Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2375

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

Merck Sharp & Dohme (UK) Limited

6 August 2021

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 restricted use within NHSScotland.

Indication under review: as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

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

In an open-label, phase III study, pembrolizumab monotherapy was associated with significantly improved progression-free survival compared with investigator's choice of chemotherapy in patients with metastatic MSI-H/dMMR colorectal cancer.

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

Chairman
Scottish Medicines Consortium

Indication

Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.[1]

Dosing Information

The recommended dose of pembrolizumab as monotherapy 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.

Testing for MSI-H/dMMR tumour status using a validated test is recommended to select patients with colorectal cancer for treatment.

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

Patients treated with pembrolizumab must be given the Patient Alert Card and be informed about the risks of pembrolizumab. Refer to the SPC for further detail.[1]

Product availability date

28 January 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 ligands PD-L1 and PD-L2. This blockade potentiates T-cell responses which stimulates immune-mediated anti-tumour activity.[1, 2]

Key evidence for this indication is from KEYNOTE-177, a, randomised, open-label phase III study. KEYNOTE-177 recruited adult patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) stage IV colorectal cancer with measurable disease according to Response Evaluation Criteria in Solid Tumour (RECIST), version 1.1. Patients had an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 or 1, adequate organ function and a life expectancy of at least 3 months. Patients had not received previous systemic treatment for stage IV disease but previous adjuvant chemotherapy for colorectal cancer was permitted if completed at least 6 months prior to randomisation.[2, 3]

Patients were randomised equally to receive pembrolizumab 200mg intravenously once every 3 weeks (n=153) or investigator's choice of chemotherapy every 2 weeks (n=154). The chemotherapy regimens were administered intravenously and included:

- mFOLFOX6: oxaliplatin 85mg/m^2 as a 2-hour infusion on day 1, leucovorin 400mg/m^2 as a 2-hour infusion on day 1, and 5-fluorouracil 400mg/m^2 on day 1, followed by 1200mg/m^2 for 2 days for a total of 2400mg/m^2 delivered by continuous infusion over 46 to 48 hours (n=11).
    - mFOLFOX6 plus bevacizumab 5mg/kg administered intravenously on day 1 (n=64).
    - mFOLFOX6 plus cetuximab 400mg/m^2 administered intravenously over 2 hours (first infusion) followed by 250mg/m^2 administered as one 1-hour infusion weekly (n=5).
- FOLFIRI: irinotecan 180mg/m^2 delivered over 30 to 90 minutes on day 1, leucovorin 400mg/m^2 delivered by infusion over 30 to 90 minutes on day 1, and 5-fluorouracil 400mg/m^2 administered as a bolus on day 1, followed by 1200mg/m^2 per day for 2 days for a total of 2400mg/m^2 delivered by continuous infusion over 46 to 48 hours (n=16).
    - FOLFIRI plus bevacizumab 5mg/kg administered intravenously on day 1 (n=36).
    - FOLFIRI plus cetuximab 400mg/m^2 administered intravenously over 2 hours [first infusion] followed by 250mg/m^2 administered as one 1-hour infusion weekly (n=11).

Treatment was continued for a maximum of 35 treatments with pembrolizumab, or until confirmed radiographic disease progression, development of unacceptable toxic effects, illness, or a decision by the physician or patient to withdraw from the study. Patients randomised to chemotherapy were permitted to cross over to receive pembrolizumab at the discretion of the investigator after disease progression confirmed by independent central review.[2, 3]

KEYNOTE-177 had two primary outcomes: progression free survival (PFS) and overall survival. PFS was defined as the time from randomisation to the first documented disease progression per RECIST v1.1 based on blinded central review or death by any cause, whichever occurred first. Overall survival was defined as the time from date of randomisation to death due to any cause. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomised patients. A hierarchical statistical testing strategy was applied to the primary outcomes and secondary outcome of objective response rate (ORR), defined as the proportion of patients achieving a complete or partial response as per RECIST v1.1 assessed by blinded central review. If only one of the primary outcomes was statistically significant, then ORR was tested at one-sided 1.25% significance level.[2, 3]

The primary analysis (interim analysis for overall survival) was conducted at the data cut-off on 19 February 2020 after a median follow-up of 28.4 months in the pembrolizumab group and 27.2 months in the chemotherapy group. Pembrolizumab demonstrated superiority compared with chemotherapy for PFS with an increase of 8.3 months. Sensitivity analyses for PFS using time to disease recurrence after curative-intent surgery and two alternative censoring rules were consistent with the primary analysis. At the data-cut off, there was no significant difference in

overall survival, although results numerically favoured pembrolizumab. Since PFS was statistically significant, ORR was formally tested but no significant difference between the pembrolizumab and chemotherapy groups was found.[2, 3] The results for the primary and secondary outcomes are presented in Table 1.

Table 1: Primary and secondary outcomes for KEYNOTE-177 study in the ITT population (data cut-off 19 February 2020)[2, 3]

	Pembrolizumab (n=153)	Chemotherapy (n=154)
Primary outcome: PFS by blinded central review per RECIST v1.1		
Median PFS	16.5 months	8.2 months
PFS Events (n)	82	113
Hazard Ratio (95% CI)	0.60 (0.45 to 0.80), p<0.001	
KM estimated PFS at 12 months	55%	37%
KM estimated PFS at 24 months	48%	19%
Primary outcome: overall survival		
Median overall survival	NR	34.8 months
Deaths (n)	56	69
Hazard Ratio (95% CI)	0.77 (0.54 to 1.09), p=0.069	
KM estimated overall survival at 12 months	78%	74%
KM estimated overall survival at 24 months	68%	60%
Secondary outcome: ORR by blinded central review per RECIST v1.1		
ORR, % (n/N)	44% (67/153)	33% (51/154)
Percent difference (95% CI)	11% (-0.2 to 21.3), p=0.028[A]	
Complete response (%)	11%	3.9%
Partial response (%)	33%	29%

ITT=intention to treat, PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumours, Cl=confidence interval, KM=Kaplan-Meier, NR=not reached, ORR=overall response rate. [A]Not significant as tested at a 1.25% one-sided significance level.

Subgroup analyses for PFS and overall survival were generally consistent with the primary analysis with the exception of subgroups by metastatic sites and mutational status. In the KRAS/NRAS mutation subgroup (n=74), no PFS advantage was demonstrated for pembrolizumab compared with chemotherapy (hazard ratio [HR]=1.19, [95% CI: 0.68 to 2.07]). The benefit of pembrolizumab compared with chemotherapy was also less favourable for patients with hepatic and/or pulmonary metastases, in particular this is noted for patients with pulmonary metastases only (n=34) (PFS HR=1.02 [95% CI: 0.42 to 2.46], overall survival HR=1.99 [0.69 to 5.44]).[2, 3]

A final analysis for overall survival was conducted at the data cut-off 19 February 2021 and the results were consistent with the interim analysis; median overall survival not reached for the pembrolizumab group compared with 36.7 months for the chemotherapy group, HR 0.74 (95% CI: 0.53 to 1.03).[4]

Patient reported outcomes were assessed as an exploratory outcome using the European Organisation for the Research and Treatment of Cancer quality of life 30 item questionnaire (EORTC QLQ-C30) which was supplemented with a colorectal cancer-specific module (QLQ-CR29)

and the EuroQol-5 dimension (EQ-5D) questionnaire. The results indicated a general trend towards improved health-related quality of life and no significant deterioration was observed.[2]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that no new safety concerns were identified in KEYNOTE-177 and that compared with chemotherapy, pembrolizumab demonstrated a favourable safety profile. However, it noted that there was an increase in gastrointestinal toxicity, including diarrhoea, abdominal pain and colitis compared with the known safety profile of pembrolizumab. In KEYNOTE-177, safety analyses were performed in all patients who underwent randomisation and received at least one dose of study medicine. At the data cut-off, the median duration of treatment in the pembrolizumab group was 11.1 months and in the chemotherapy group was 5.7 months. Any treatment-emergent adverse event (AE) was reported by 97% (149/153) of patients in the pembrolizumab group and 99% (142/143) in the chemotherapy group and these were considered treatment-related in 80% and 99% respectively. In the pembrolizumab and chemotherapy groups respectively, patients reporting a grade 3 or higher treatment-related AE were 22% versus 66%, patients with a reported serious treatment-related AE were 16% versus 29%, the proportion of treatment-related AEs that led to dose interruptions were 23% versus 59% and patients discontinuing therapy due to an AE was 9.8% versus 5.6%.[2, 5]

The most frequently reported treatment-related AEs of any grade with an incidence >10% in the pembrolizumab group versus the chemotherapy group were: diarrhoea (25% versus 52%), fatigue (21% versus 44%), pruritus (14% versus 4.9%), nausea (12% versus 55%), aspartate aminotransferase (AST) increased (11% versus 4.9%), rash (11% versus 7.7%), arthralgia (10% versus 1.4%) and hypothyroidism (10% versus 0%).[2, 3]

Immune-related AEs and infusion reactions were reported by 31% of patients in the pembrolizumab group and 13% of patients in the chemotherapy group, these were grade 3 or higher in 9.2% and 2.1% respectively. Compared with the reference data set (n=5884), which represents the established safety profile for pembrolizumab from 18 studies, patients in the pembrolizumab group of KEYNOTE-177 experienced a similar frequency of hypothyroidism (12% versus 11%), a higher incidence of colitis (6% versus 2%), adrenal insufficiency (2.6% versus 0.8%) and hepatitis (2.6% versus 1%). However, when adjusted for exposure, differences tended to be reduced.[2]

Summary of clinical effectiveness issues

Colorectal cancer is clinically defined by its tissue of origin in the colon or rectum, but is heterogeneous in terms of genetic classification. Approximately 12% to 15% of patients with colorectal cancer and 4% with metastatic colorectal cancer have tumours with dMMR that results in the inability of cells to recognise and repair spontaneous mutations. This causes a very high tumour mutation burden and altered microsatellite sequences that render these tumours high in

microsatellite instability (MSI-H). Evidence suggests that patients with MSI-H/dMMR metastatic colorectal cancer demonstrate less favourable PFS and overall survival outcomes compared with patients who have microsatellite stable (MSS) tumours following treatment with first-line therapies.[2, 3] Current guidelines recommend combination treatment with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CAPOX) or 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) as the preferred first-line options for patients with metastatic colorectal cancer. Epidermal growth factor receptor (EGFR) antibodies, cetuximab or panitumumab, may be used in combination with FOLFOX or FOLFIRI chemotherapy regimens as a first-line option for patients with EGFR-expressing RAS wild-type metastatic colorectal cancer. Bevacizumab is a vascular endothelial growth factor (VEGF) antibody licensed for use in combination with fluoropyrimidine-based chemotherapy for metastatic carcinoma of the colon or rectum but is not recommended for use in NHSScotland.[6, 7] Surgical intervention should be considered for patients whose metastases are suitable for resection either initially or after chemotherapy.[8] Clinical experts consulted by SMC considered pembrolizumab fills an unmet need for this indication due to favourable results of the KEYNOTE-177 study. Pembrolizumab meets SMC end of life criteria for this indication.

In KEYNOTE-177, at the 19 February 2020 data cut-off, pembrolizumab demonstrated a statistically significant improvement in PFS (assessed by central review) of 8.3 months compared with chemotherapy, which the EMA considered clinically meaningful. This was not supported by overall survival or ORR as these outcomes did not demonstrate a statistically significant between group difference. The beneficial effects of pembrolizumab were less favourable in the subgroup of patients with a KRAS/NRAS mutation and in patients with pulmonary only or pulmonary and hepatic metastases.[2, 3] However, the sample size in these groups are limited and KEYNOTE-177 was not powered to detect differences in subgroups therefore these results should be interpreted with caution.

KEYNOTE-177 had an open-label study design because of marked differences between treatments. To minimise the risk of assessment bias, subjective outcomes (PFS and ORR) were analysed by blinded central review in accordance with validated tumour response criteria RECIST 1.1 which was endorsed by the EMA. However, the open-label study design may bias other subjective outcomes including safety and patient-reported outcomes. A large proportion of patients in the chemotherapy group (59%) received subsequent anti-PD-1/anti-PD-L1 therapy, through either crossover or subsequent anticancer treatment, which may have a confounding impact on overall survival and safety profile. Sensitivity analyses were carried out to assess the impact of crossover on overall survival, the results indicated lower hazard ratios compared with the primary analysis; however, no definitive conclusions could be drawn. The EMA noted that pembrolizumab was not expected to have a detrimental effect on overall survival.[2] In the main study, pembrolizumab was continued for a maximum of 2 years, therefore, evidence of efficacy beyond this treatment period is limited. KEYNOTE-177 excluded patients with an ECOG performance score greater than 1, which may affect the generalisability of results to less fit patients who may still be considered suitable for treatment.

The comparator arm in KEYNOTE-177 was investigator's choice of six preselected chemotherapy regimens and although the study was not powered to compare pembrolizumab with individual regimens, the EMA noted that a consistent PFS and overall survival benefit was observed when analysed alone or grouped. However, approximately 70% of patients in this group received treatment combinations that included bevacizumab. Although bevacizumab is associated with improved outcomes in patients with metastatic colorectal cancer it is not recommended for use in NHSScotland and therefore does not represent standard of care in clinical practice.[6] The submitting company considered this would provide a conservative estimate of the relative effectiveness of pembrolizumab. There is no direct evidence comparing pembrolizumab with CAPOX or with panitumumab in combination with FOLFOX or FOLFIRI, which are recommended first-line treatment options and represent relevant comparators in clinical practice in Scotland. Guidelines indicate CAPOX has similar activity and safety to FOLFOX.[6]

The introduction of pembrolizumab for this indication would represent the first specific and targeted treatment for patients with MSI-H or dMMR colorectal cancer. Clinical experts consulted by SMC considered that pembrolizumab is a therapeutic advancement due to the favourable outcomes and toxicity profile compared with chemotherapy as demonstrated in KEYNOTE-177. The introduction of pembrolizumab is likely to be associated with less oncology administration time in comparison with standard chemotherapy regimens. Monitoring and management of immune-related reaction will be required. A companion diagnostic, testing for dMMR or MSI-H status, will be necessary to select eligible patients, contact local laboratory for information.

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

Summary of comparative health economic evidence

The submitting company provided a cost utility analysis of pembrolizumab compared with standard of care treatment(s) used in Scotland for the first line treatment of adults with metastatic microsatellite instability-high MSI-H or mismatch repair deficient (dMMR) colorectal cancer.

Consistent with SIGN guidelines, patients could receive cetuximab in addition to FOLFOX or FOLFIRI) as part of the standard care arm. The standard care arm was based on treatments received in the KEYNOTE-177 trial but the submitting company also provided results against a comparator of capecitabine and oxiliplatin (CAPOX) also used in clinical practice in Scotland. In the model the clinical efficacy of CAPOX was assumed to be equivalent to the standard of care arm data used to populate the model from KEYNOTE-177.

A state transition model was chosen, although the surgical states in the model require a partitioned survival analysis based on observational data from out with the main KEYNOTE-177 study that provided most of the clinical information to parameterise the model.[9-11] In addition, the economic model includes separate post-surgical pre-progression and post-progression states separate to non-surgical treatment. Results were provided separately by the submitting company with these surgical states removed. For the five state model, patients start off in the 'progression

free' health state and can remain in this state or move to 'progressed disease', or 'death' at the end of each weekly cycle. However, patients can only transition to the 'post-surgery progression free' state (and then if progression of disease happens the 'post-surgery progressed disease' state) once at the end of week 12. If patients move to the 'post-surgery progression free' state at that time, they can then stay in this state or move to 'post-surgery progression' or 'death' states; they cannot move to the 'progressed disease' state because this is only for non-surgical patients.

The time horizon for the model was 40 years. This was reduced to 30 years in sensitivity analysis and a further scenario analysis reducing the time horizon to 20 years was also provided by the submitting company. Data were extrapolated beyond the time frame of the KEYNOTE-177 using 20 week piecewise approach for progression free survival and time to treatment progression, as proportional hazard assumptions were not met. Justification for the 20 week piecewise approach was that because the first and second on-study imaging in KEYNOTE-177 took place every 9 weeks potential cut-points of both 10 and 20 weeks would occur when imaging changes would be notable, and the submitting company chose the 20 week piecewise extrapolations as most appropriate based on visual fit. For post progression survival (excluding surgical patients), only the pembrolizumab arm was used to account for the extent of crossover in the study for patients in the standard of care arm.

Utility values were based on EQ-5D data collected during the study whereby data for each treatment arm were used until progression when data were pooled across treatment arms. Disutilities were included separately for adverse events (i.e. in addition to any reduction in EQ-5D score that an adverse event could have) and applied as a one-off treatment specific disutility and applied in cycle 1. Key health state-utility values used in the model are summarised in Table 2.

Table 2: Utility values used in the cost-effectiveness analysis

Health state	Pembrolizumab	Standard of care
Progression free	0.85	0.80
Progressed disease	0.73	0.73
Post-surgery progression free	0.85	0.85
Post-surgery progressed disease	0.75	0.75
One-off QALY loss due to AEs	0.03	0.04

AE = adverse events, QALY = quality-adjusted life year, NA = not applicable

Resource use was estimated from KEYNOTE-177 study data and an existing NICE MTA (TA439) in colorectal cancer and included medicines costs, administration costs, accounting for missed doses, adverse event costs, subsequent treatment costs, disease management costs and the costs of end of life.[12] A stopping rule of a maximum of 35 treatment cycles was applied to costs (based on the KEYNOTE-177 trial dosing schedule of every 3 weeks), but time on treatment data in the submission indicated that a small number of patients were still being treated after 2 years, which is likely to reflect continued treatment until BICR confirmation of progression in the trial. Routine sources (NHS Reference Costs) or existing published literature (including previous NICE MTAs) were used to source unit costs to apply to resource use items.[12-14]

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

List price data comparing pembrolizumab with a) standard of care and b) CAPOX are provided in Tables 3a and 3b below.

Table 3a: Base case results at list prices vs standard of care

Technologies	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
SoC	-	-	-
Pembrolizumab	£55,601	1.674	£33,221
Abbreviations: Inc, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years			

Table 3b: Base case results at list prices vs CAPOX

Technologies	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
CAPOX	-	-	-
Pembrolizumab	£96,516	1.674	£57,855
Abbreviations: Inc, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years			

Scenario analyses were provided separately against each comparator of interest and further data excluding the surgical states of the model were also provided. These are shown in Table 4 below at list prices.

Table 4: Scenario analyses at list prices against standard of care and CAPOX comparators for the 5 state (base case) model and 3 state (excluding surgery) model respectively.

Model setting	**Scenario**	**ICER vs SoC 5 state model**	**ICER vs CAPOX 5 state model**	**ICER vs SoC 3 state model**	**ICER vs CAPOX 3 state model**
Base case	-	£33,221	£57,855	£27,864	£49,058
Time horizon	30 years	£33,268	£58,041	£27,889	£49,219
Time to progression and Progression-free survival	Piecewise, with 20-week cut-point, Weibull thereafter	£31,417	£54,907	£27,492	£48,714

(Pembrolizumab & SoC)					
Post-progression Survival (Pembrolizumab & SoC)	Full parametric fit, lognormal	£33,431	£59,013	£27,863	£49,908
Data source: Post-surgery survival	Adams (2004)	£33,245	£57,994	£27,864	£49,058
Post- surgery parametric survival model: PFS and OS	Generalised gamma	£33,227	£57,885	£27,864	£49,058
Assumption of vial wastage	Yes – vial wastage assumed	£31,788	£57,835	£26,642	£49,039
Pembrolizumab treatment regimen & Consultant outpatient visits (Pembro-treated patients)	Q3W	£36,282	£59,473	£30,678	£50,825
Three-state model structure excluding surgery	Surgery excluded, modelling outcomes based on ITT pop.	£27,864	£49,058	£27,864	£49,058
PFS health state utility	PFS utility value based on pooled EQ-5D data	£35,689	£62,169	£33,844	£62,169
MSI-H Testing	50% of patients already tested in clinical practice (50% of testing costs excluded)	£34,699	£59,338	£34,699	£59,338

One way sensitivity analysis found that the study was sensitive to resource use and costs of treatment at list prices for all treatments including administration costs and the costs of best supportive care and resource use assumptions about consultant appointments. The submitting company provided a further scenario analysis that assumed equivalency of administration costs between pembrolizumab and the standard of care, which did increase the base case ICER at list price from £33,221 to £47,600 per QALY gained. However, clinical experts consulted by SMC indicated that the base case assumptions were more likely to reflect clinical practice in Scotland as standard of care treatments can require longer infusion times and the use of a peripherally inserted central catheter (PICC) line.

The main weaknesses in the model related to:

- The structural inclusion of surgical states separately to the main pathway of care experienced by patients in the underlying clinical data from KEYNOTE-177 (most of whom did not have surgery); there does not seem to be a difference by treatment arm in terms of the QALYs gained for these patients (although QALY gains are different to those who do not receive surgery). Additional observational data also had to be used to populate the surgical states. However, additional results that were requested for the 3-state model (without surgery) indicated that ICERs for the model with surgical states were consistently higher than those ICERs for the 3-state model, and, therefore, potentially the 5 state model is the more conservative choice. Clinical experts also advised SMC that surgical intervention (particularly for liver metastases) is a valid option for a small proportion of patients in Scotland (consistent with the KEYNOTE-177 trial data) and so the 5 state model is likely a reasonable reflection of clinical practice.
- The choices used in the extrapolation of progression-free survival, time on treatment and time to progression as scenario analysis choices were not always considerably different from the base case choice. However, it was notable that the base case choice was usually the most conservative option according to visual fit. Further comment was also provided by the submitting company on the rationale for using to use a 20 week piecewise approach rather than full parametric (no cut points) or a 10 week cut off.
- The inclusion of bevacizumab treatment in the KEYNOTE-177 study even though it is not accepted for use for this indication in Scottish clinical practice and assumptions about how these patients were assumed to be treated in Scottish clinical practice in the model (assumed equivalence of cetuximab treatment) to some extent cannot be helped. The submitting company provided further data for the model that excluded the bevacizumab patients from the ITT analysis. The list price ICERs for this analysis compared with standard of care rose from to £33,221 in the base case to £43,365 and compared with CAPOX falls from £57,855 in the base case to £53,359. Excluding bevacizumab completely does considerably reduce the sample size of trial participant data to draw from, and so it is important to treat these results with caution given the increased uncertainty. Additionally, cetuximab is licensed for use in combination with FOLFOX or FOLFIRI only for patients with EGFR-expressing RAS wild-type metastatic colorectal cancer and so the total costs for the base case analysis whereby cetuximab has been assumed to be provided to all those in the standard of care arm who had bevacizumab in the KEYNOTE-177 trial, will overestimate the use of cetuximab (and its costs) compared to standard of care in clinical practice in Scotland.
- Assumptions about subsequent therapies in the model given what is provided in Scottish clinical practice were not always clear and so we requested the submitting company provide an analysis that removes the use of cetuximab in subsequent lines of therapy (given the assumptions that had to be made in the model regarding treatment of KEYNOTE-177 trial participants who had received bevacizumab as first line treatment even though this is not accepted for use in Scotland). Removing cetuximab from subsequent lines of therapy raised the base case ICER slightly against standard of care (the comparator

affected by this issue) from £33,221 to £33,451 at list prices (these patients were assumed to receive FOLFIRI monotherapy in subsequent line therapy instead).

- The time horizon given this treatment is for end of life was, despite scenario analysis testing, still considerably long. The submitting company provided results for a time horizon of 20 years and results again show only a small effect on the ICERs, which increase from £33,221 to £34,050 against standard of care and from £57,855 to £59,973 against CAPOX at list prices.

Summary of patient and carer involvement

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

- We received a patient group submission from Bowel Cancer UK, which is a registered charity.
- Bowel Cancer UK has received 1.2% pharmaceutical company funding in the past two years, including from the submitting company.
- A diagnosis of bowel cancer can be life changing for those diagnosed, as well as their friends and family, and is even more acute for those at the metastatic stage of the disease when it is harder to treat and there is a low chance of survival.
- Current treatment options for advanced bowel cancer are extremely limited, with many being unable to access a treatment that could prolong their life.
- Pembrolizumab would provide a valued immunotherapy and targeted treatment option for this cancer. The administration of pembrolizumab is patient friendly, with fewer hospital visits and shorter duration of each cycle. The side effects are also often less debilitating than current chemotherapy treatments. Those who have received this medicine report that it offers them greater hope, extended life, additional treatment choice and fewer side effects than chemotherapy, giving them better quality of life.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline, SIGN 126: Diagnosis and management of colorectal cancer, in 2011 which was updated in 2016. This guideline states that the optimal treatment strategy for patients with metastatic colorectal cancer should be determined following discussion at a multidisciplinary team meeting and is dependent on the site and extent of metastatic disease and the performance status, organ function and comorbidity of the patient. The following treatment recommendations are made:

- Surgical resection should be considered for all patients with resectable liver metastases.
- All patients with metastatic colorectal cancer should be considered for chemotherapy.

- Combination treatment with 5-FU/leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/ leucovorin/irinotecan are the preferred options in patients with good performance status and organ function.
- Consider raltitrexed for patients with metastatic colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable.
- Cetuximab should be considered in combination with 5-FU/leucovorin/oxaliplatin or 5-FU/ leucovorin/irinotecan chemotherapy as first-line treatment for patients with RAS wild-type metastatic colorectal cancer. The use of cetuximab in combination with oxaliplatin and capecitabine cannot currently be recommended.[6]

National Institute for Health and Care Excellence (NICE) pathway: Managing metastatic colorectal cancer, updated 3 March 2021, recommends capecitabine or intravenous 5-FU/folinic acid as first line chemotherapy treatment options. Cetuximab or panitumumab in combination with 5-fluorouracil/leucovorin/oxaliplatin or 5-fluorouracil/leucovorin/irinotecan are first line options for previously untreated patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer.[15]

European Society of Medical Oncology (ESMO) published clinical practice guidelines in September 2014; Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. This guideline makes the following recommendations for systemic treatment:

- The backbone of first line palliative chemotherapy alone and in combination with targeted agents is 5-fluorouracil/leucovorin or capecitabine.
- 5-fluorouracil/leucovorin in combination with oxaliplatin or irinotecan are associate with higher response rates, longer PFS and better survival. Both triplet regimens have similar activity and are partners for biologics but have a distinct toxicity profile.7
- Capecitibine plus oxaliplatin is an alternative to 5-fluorouracil/leucovorin/oxaliplatin based on similar activity and safety profiles.
- Anti-VEGF antibody, bevacizumab has been shown to increase survival, PFS and response rate when used in combination with 5-fluorouracil/ leucovorin/irinotecan or capecitabine alone. It also improved PFS when given in a fluoropyrimidine plus oxaliplatin in the first-line treatment of metastatic colorectal cancer.
- Anti-EGFR antibodies cetuximab and panitumumab are recommended in combination with chemotherapy in the first-line treatment of (K)RAS-wild type metastatic colorectal cancer. Cetuximab added to 5-fluorouracil/ leucovorin/irinotecan, demonstrated a survival, PFS and response rate benefit for the first line treatment of (K)RAS-wild type patients, an improved PFS and response rate was also demonstrated when added to 5-fluorouracil/leucovorin/oxaliplatin. Panitumumab increases ORR, PFS and overall survival when added to 5-fluorouracil/leucovorin/oxaliplatin in the first-line treatment of RAS wild-type metastatic colorectal cancer.[8]

Additional information: comparators

5-fluorouracil, leucovorin and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CAPOX) or 5-fluorouracil, leucovorin and irinotecan (FOLFIRI). Cetuximab or panitumumab, in combination with FOLFOX or FOLFIRI for patients with EGFR-expressing RAS wild-type metastatic colorectal cancer.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Pembrolizumab	200mg every 3 weeks or 400mg every 6 weeks via intravenous infusion.	91,173

Costs from BNF online on 02 June 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 70 patients eligible for treatment with pembrolizumab in year 1 and 59 patients in year 5. The estimated uptake rate was 30% in year 1 and 85% in year 5. This resulted in 21 patients estimated to receive treatment in year 1 rising to 50 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines 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 9 July 2021.

**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.