SMC2660

pembrolizumab 25mg/mL 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, 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: in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor 2 (HER2)-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1.

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

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

This advice replaces advice in SMC2420 only relating to patients with HER2-negative gastro-oesophageal junction adenocarcinoma expressing PD-L1.

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 for this indication is 200 mg every 3 weeks or 400 mg every 6 weeks administered via intravenous infusion over 30 minutes; patients should be treated until disease progression or unacceptable toxicity.[1]

1.2. Disease background

Gastric cancer is the fifth most common cancer worldwide, and the fourth leading cause of death with an estimated 768,793 deaths in 2020.[2] In the UK, gastric cancer accounts for 2% of all new cancer cases, making it a significant ongoing risk to health. Evidence suggests that approximately 50% of gastric cancers in the UK occur in people aged 75 years and older; it is twice as frequent in men than women.[3, 4] Gastric cancer is often diagnosed at an advanced stage due to a lack of specific symptoms, and curative treatments are not appropriate for a large proportion (approximately 60%) of patients.[5] Survival rates at 12 months after diagnosis of metastatic gastric/gastro-oesophageal cancer are estimated to be as low as 20%.[4]

Current guidelines recommend human epidermal growth factor receptor 2 (HER2) testing for people with metastatic oesophago-gastric adenocarcinoma.[2, 6, 7] The expression of PD-L1 is associated with poor prognosis in patients with gastric cancer and the European Society for Medical Oncology (ESMO) guidelines recommend that HER2 status and PD-L1 combined positive score (CPS) should be evaluated in patients with metastatic or locally advanced gastric cancer to tailor first-line treatment in combination with chemotherapy.[2]

1.3. Treatment pathway and relevant comparators

Current guidelines recommend dual therapy with a fluoropyrimidine (5-fluorouracil or capecitabine) in combination with a platinum-containing agent (cisplatin or oxaliplatin), or as triple therapy with epirubicin[6], as the standard of care in patients with advanced metastatic HER2-negative gastric or gastro-oesophageal junction cancer.[2]

In September 2022, SMC issued advice that nivolumab in combination with fluoropyrimidine and platinum-based combination chemotherapy is accepted for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5 (SMC2458). SMC issued advice in May 2022 that pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy, is accepted for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10. This was restricted to a two-year clinical stopping rule (SMC2420).

Clinical experts consulted by SMC confirmed that the only current treatment options for those with a CPS of 1 to 4 is the use of dual chemotherapy with a fluoropyrimidine and platinum-

containing agent, either capecitabine plus oxaliplatin (CAPOX) or cisplatin plus 5-fluorouracil (FP). The addition of nivolumab is also an option for those with a CPS≥ 5.

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-859 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	KEYNOTE-859 study[8, 9]
Study Design	An international, randomised, placebo-controlled, double-blind, phase III study.
Eligible Patients	• Aged 18 years and over. • Previously untreated, unresectable locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma. • Measurable disease per RECIST 1.1 as assessed by investigator. • Known PD-L1 status (CPS <1, ≥1). • ECOG PS status of 0 or 1.
Treatments & randomisation	Patients were randomised equally to receive either IV pembrolizumab (200 mg on day 1 of every 3-week cycle for up to a maximum of 35 cycles) plus chemotherapy or placebo plus chemotherapy. The chemotherapy options (see dose below) permitted in the study were either cisplatin plus 5-fluorouracil (FP) or capecitabine plus oxaliplatin (CAPOX); the two chemotherapy regimen choices (FP or CAPOX) had to be chosen by the investigator prior to randomisation. Crossover was not permitted, and patients continued on the chosen chemotherapy regimen throughout the study. Treatment continued until disease progression, death, unacceptable toxicity or the maximum number of cycles was reached. • Cisplatin: 80 mg/m^2, IV infusion, day 1 of each 3-week cycle (which may be capped at 6 cycles as per local country guidelines). • 5 fluorouracil: 800 mg/m^2, IV infusion, continuous on days 1 to 5 of each 3-week cycle. • Oxaliplatin: 130 mg/m^2, IV infusion, day 1 of each 3-week cycle (which may be capped at 6 cycles as per local country guidelines). • Capecitabine: 1000 mg/m^2, orally twice per day on day 1 to 14 of each 3-week cycle. Randomisation was stratified by PD-L1 expression (CPS ≥ 1 or < 1), chemotherapy regimen (FP or CAPOX), and geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World).
Primary outcome	OS, defined as the time from randomisation and death due to any cause.
Secondary outcomes	• PFS (as per RECIST 1.1 assessed by BICR), 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. • ORR (as per RECIST 1.1 assessed by BICR), defined as the proportion of patients who

	had a complete or partial response.
Statistical analysis	Efficacy analyses were performed first in the CPS ≥ 10 subpopulation, then the CPS ≥ 1 subpopulation and then the ITT population, which included all randomised patients. Adjustment for multiplicity testing was based on Maurer and Bretz[10] graphical approach and formal testing was carried out in a sequential manner in for the primary (OS) and secondary outcomes (PFS and ORR) in each of the three patient populations. One interim analysis was planned approximately 12 months after the last patient was randomised and 403 deaths had occurred in the CPS ≥ 10 subpopulation.

Abbreviations: BICR = blinded independent central review; CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; ITT = intention-to-treat; IV = intravenous; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

The licensed indication is for patients with a CPS ≥1; therefore, the evidence supporting this comes from the subpopulation of patients with CPS ≥1 (78% [1235/1579] of the ITT population).[9]

At the planned interim analysis (data cut-off 03 October 2022), pembrolizumab plus chemotherapy resulted in statistically significant improvements in the primary and hierarchically tested secondary outcomes (OS, PFS by BICR and ORR by BICR) when compared with placebo plus chemotherapy in each study population: CPS ≥ 10 subpopulation, CPS ≥ 1 subpopulation and the ITT population.[8, 9] Results for the CPS ≥ 1 subpopulation, representing the licensed indication are presented in Table 2.2. Since the primary and secondary outcomes were all met at the interim analysis, no further formal analysis was performed. The submitting company provided results of updated post-hoc analysis for OS and PFS in the CPS ≥1 subpopulation (data cut-off August 2023) which was used to reassess survival extrapolations in the cost-effectiveness analyses; these results were similar to those from interim analysis one (data cut-off 03 October 2022).

Table 2.2 Results of primary and selected secondary outcomes from KEYNOTE-859 in the PD-L1 CPS ≥1 subpopulation at the interim analysis (data cut-off 03 October 2022).[8, 9]

PD-L1 CPS≥1 subpopulation		
	Pembrolizumab + chemotherapy (n=618)	**Placebo + chemotherapy (n=617)**
Median follow-up (range in months)	13.0 months (0.2 to 45.9)	11.5 months (0.1 to 45.5)
Primary outcome: overall survival		
Deaths, n	464	526
Median OS	13.0 months	11.4 months
HR (95% CI), p-value	0.74 (0.65 to 0.84), p<0.001	
KM estimated OS at 12 months	52%	46%
KM estimated OS at 24 months	30%	18%
Secondary outcome: progression-free survival (as per RECIST 1.1 assessed by BICR)		
PFS events, n	443	483
Median PFS	6.9 months	5.6 months
HR (95% CI), p-value	0.72 (0.63 to 0.82), p<0.001	
KM estimated PFS at 12 months	29%	18%
KM estimated PFS at 24 months	20%	7.9%

Secondary outcome: objective response rate (as per RECIST 1.1 assessed by BICR)		
ORR, n (%)	322 (52%)	263 (43%)
Difference in ORR, % (95% CI), p-value	9.5% (3.9 to 15), p=0.00041	
Complete response, n (%)	61 (9.9%)	36 (5.8%)
Partial response, n (%)	261 (42%)	227 (37%)

Abbreviations: CI = confidence intervals; CPS = combined positive score; HR = hazard ratio; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

Evidence was presented from an exploratory post-hoc subgroup analyses in patients with CPS ≥ 5 and CPS ≥ 1 to < 5 (data cut-off 03 October 2022). For the CPS ≥ 5 subpopulation (49% [767/1579] of the ITT population), a greater treatment effect was observed in the pembrolizumab plus chemotherapy group compared with placebo plus chemotherapy group for OS (HR 0.70 [95% CI: 0.60 to 0.82]) and PFS (HR 0.69 [95% CI: 0.58 to 0.81]). For the CPS ≥ 1 to < 5 subpopulation (30% [468/1579] of the ITT population), a similarly positive treatment benefit was observed in the pembrolizumab plus chemotherapy group compared with placebo plus chemotherapy for OS (HR 0.78 [95% CI: 0.64 to 0.95]) and PFS (HR 0.78 [95% CI: 0.64 to 0.96]).[8] On request, the submitting company provided updated economic analyses using survival data (from the August 2023 data cut-off) in the sub-population with CPS ≥ 5, and updated survival analysis in the CPS ≥ 1 sub-population.

2.2. Health-related quality of life outcomes

The study used Health related quality of life (HRQoL) questionnaires including the Eastern Cooperative Oncology Group (EORTC) core quality of life questionnaire-C30 (EORTC QLQ-C30), the disease specific EORTC quality of life questionnaire - Gastric Cancer Module (EORTC QLQ-STO-22) and the generic European Quality of Life Five Dimension Five Level (EQ-5D-5L). Overall, results from the exploratory analyses of these outcomes did not show any clinically meaningful differences between the two treatment groups, and a positive trend was only seen for selected items in selected analyses of EORTC QLQ-C30 in those with a CPS≥10; however, there was an improvement in pain (measured by the EORTC-QLQ-STO22 pain scale) in favour of pembrolizumab plus chemotherapy for the ITT population and all subgroups.[8, 9]

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

A Bayesian network meta-analysis (NMA) was performed to compare the efficacy of pembrolizumab with nivolumab when used in combination with fluoropyrimidine and platinum-containing doublet chemotherapy. The main analysis focused on patients with tumours expressing CPS ≥ 5. However, due to methodological uncertainties, sensitivity analyses were conducted based on CPS ≥ 1 and CPS ≥ 10.

The NMA results suggested that pembrolizumab and nivolumab have similar effect on OS and PFS when used in addition to fluoropyrimidine and platinum-containing doublet chemotherapy.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis (NMA) using fixed effects.
Population	Adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma with CPS ≥5.
Intervention	Pembrolizumab plus fluoropyrimidine and platinum-containing doublet chemotherapy. Nivolumab plus fluoropyrimidine and platinum-containing doublet chemotherapy.
Comparators	Fluoropyrimidine and platinum-containing doublet chemotherapy.
Studies included	KEYNOTE-859[9] and CheckMate-469.[11]
Outcomes	Primary outcomes in populations CPS ≥ 5: • OS, defined as the time from randomisation to death due to any cause. • PFS, defined as the time from randomisation to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. Sensitivity analysis repeated the primary outcome analysis but in populations CPS ≥1 and CPS ≥ 10.
Results	The submitting company presented results of the NMA for pembrolizumab plus doublet chemotherapy which was compared to nivolumab plus doublet chemotherapy via the common comparator, doublet chemotherapy alone. The results suggest there is similar efficacy between the treatments, irrespective of PD-L1 status.

Abbreviations: CPS = combined positive score; HER2 = human epidermal growth factor receptor 2; OS = overall survival; PFS = progression-free survival.

3. Summary of Safety Evidence

No new safety concerns were identified in KEYNOTE-859 and the safety profile of the immuno-chemotherapy combination reflected the known and established individual safety profiles of pembrolizumab and the chemotherapy regimens administered.[8]

Safety analyses were performed in the treated population, which included those who had received at least one dose of study treatment in the KEYNOTE-859 study (n=1572). As of the October 2022 data cut-off, any treatment emergent adverse event (AE) was reported by 99% (776/785) of patients in the pembrolizumab plus chemotherapy group and 98% (771/787) in the placebo plus chemotherapy group and these were considered treatment-related in 96% and 94% respectively.[8]

In the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups respectively, patients reporting a grade 3 or higher AE were 75% versus 70%, and these were considered treatment-related in 59% and 51%. The most frequently reported treatment-related grade 3 or higher AEs (with an incidence ≥3% in either group) respectively were: decreased neutrophil count (9.2% versus 7.4%), anaemia (8.2% versus 6.5%), neutropenia (7.0% versus 7.6%), platelet count decreased (7.0% versus 4.6%), diarrhoea (5.9% versus 4.7%), vomiting (4.5% versus 4.1%), fatigue (3.4% versus 4.1%), hypokalaemia (3.3% versus 2.3%), nausea (3.3% versus 3.7%), palmar-plantar erythrodysaesthesia syndrome (3.1% versus 1.8%), and peripheral neuropathy (1.3% versus 3.2%).[8]

In the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups respectively, a serious AE was reported in 45% versus 40% of patients, and a treatment-related serious AE was reported in 23% versus 19%.

Patients with a discontinuation of any study treatment due to treatment-related AEs were 26% versus 20%. 8.7% and 5.1% discontinued pembrolizumab or placebo; 24% and 20% discontinued any chemotherapy; and 4.2% and 3.3% discontinued all drugs.[8, 9] Patients who died due to a treatment-related adverse event were 1.0% versus 2.0% of the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups respectively.

The incidence of AEs in the licensed population (with CPS ≥ 1) were similar to the overall population.[8]

The number of patients with AEs resulting in death was similar in the pembrolizumab plus chemotherapy group (8.2%) and placebo plus chemotherapy group (7.4%). Eight deaths (1.3%) in the pembrolizumab plus chemotherapy group and 16 deaths (2.6%) in the placebo plus chemotherapy group were treatment-related.[8]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Evidence to support the indication under review is based on the subpopulation of KEYNOTE-859 with CPS ≥ 1, which accounted for 78% of the ITT population. The study design controlled for multiplicity to hierarchically test the primary and secondary outcomes in each of the three study populations (CPS ≥ 1, CPS ≥ 10, and the full ITT population). The results demonstrated that the addition of pembrolizumab to fluoropyrimidine and platinum-based chemotherapy significantly improved OS, PFS and ORR in patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
- The baseline characteristics in the CPS ≥ 1 subpopulation, as well as the ITT population, and CPS ≥ 10 subpopulation, were generally consistent with all participants, and balanced between both treatment groups.[8]
- Despite the limited magnitude of these improvements (an approximate OS gain of 2 months in the CPS ≥ 1 subpopulation), these could be considered clinically meaningful given that the current life expectancy in this patient population is very poor.[8]
- Most patients in KEYNOTE-859 received CAPOX (86%), with the other 14% of patients receiving FP as their combination chemotherapy; these two regimens are used for this population in Scottish clinical practice. Oxaliplatin-containing regimens (like CAPOX) may be preferred over cisplatin - containing regimens (FP) due to its more favourable toxicity profile. Whilst other chemotherapy regimens that are potentially used within NHSScotland for this patient population, such as FOLFOX (5-fluorouracil plus oxaliplatin) and XP (capecitabine plus cisplatin), were not an option for patients in KEYNOTE-859, ESMO guidelines suggest that the platinum-based chemotherapy options, cisplatin and oxaliplatin are equally effective[2]; and the fluoropyrimidines, 5-fluorouracil and capecitabine, are deemed clinically equivalent, which is

consistent with the wider literature.[12-14] This suggests that the choices and proportions of the chemotherapy regimens used in KEYNOTE-859 are consistent with Scottish clinical practice.

- The safety profile of pembrolizumab is already well established and KEYNOTE-859 provides additional knowledge relevant to this patient population.

4.2. Key uncertainties

- Nivolumab is recognised as a relevant comparator for those patients with a CPS ≥ 5. Despite the observed potential treatment benefit of pembrolizumab plus chemotherapy observed in the CPS ≥ 5 subpopulation (see section 2.2), less favourable results were reported for OS and PFS in the smaller CPS ≥ 5 to <10 subpopulation (15% [231/1579] of the full ITT population). It was noted that the lack of benefit in the comparatively higher PD-L1 expression group is not biologically plausible. Various factors may have negatively impacted the accuracy of the PD-L1 scores at the CPS 5 cut-off, including this cut-off point was not analytically validated, pre-specified or stratified, and no pathologist training was conducted in KEYNOTE-859.The results of these exploratory analyses should be interpreted with caution. however, based on using CPS as a continuous score, there appears to be an association between higher CPS scores and efficacy in the pembrolizumab plus chemotherapy group in the CPS ≥1 and ≥5 subgroups.[8]
- The treatment benefit for pembrolizumab plus chemotherapy observed in the KEYNOTE-859 study appeared to be driven by patients with a higher CPS level, potentially concealing a lack of benefit in those with a lower CPS level in the ITT efficacy analyses. However, the results from the additional exploratory and retrospective analyses do provide some reassurance in this regard.[8]
- There are some uncertainties about the generalisability of KEYNOTE-859 to the eligible population in Scottish practice. In the UK, gastric cancer is most common in people with black ethnicity;[15] however, there was a notable underrepresentation of black or African American participants in KEYNOTE-859. Additionally, evidence suggests that approximately 50% of new gastric cancers in the UK between 2015 to 2017 were in adults aged 75 years and over.[4] However, in the CPS ≥ 1 subpopulation in KEYNOTE-859, only 40% of patients were ≥65 years of age and only 7.5% were ≥75 years of age.[8] Finally, males accounted for 70% of the CPS ≥ 1 subpopulation in KEYNOTE-859 and may be overrepresented in KEYNOTE-859 compared with the clinical population in Scotland.[4] Additionally, only relatively fit patients (with ECOG performance status of 0 to 1) were recruited in this study.[8]
- In KEYNOTE-859, it was noted that cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. However, approximately 50% of patients were on treatment for at least 6 months (6 cycles of chemotherapy every 3 weeks would usually take up to 18 weeks).[8] Within NHSScotland, these treatments (for example CAPOX) are usually given for 6 to 8 cycles.
- There were a number of limitations with the NMA including the methodological limitations of the CPS ≥ 5 cut-off. As described, in KEYNOTE-859 the PD-L1 score at the CPS 5 cutoff was not a validated biochemical measure, and it was a post hoc analysis. Hence, there is reduced confidence in the statistical inferences made. Heterogeneity was observed in the NMA based on the descriptive statistics, and inclusion of participants who were previously treated with

chemotherapy in the CheckMate-649 study. However, other characteristics appeared similar between the studies based on descriptive statistics. Overall, the conclusions of the NMA appear reasonable.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that the addition of pembrolizumab to chemotherapy is a therapeutic advancement due to the favourable results (for OS and PFS) demonstrated in the KEYNOTE-859 study. They noted that patients with HER2-negative tumours expressing PD-L1 with a CPS of 1 to 4 do not currently have access to immunotherapy.

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 chemotherapy chair time. Also, the potential of immune related side effects might lead to frequent monitoring appointment, more hospital visits and hospital admission for severe cases.

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

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	30 years.
Population	The submitting company requested SMC consider pembrolizumab in combination with fluoropyrimidine and platinum-containing containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma whose tumours express CPS ≥1.
Comparators	Two comparators were used, with comparisons dependent on the patient's CPS level: • doublet chemotherapy for all patients expressing a CPS ≥1 and, • in patients expressing CPS≥5, nivolumab plus doublet chemotherapy.
Model description	A partitioned survival analysis was used, with three mutually exclusive health states: progression free, progressed disease and death. All patients entered the economic model in the progression free health state and were treated with pembrolizumab plus doublet chemotherapy or a comparator treatment. The proportion in this health state was determined by the PFS curve. In subsequent cycles, patients remained progression free and continued first line treatment, remained progression free and discontinued first line treatment, progressed (where subsequent treatments could be received with a one-off cost) or died. The proportion receiving first line treatment was represented by the time on treatment (ToT) curves. The proportion of patients in the progressed disease state was calculated as

	the difference between the PFS and OS curves. Following progression, in subsequent cycles progressed patients remained progressed or died.
Clinical data	PFS, OS and ToT clinical data were sourced from the August 2023 data-cut of the KEYNOTE-859 study for the pembrolizumab plus doublet chemotherapy and doublet chemotherapy arms. Further clinical data from KEYNOTE-859 used in the economic analysis were baseline characteristics, the proportions of patients receiving each doublet chemotherapy regimen in the pembrolizumab plus doublet chemotherapy and doublet chemotherapy arms, and adverse events (Grade 3 plus adverse events occurring in at least 3% of patients in the ITT population). PFS and OS outcomes from the NMA were used in the nivolumab plus doublet chemotherapy arm. In the nivolumab plus doublet chemotherapy arm, the doublet chemotherapy regimen proportions were from the CheckMate 649 study. Adverse event data for nivolumab were also from the CheckMate 649 study (ITT population).
Extrapolation	In the CPS≥1 population, KEYNOTE-859 OS and PFS data were independently extrapolated in each of the pembrolizumab plus doublet chemotherapy and doublet chemotherapy arms, using data from the CPS≥1 population. The spline 3 knot odds was used to extrapolate OS in the pembrolizumab plus doublet chemotherapy and doublet chemotherapy arms, with the spline 2 knot hazards used for PFS extrapolations in both arms. The ToT Kaplan-Meier data in the CPS≥1 population (in combination with maximum treatment durations for chemotherapy of 6 cycles) were directly used for these treatments. In the CPS≥5 population, time-varying hazard ratios were applied in preference to constant hazard ratios, given the company-assessed violation of proportional hazards in overall survival. The overall survival model selected was the first-order fractional polynomial (P1=1, P2=0.5, scale and 2nd shape). The second-order FP (P1=0, P2=0.5, scale and 2nd shape) is used to inform PFS in the base case analysis. As ToT was not an endpoint in the NMA, it was assumed that nivolumab had the same ToT as pembrolizumab (that is, a hazard ratio of 1 was applied).
Quality of life	Utility values were derived from KEYNOTE-859 EQ-5D data. Time-to-death utilities from pooled treatment arms were used. The model placed caps on utility values to prevent them exceeding the baseline general population utility value. Adverse event disutility values were applied as a one-off QALY loss in the first model cycle.
Costs and resource use	Costs included in the model were medicine acquisition, administration, adverse events, subsequent treatments, disease management and end-of-life costs. A relative dose intensity was applied to medicine costs. PD-L1 testing costs were not included, due to this being administered in both arms and having no impact on incremental costs.
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. A PAS discount is in place for nivolumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results.

6.3. Sensitivity analyses

Descriptions of the key scenario analyses that were provided are summarised in Tables 6.3.1 and 6.3.2.

Table 6.3.1 Scenario analysis results – CPS ≥1

	Parameter	Base case	Scenario
	Base case	-	-
1	Time horizon	30 years	10 years
2	OS extrapolations (both arms)	Independent spline 3 knot odds	Independent spline 2 knot hazards
3	PFS extrapolations (both arms)	Independent spline 2 knot odds	Independent spline 1 knot hazards
4	Chemotherapy time on treatment	18-week (6 treatment cycles)	Matched to KEYNOTE-589 data
5	Pembrolizumab time on treatment	Matched to KEYNOTE-589 data	2 year (104 week) stopping rule
6	Treatment waning (pembrolizumab)	Excluded	Included (years 7 to 9)
7	RDI	Include	Exclude
8	Chemotherapy regimens	KEYNOTE-859. 84.5% CAPOX/XELOX 14.5% FP. Both arms.	80% CAPOX/XELOX 20% FOLFOX. Both arms.
9	Utility values	Time-to-death	Health state
10	Utility values	No age adjustment	Age adjustment
11	Combine 4 and 8		

Abbreviations: Incr. = Incremental; ICER =incremental cost-effectiveness ratio; PFS = progression free survival; OS: overall survival; QALY = quality-adjusted life year; RDI =Relative dose intensity; CAPOX/XELOX = Oxaliplatin and capecitabine; FP = cisplatin plus 5-fluorouracil

Table 6.3.2 Scenario analysis results – CPS ≥5

	Parameter	Base case	Scenario
	Base case	-	-
1	Time horizon	30 years	10 years
2	OS extrapolations (pembrolizumab arm)	Independent spline 3 knot odds	Independent spline 2 knot odds
3	PFS extrapolations (both arms)	Independent spline 2 knot odds	Independent spline 1 knot hazards
4	Chemotherapy time on treatment	18-week (6 treatment cycles)	Matched to KEYNOTE-589 data
5	Pembrolizumab and nivolumab time on treatment	Matched to KEYNOTE-589 data	2 year (104 week) stopping rule
6	Treatment waning (pembrolizumab and nivolumab)	Excluded	Included (years 7 to 9)
7	RDI	Include	Exclude
8	Chemotherapy regimens	KEYNOTE-859. 84.5% CAPOX/XELOX 14.5% FP. Both arms.	80% CAPOX/XELOX 20% FOLFOX. Both arms.
9	Utility values	Time-to-death	Health state
10	Utility values	No age adjustment	Age adjustment
11	Nivolumab vs pembrolizumab PFS and OS hazard ratios	Fractional polynomial models (equivalent to time varying hazard	Constant hazard ratios of PFS=OS=1

		ratios)	
12	Nivolumab vs pembrolizumab ToT hazard ratios	ToT=1	Lower bound ToT = 0.8
13			Upper bound ToT = 1.2
14	Combine 4 and 8	-	-

Abbreviations: Incr. = Incremental; ICER =incremental cost-effectiveness ratio; PFS = progression free survival; OS: overall survival; PFS: progression free survival; QALY = quality-adjusted life year; RDI =Relative dose intensity; CAPOX/XELOX = Oxaliplatin and capecitabine; FP = cisplatin plus 5-fluorouracil; ToT = time on treatment.

6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for locally advanced unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma.
- KEYNOTE-859 time on treatment data used for pembrolizumab plus doublet chemotherapy and doublet chemotherapy were mature.
- The ranges used to vary parameters in one-way deterministic sensitivity analysis were appropriate.

6.5. Key uncertainties

- The base case analysis was performed for CPS ≥1 and CPS ≥5 sub-populations. Based on SMC expert responses, it is reasonable to expect that only CPS ≥1 to CPS <5 patients would receive doublet chemotherapy. Therefore, the inclusion of data from CPS ≥5 patients in the efficacy estimates in the CPS ≥1 analysis may have led to bias. The company did not provide additional economic analysis in the CPS ≥1 to CPS <5 sub-population but did provide overall survival hazard ratios in the CPS ≥ 1to CPS <5 sub-population (0.78, 95% confidence interval 0.64 to 0.95) to highlight similarity with the CPS ≥1 sub-population overall survival (0.74, 95% confidence interval 0.65 to 0.84). While those hazard ratio were similar, the overlapping of the subgroup populations was still identified as a source of uncertainty.
- The doublet chemotherapy regimens used in the base case of the economic model matched those from the KEYNOTE-859 study. Those regimens are likely different from what would be observed in Scottish clinical practice. Notably, the FOLFOX regimen was not used in the pembrolizumab plus doublet chemotherapy or doublet chemotherapy arms, but was highlighted as a treatment option by experts consulted by SMC. As noted in the clinical section, the expected effect on the estimated treatment efficacy was minimal, but there are cost implications which were relevant for the economic results. Scenarios exploring alternative treatment regimen, thought to more closely match Scottish practice, showed there was some upward variation in the ICER (Tables 6.3.1, 6.3.2, Scenario 8).
- The NMA was subject to limitations. As the company viewed the proportional hazards assumption to not be met, time varying hazard ratios were used through the application of fractional polynomial models. However, given the ITC results suggested similar efficacy between the treatments, scenarios considering constant hazard ratios were still considered, generating variation in the ICER (Table 6.3.2, Scenario 11). In addition, there was an

assumption of equal time on treatment for pembrolizumab and nivolumab, with the ICER showing variation when exploring this (Table 6.3.2, Scenarios 12 and 13).

- The utility values used in the economic model were subject to limitations. Firstly, it was not possible to compare the time-to-death utilities used in the base case with those from literature (as these were defined for health states). Although the scenario health state utility values were aligned to literature in the progression free health state (although towards the upper bound), they were higher than those in literature for progressed disease. Limited data EQ-5D data collection post-progression was likely the cause of this uncertainty. However, scenario analysis using the KEYNOTE-859 health state utility values had a minor impact on the ICER (Tables 6.3.1 and 6.3.2, Scenario 9), with a minor impact also observed when using the lowest literature progression utility value of 0.577 from NICE TA179/TA208. Secondly, age adjustment for utilities was not performed in the base case, although when applied a minor impact was observed on the ICER (Tables 6.3.1, 6.3.2 Scenario 10). Thirdly, utility values for ≥360 days to death compared to the baseline general population also appeared high (0.8434 and 0.8401 in patients expressing CPS ≥1 and CPS ≥10, respectively). However, utility variation in one-way deterministic sensitivity analysis showed a limited impact on the ICER. In sum, although uncertainties were present with utility values, scenario analyses showed a limited impact on the ICER.
- There was some uncertainty on how long patients in Scotland would receive cisplatin or oxaliplatin treatment, and how that related to the time on treatment observed in the KEYNOTE-589 study. Treatment in Scotland may be capped at 6 cycles, although the SMC also received clinical feedback that treatment may extend beyond that point. The base case analysis assumed that chemotherapy would last for 6 cycles. Scenarios showed that matching the time on treatment to that observed in the KEYNOTE-589 study, where some patients did receive longer chemotherapy treatment, had a relatively modest impact on ICERs, and the direction of that change depended upon the comparator (Table 6.3.1, 6.32 Scenario 4).

*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

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).[6]

European Society for Medical Oncology (ESMO) guidelines, Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Published 2022.[2]

9. Additional Information

9.1. Product availability date

26 January 2024.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
Pembrolizumab	**200 mg intravenously every 3 weeks or 400 mg every 6 weeks.**	**3-week cycle: 5,260** **6-week cycle: 10,520**

Costs from BNF online on 01 April 2024. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 89 patients eligible for treatment with pembrolizumab in year 1 and 86 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.**

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This assessment is based on data submitted by the applicant company up to and including 16 May 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.