Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2420

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

Merck Sharp & Dohme Ltd

8 April 2022

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

ADVICE: following a full submission assessed under the end of life medicine process

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

Indication under review: In combination with platinum and fluoropyrimidine based chemotherapy, 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.

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

In a phase III study, pembrolizumab in combination with chemotherapy was associated with significantly improved progression-free survival and overall survival compared with chemotherapy alone.

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

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

Chairman
Scottish Medicines Consortium

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Indication

In combination with platinum and fluoropyrimidine based chemotherapy, 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.[1]

Dosing Information

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

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

The Summary of product characteristics (SPC) gives recommendations for withholding or discontinuing treatment to manage adverse reactions. No dose reductions are recommended. Tumour expression of PD-L1 should be confirmed using a validated test to select eligible patients for treatment.

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Refer to the SPC for further detail.[1]

Product availability date

27 July 2021
Pembrolizumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Pembrolizumab is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor found in T-cells and blocks its interaction with its ligands PD-L1 and PD-L2. This blockade potentiates T-cell responses, which stimulate immune-mediated anti-tumour activity.[1, 2]

Evidence to support the efficacy and safety of pembrolizumab for this indication is from KEYNOTE-590, a randomised, double-blind, phase III study that recruited adult patients aged ≥18 years with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or Siewert type 1 adenocarcinoma of the gastro-oesophageal junction. Eligible patients had measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) as determined by

investigator or radiology assessment, adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were randomised equally to receive pembrolizumab 200mg every 3 weeks for up to 35 cycles (n=373) or placebo (n=376), both in combination with chemotherapy: cisplatin 80mg/m^2 on day 1 of each 3-week cycle and 5-fluorouracil 800mg/m^2 per day on day 1 to day 5 of each 3-week cycle for up to six cycles, all treatments were administered intravenously. Treatment continued until unacceptable toxicity, disease progression or a maximum of 24 months. Patients in the pembrolizumab group were permitted to continue beyond the first RECIST v1.1 defined disease progression if clinically stable until the first radiographic evidence of disease progression. Randomisation was stratified according to geographical region (Asia or non-Asia), histology (oesophageal squamous cell carcinoma or adenocarcinoma), and ECOG performance status (0 or 1).[2, 3]

KEYNOTE-590 had dual primary outcomes: progression-free survival (PFS) and overall survival. PFS was defined as the time from randomisation to first disease progression per RECIST v1.1 as assessed by the investigator or death due to any cause, whichever occurred first. Overall survival was defined as the time from randomisation to death due to any cause. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. A hierarchical testing strategy was applied to the primary outcomes for the ITT population and pre-specified subgroups including: patients with oesophageal squamous cell carcinoma, patients with oesophageal squamous cell carcinoma and PD-L1 combined positive scores (CPS) ≥10 and all patients with CPS≥10. The marketing authorisation has been granted in patients with a CPS≥10 therefore other patient populations will not be discussed further.[2, 3]

An interim analysis (final analysis for PFS) was conducted on 02 July 2020 with a median follow-up of 12.6 months for the pembrolizumab group and 9.8 months for the placebo group. Pembrolizumab in combination with chemotherapy demonstrated a statistically significant improvement in overall survival and PFS compared with chemotherapy alone in patients with PD-L1 CPS≥10. The results for the primary and key secondary outcomes are presented in Table 1.[2, 3]

Table 1: Primary and secondary outcomes from KEYNOTE-590 in patients with PD-L1 CPS≥10 (data cut-off 2 July 2020)[2, 3]

	Patients with PD-L1 CPS≥10[a]	
	Pembrolizumab + chemotherapy n=186	**Placebo + chemotherapy n=197**
Primary outcome: Overall survival		
Deaths, n	124	165
Median overall survival, months	13.5	9.4
Hazard ratio, 95% CI	0.62 (0.49 to 0.78), p<0.001	
KM estimated overall survival at 24 months	31%	15%
Primary outcome: Progression-free survival assessed by investigator per RECISTv1.1		
Events, n	140	174
Median PFS, months	7.5	5.5
Hazard ratio, 95% CI	0.51 (0.41 to 0.65), p<0.001	
KM estimated PFS at 18 months	21%	5.4%
Secondary outcome: Objective response rate assessed by investigator per RECISTv1.1		
Objective response rate[b]	51%	27%

Complete response	5.9%	2.5%
Partial response	45%	24%

CI: confidence interval, CPS: combined positive score, ITT: intention-to-treat, KM: Kaplan-Meier, PD-L1: programmed cell death-1 ligand-1, PFS: progression-free survival, RECIST v1.1: Response Evaluation Criteria in Solid Tumours version 1.1. [a]PD-L1 CPS is defined as the number of PD-L1-positive cells (tumour cells, macrophages, and lymphocytes) divided by the total number of viable tumour cells. PD-L1-positive tumours had CPS of 10 or more in this study. [b]Proportion of patients with complete or partial response.

Sensitivity analyses of PFS and objective response rate (ORR) assessed by blinded independent central review (BICR) were similar with investigator assessed results for patients with PD-L1≥10 (PFS Hazard ratio [HR]: 0.60 [95% CI: 0.48 to 0.75], ORR 48% versus 28% in the pembrolizumab and placebo groups respectively).[2, 3]

Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in Oesophageal Cancer 18 (EORTC QLQ-OES18) and EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire in the overall study population. For the EORTC QLQ-C30, there was no significant difference in least squares mean (LSM) change from baseline to week 18 in global health status (GHS)/QoL status between groups (LSM difference -0.10 [95% CI: -3.40 to 3.20]). For the EORTC QLQ-OES18, the LSM change from baseline to week 18 favoured the pembrolizumab plus chemotherapy group (-4.78 versus -1.85) but there were no significant between group differences for the reflux or dysphagia subscales. For EQ-5D-5L, LSM change from baseline to week 18 was similar between treatment groups.[2, 4]

Summary of evidence on comparative safety

No new safety concerns were identified in KEYNOTE-590; the safety profile of the immuno-chemotherapy combination reflected the known and established individual safety profiles of pembrolizumab, cisplatin and 5-fluorouracil. Treatment with pembrolizumab plus chemotherapy was associated with an increase in toxicity with patients aged ≥75 years, which may affect the tolerability of the treatment regimen in this patient population. In the KEYNOTE-590, safety analyses were performed in all patients who had received at least one dose of study medicine. At data cut-off, the median duration of treatment with pembrolizumab plus chemotherapy was 5.7 months and with placebo plus chemotherapy was 5.1 months. Any treatment-emergent adverse event (AE) was reported by 100% (370/370) of patients in the pembrolizumab group and 99% (368/370) in the placebo group and these were considered treatment-related in 98% and 97%, respectively. In the pembrolizumab and placebo groups, patients reporting a grade 3 or higher AE were 86% versus 83%, patients with a reported serious AE were 55% in both groups, and patients discontinuing therapy due to an AE was 24% versus 20%.[2, 3]

The most frequently reported treatment-related AEs of any grade with an incidence >20% in the pembrolizumab group versus the placebo group were: nausea (63% versus 59%), decreased appetite (39% versus 32%), anaemia (39% versus 44%), fatigue (36% versus 29%), decreased neutrophil count (36% versus 29%), vomiting (30% versus 27%), diarrhoea (26% versus 23%),

neutropenia (26% versus 24%), stomatitis (26% versus 25%), decreased white blood cells (24% versus 19%).[2, 3]

Immune-mediated AEs and infusion reactions are known AEs of special interest associated with pembrolizumab. These occurred in 26% of patients in the pembrolizumab group and 12% of patients in the placebo group; the most common were hypothyroidism (11% versus 6.5%), pneumonitis (6.2% versus 0.8%), and hyperthyroidism 5.7% versus 0.8%). The majority of cases were mild or moderate in severity. Deaths due to AEs of special interest occurred in two patients in the pembrolizumab group (pneumonitis and interstitial lung disease) and one patient in the placebo group (pneumonitis).[2, 3]

Summary of clinical effectiveness issues

Oesophageal cancer is the seventh most common cancer and sixth leading cause of cancer deaths worldwide; incidence increases with age, peaking in the seventh and eighth decades of life. There are two main histological subtypes: adenocarcinoma and squamous cell carcinoma. Adenocarcinoma is the most common histological subtype in the UK; it is more prevalent in men and risk factors include obesity and chronic gastro-oesophageal reflux disease. Risk factors for squamous cell carcinoma include smoking and alcohol consumption.[5, 6] Patients with unresectable advanced or metastatic oesophageal cancer and HER2-negative gastroesophageal junction cancer with a good performance status and no significant comorbidities are considered for palliative chemotherapy. First-line options include doublet treatment with a fluoropyrimidine (5-fluorouracil or capecitabine) in combination with a platinum agent (cisplatin or oxaliplatin), or triplet therapy with the addition of epirubicin to fluoropyrimidine plus platinum agent. Clinical experts consulted by SMC indicated that doublet chemotherapy with oxaliplatin and capecitabine is the predominant treatment in Scotland. Eligible patients should also be considered for entry into clinical trials and other palliative treatments may be offered including radiotherapy (for example, brachytherapy) or endoscopic therapies (for example, stents) for the symptomatic relief of obstruction or dysphagia. Most patients with oesophageal cancer present with advanced disease; the prognosis for metastatic oesophageal cancer is poor with an overall 5-year survival rate of 5%.[5, 7]

Pembrolizumab meets SMC end of life criteria for this indication.

In KEYNOTE-590, pembrolizumab in combination with cisplatin and 5-fluorouracil demonstrated a statistically significant 4.1 month improvement in overall survival and 2 month improvement in PFS compared with chemotherapy alone in patients whose tumours expressed PD-L1 CPS≥10. These results were considered clinically relevant and were supported by a 24% increase in ORR in this patient population.

There were some limitations associated with KEYNOTE-590. PFS and ORR were assessed by the investigator, which may have introduced potential assessment bias. In a sensitivity analysis using blinded independent central review to determine PFS and ORR, the results were consistent with the investigator assessment. In KEYNOTE-590, pembrolizumab was continued for up to 2 years; therefore evidence of efficacy beyond this treatment period is limited. The number of patients in KEYNOTE-590 aged ≥75 years with PD-L1 CPS≥10 (n=32) is too small to draw conclusions on efficacy.[1] In the overall population, the benefit from the addition of pembrolizumab to

chemotherapy in patients aged ≥75 years (n=69) was modest (overall survival HR: 0.98 and PFS HR: 0.93); there was also a trend towards increased toxicity which may influence treatment selection in this older patient population. However KEYNOTE-590 was not powered to detect differences between subgroups and therefore results should be interpreted with caution. In patients with PD-L1 CPS≥10, the proportion with squamous cell carcinoma (75%) and the proportion of Asian patients (56%) is higher than in the Scottish population, which could affect the generalisability of study results.[2, 3]

KEYNOTE-590 evaluated pembrolizumab when added to cisplatin and 5-fluorouracil chemotherapy. There is no direct or indirect evidence for pembrolizumab in combination with other platinum or fluoropyrimidine regimens that may be used in clinical practice. The submitting company assumed that alternative doublet regimens including oxaliplatin or cisplatin in combination with 5-fluorouracil or capecitabine or triplet regimens with epirubicin were clinically equivalent. SMC clinical experts agreed that this was a reasonable assumption.

Clinical experts consulted by SMC considered that the addition of pembrolizumab to chemotherapy represents a therapeutic advancement due to the favourable results demonstrated in the KEYNOTE-590 study. They considered that it would be used according to the licensed indication in patients whose tumours express PD-L1 CPS≥10. The introduction of pembrolizumab may impact the service and patient as additional time will be required in the oncology day unit for administration and treatment may continue beyond the standard number of chemotherapy cycles.

Companion diagnostic, testing for PD-L1 status, is required: contact local laboratory for information.

Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma is a severe condition with a poor prognosis. The disease is associated with significant morbidity including bleeding, pain and life changing dysphagia. Other symptoms include weight loss, hoarseness, cough, feelings of persistent heartburn and indigestion. The diagnosis is devastating and has a huge impact on the patient and their family.
- There is a high unmet need for patients with this condition as treatment options are limited. Pembrolizumab in combination with standard platinum and fluoropyrimidine based chemotherapy would provide suitable patients with an additional treatment option which is associated with a significantly improved survival and minimal additional toxicity.
- Pembrolizumab is expected to have a positive impact on wellbeing and quality of life. Improved patient survival could offer additional quality time for patients to spend time with

family and friends. Patients may be able to live independently for longer and reduce the impact of care burden for family and carers. Improved disease control may delay the progression of debilitating symptoms and reduce the reliance on regular care and support from health services for day to day living and symptom management.

- PACE participants agreed that pembrolizumab should be used as per the licensed indication for this condition.

Additional Patient and Carer Involvement

We received a patient group submission from OCHRE, 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.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating pembrolizumab within its full licensed indication. In the model, 200mg of pembrolizumab was administered every three weeks for up to two years, in combination with cisplatin and 5-fluorouracil (5FU). Analysis and results were prepared using a variety of comparators including those used in the KEYNOTE-590 study (cisplatin and 5FU), a blended comparator of doublet and triplet chemotherapy treatments and each of the separate doublet and triplet therapies in isolation. The company reported having been unable to conduct an indirect comparison with alternative chemotherapies to cisplatin and 5FU, so instead the analysis made the assumption that all chemotherapy treatments have equal clinical and safety profiles. This was judged as an appropriate assumption by clinicians consulted by the company and SMC.

According to clinical experts consulted by SMC, the treatment most commonly used in Scottish practice is capecitabine and oxaliplatin. Results using this combination as a comparator were available, however, given the assumed equivalence and modest price differential across chemotherapy treatments, all base case results fell within a small range.

The analysis consisted of a standard three-state partitioned survival model, grouping people between PFS, post-progression survival and death. A separate partition was applied to represent the time spent on treatment. A lifetime horizon of 30 years was used, and a one-week cycle length applied.

Individual patient level data, from the PD-L1 CPS≥10 subgroup of the KEYNOTE-590 study[3], were used as the main source of clinical evidence. The company fitted parametric curves to these data in a manner consistent with the guidance issued by the NICE decision support unit.[8] Separately fitted piecewise log-normal curves were used to extrapolate for overall survival. These used the study data in its raw form up until week 40, after which the parametric curves were applied. The appropriateness of these projections were assessed through statistical fit, visual fit, comparison to external data and clinical opinion.

For PFS, the raw study data was used up to week 10 after which point separately fitted log-logistic parametric curves were applied. The appropriateness of these projections was assessed through statistical and visual fit. Given the maturity of the data PFS was less of a source of uncertainty than overall survival.

Within the base case, no treatment waning was assumed, and so the effectiveness of pembrolizumab was maintained until death.

EQ-5D-5L data were collected from participants in the KEYNOTE-590 trial and valued at individual level, before being converted to the 3L equivalent using the van Hout et al. (2012)[9] cross walk algorithm. These data were pooled across both treatment arms as well as across the full study population (including the PD-L1 CPS<10 population). A time-to-death approach was taken, using a linear mixed-effects model regression to estimate utility values for 0-29, 30-89, 90-179, 180-359 and 360+ days until death. Additionally a disutility of grade 3+ AE events was estimated. An age adjustment was applied through an index formed from general population values. Some of the initially estimated utility values for those with oesophageal cancer, but a long life expectancy, were higher than predicted for member of the general population. As a result, a cap was applied, setting the general population value as a maximum.

Treatment costs included in the model were for medicine acquisition, administration and the treatment of AEs, for both first-line and second-line treatments. There were additional state specific costs, with those in the pre-progressed state assumed to utilise CT scans, full blood counts, renal function tests, hepatic function tests and consultation visits. Those in the in the progressed state were assumed to utilise consultation visits only. At the time of death, a one off end of life cost was applied. Costs for PD-L1 testing were also included, adjusted to match the proportion of CPS≥10 patients included in the KEYNOTE-590 study (51.1%) meaning approximately two tests needed to be carried out for every positive result. The cost of each test was assumed to be £43.53.

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.

The base case results for the comparison between pembrolizumab plus cisplatin and 5FU and cisplatin and 5FU are shown in the table below. As noted above, a variety of comparators are available, but there is limited variation in overall results. Additionally, sensitivity analysis was only provided for the comparator used in the KEYNOTE-590 study, making it the most relevant for consideration.

Table 2: Base case results, KEYNOTE-590 study comparator (PAS price)

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab plus chemotherapy	-	-	-
chemotherapy	£30,587	1.05	£32,051

Abbreviations: ICER = Incremental cost effectiveness estimate, QALY = Quality adjusted life year

A range of sensitivity and scenario analyses were presented, with the key scenarios summarised below. Note that the company identified a minor modelling error resulting in a small reduction in the base case ICER. The company did not provide updated scenario modelling to reflect this correction, however it was not expected to have a significant influence on these results.

Table 3: Selected scenario analysis, KEYNOTE-590 study comparator (PAS price)

#	Base case	Description	Inc. costs (£)	Inc. QALYs	ICER (£)
1	OS – Log-normal distribution	OS – Log-logistic distribution	30,217	0.80	37,861
2		OS – Generalised gamma distribution	31,894	0.95	31,706
3**Error! Reference source not found.**	No treatment waning effect	Treatment waning on OS initiated at 5 years, completed at 7 years	30,170	0.72	41,923
4	Dose intensities matched to KEYNOTE-590 study	Assuming 100% dose intensity	32,202	0.90	35,914
5**Error! Reference source not found.**	Time-to-death utilities	Health-state utilities	30,287	0.80	37,795
6**Error! Reference source not found.**	Time horizon 30 years	Time horizon 10 years	29,590	0.63	46,680
7		Time horizon 20 years	30,094	0.83	36,260
8		Time horizon 40 years	30,346	0.91	33,496

Abbreviations: PAS: Patient Access Scheme, ICER = Incremental cost effectiveness estimate, QALY = Quality adjusted life year, OS = Overall survival, RDI = Relative dose intensity

Additional combined scenarios were requested and provided by the company.

Table 4: Combined scenario analysis, KEYNOTE 590 study comparator (PAS price)

#	Base case	Description	Inc. costs (£)	Inc. QALYs	ICER (£)
1**Error! Reference source not found.**	No treatment waning effect / time-to-death utilities	Treatment waning on OS / health-state utilities	30,170	0.66	45,877
2	No treatment waning effect / time-to-death utilities / study RDI	Treatment waning on OS / health-state utilities / 100% RDI	32,085	0.66	48,790
3**Error! Reference**	No treatment waning effect / time-to-death	Treatment waning on OS / health-state	30,070	0.64	47,170

#	Base case	Description	Inc. costs (£)	Inc. QALYs	ICER (£)
source not found.	utilities / 30 year time horizon	utilities / 20 year time horizon			

Abbreviations: PAS: Patient Access Scheme, ICER = Incremental cost effectiveness estimate, QALY = Quality adjusted life year, OS = Overall survival, RDI = Relative dose intensity

The strengths of the economic case were identified as:

- The modelling approach taken followed standard practice for oncology, using a three-state partitioned survival model.
- Clinical evidence on the efficacy of pembrolizumab in combination with chemotherapy came from a large, randomised, double-blind phase III trial.
- While a source of uncertainty, the extrapolation of overall survival was validated through visual fit, statistical fit, external data and clinical opinion.
- The data for PFS were largely mature at the end of the study. For time on treatment, the data were fully mature.

The limitations of the economic case were identified as:

- The assumption of clinical equivalence between comparators was underpinned by evidence and clinical opinion but remained a source of uncertainty which was not explored in sensitivity analysis.
- No waning effect was assumed after the completion of the maximum of 2 years of pembrolizumab treatment. The clinical plausibility of that was uncertain. As can be seen in Scenario 3 in Table 2, its inclusion increases the ICER by a substantial amount.
- The extrapolation of overall survival remains uncertain. Both the log-logistic and generalised gamma functions were felt to show similar plausibility to the log-normal function. Their use increases and decreases the ICER (see Scenario 1 and 2, Table 2). Further, the break point used in the piecewise modelling remains a source of uncertainty. Alternative options were not explored in sensitivity analysis, meaning the effect of change its location were unknown.
- There was some uncertainty on the validity of the time-to-death approach taken for utility values, for example leading to inappropriately high utility values when a person is approximately a year or more from death. The alternative of health-state utilities, which is a method frequently employed within SMC submissions, increases the ICER (see Scenario 5 in Table 2). Both results above were derived from the full KEYNOTE 590 population, not just those from the PD-L1 CPS≥10 population, and it was unclear whether these groups had different utility profiles.

The Committee also 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 accepted pembrolizumab for restricted use in NHSScotland.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published in 2018 'Oesophago-gastric cancer: assessment and management in adults' (National guideline 83). For patients with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities these guidelines recommend the following palliative first-line chemotherapy combinations: doublet treatment with 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin or triplet treatment with 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.[7]

The European Society for Medical Oncology (ESMO) published in 2016 'Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. For patients with advanced/metastatic oesophageal cancer, these guidelines recommend chemotherapy with cisplatin plus 5-fluorouracil for palliative treatment in selected patients, particularly for patients with adenocarcinoma who have a good prognostic score. In addition, oxaliplatin in combination with fluoropyrimidine agents are newer alternative regimens. Also, infusional 5-fluorouracil may be replaced by capecitabine if combination if the swallowing of tablets is not compromised. Taxanes are recommended in first-line combinations or as monotherapy in second-line therapy. For patients with squamous cell carcinoma, palliative chemotherapy is considered less effective. Cisplatin-based combinations have shown increased response rates but no survival gain compared with monotherapy. Overall, results with palliative chemotherapy are inferior to those in adenocarcinoma. Therefore, best supportive care or palliative monotherapy should also be considered.[5]

Additional information: comparators

Doublet chemotherapy with cisplatin or oxaliplatin in combination with 5-fluorouracil or capecitabine. Triplet chemotherapy with the addition of epirubicin.

Additional information: list price of medicine under review

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

Costs from BNF online on 15.12.21. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 151 patients eligible for treatment with pembrolizumab in year 1 and 161 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

1. Merck Sharp & Dohme (UK) Limited. Pembrolizumab concentrate for solution for infusion (Keytruda®). Summary of product characteristics. Electronic Medicines Compendium. Last updated: 3 December 2021. Available at: https://www.medicines.org.uk/emc/product/2498/smpc#gref.

2. The European Medicines Agency (EMA) European Public Assessment Report. Pembrolizumab (Keytruda®). 20 May 2021. EMA/331504/2021 Available at: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0097-epar-assessment-report-variation_en.pdf

3. Sun et al., Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021; 398: 759–71.

4. Mansoor W, Kulkarni AS, Kato K, Sun J-M, Shah MA, Enzinger PC*, et al.* Health-related quality of life (HRQoL) of pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase III KEYNOTE-590 study. Journal of Clinical Oncology. 2021;39(3_suppl):168-.

5. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D, on behalf of the Esmo Guidelines Committee ceo. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016;27(August 2003):v50-v7.

6. Cancer Research UK. Oesophageal cancer: Types. Last reviewed: August 2019. Available at: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/stages-types-and-grades/types.

7. National Institute for Health and Care Excellence (NICE). Oesophago-gastric cancer: Assessment and management in adults. NICE guideline (NG83). Published: 24 January 2018. Available at: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations#palliative-management-2.

8. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Sheffield: Report by the Decision Support Unit. 2011(0).

9. Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

This assessment is based on data submitted by the applicant company up to and including 11 February 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.