios sufficiently capture patients' quality of life over the course of the model compared to the final year prior to death, particularly for the progressed disease state as additional literature values suggest health state utility could be lower in practice.

7. Conclusion

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 the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept pembrolizumab for use in NHSScotland.

8. Guidelines and Protocols

There are no recent SIGN guidelines for the management of gastric cancer.

National Institute for, Health Care, Excellence NICE (83) Oesophago-gastric cancer: assessment and management in adults, published 2018 (last updated 2023). [7]

European Society for Medical Oncology (ESMO) guidelines, Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Published 2022. [8]

9. Additional Information

9.1. Product availability date

24 October 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
Pembrolizumab	**200 mg of pembrolizumab every 3 weeks or 400 mg every 6 weeks administered via intravenous infusion**	**3-week cycle: 5,260** **6-week cycle: 10,520**

Costs from BNF online on 07/03/2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues.

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

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

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

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

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

Advice context:

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

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