NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission summary** from Merck Sharp & Dohme
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Bowel Cancer UK
4. **Evidence Review Group report** prepared by BMJ Group
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from** Merck Sharp & Dohme
7. **Expert personal perspectives and Technical engagement responses from experts:**
   a. Dr Kai-Keen Shiu – clinical expert, nominated by MSD
   b. Dr Mark Saunders – clinical expert, nominated by Bowel Cancer UK
   c. Hayley Crawley – patient expert, nominated by Bowel Cancer UK
   d. Momenul Haque– patient expert, nominated by Bowel Cancer UK
8. **Technical engagement responses from consultees and commentators:**
   a. Promega
9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Document B

Company evidence submission

September 2020

File name	Version	Contains confidential information	Date
Pembrolizumab 1L MSI-H-dMMR mCRC ID1498 Document B Final	1.0	Yes	30-SEP-2020

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's proposed full marketing authorisation for this indication.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatched repair deficiency (dMMR).	Adults with mCRC with high MSI-H or dMMR.	N/A
Intervention	Pembrolizumab	Pembrolizumab	N/A
Comparator(s)	**For all patients** • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine • Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) **For patients with RAS wild-type mCRC**	**For all patients** • Folinic acid plus fluorouracil plus oxaliplatin FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) **For patients with RAS wild-type mCRC** • Panitumumab in combination with FOLFOX or FOLFIRI **For patients with EGFR expressing, RAS wild-type mCRC**	• *Tegafur with uracil (in combination with folinic acid)* is not a relevant comparator for this appraisal as this regimen is no longer available as it was discontinued in the UK (1, 2). • *Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable)* is not a relevant comparator for this appraisal as this is only very rarely used in UK clinical practice. • *Capecitabine* is not a relevant comparator for this appraisal as it is used in elderly and frail patients who have a poor performance status (i.e. Eastern Cooperative Oncology Group [ECOG] performance status score of ≥2).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Panitumumab in combination with FOLFOX or FOLFIRI **For patients with EGFR expressing, RAS wild-type mCRC** • Cetuximab in combination with FOLFOX or folinic acid plus fluorouracil plus irinotecan (FOLFIRI)	• Cetuximab in combination with FOLFOX or folinic acid plus fluorouracil plus irinotecan (FOLFIRI)	
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	N/A

B.1.2 Description of the technology being appraised

Table 2 Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAB) of the IgG4/kappa isotype designed to exert a dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its associated ligands, PD-L1 and PD-L2 which appear on the antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour inactivity.
Marketing authorisation/CE mark status	The technology does not currently have a UK marketing authorisation/CE marking for the indication in this submission. The expected date of the opinion from the Committee for Human Medicinal Products is in February 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indications in the UK: • KEYTRUDA as monotherapy is indicated for the first-line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. Current indications in the UK: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-

	L1with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL)who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS)≥10. • KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. • KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)in adults whose tumours express PD-L1 with a ≥50%TPS and progressing on or after platinum-containing chemotherapy. • KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.
Method of administration and dosage	Pembrolizumab as monotherapy 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W)
Additional tests or investigations	Polymerase chain reaction (PCR) test for microsatellite instability high (MSI-H) and immunohistochemistry (IHC) test for mismatch repair deficiency (dMMR).
List price and average cost of a course of treatment	£2,630 per 100mg vial.
Patient access scheme (if applicable)	A Commercial Access Agreement has been arranged with NHS England.

B.1.3 Health condition and position of the technology in the treatment pathway

Health condition

Metastatic colorectal cancer

Colorectal cancer (CRC) is a malignant tumour arising from the lining of the large intestine (colon and rectum) (3). Metastatic CRC (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer often first spreads to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones (3).

Epidemiology and aetiology

Worldwide, CRC is the second most common type of cancer that can be found in both men and women and in 2018 1.8 million new cases were recorded, which resulted in 861,000 deaths (4). In Europe, CRC is also the second highest cause of cancer mortality rates with 500,000 diagnosed cases and 243,000 deaths (5). In the UK, CRC is the 4th most common type of cancer in the UK, accounting for 12% of all new cancer cases. Between 2014-2016, 42,042 new cases of CRC have been reported. In the UK, CRC is more common amongst men than women. 44% of bowel cancer cases are in females and 56% are diagnosed in males (6).

Some of the major risk factors for CRC include a family history of the disease, older age and lifestyle. CRC is associated with higher socioeconomic countries, such as the UK (7). The risk of developing CRC over a person's lifetime increases if there is a family history of CRC. An individual's relative risk is related to the degree of family history (3). There is also the risk of developing CRC as a result of inherited conditions or syndromes associated with certain gene changes, the most common associated diseases that increase relative risk for CRC are familial adenomatous (germline mutations in the APC gene), Peutz-Jeghers syndrome (germline mutations in STK11) and hereditary non-polyposis colorectal cancer (HNPCC). With increasing age, the relative risk of developing CRC increases. Developing CRC before the age of 40 is relatively uncommon. Incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter. Ninety percent (90%) of CRC have been diagnosed in patients at the age of 45 years and over. The ages associated most commonly with CRC is between 85-89. Lastly, lifestyle factors can have a significant impact on the possibility of developing CRC over a

person's lifetime. Smoking, drinking, a poor diet and low levels of activity can all increase the likelihood of a person to develop CRC over their lifetime.

Classical symptoms of bowel cancer can include unexplained weight loss, a persistent change in bowel habit (including diarrhoea or constipation or a change in stool consistency), rectal bleeding or blood mixed in with stool, persistent abdominal discomfort (such as cramps, bloating or pain), nausea, fatigue, rectal tenesmus (a feeling of incomplete bowel emptying) and a palpable mass on rectal examination. There were over 16,000 bowel cancer deaths registered in England between 2015-2017 (8, 9). Sites of metastases include the liver, lymph nodes, the lung, bones and the brain. One-year net survival for patient diagnosed at Stage 4 lies at 44% as 2013-2017 data shows. One-year survival is also significantly higher for males than for females. Five-year net survival lies at 10% for patients diagnosed in Stage 4 and there is no significant difference in the five-year net survival rate between men and women (8).

There are two methods of staging CRC. Modern clinical staging utilises a numbering system (summarised in Table 3 and Table 4) (10). The classical method is via the Dukes' system, the relationship/comparison between the modern TMN system and the classical Dukes' system is summarised in Table 5 (11).

Table 3 Summary of the TMN staging system for colorectal cancer (10, 12)

T (tumour) **How far the tumour has grown through the bowel wall**	**N (nodes)** **Whether the cancer has spread to nearby lymph nodes**	**M (metastases)** **Whether the cancer has spread (metastasised) to other parts of the body**
T1 - the tumour is in the inner layer of the bowel	N0 – no lymph nodes contain cancer cells	M0 – the cancer hasn't spread to other parts of the body
T2 – the tumour has grown into the muscle layer of the bowel wall	N1 – cancer cells in up to three nearby lymph nodes	M1 – the cancer has spread to other parts of the body, like the liver or lungs
T3 – the tumour has grown into the outer lining of the bowel wall	N2 – cancer cells in four or more nearby lymph nodes	
T4 – the tumour has grown through the outer lining of the bowel wall		

Table 4 Summary of the numbering staging system based on the TMN staging system (10, 12)

Stage 1 (I)	**Stage 2 (II)**	**Stage 3 (III)**	**Stage 4 (IV)**
T1 or T2	T3 or T4	Any T	Any T
N0	N0	N1 or N2	Any N
M0	M0	M0	M1

Table 5 Comparison between the Dukes' staging system and the TMN staging system (10-12)

Dukes' A	Dukes' B	Dukes' C	Dukes' D
TNM stage 1	TNM stage 2	TNM stage 3	TNM stage 4
The cancer has grown into the inner layer or muscle layer of the bowel wall. It has not spread to the lymph nodes or other parts of the body.	The cancer has grown through the muscle layer or outer layer. It may be growing into tissues near the bowel but has not spread to the lymph nodes or other parts of the body.	The cancer is any size and has spread to nearby lymph nodes. It has not spread to other parts of the body.	The cancer is any size. It may or may not have spread to nearby lymph nodes but it has spread to other parts of the body, like the liver or lungs.

Despite the availability of a CRC screening programme for men and women aged 60 to 74 since 2015, most patients are patients are diagnosed at a late stage (52-56%, Stage III and Stage IV), rather than an early stage (44-48% are diagnosed at stage I or II). Around 23-26% of bowel cancer patients have metastases at diagnosis (stage IV). Studies generally report a 30%-40% recurrence rate (13). Patients with R/M have a poor prognosis with only ≈5% of men and ≈10% of women with stage 4 bowel cancer surviving for more than 5 years after they're diagnosed (14).

Microsatellite instability and DNA mismatch repair

Colorectal cancers may be divided via molecular phenotype into tumours with normal DNA MMR function and those with DNA MMR deficiency (dMMR). DNA mismatch repair (MMR) deficiency results in mutations, tumour development and progression. DNA MMR-deficient tumours are associated with a higher rate of MSI mutations (15). Microsatellite instability (MSI), a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides (microsatellites) during DNA replication and failure of the MMR system to correct errors in nucleotide repeat markers. Tumours with MSI are classified as MSI-H based on the extent of instability in the markers tested by polymerase chain reaction (PCR) or immunohistochemistry (IHC) (15). Approximately 15% of people with early stage CRC show high MSI, whereas around 4% of metastatic disease show high MSI (16, 17). NICE diagnostics guidance (DG27) recommends testing all people with CRC, when first diagnosed using immunohistochemistry for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair (18).

Data from clinical studies in early stage (stage I-III) CRC indicate that MSI-H/dMMR CRC have a better prognosis compared to microsatellite stable CRC (19). However, in the

metastatic setting, a pooled analysis of phase III studies in first-line treatment of mCRC showed that median PFS and OS were significantly worse for patients with MSI-H/dMMR than without (PFS: 6.2 vs. 7.6 months, respectively; HR, 1.33; 95% confidence interval (CI) 1.12–1.57; P = 0.001; OS: 13.6 vs. 16.8 months, respectively; HR, 1.35; 95% CI, 1.13–1.61; P = 0.001) (20).

Treatment pathway

Treatment for mCRC aims to prolong survival and improve quality of life. Worldwide, there is no approved 1L MSI-H/dMMR-specific therapy, and the standard of care (SOC) treatments for patients with MSI-H/dMMR CRC are the same as that used to treat CRC patients in general. Treatment for mCRC can involve a combination of surgery (to resect the primary tumour or the metastases), chemotherapy (to make the tumour or metastases resectable, or to manage the cancer), biological therapy, and radiotherapy.

For mCRC, NICE recommend that initial chemotherapy can be given alone, or combined with biological epidermal growth factor receptor (EGFR) inhibitors for patients with RAS wild-type disease, as specified in NICE guidance documents NG151, TA61 and TA439 (1, 21, 22). It should be noted that bevacizumab-containing regimens are not reimbursed in routine clinical practice in the UK (21, 23-25), though they are recommended standards of care in international treatment guidelines for this indication published by the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and Japanese Society for cancer of the Colon and Rectum (JSCCR) (26-28). A comparison of the treatment regimens for mCRC recommended in different guidelines is shown in Table 6.

For this submission, pembrolizumab is positioned as a treatment for patients with untreated MSI-H/dMMR mCRC.

Table 6 Comparison of treatment regimens for mCRC recommended by different guidelines

Guideline producing organisation	National Institute of Health and Care Excellence (NICE) (21-23)	National Comprehensive Cancer Network (NCCN) (26)	European Society for Medical Oncology (ESMO) (27)	Japanese Society for cancer of the Colon and Rectum (JSCCR) (28)
Systemic therapies recommended for the 1st-line treatment of mCRC	• Folinic acid plus fluorouracil plus oxaliplatin FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Panitumumab in combination with FOLFOX or FOLFIRI (only for patients with RAS wild-type mCRC) • Cetuximab in combination with FOLFOX or FOLFIRI (only for patients with EGFR expressing, RAS wild-type mCRC) • Capecitabine plus oxaliplatin (XELOX/CAPOX) • Capecitabine monotherapy • Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil are not	• FOLFIRI with or without bevacizumab, panitumumab, or cetuximab* • FOLFOX with or without bevacizumab, panitumumab, or cetuximab* • Capecitabine plus oxaliplatin (CAPEOX) with or without bevacizumab • Leucovorin, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) with or without bevacizumab *Targeted therapy drugs panitumumab and cetuximab should only be used for left-sided tumours that have normal KRAS and NRAS genes.	Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated. The VEGF antibody bevacizumab should be used in combination with: • the cytotoxic doublets FOLFOX/CAPOX/FOLFIRI, • the cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal—and potentially also in fit patients with tumour BRAF mutations, • fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment. EGFR antibodies should be used in combination with: • FOLFOX/FOLFIRI, • capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies.	• FOLFOX/CAPOX/S-1 plus oxaliplatin (SOX) + bevacizumab • FOLFIRI + bevacizumab • FOLFOX + cetuximab/panitumumab* • FOLFIRI + cetuximab/panitumumab* • FOLFOXIRI or FOLFOXIRI + bevacizumab • Fluorouracil/capecitabine/uracil or tegafur + leucovorin/S-1 + bevacizumab or cetuximab/panitumumab* *Indicated for patients who are RAS-wildtype only.

Guideline producing organisation	National Institute of Health and Care Excellence (NICE) (21-23)	National Comprehensive Cancer Network (NCCN) (26)	European Society for Medical Oncology (ESMO) (27)	Japanese Society for cancer of the Colon and Rectum (JSCCR) (28)
	tolerated or unsuitable)			

B.1.4 Equality considerations

No equity or equality considerations are anticipated.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

To identify and select relevant studies, a systematic literature review (SLR) search was carried out in accordance with NICE guidance, according to a previously prepared protocol to identify relevant studies to inform indirect comparisons between pembrolizumab and the relevant comparator treatments for this appraisal as described in

Table 1. Please refer to Appendix D for full details of the process and methods undertaken.

B.2.2 List of relevant clinical effectiveness evidence

A SLR was performed to identify all relevant published and unpublished randomised controlled trials (RCTs) and non-randomised clinical trials (non-RCTs) relating to pembrolizumab as per the final scope in

Table 1.

A single trial was identified from the SLR that provided clinical effectiveness information on pembrolizumab in the patient population of relevance to this submission (first-line treatment of stage IV MSI-H/dMMR CRC) (Table 7). At the time of the SLR search, unpublished evidence from KEYNOTE-177 was available.

KEYNOTE-177 is a Phase 3 randomised, active-controlled, multi-site, open-label study that compared pembrolizumab monotherapy or standard of care in patients with stage IV MSI-H/dMMR CRC who had not had prior systemic therapy for stage IV CRC.

Table 7 Clinical effectiveness evidence

Study	A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)				
Study design	Randomised, active-controlled, multi-site, open-label study				
Population	Male or female patients of at least 18 years of age with MSI-H or dMMR stage IV CRC. Patients without prior systemic therapy for stage IV CRC.				
Intervention(s)	• Pembrolizumab				
Comparator(s)	• Standard of Care				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-177 is the only available trial with data for pembrolizumab in this indication				

Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	N/A

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Summary of the methodology of the KEYNOTE-177 study

Trial design

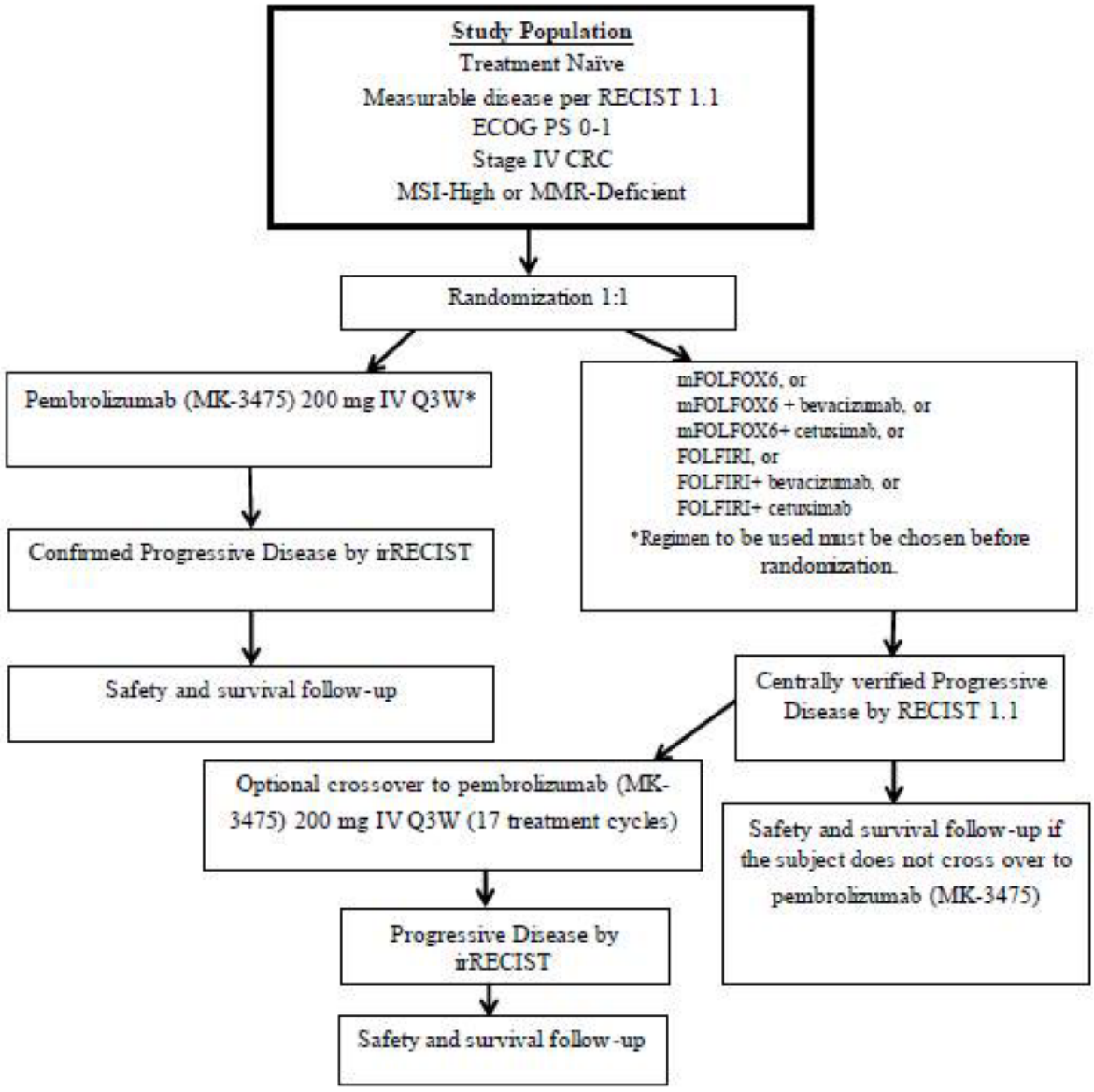
The KEYNOTE-177 study was a two-arm, multicentre, international, randomised, open-label, controlled study of pembrolizumab monotherapy versus standard chemotherapy in patients who have stage IV Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) CRC. MSI, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers. Patients were required to have at least 1 measurable lesion by Response Evaluation Criteria in Solid Tumours (RECIST 1.1) for response assessment. Patients were randomised in a 1:1 ratio to receive pembrolizumab (experimental arm) or the investigator's choice of SOC chemotherapy (control arm). The chemotherapy to be used was chosen before randomisation. Treatment allocation/randomisation occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). No stratification based on age, sex, or other characteristics were used in this study. The design of the KEYNOTE-177 study is summarised in the diagram in Figure 1.

Pembrolizumab arm patients received up to 35 administrations of pembrolizumab (approximately 2 years) in the Initial Treatment Phase. Patients who stopped pembrolizumab with locally confirmed complete response (CR), or stable disease (SD) or better at the end of the Initial Treatment Phase may be treated in a Second Course Treatment Phase with up to 17 administrations of pembrolizumab.

Control arm subjects with progressive disease (PD) per RECIST 1.1 as verified by a blinded independent central imaging vendor who met all crossover criteria had an option to receive

pembrolizumab in the Crossover Phase. This may be followed by 17 additional treatments in the Second Course Treatment Phase.

Figure 1 KEYNOTE-177 study design diagram



Eligibility criteria

Male/female patients with MSI-H/dMMR mCRC were enrolled in this study.

Patient inclusion criteria

In order to be eligible for participation in this trial, the subject must:

1. Provide written informed consent for the study.

2. Be male or female who is ≥ 18 years of age on the date of signing informed consent.

3. Have locally confirmed dMMR or MSI-H stage IV CRC.

4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 10 days prior to treatment initiation.

5. Have life expectancy of at least 3 months.

6. Have measurable disease at baseline based on RECIST 1.1 as determined by the local site Investigator/radiology assessment.

7. Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

8. Female patients of childbearing potential must be willing to use an adequate method of contraception for the course of the study starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm and 120 days for pembrolizumab arm, whichever is later.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male patients of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm and 120 days for pembrolizumab arm, whichever is later.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. Demonstrate adequate organ function as defined in Table 8. All screening laboratory assessment should be performed within 10 days prior to treatment initiation.

Table 8 Adequate organ function laboratory values

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1,500/μL
Platelets	≥100,000/μL
Haemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	

Creatinine OR	≤1.5 × upper limit of normal (ULN) OR
Measured or calculated[a] creatinine clearance [Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl)]	≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 ULN
Aspartate aminotransferase (AST) [Serum glutamic oxaloacetic transaminase (SGOT)] and Alanine Aminotransferase (ALT) [Serum Glutamic Pyruvic Transaminase (SGPT)]	≤2.5 × ULN OR ≤5 × ULN for subjects with liver metastases
Albumin	>2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant Therapy as long as PT or partial prothrombin time (PTT) is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant Therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] Creatine clearance calculated per institutional standard

Patient exclusion criteria

Patients were excluded from participating in the trial if the patient:

1. Has received prior systemic therapy for stage IV CRC. Patients may have received prior adjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to randomisation.

2. Is currently participating and receiving study medication in another study, or has participated in a study of an investigational agent and received study medication, or used an investigational device within 4 weeks of randomisation.

3. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomisation.

5. Has had radiation therapy within 4 weeks prior to randomisation of study medication and who has not recovered to baseline from adverse events due to radiation therapy. Patients who have been given palliative radiotherapy to peripheral sites (e.g., bone metastasis) may enter the study before 4 weeks have elapsed but must have recovered from any acute adverse effects.

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they have stable brain metastases (without evidence of progression by imaging as confirmed by magnetic resonance imaging [MRI] if MRI was used at prior imaging, or confirmed by computed tomography [CT] imaging, if CT used at prior imaging, at least 4 weeks prior to the first dose of study medication; also, any neurologic symptoms must have returned to baseline], and have not used steroids for brain metastases for at least 28 days prior to study initiation. This exception does not include carcinomatous meningitis, as patients with carcinomatous meningitis are excluded regardless of clinical stability.

7. Has had major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomisation.

8. Has received prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or anti-CTLA-4 agent, etc).

9. Has another malignancy that is progressing or requires active treatment. Exceptions include non-melanomatous skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma.

10. Has received a live vaccine within 30 days of planned start of study medication.

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

France and UK only: Has a history or current evidence of any condition, (i.e., known allergy, hypersensitivity, or contraindication to fluorouracil, leucovorin, oxaliplatin, irinotecan, bevacizumab, or cetuximab or any components used in their preparation if such is applicable in the investigator's choice of chemotherapy for this study), therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

12. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

13. Has known history of, or any evidence of interstitial lung disease or active, non-infectious pneumonitis.

14. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

15. Has an active infection requiring systemic therapy.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study medication for SOC or 120 days after the last dose of study medication in the pembrolizumab arm.

Settings and locations where the data were collected

The KEYNOTE-177 study was conducted at 120 centres (hospitals or medical centres) in 23 countries (Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, the UK, and the USA). Six centres were located in the UK.

Trial drugs and concomitant medications

Trial treatments

The treatments used in the KEYNOTE-177 study are outline in Table 9.

Table 9 Study medication

Study Medication	Dose/Potency	Dose Frequency	Route of Administration	Use
Pembrolizumab	200 mg IV over 30 minutes	Q3W	IV infusion	Experimental
mFOLFOX6	mFOLFOX6: • Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 • Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 • 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m2 over 46-48 hours) IV continuous infusion	Q2W	IV infusion	Standard of care
mFOLFOX6 + bevacizumab	mFOLFOX6: • Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 • Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 • 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m2 over 46-48 hours) IV continuous infusion Bevacizumab 5 mg/kg IV, day 1	Q2W	IV infusion	Standard of care
mFOLFOX6 + cetuximab	mFOLFOX6: • Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 • Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 • 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion Cetuximab: 400 mg/m2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour weekly	Q2W	IV infusion	Standard of care
FOLFIRI	FOLFIRI: • Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 • Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 • 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion	Q2W	IV infusion	Standard of care

Study Medication	Dose/Potency	Dose Frequency	Route of Administration	Use
FOLFIRI +bevacizumab	FOLFIRI: • Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 • Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 • 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion Bevacizumab 5 mg/kg IV, day 1	Q2W	IV infusion	Standard of care
FOLFIRI +cetuximab	FOLFIRI: • Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 • Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 • 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion Cetuximab: 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour weekly	Q2W	IV infusion	Standard of care

*or levoleucovorin 200mg/m^2

Concomitant medications

Medications or vaccinations specifically prohibited in the exclusion criteria were not allowed during the ongoing trial. If there was a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination was required.

Acceptable concomitant medications and therapy

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the local and institutional standards of medical care. In addition, local therapy for palliation is permitted after consultation with the Sponsor. All concomitant medications were recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occurred during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications taken by the patient from the date of first dose of study medication and 30 days after the last dose of study medication were recorded. Concomitant medications administered more than 30 days after the last dose of study medication were recorded for SAEs.

Prohibited concomitant medications and therapy

Patients were prohibited from receiving the therapies listed below during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this study.

- Antineoplastic systemic chemotherapy or immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Local therapy for palliation after consultation with Sponsor
- Live vaccines within 30 days prior to the first dose of study medication and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

- For pembrolizumab: glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic aetiology. The use of physiologic doses of corticosteroids (prednisone 10 mg orally per day, or equivalent) may be approved after consultation with the Sponsor.
    - Note: Inhaled steroids are allowed for the management of asthma
    - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.

Outcomes assessed

Primary efficacy endpoints

Progression-free survival (PFS) – RECIST 1.1 assessed by central imaging vendor:

Progression-free-survival (PFS) is defined as the time from randomisation to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first.

Overall Survival:

Overall Survival (OS) is defined as the time from randomisation to death due to any cause. Patients without documented death at the time of analysis will be censored at the date of last known contact.

Secondary efficacy endpoints

Overall Response Rate (ORR) – RECIST 1.1 assessed by central imaging vendor:

Overall response rate is defined as the proportion of the patients in the analysis population who have a complete response (CR) or partial response (PR).

Exploratory endpoints

Progression-free survival 2 (PFS2):

Progression-free survival 2 (PFS2) is defined as the time from randomisation to disease progression on the next line of therapy, or death from any cause, whichever first.

Progression-free survival (PFS) – irRECIST assessed by central imaging vendor:

Progression-free-survival (PFS) is defined as the time from randomisation to the first confirmed disease progression or death due to any cause, whichever occurs first.

Duration of Overall Response (DOR) – RECIST 1.1 by central imaging vendor:

For patients who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of first documented disease progression or death.

Surgical conversion rate:

The surgical conversion rate is the rate of patients who become eligible and undergo resection with curative intent as a result of study therapy.

Safety endpoints

All adverse events that occurred after the consent form was signed but before treatment allocation/randomisation were reported by the investigator if they caused the patient to be excluded from the trial, or were the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomisation through 30 days following cessation of treatment, all adverse events were reported by the investigator. Such events were recorded at each examination on the Adverse Event case report forms/worksheets. The investigator made every attempt to follow all patients with nonserious adverse events for outcome.

Summary of the baseline characteristics of trial participants

The summary of the baseline characteristics of the KEYNOTE-177 trial participants is shown in Table 10. Baseline characteristics were generally balanced between the two treatment groups in the ITT population.

The majority of participants in the trial were white (74.6%) with a median age of 63.0 years and had an ECOG performance status score of 0 (51.8%) or 1 (48.2%). The proportion of male and female participants in the trial was similar. Most participants (72.3%) were from the Western Europe/North America region and 15.6% were from the Asia region. The majority (73.0%) of participants did not receive prior adjuvant and/or neoadjuvant systemic therapy. One participant in the SOC group had a negative MSI-H status after reporting a positive MSI-H status at screening. The majority (68.1%) of participants in both treatment groups had right-sided tumours and over 40% of participants had KRAS/NRAS or BRAF V600E mutations.

Table 10 Summary of KEYNOTE-177 study patient baseline characteristics

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	153		154		307	
Gender						
Male	71	(46.4)	82	(53.2)	153	(49.8)
Female	82	(53.6)	72	(46.8)	154	(50.2)
Age (Years)						
<65	80	(52.3)	83	(53.9)	163	(53.1)
>=65	73	(47.7)	71	(46.1)	144	(46.9)
Subjects with data	153		154		307	
Mean	61.9		60.6		61.2	
SD	14.9		14.8		14.8	
Median	63.0		62.5		63.0	
Range	24 to 93		26 to 90		24 to 93	
Age (Years)						
<=70	105	(68.6)	112	(72.7)	217	(70.7)
>70	48	(31.4)	42	(27.3)	90	(29.3)
Race						
ASIAN	24	(15.7)	26	(16.9)	50	(16.3)
BLACK OR AFRICAN AMERICAN	9	(5.9)	5	(3.2)	14	(4.6)
WHITE	113	(73.9)	116	(75.3)	229	(74.6)
Missing	7	(4.6)	7	(4.5)	14	(4.6)
Ethnicity						
HISPANIC OR LATINO	11	(7.2)	10	(6.5)	21	(6.8)
NOT HISPANIC OR LATINO	128	(83.7)	131	(85.1)	259	(84.4)
NOT REPORTED	10	(6.5)	10	(6.5)	20	(6.5)
UNKNOWN	2	(1.3)	2	(1.3)	4	(1.3)
Missing	2	(1.3)	1	(0.6)	3	(1.0)
Geographic Region						
Asia	22	(14.4)	26	(16.9)	48	(15.6)
Western Europe/North America	109	(71.2)	113	(73.4)	222	(72.3)
Rest of World	22	(14.4)	15	(9.7)	37	(12.1)
ECOG						
0	75	(49.0)	84	(54.5)	159	(51.8)
1	78	(51.0)	70	(45.5)	148	(48.2)
Site of Primary Tumour*						
Right	102	(66.7)	107	(69.5)	209	(68.1)
Left	46	(30.1)	42	(27.3)	88	(28.7)
Other	4	(2.6)	5	(3.2)	9	(2.9)
Missing	1	(0.7)	0	(0.0)	1	(0.3)
Metastases Location						
Hepatic or pulmonary	86	(56.2)	73	(47.4)	159	(51.8)
Other Metastases	67	(43.8)	81	(52.6)	148	(48.2)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Diagnosed Stage						
Recurrent	80	(52.3)	74	(48.1)	154	(50.2)
Newly diagnosed stage	73	(47.7)	80	(51.9)	153	(49.8)
Prior Systemic Therapy						
Adjuvant only	33	(21.6)	37	(24.0)	70	(22.8)
Neoadjuvant only	2	(1.3)	3	(1.9)	5	(1.6)
Neoadjuvant and adjuvant	3	(2.0)	5	(3.2)	8	(2.6)
None	115	(75.2)	109	(70.8)	224	(73.0)
Mutation Status[**]						
BRAF/KRAS/NRAS all wild type	34	(22.2)	35	(22.7)	69	(22.5)
KRAS/NRAS mutant and BRAF V600E not mutant	33	(21.6)	38	(24.7)	71	(23.1)
BRAF V600E mutant and KRAS/NRAS not mutant	34	(22.2)	40	(26.0)	74	(24.1)
BRAF V600E and KRAS/NRAS mutant	0	(0.0)	3	(1.9)	3	(1.0)
Other	52	(34.0)	38	(24.7)	90	(29.3)
MSI-High Status[#]						
Positive	153	(100.0)	153	(99.4)	306	(99.7)
Negative	0	(0.0)	1	(0.6)	1	(0.3)
Oncologic Surgery with Curative Intent[##]						
Received surgery with curative-intent	14	(9.2)	13	(8.4)	27	(8.8)
Did not receive surgery with curative-intent	139	(90.8)	141	(91.6)	280	(91.2)

[*] If there were primary tumours in both left side and right side, the subject would be categorized into Other.

[**] When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other.

[#] MSI status by PCR test or IHC test at local site laboratory.

[##] Oncologic surgery that was with curative intent and occurred after subject randomisation and before initiation of new anti-cancer therapy, crossover treatment and second course treatment.

Database Cutoff Date: 19FEB2020.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Objectives and hypotheses

Primary objectives and hypotheses

In patients with stage IV MSI-H or dMMR CRC treated with first-line (1L) pembrolizumab versus SOC chemotherapies,

1. Objective: To compare Progression-Free Survival (PFS) per RECIST 1.1 by central imaging vendor.

   Hypothesis (H1): Pembrolizumab prolongs PFS per RECIST 1.1 by central imaging vendor compared to SOC chemotherapies.

2. Objective: To compare Overall Survival (OS).

   Hypothesis (H2): Pembrolizumab prolongs OS compared to SOC chemotherapies.

The study was considered to have met its primary objective if pembrolizumab is superior to SOC chemotherapies in either of the two primary endpoints.

Secondary objectives and hypotheses

In patients with stage IV MSI-H or dMMR CRC treated with 1L pembrolizumab versus SOC chemotherapies,

1. Objective: To compare Overall Response Rate (ORR) per RECIST 1.1 by central imaging vendor.

   Hypothesis (H3): Pembrolizumab improves ORR compared to SOC chemotherapies

2. Objective: To evaluate the safety and tolerability profiles.

Exploratory objectives

1. Objective: To evaluate Progression-Free Survival 2 (PFS2).

2. Objective: To evaluate Progression-Free Survival (PFS) per irRECIST by central imaging vendor.

3. Objective: To evaluate Duration of Response (DOR) per RECIST 1.1 by central imaging vendor.

4. Objective: To evaluate score change of health-related quality-of-life using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ- CR29 from baseline among subjects treated with pembrolizumab compared to SOC chemotherapies.

5. Objective: To characterize utilities using EuroQoL EQ-5D among subjects treated with pembrolizumab (MK-3475) compared to SOC chemotherapies.

6. Objective: To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumour) will be analysed for association with clinical data collected in this study.

7. Objective: To evaluate the surgical conversion rate among subjects treated with pembrolizumab compared to SOC chemotherapies.

Analysis populations

Efficacy analysis populations

The Intention-to-Treat (ITT) population served as the population for primary efficacy analysis. All randomised patients were included in this population. Patients were included in the treatment group to which they are randomised. ITT population consists of all randomised subjects whether or not treatment was administered. Any patient who received a treatment randomisation number was considered to have been randomised.

Safety analysis populations

The All Subjects as Treated (ASaT) population was used for the analysis of safety data in this study. The ASaT population consists of all randomised patients who received at least one dose of study medication. Patients were included in the treatment group corresponding to the study medication they actually received for the analysis of safety data using the ASaT population. For most patients this was the treatment group to which they are randomised. patients who take incorrect study medication for the entire treatment period were included in the treatment group corresponding to the study medication actually received. Any patient who received the incorrect study medication for one cycle but received the correct treatment for all other cycles were analysed according to the correct treatment group and a narrative was provided for any events that occur during the cycle for which the patient was incorrectly dosed.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study medication was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

Statistical methods

Statistical methods for efficacy analyses

A summary of the primary analysis approach for primary and secondary efficacy endpoints is shown in Table 11 and described in more detail in the following subsections.

Table 11 Analysis strategy for key efficacy endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by central imaging vendor	Test: Log-rank test. Estimation: Cox model with Efron's tie handling method.	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Log-rank test. Estimation: Cox model with Efron's tie handling method.	ITT	Censored at the date of last known contact
Secondary Endpoint			
ORR per RECIST 1.1 by central imaging vendor	Test: Miettinen and Nurminen method.	ITT	Patients with missing data are considered as non-responders.

Progression-free survival

The non-parametric Kaplan-Meier method was used to estimate the PFS curve in each treatment group. The treatment difference in PFS was assessed by the log-rank test and the P-value was provided. A Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the Cox model with Efron's method of tie handling and with a single treatment covariate was reported.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the patients who have PD, the true date of disease progression was approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by central imaging vendor, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses were performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, we performed several sensitivity analyses with a different set of censoring rules. The first sensitivity analysis was the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer

treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for patients without documented PD or death. The censoring rules for primary and sensitivity analyses are summarised in Table 12. Surgical patients (i.e., those who have surgery with curative intent) were censored at the surgical date in the PFS analysis.

The proportional hazards assumption on PFS were examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for PFS were plotted for the comparison between pembrolizumab and the SOC chemotherapies arm. If the curves were not parallel, indicating that hazards were not proportional, supportive analyses were conducted to account for the possible non-proportional hazards effect associated with immunotherapies (e.g., using Restricted Mean Survival Time (RMST) method, parametric method etc.).

Table 12 Censoring rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study medication; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; ≥2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented at any time after ≥2 consecutive missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessment	Progressed at date of documented PD or death

Note: Surgical patients were censored at the surgical date in the PFS primary, sensitivity 1 and 2 analyses. PD: progressive disease, PFS: progression-free survival.

Overall survival

The non-parametric Kaplan-Meier method was used to estimate the survival curves. The treatment difference in survival was assessed by the log-rank test. A Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the Cox model with a single treatment covariate was reported.

Since patients in the SOC chemotherapies arm were allowed to switch to the pembrolizumab treatment after progressive disease, adjustment for the effect of crossover on OS were performed as a sensitivity analysis based on recognised methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (29), two-stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods. An additional OS sensitivity analysis was performed with survival dates censored at the start of crossover treatment or the start of first subsequent immune checkpoint inhibitor treatment, whichever occurred first.

Overall response rate

The Miettinen and Nurminen method was used for comparison of the Overall Response Rate between the treatment arms (30). The point estimate, 95% Confidence Interval for the difference in response rate between the pembrolizumab arm and the SOC chemotherapies arm are provided. Patients without response data were counted as non-responders.

Statistical methods for safety analyses

Adverse events

Adverse events (AEs) were coded using the standard MedDRA and grouped system organ class. AEs were graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Tiered approach

The analysis of safety results followed a tiered approach (Table 13). The tiers differ with respect to the analyses that were performed. “Tier 1” safety endpoints were subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. For these analyses, there were no Tier 1 events. Other safety parameters were considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) that are not prespecified as Tier-1 endpoints were classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences and predefined limits of change belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, that are not pre-specified as Tier-1 endpoints were considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values are provided by treatment group.

Based on the mechanism of action of pembrolizumab and safety data observed in historic pembrolizumab studies to date, there are no events of interest that warrant classification as Tier I events for this protocol. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug-related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death were considered Tier 2 endpoints. 95% confidence intervals (Tier 2) are provided for between-treatment differences in the percentage of patients with events; these analyses were performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

In the primary safety comparison between pembrolizumab and SOC chemotherapies, patients who crossed over to pembrolizumab were censored at time of crossover (i.e., AEs occurring during treatment with pembrolizumab were excluded for control-arm patients). An exploratory safety analysis was conducted for the crossover population including all safety events starting from the date of randomisation.

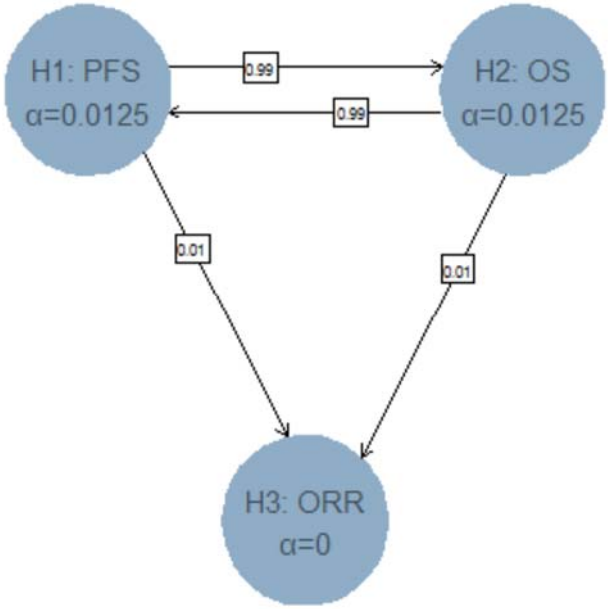
Table 13 Analysis strategy for safety parameters

Safety Tier	Safety Endpoint	95% Confidence Interval for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of patients in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of patients in all of the treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

Multiplicity

The overall type I error over the primary endpoints (PFS and OS) and the secondary endpoint (ORR) is strongly controlled at 2.5% (one-sided), with initially 1.25% allocated to the PFS hypothesis, 1.25% to the OS hypothesis, and 0% to the ORR hypothesis. An extension of the graphical method of Maurer and Bretz is used to strongly control the overall Type I error rate for testing of multiple endpoints at the 2.5% 1-sided level (Anderson et al, unpublished data, 2018) (31). Figure 2 shows the initial 1-sided α-allocation for each hypothesis in the ellipse representing the hypotheses. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. The transfer weights of 0.01 from OS and PFS to ORR essentially imply that if null hypotheses for both OS and PFS are rejected that an ORR benefit may be tested at the 2.5% 1-sided level; if only 1 of OS or PFS null hypotheses are rejected, then ORR would be tested at the 0.0125% 1-sided level.

Figure 2 Multiplicity strategy



Sample size and power calculations

The primary objective of this study is to evaluate the efficacy of pembrolizumab compared to the standard of care with respect to PFS and OS for patients with microsatellite instability-high or mismatch repair deficient stage IV CRC. Approximately 300 patients were planned to be enrolled.

PFS analysis

The final PFS analysis was planned to be performed at the time of Interim Analysis 2 when approximately 209 PFS events have occurred or 24 months after last subject randomised, whichever occurred first. With 209 PFS events, the study has ~98% power for PFS to detect a hazard ratio (pembrolizumab vs. SOC) of 0.55 at the 1.25% (one-sided) significance level. If fewer than 209 events are observed 24 months after last subject randomised, the power will be lower; for example, if 192 events are observed, then the study has 97% power for PFS.

The sample size calculations are based on the following assumptions: 1) PFS follows an exponential distribution with a median of 10 months in the SOC arm; 2) an enrolment period of 30 months from first patient randomised and a minimum of 13 months follow-up after enrolment completion; and 3) a yearly dropout rate of 5%.

OS analysis

The final OS analysis was planned to be performed after approximately 190 OS events have occurred or 12 months after Interim Analysis 2, whichever occurred first. With 190 OS events, the study has ~85% power for OS to detect a hazard ratio (pembrolizumab vs. SOC) of 0.62 at the 1.25% (one-sided) significance level. If fewer than 190 events are observed 12 months after Interim Analysis 2, the power will be lower; for example, if 170 events are observed, then the study has 80% power for OS. However, due to the anticipated high crossover rate, the actual power could be substantially lower.

The sample size calculations are based on the following assumptions: 1) OS follows an exponential distribution with a median of 24 months in the SOC arm; 2) an enrolment period of 30 months from first subjects randomised and a minimum of 33.5 months follow-up after enrolment completion; and 3) a yearly dropout rate of 2%.

ORR analysis

ORR is a secondary endpoint. The ORR analysis was planned to be conducted when either PFS or OS null hypothesis is rejected. The study has 92% power to demonstrate the superiority of pembrolizumab over SOC at one-sided 2.5% α-level, if the underlying treatment difference in ORR is 19%, assuming a 50% response rate in the SOC arm.

Subgroup analyses and effect of baseline factors

To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the two primary endpoints are estimated and plotted within each category of the following classification variables:

- Age category (≤70 years vs. >70 years).
- Geographic region (Asia vs. Western Europe/North America vs. Rest of World).
- Hepatic or pulmonary metastases vs other metastases.
- Recurrent vs newly diagnosed stage IV CRC.
- BRAF wild-type vs. BRAF V600E.
- Site of primary tumour (right vs. left).
- Surgical vs non-surgical subjects, where surgical patients are those who have surgery with curative intent.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for each trial included in the network meta-analyses is shown in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

Please note that all clinical effectiveness results shown in section B.2.6 are from the KEYNOTE-177 study second interim analysis (IA2, data cut-off date: 19-FEB-2020), as the final analysis has not yet been reached.

Pembrolizumab versus SOC (ITT population) data from the KEYNOTE-177 study

The KEYNOTE-177 study results presented in this section are for the total ITT population of the study. It should be noted that the KEYNOTE-177 was a global trial and included a high proportion of patients in the SOC arm (70%, see Table 16) who were treated with a bevacizumab-containing regimen. As bevacizumab is not reimbursed for use in UK clinical practice in this indication, subgroup/sensitivity analyses have been conducted which exclude those patients who were chosen to receive a bevacizumab-containing chemotherapy prior to randomisation (the chemotherapy regimen to be given to any patient if they were randomised to the SOC arm was chosen before randomisation occurred, as part of the study protocol as described in Document B section B.2.3). These subgroup/sensitivity analyses are shown in Appendix L and should be interpreted with caution due to the much smaller population/sample size in this subpopulation compared to the overall population (99 patients versus 307 patients).

Patient disposition

A total of 852 participants were screened and 307 were randomised (153 in the pembrolizumab group, 154 in the SOC group) (Figure 3 and Table 14). Investigator's choice of SOC treatment is summarised in Table 16.

The proportion of participants who discontinued treatment was lower in the pembrolizumab group compared with the SOC group. In the pembrolizumab group, 58 participants (37.9%) had discontinued from the trial, 94 participants (61.4%) had discontinued from pembrolizumab treatment, and 57 participants (37.3%) had completed pembrolizumab treatment as of the data cut-off. The primary reason for treatment discontinuation was PD (32.7%). Treatment was ongoing in 2 participants (1.3%) as of the data cut-off (Table 15).

In the SOC group, 75 participants (48.7%) had discontinued from the trial, and 137 participants (95.8%) had discontinued from SOC treatment. The primary reason for treatment discontinuation was PD (60.1%). Treatment was ongoing in 6 participants (4.2%) (Table 15).

As of the data cut-off, 56 participants (36.4%) in the SOC group had crossed over to pembrolizumab treatment (Table 15). In the crossover segment, 30 participants (53.6%) had discontinued from pembrolizumab treatment as of the data cut-off, with PD as the primary reason for discontinuation (Table 15).

Approximately 46.9% of participants across the 2 treatment groups received new oncological medications as next line therapy following discontinuation from study treatment, including 9 (5.5%) and 35 (22.7%) participants in the pembrolizumab and SOC groups (those who did not cross over) who received subsequent anti-PD-1/anti-PD-L1 therapy. Approximately 59% of participants in the SOC group received subsequent checkpoint inhibitor treatments, which includes the participants in the SOC group who crossed over to pembrolizumab treatment within the study and those in the SOC group who received other subsequent anti-PD-1/anti-PD-L1 therapy.

Figure 3 KEYNOTE-177 participant flow diagram

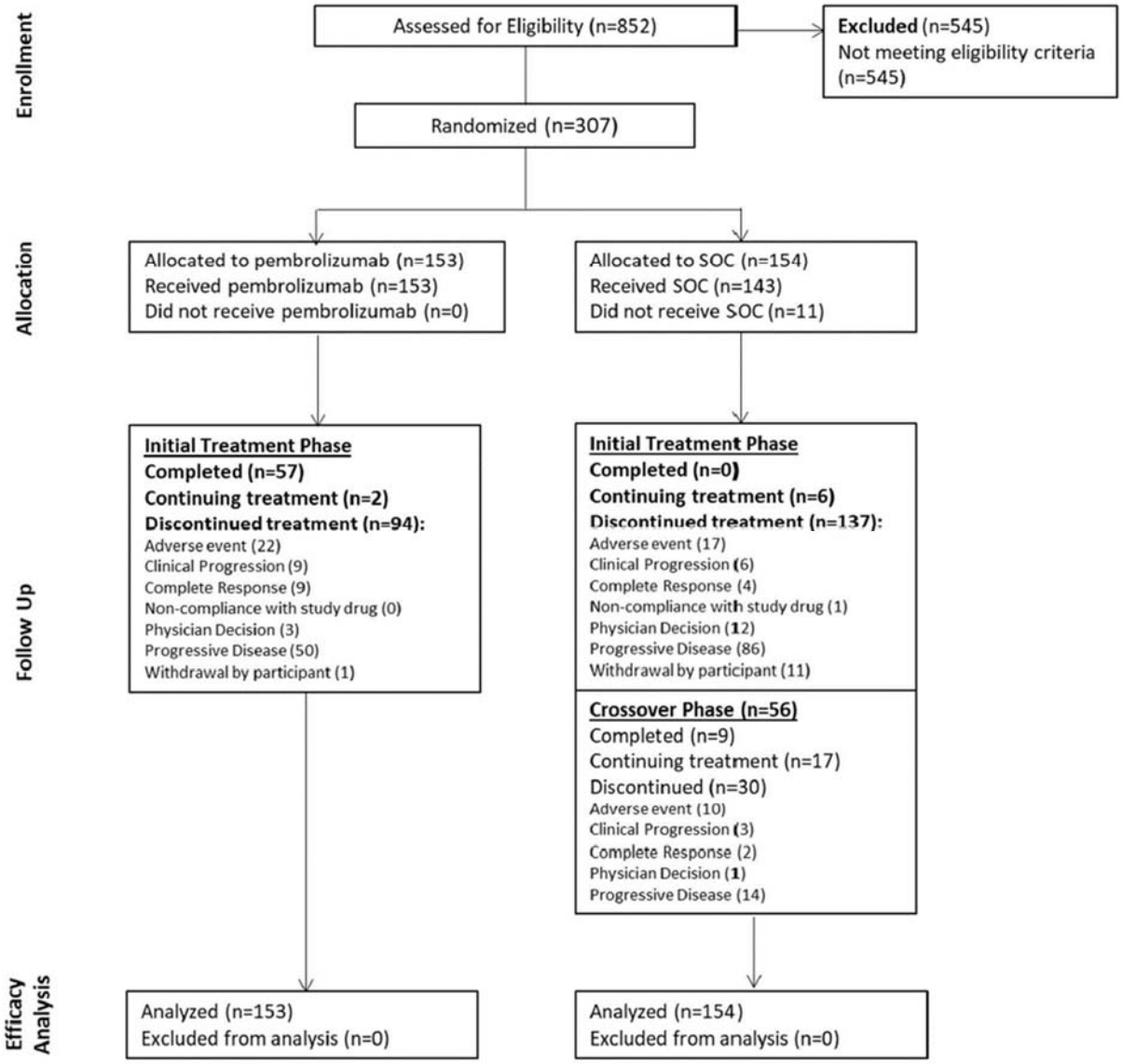


Table 14 Study population

	Pembrolizumab	SOC	Total
Number of Subjects Screened			852
Number of Subjects (Planned Treatment) (ITT)	153	154	307
Number of Subjects Received Treatment (Actual Treatment) (ASaT)	153	143	296
Number of Subjects Did not Receive Treatment	0	11	11
Number of Subjects Discontinued Study Medication (Actual Treatment)	94	137	231
Number of Subjects Crossed Over to Pembrolizumab	0	56	56
Database Cutoff Date: 19FEB2020.			

Table 15 Disposition of patients

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	153		154		307	
Status for Trial						
Discontinued	58	(37.9)	75	(48.7)	133	(43.3)
Death	56	(36.6)	66	(42.9)	122	(39.7)
Lost To Follow-Up	2	(1.3)	0	(0.0)	2	(0.7)
Withdrawal By Subject	0	(0.0)	9	(5.8)	9	(2.9)
Subjects Ongoing	95	(62.1)	79	(51.3)	174	(56.7)
Status for Study Medication in Trial Segment Treatment						
Started	153		143		296	
Completed	57	(37.3)	0	(0.0)	57	(19.3)
Discontinued	94	(61.4)	137	(95.8)	231	(78.0)
Adverse Event	22	(14.4)	17	(11.9)	39	(13.2)
Clinical Progression	9	(5.9)	6	(4.2)	15	(5.1)
Complete Response	9	(5.9)	4	(2.8)	13	(4.4)
Non-Compliance With Study Drug	0	(0.0)	1	(0.7)	1	(0.3)
Physician Decision	3	(2.0)	12	(8.4)	15	(5.1)
Progressive Disease	50	(32.7)	86	(60.1)	136	(45.9)
Withdrawal By Subject	1	(0.7)	11	(7.7)	12	(4.1)
Subjects Ongoing	2	(1.3)	6	(4.2)	8	(2.7)
Status for Study Medication in Trial Segment Crossover						
Started	0		56		56	
Completed	0	(0.0)	9	(16.1)	9	(16.1)
Discontinued	0	(0.0)	30	(53.6)	30	(53.6)
Adverse Event	0	(0.0)	10	(17.9)	10	(17.9)
Clinical Progression	0	(0.0)	3	(5.4)	3	(5.4)
Complete Response	0	(0.0)	2	(3.6)	2	(3.6)
Physician Decision	0	(0.0)	1	(1.8)	1	(1.8)
Progressive Disease	0	(0.0)	14	(25.0)	14	(25.0)
Subjects Ongoing	0	(0.0)	17	(30.4)	17	(30.4)
Database Cutoff Date: 19FEB2020.						

Table 16 Investigator's choice of standard of care treatment

	SOC (N=143)	
	n	(%)
FOLFIRI	16	11.2
FOLFIRI + bevacizumab	36	25.2
FOLFIRI + cetuximab	11	7.7
mFOLFOX6	11	7.7
mFOLFOX6 + bevacizumab	64	44.8
mFOLFOX6 + cetuximab	5	3.5
Database Cutoff Date: 19FEB2020		

Follow-up duration and extent of exposure

Median duration of follow-up at the time of data cut-off was 28.4 months (range: 0.2, 48.3 months) and 27.2 months (range: 0.8, 46.6 months) in the pembrolizumab and SOC groups, respectively (Table 17). Treatment exposure is summarised in Table 18 and Table 20.

Table 17 Summary of follow-up duration

Follow-up duration (months)[†]	Pembrolizumab (N=153)	SOC (N=154)	Total (N=307)
Median (Range)	28.4 (0.2, 48.3)	27.2 (0.8, 46.6)	27.6 (0.2, 48.3)
Mean (SD)	25.1 (13.4)	23.5 (12.5)	24.3 (12.9)

[†] Follow-up duration is defined as the time from randomisation to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 19FEB2020

Table 18 Summary of treatment exposure

	Pembrolizumab (N=153)	SOC (N=143)
Study Duration On-Therapy (months)		
Mean	13.3	8.3
Median	11.1	5.7
SD	10.2	8.0
Range	0.0 to 30.6	0.1 to 39.6

Database Cutoff Date: 19FEB2020.

Table 19 Exposure duration (ASaT population)

	Pembrolizumab (N=153)		SOC (N=143)	
	n	(%)	n	(%)
Duration of Exposure				
> 0 months	153	(100.0)	143	(100.0)
>= 1 months	134	(87.6)	133	(93.0)
>= 2 months	122	(79.7)	114	(79.7)
>= 3 months	112	(73.2)	104	(72.7)
>= 6 months	96	(62.7)	65	(45.5)
>= 12 months	73	(47.7)	32	(22.4)

Each subject is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Database Cutoff Date: 19FEB2020

Overall survival

In previously untreated participants with advanced MSI-H/dMMR CRC, pembrolizumab provided a trend toward favourable OS compared with SOC.

- The HR for OS was 0.77 (95% CI: 0.54, 1.09; p=0.0694) (Table 20). The success criterion for OS was not met when compared to the p-value boundary of 0.0053; however, a trend toward improved survival for pembrolizumab was observed.
- Median OS was not reached (95% CI: not reached) in the pembrolizumab group versus 34.8 months (95% CI: 26.3, not reached) in the SOC group (Table 20).
- The KM curves demonstrate an increasingly pronounced separation, with the pembrolizumab group reaching a plateau at approximately 35 months, indicating a consistent and clinically meaningful long-term benefit with pembrolizumab (Figure 4 and Table 21).
- Despite the high number of participants (59%) in the SOC group who received a PD-1/PD-L1 inhibitor, after discontinuing initial study treatment, the KM curves for OS demonstrated a clinically meaningful improvement in survival for the pembrolizumab group (Figure 4).

Analyses by pre-specified subgroups, as shown in the forest plot in Figure 5, support the consistency of the overall OS results across subgroups.

No adjustment for SOC-arm treatment crossover

Table 20 Analysis of overall survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab	153	56 (36.6)	3794.5	1.5	NR (NR, NR)	77.8 (70.3, 83.6)
SOC	154	69 (44.8)	3430.2	2.0	34.8 (26.3, NR)	74.0 (66.2, 80.3)
					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab vs. SOC					0.77 (0.54, 1.09)	0.0694

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
§ One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 19FEB2020.

Figure 4 Kaplan-Meier estimates of overall survival (ITT population), database cut-off date 19-FEB-2020

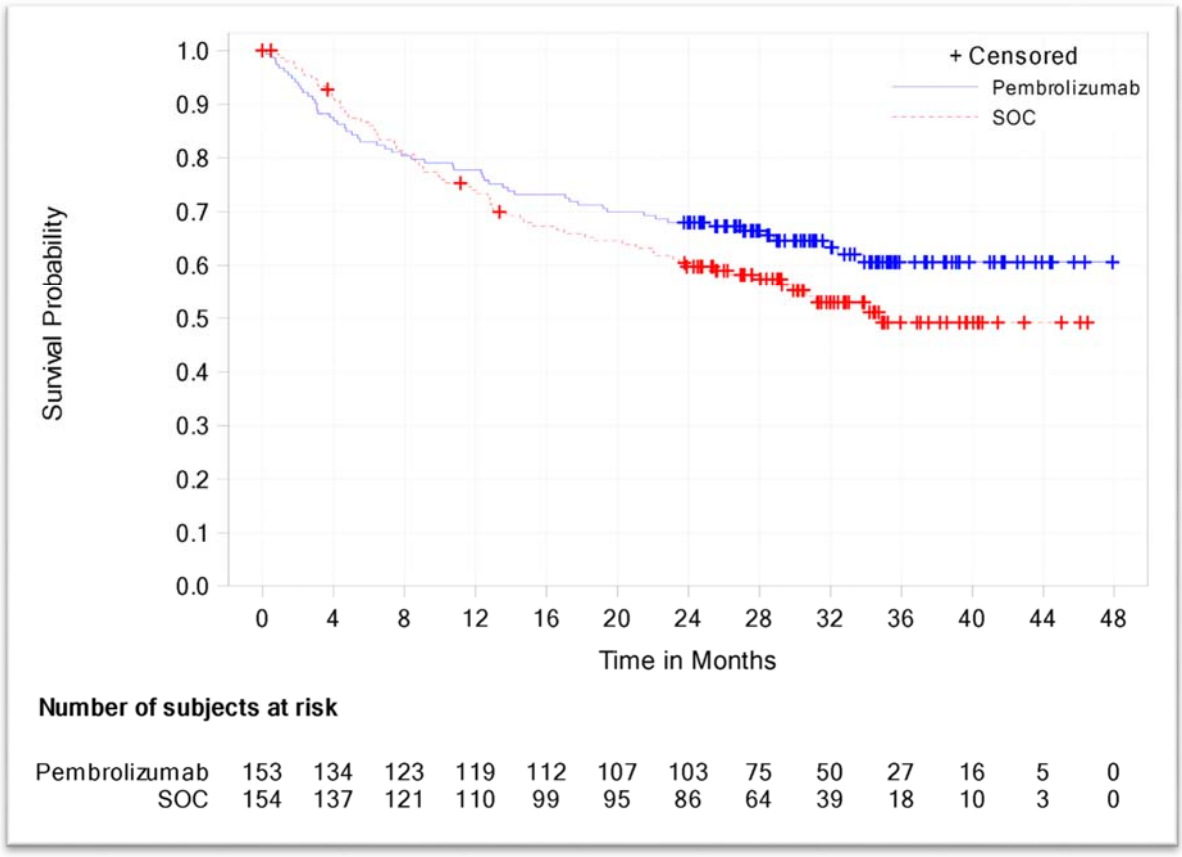
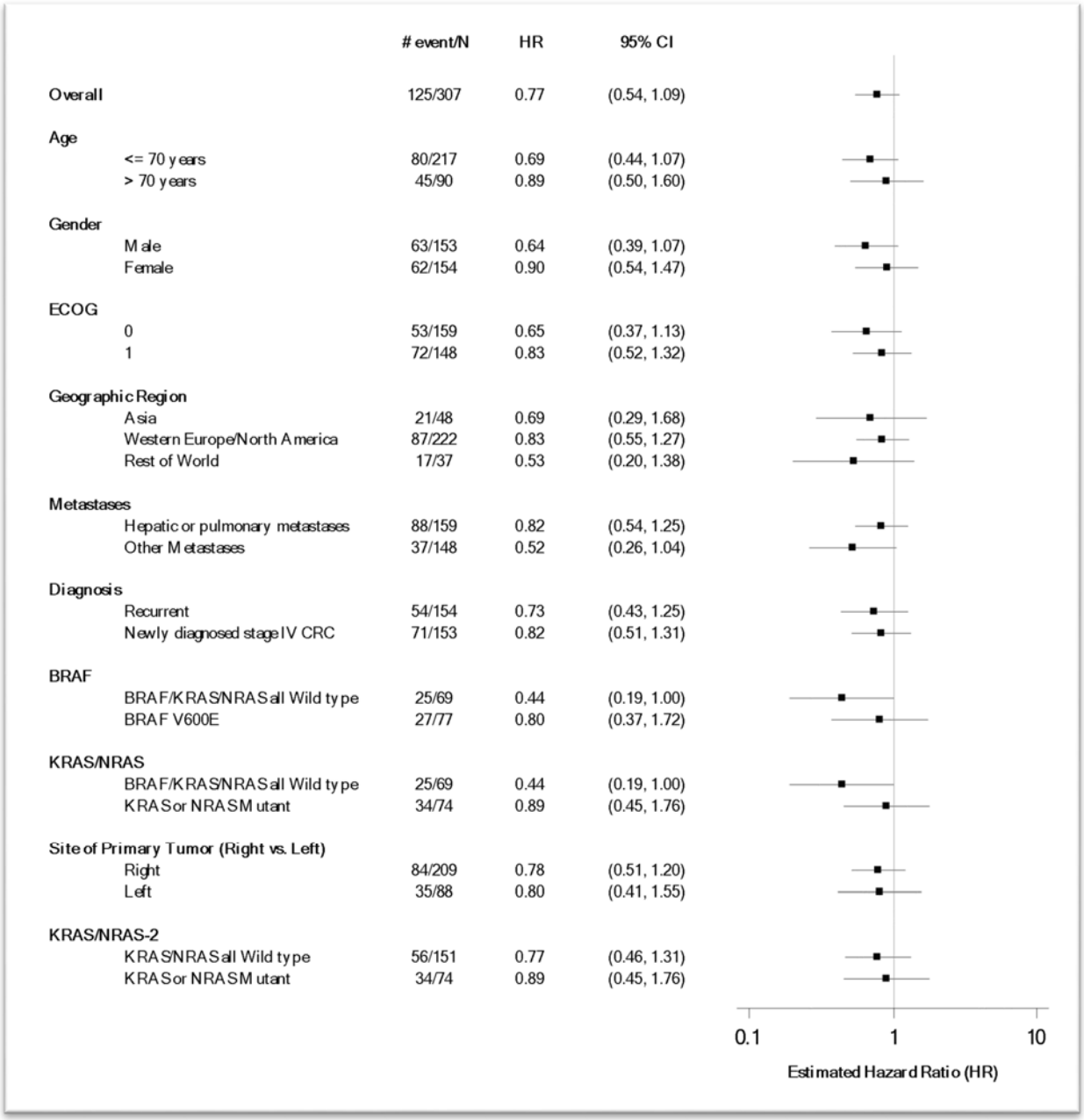


Table 21 Overall survival rate over time (ITT population)

	Pembrolizumab (N=153) % (95% CI)†	SOC (N=154) % (95% CI)†
Overall Survival rate at time point		
6 months	83.0 (76.1, 88.1)	86.0 (79.4, 90.7)
9 months	79.7 (72.5, 85.3)	78.7 (71.3, 84.4)
12 months	77.8 (70.3, 83.6)	74.0 (66.2, 80.3)
18 months	71.2 (63.4, 77.7)	65.9 (57.7, 72.9)
24 months	68.0 (59.9, 74.7)	59.8 (51.5, 67.2)

† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 19FEB2020.

Figure 5 Analysis of overall survival by subgroup factors (ITT population), based on Cox regression model with Efron's method of tie handling with treatment as a covariate, database cut-off date: 19-FEB-2020



SOC-arm treatment crossover adjustment

Sensitivity analyses of OS were also conducted with adjustment for crossover (i.e. subsequent anti-PD-1/PD-L1 therapy use in the SOC group) using three models recommended in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16: *Adjusting Survival Time Estimates in the Presence of Treatment Switching* (32): the

simplified 2-stage, the rank preserving structural failure time (RPSFT), and the inverse probability of censoring weighting (IPCW) models.

Each of these sensitivity analyses suggest that subsequent anti-PD-1/PD-L1 therapy may have impacted the primary OS results and show clinically meaningful improvement in OS in favour of pembrolizumab. The results of these analyses are shown in the subsections below, in summary:

- The analysis of OS adjusted for crossover using the simplified 2-stage model resulted in an HR of 0.59 (95% CI: 0.30, 1.19) (Table 24).
- The analysis of OS adjusted via the RPSFT model resulted in an HR of 0.68 (95% CI: 0.40, 1.14) (shown in Appendix L).
- The analysis of OS adjusted the IPCW model resulted in an HR of 0.59 (95% CI: 0.32, 1.24) (shown in Appendix L).

Treatment crossover adjusted via the 2-stage simplified method

Patient disposition for Stage1:

In the KEYNOTE-177 study, 154 patients were randomised to the SOC arm of which 56 (36.4%) patients switched over to pembrolizumab monotherapy after discontinuation of the protocol treatment (direct switchover). Besides the 56 patients who switched over to pembrolizumab monotherapy within the by-protocol allowed switching-over scenario, another 35 patients switched, outside of this scenario, to other anti-PD1/PD-L1 therapy (indirect switchover).

Therefore, of the 154 patients randomised to control arm, a total of 91 (59.1%) patients switched over to pembrolizumab monotherapy or other anti-PD1/PD-L1 therapy (direct + indirect switchover). Of these 91 patients who switched, 69 had disease progression hence met the eligibility criteria for switch-over. In 63 control patients who did not switch to pembrolizumab monotherapy or other anti-PD1/PD-L1 therapy, 18 patients had disease progression and hence met the eligibility criteria for switching. Therefore, a total of 87 eligible patients (69 switchers vs 18 non-switchers) were included in the first stage model to estimate the acceleration factor. The breakdown of the disposition of the control group is displayed in Figure 6.

Figure 6 Breakdown of the disposition of the SOC arm of the KEYNOTE-177 study (ITT population)

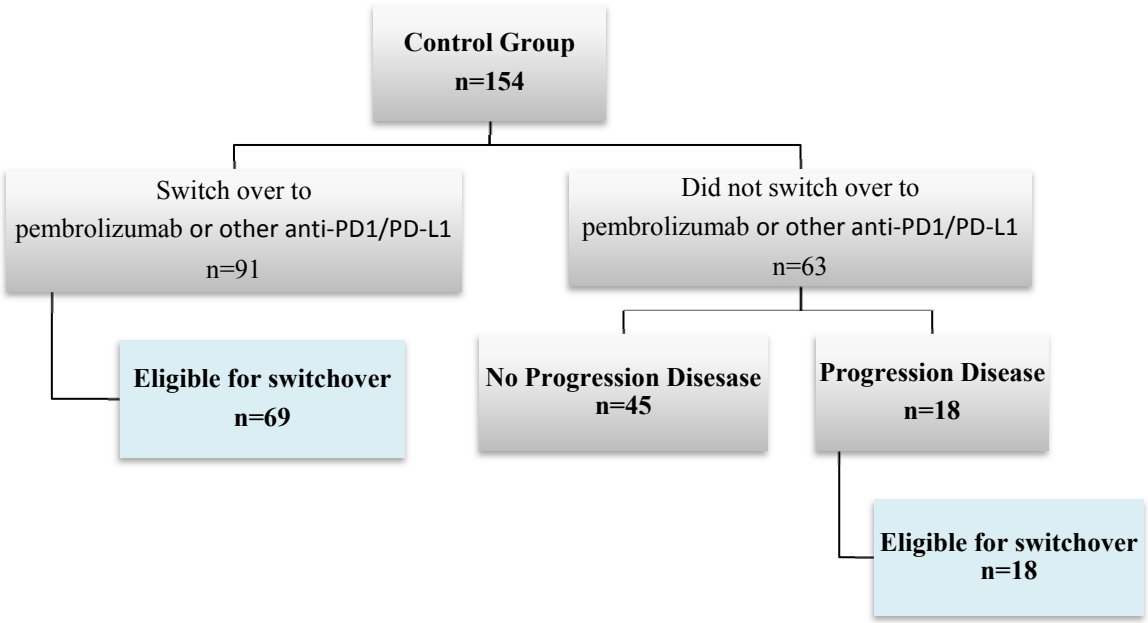
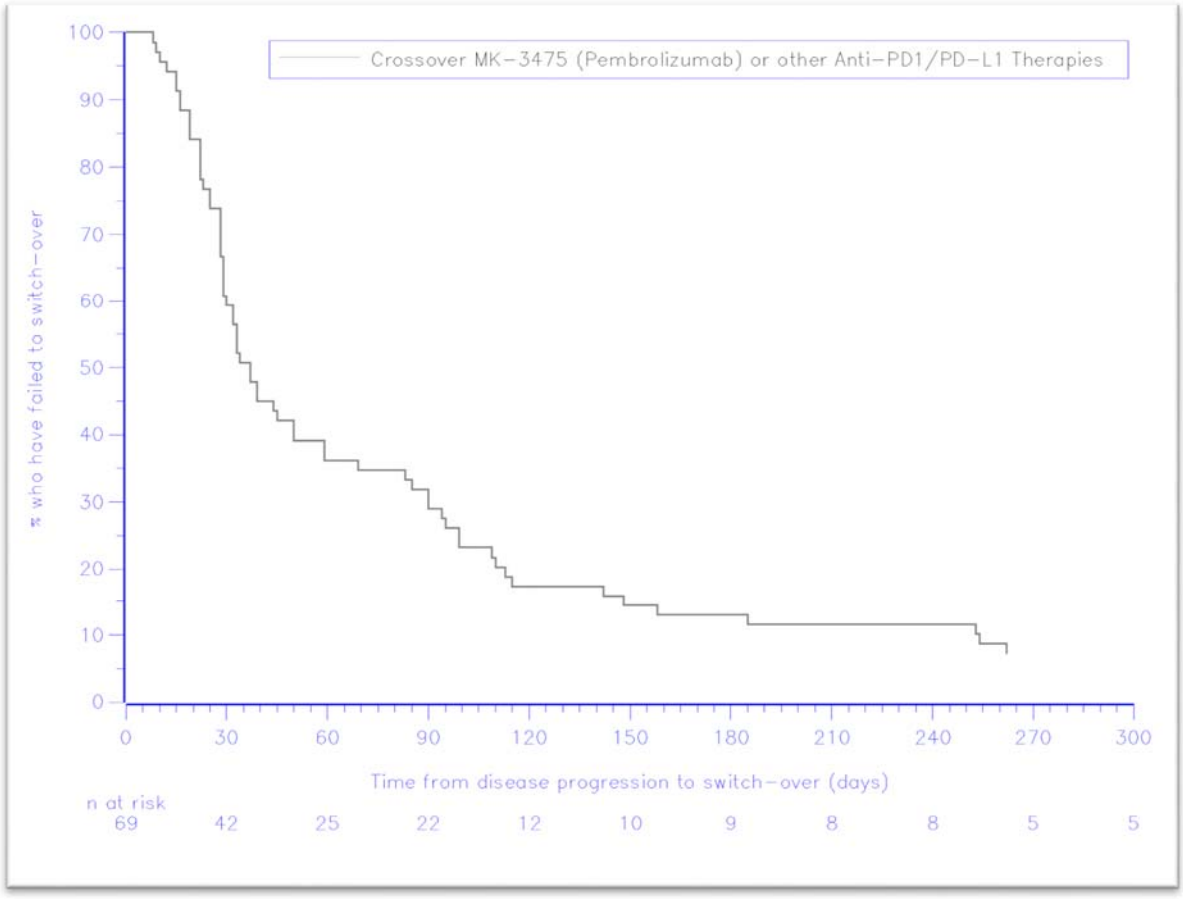


Figure 7 illustrates the probability of not receiving the pembrolizumab monotherapy or other anti-PD1/PD-L1 therapy after disease progression using a Kaplan-Meier curve in the 69 patients who were eligible for switch-over and actually switched over. Approximately two thirds of the patients switched over within 83 days after disease progression, with a median time from disease progression until switching of 37 days. The two-stage method relies on the assumption of no time-dependent confounding between disease progression and switch-over. Although it took a bit longer time for some patients to switch-over, the bias was likely to be small because the majority of switching occurred shortly after disease progression.

Figure 7 Kaplan-Meier Curves of Time to Switch-over from Disease Progression Switching Patients from Control arm eligible for switch-over to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies



Patient characteristics at baseline and at disease progression (secondary baseline) are compared in switchers vs. non-switchers in Table 22. Notable difference (p-value <0.05) was observed for geographic region (Asia vs Western Europe/North America vs Rest of the World) and tumour size at time of progression.

Table 22 Characteristics of patients from SOC arm eligible for switch-over to pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies, comparison of switchers vs. non-switchers, (Stage 1 model)

Characteristic	Study: 3475-177		
	Switchers N=69	Non-Switchers N=18	p-value ‡ Switchers vs Non-Switchers
Age (Years)			
Mean (SD)	58.8 (14.6)	62.5 (11.0)	
Median (Range)	61.0 (26.0-87.0)	66.5 (45.0-81.0)	0.3214
Gender			
Male	31 (44.9)	10 (55.6)	
Female	38 (55.1)	8 (44.4)	0.4211
Race			
Asian	10 (14.5)	5 (27.8)	
Black or African American	2 (2.9)	0 (0.0)	

Characteristic	Study: 3475-177		
	Switchers N=69	Non-Switchers N=18	p-value ‡ Switchers vs Non-Switchers
White	54 (78.3)	11 (61.1)	
Other	3 (4.3)	2 (11.1)	0.2429
Geographic Region			
Asia	10 (14.5)	5 (27.8)	
Rest of World	3 (4.3)	3 (16.7)	
Western Europe/North America	56 (81.2)	10 (55.6)	0.0424
BRAF Mutation Status			
BRAF V600E	21 (30.4)	6 (33.3)	
Wild type	32 (46.4)	7 (38.9)	
Other	16 (23.2)	5 (27.8)	0.8429
KRAS/NRAS Status			
BRAF/KRAS/NRAS all Wild type	18 (26.1)	6 (33.3)	
KRAS or NRAS Mutant	17 (24.6)	3 (16.7)	
Other	34 (49.3)	9 (50.0)	0.6929
ECOG at Time of Progression			
0	19 (27.5)	5 (27.8)	
1	50 (72.5)	13 (72.2)	1.0000
Site of Primary Tumor			
Left	14 (20.3)	4 (22.2)	
Right	53 (76.8)	13 (72.2)	
Other	2 (2.9)	1 (5.6)	0.6645
Metastases location			
Hepatic	27 (39.1)	9 (50.0)	
Other	42 (60.9)	9 (50.0)	0.4044
Time to Progression			
Mean (SD)	237.0 (195.6)	219.2 (228.2)	
Median (Range)	182.0 (30.0-869.0)	129.0 (58.0-940.0)	0.7405
Carcinoembryonic Antigen (CEA) at Time of Progression			
Subjects with data	68	17	
Mean (SD)	196.9 (970.0)	38.2 (59.7)	
Median (Range)	7.0 (0.5-7550.0)	12.5 (0.5-205.4)	0.5040
Tumor size at Time of Progression			
Mean (SD)	81.7 (66.8)	139.4 (114.4)	
Median (Range)	62.8 (0.0-320.0)	86.7 (5.0-323.1)	0.0069

† Patients were eligible to switch if they had RECIST v1.1 documented progression per IRC.
‡ Two-sided p-values based on Chi-square or Fisher's exact test for categorical variables and t-test for continuous variables.
§ Secondary baseline defined as time of disease progression.
Database Cutoff Date: 19Feb2020.

Estimation of the acceleration factor in Stage 1:

The parametric survival model was fitted to the post progression survival of the 87 subjects who had documented disease progression in the chemotherapy arm. Specifically, the Log-normal distribution was fitted for the parametric model for the survival time post progression

(AIC = 190.40). The model was adjusted for covariates as defined in the statistical analysis plan and converged.

Parameter estimates of the full model are shown in Table 23. Switching factor (switch from control to pembrolizumab or other anti-PD1/PD-L1 therapies versus no switch from control to pembrolizumab or other anti-PD1/PD-L1 therapies), age, gender, BRAF mutation status, site of primary tumour, ECOG at time of progression, time to progression and tumour size at time of progression are significant covariates for evaluating time to survival after disease progression in switchers vs. non-switchers (with a p-value <0.05 for these covariates).

Table 23 Parameter estimates - Stage 1 model (lognormal distribution), patients from the SOC arm eligible for switch-over to pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies

Parameter	Estimate	Standard Error	95% CI	p-value
Intercept	5.13	1.13	(2.92,7.34)	<.001
Switching Factor (Switchers vs. Non-switchers)	1.40	0.37	(0.68,2.12)	<.001
Age	-0.03	0.01	(-0.05,-0.00)	0.043
Gender	1.09	0.35	(0.41,1.78)	0.002
Race - Asian	0.33	1.25	(-2.13,2.79)	0.794
Race - Black or African American	-0.62	0.97	(-2.53,1.28)	0.521
Race - Other	0.78	0.62	(-0.43,2.00)	0.207
Region - Asia	-0.66	1.20	(-3.00,1.68)	0.582
Region - Rest of World	-0.87	0.61	(-2.07,0.33)	0.156
BRAF Mutation Status - BRAF V600E	-0.44	0.64	(-1.70,0.81)	0.491
BRAF Mutation Status - Other	-1.45	0.61	(-2.65,-0.26)	0.017
KRAS/NRAS Status - BRAF/KRAS/NRAS All Wild Type	-0.36	0.66	(-1.65,0.94)	0.589
KRAS/NRAS Status - KRAS or NRAS Mutant	-0.16	0.55	(-1.24,0.92)	0.773
Site of Primary Tumor - Left	-0.94	0.45	(-1.81,-0.06)	0.036
Site of Primary Tumor - Other	-1.59	0.80	(-3.17,-0.02)	0.047
Metastases location	-0.06	0.36	(-0.77,0.65)	0.869
ECOG at Time of Progression †	0.98	0.45	(0.09,1.87)	0.031
Time to Progression †	0.00	0.00	(0.00,0.00)	0.023
CEA at Time of Progression †	-0.00	0.00	(-0.00,0.00)	0.812
Tumor Size at Time of Progression †	-0.01	0.00	(-0.01,-0.00)	0.015
Convergence Statistics			AIC	190.40

‡ Lognormal parametric survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: Age , Gender (Male vs Female), Race (White vs. Asian vs. Black or African American vs. Other), Geographic region (Asia vs. Rest of World vs. Western Europe/North America), BRAF Mutation Status (BRAF V600E vs. Other vs. Wild type), KRAS/NRAS Status (KRAS and NRAS wild type vs. KRAS or NRAS mutant vs. Other), ECOG Performance Status at Time of Progression (0 vs 1), Site of Primary Tumor (Left vs Right vs Other), Metastases location (Hepatic vs Other), Carcinoembryonic Antigen (CEA) at Time of Progression, Time to Progression and Tumor size at Time of Progression

§ Patients were eligible to switch if they had RECIST v1.1 documented progression per IRC.

† Secondary baseline defined as time of disease progression.

Database Cutoff Date: 19Feb2020.

The estimated acceleration factor and its 95% CI are 4.047 (1.967, 8.327), as listed in Table 24. This acceleration factor is used to adjust the survival time of the 91 patients who switched from control arm to pembrolizumab monotherapy or other anti-PD1/PD-L1 therapies, and the survival period after treatment switch is reduced by approximately 75.3% as compared to the unadjusted observed data.

Estimation of treatment effect:

Table 24 present the results of the analysis of OS adjusting for treatment switch from control arm to pembrolizumab or other anti-PD1/PD-L1 therapies, including Kaplan-Meier estimates of OS and estimation of treatment effect. No re-censoring to adjusted survival or censored survival times is applied (primary approach).

Without re-censoring, the number of events in the control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (i.e., 69 events). The adjusted HR for OS is 0.59 (95% CI: 0.30, 1.19) for the pembrolizumab arm vs. the control arm. The two-sided p-value is retained from the ITT analysis. Note that the estimated acceleration factor is relatively high with a wide confidence interval. Therefore, the results from the two-stage analysis should be interpreted cautiously.

Table 24 Analysis of Overall Survival | Without Re-censoring, Comparison Pembrolizumab 200 mg Q3W versus Chemotherapy, Adjusting for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis, ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Pembrolizumab 200 mg vs. Control		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]	p-Value[¶¶]
Control	154	69 (44.8)	3430.2	2.0	34.8 (26.3, .)	74.0 (66.2, 80.3)	---	---	---
Control, Adjusted[¶]	154	69 (44.8)	2389.1	2.9	23.5 (16.6, .)	69.3 (61.1, 76.1)	---	---	---
Pembrolizumab 200 mg	153	56 (36.6)	3794.5	1.5	Not Reached (., .)	77.8 (70.3, 83.6)	0.59 (0.30, 1.19)	0.1399	0.1388

Stage 1 model[††]	Acceleration factor[‡‡]
[§] Controls eligible to cross-over to pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies, patients switching vs patients not switching	4.047 (1.967, 8.327)

[¶] Survival times shrunk for the patients who crossed-over to Pembrolizumab 200 mg Q3W treatment or Other Anti-PD1/PD-L1 Therapies.

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with treatment as a covariate. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[‖] Two-sided p-value based on Log-rank test, ITT population, analysis not adjusted for treatment switch.

[¶¶] Two-sided p-value based on Cox model, ITT population, analysis not adjusted for treatment switch.

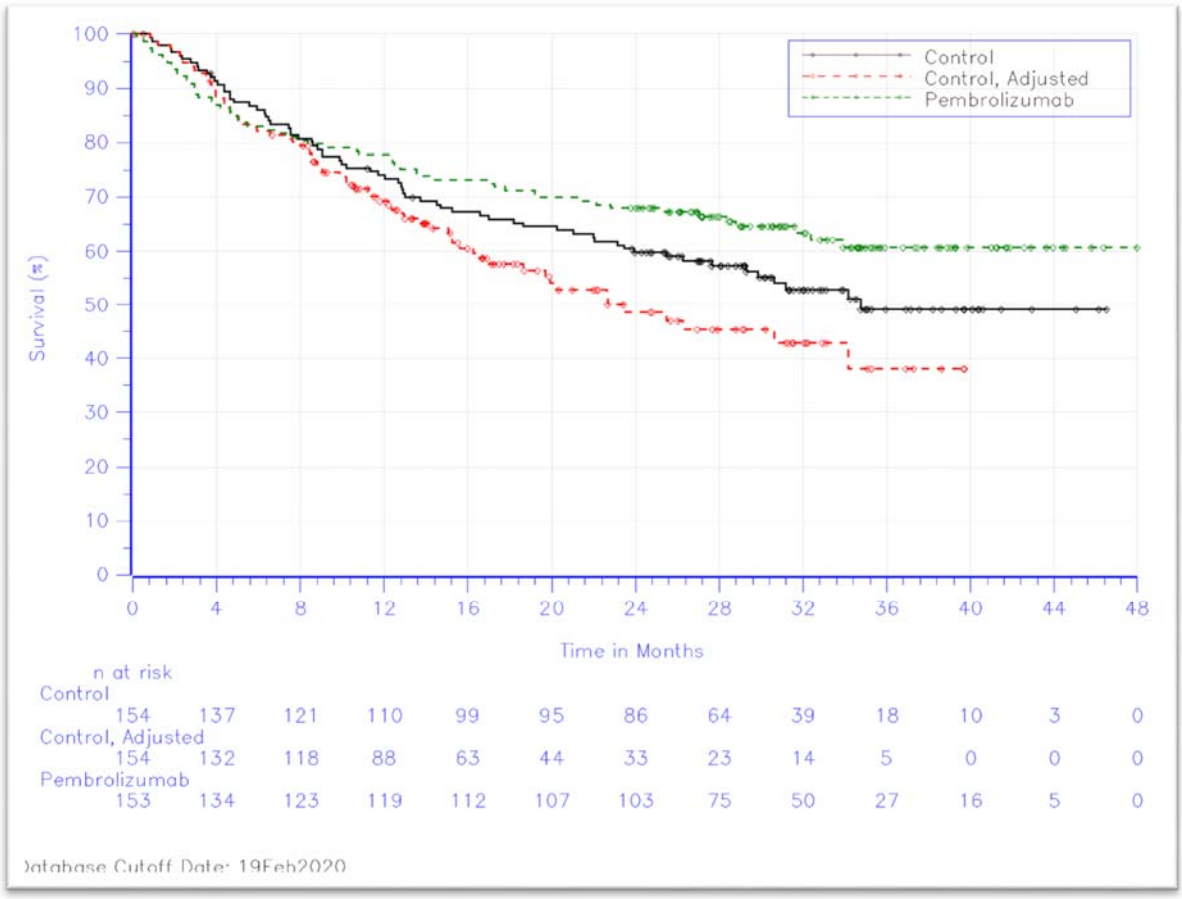
[††] Lognormal parametric survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: Age, Race (White vs. Asian vs. Black or African American vs. Other), Gender (Male vs Female), Geographic region (Asia vs. Rest of World vs. Western Europe/North America), BRAF Mutation Status (BRAF V600E vs. Wild type vs. Other), KRAS/NRAS Status (KRAS and NRAS wild type vs. KRAS or NRAS mutant vs. Other), ECOG performance status (0 vs.1), Site of primary tumour (Left vs Right vs Other), Metastases location (Hepatic vs Other), Carcinoembryonic Antigen (CEA) at time of progression, Time to progression and Tumour size at time of progression.

[§] Patients were eligible to switch if they had RECIST v1.1 documented progression per IRC.

[‡‡] Acceleration factor used to shrink the survival time of control patients who crossed-over to Pembrolizumab 200 mg Q3W treatment or Other Anti-PD1/PD-L1 Therapies. The corresponding estimate and the 95% CI are derived from Stage 1 Lognormal model.

Database Cutoff Date: 19Feb2020.

Figure 8 Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-stage Analysis, Without Re-censoring, ITT Population



Selection of the most appropriate method for crossover adjustment

Based on the guidance given in NICE DSU TSD 16 (32) and the characteristics of the KEYNOTE-177 study, adjustment via the simplified 2-stage method is likely to be the most appropriate in this case:

- The RPSFT method was designed primarily to address the issue of treatment non-compliance in RCTs (and therefore less relevant in the context of the KEYNOTE-177 study) and is primarily limited by the "common treatment effect" assumption which becomes invalid if patients who switch on to on a treatment part way through a trial experience a different treatment effect compared to patients originally randomised to that treatment group. Given that switching in the KEYNOTE-177 study is permitted only after disease progression, at which time the capacity for a patient to benefit from subsequent anti-PD-1/PD-L1 therapy is likely to be different compared to pre-progression, the "common treatment effect" assumption is unlikely to be clinically plausible in this case and consequently the RPSFT method is unlikely to be the most appropriate.
- The IPCW method represents a type of Marginal Structural Model that was originally developed for use with observational data, and has "no unmeasured confounder" as a key assumption (i.e. data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring [switching] and models of censoring risk must be correctly specified). This assumption is particularly problematic in the context of KEYNOTE-177 as the RCT's dataset is smaller than observational datasets and some key predictors of treatment switching (e.g. patient preference for switching) are not collected. Consequently, the IPCW method is also unlikely to be the most appropriate method for the analysis of data from KEYNOTE-177.

- In contrast, the simplified 2-stage model approach is particularly suitable for adjusting for the type of treatment switching observed in KEYNOTE-177 and other oncology RCTs when switching is only permitted soon after disease progression, i.e. a timepoint that can be used as a secondary "baseline" under the assumption that all patients are at a similar stage of disease at the point of disease progression (a reasonable assumption in the context of the KEYNOTE-177 study design). Unlike the RPSFT method, the simple 2-stage method does not require the "common treatment effect" assumption (which is unlikely to be clinically plausible as described previously) as the initial step of this approach involves estimating a treatment effect specifically for switchers. Furthermore, during stage 1 of the s-stage method, the switch effect was estimated after adjustment for other covariates – only subjects who did have a progression were considered in stage 1 and the switch effect was quantified by means of an acceleration factor. The estimated post-progression treatment acceleration factor was 4.05 (95% CI: 1.97, 8.33). This point estimate suggests that switching to pembrolizumab monotherapy or other anti-PD1/PD-L1 therapy increases survival time by a large factor of 4.05. This large factor could suggest that the assumption of no unmeasured confounders may not be met which further supports the argument the RPSFT model is less likely to be appropriate.

It should be noted that the simplified 2-stage method of adjustment was also chosen as the most appropriate and used as the base-case for two recent pembrolizumab NICE appraisals (TA428 for treating PD-L1-positive non-small-cell lung cancer after chemotherapy and TA519 for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy).

It should also be noted that due to the very small sample size available for the analysis using only those patients from the KEYNOTE-177 who did not receive bevacizumab (a subgroup/sensitivity analysis shown in Appendix L), only adjustment via the RPSFT method was possible.

Progression-free survival

A statistically significant and clinically meaningful improvement in PFS was observed in the pembrolizumab group compared to the SOC group:

- The HR for PFS was 0.60 (95% CI: 0.45, 0.80; p-value=0.0002) in favour of pembrolizumab, representing a 40% reduction in the risk of disease progression or death (Table 25). Pembrolizumab was superior to SOC compared to the p-value boundary of 0.0117.
- Median PFS was approximately double that of the SOC group: 16.5 months (95% CI: 5.4, 32.4) versus 8.2 months (95% CI: 6.1, 10.2) (Table 25).
- By KM estimation, the PFS rate at 6 months was similar in the pembrolizumab and SOC groups but was higher in the pembrolizumab group at 12 months (55.3% vs 37.3%) and 24 months (48.3% vs 18.6%) (Table 26 and Figure 9).
- The KM curves for PFS demonstrate an increasingly pronounced separation with the pembrolizumab group reaching a plateau around 40%, indicating a consistent and clinically meaningful long-term benefit with pembrolizumab (Figure 9).
- Analyses of PFS by prespecified subgroups were generally consistent with the primary findings, as shown in the forest plot, with all CIs overlapping the CI for the primary PFS HR (Figure 10). These results should be interpreted with caution, as the study was not powered to demonstrate improvement in subgroups.

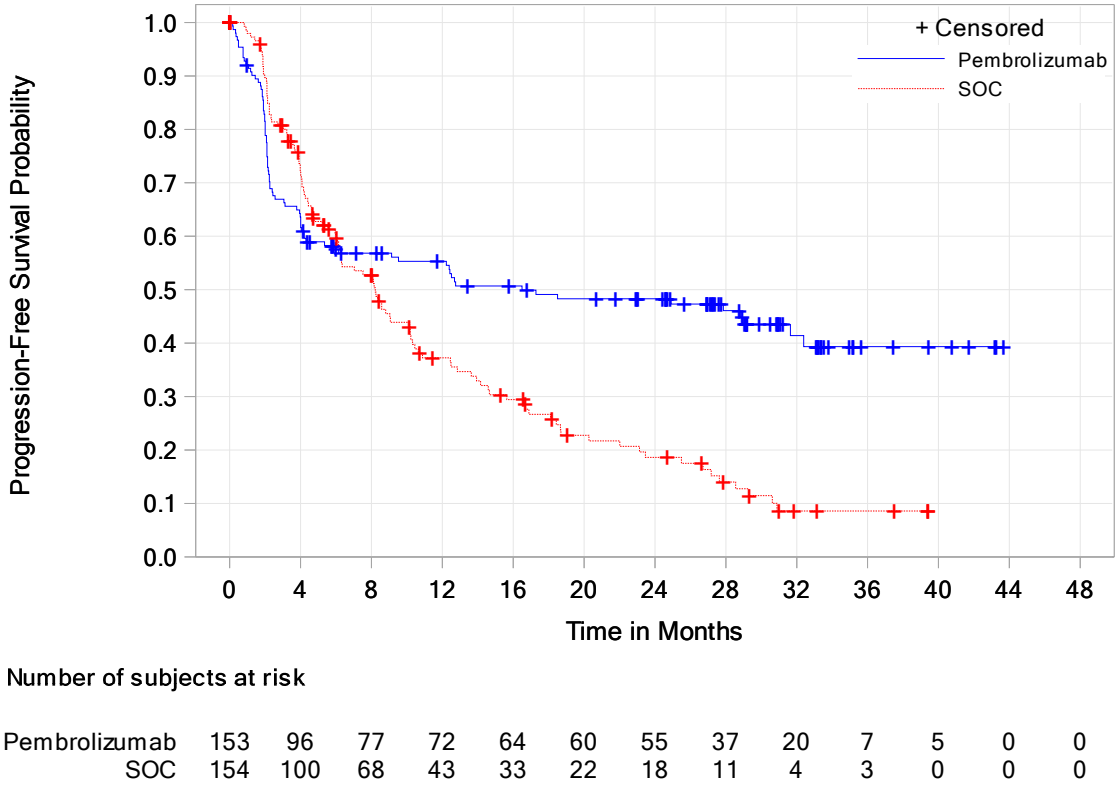
Table 27 summarises event and censoring used in the analysis of PFS.

Table 25 Analysis of progression-Free Survival (Primary Analysis) By Central Imaging Vendor per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Month 12 in % [†] (95% CI)
Pembrolizumab	153	82 (53.6)	2238.8	3.7	16.5 (5.4, 32.4)	55.3 (47.0, 62.9)
SOC	154	113 (73.4)	1487.3	7.6	8.2 (6.1, 10.2)	37.3 (29.0, 45.5)
					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab vs. SOC					0.60 (0.45, 0.80)	0.0002

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 19FEB2020.

Figure 9 Kaplan-Meier estimates of progression-free survival by central imaging vendor per RECIST 1.1 (ITT population), database cut-off date: 19-FEB-2020



Number of subjects at risk

Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
SOC	154	100	68	43	33	22	18	11	4	3	0	0	0

Table 26 Progression-free survival rate over time by central imaging vendor per RECIST 1.1 (ITT population)

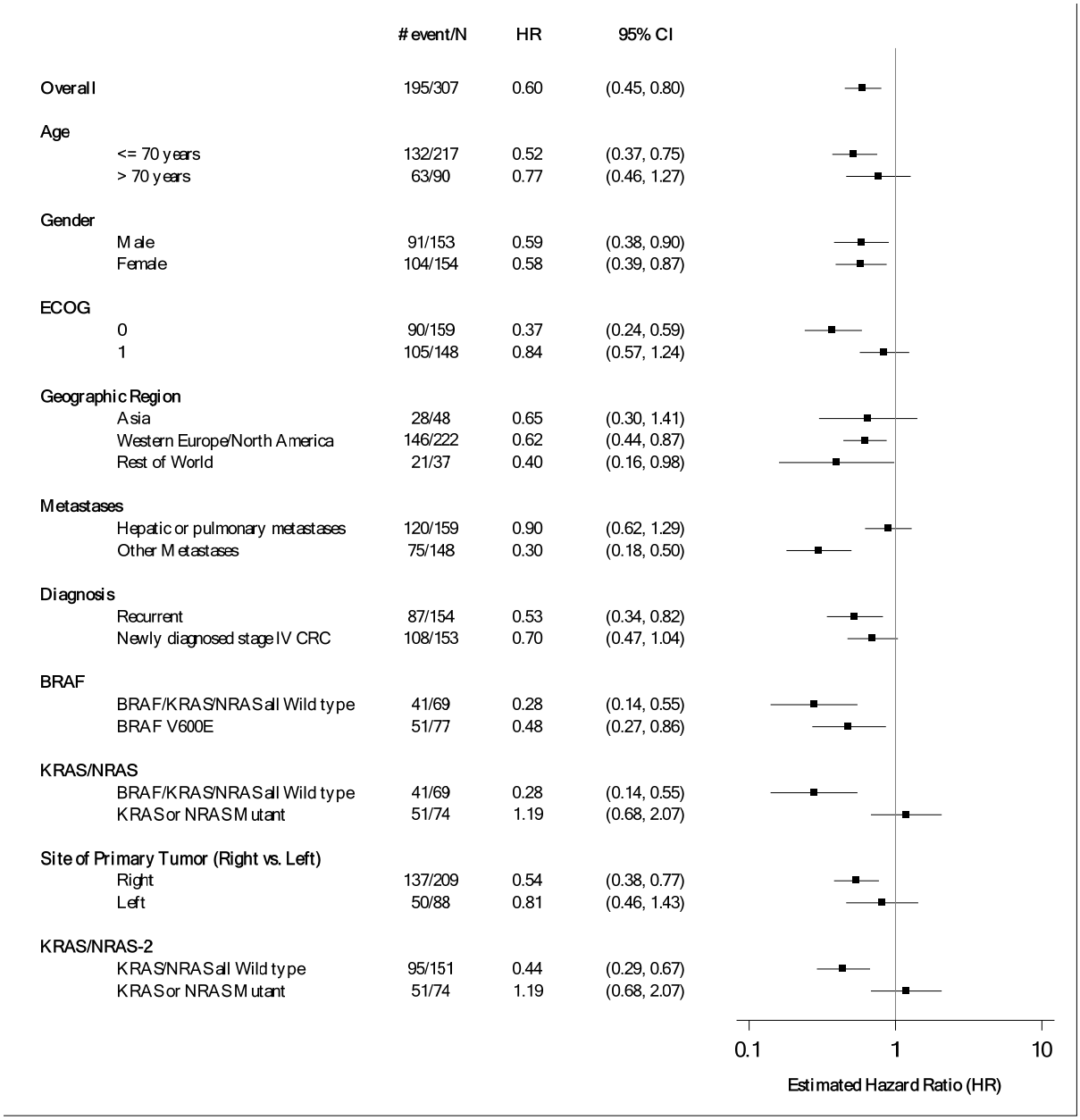
	Pembrolizumab (N=153) % (95% CI)†	SOC (N=154) % (95% CI)†
Progression-Free Survival rate at time point		
6 months	57.6 (49.3, 65.0)	59.7 (51.1, 67.3)
9 months	56.8 (48.5, 64.3)	45.5 (36.9, 53.7)
12 months	55.3 (47.0, 62.9)	37.3 (29.0, 45.5)
18 months	49.1 (40.7, 57.0)	26.7 (19.2, 34.7)
24 months	48.3 (39.9, 56.2)	18.6 (12.1, 26.3)

† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 19FEB2020.

Table 27 Summary of event and censoring description for progression-free survival by central imaging vendor per RECIST 1.1 (ITT population)

	Pembrolizumab (N=153) n (%)	SOC (N=154) n (%)
Subjects with Events	82 (53.6)	113 (73.4)
Documented progression	65 (42.5)	86 (55.8)
Death	17 (11.1)	27 (17.5)
Subjects Censored	71 (46.4)	41 (26.6)
Curative-intent surgery	12 (7.8)	12 (7.8)
New anti-cancer therapy	5 (3.3)	15 (9.7)
Last radiologic assessment showing no progression	53 (34.6)	10 (6.5)
No adequate post-baseline imaging assessment	1 (0.7)	4 (2.6)
Database Cutoff Date: 19FEB2020.		

Figure 10 Analysis of progression-free survival by subgroup factors by central imaging vendor per RECIST 1.1 (ITT population), based on Cox regression model with Efron's method of tie handling with treatment as a covariate, database cut-off date 19-FEB-2020



Rate of response

Pembrolizumab treatment provided a clinically meaningful improvement in ORR when compared with SOC treatment at IA2. Comparing the ITT population in the pembrolizumab group with the SOC group:

- The overall response rate (ORR) as defined by BICR per RECIST 1.1 was higher: 43.8% (95% CI: 35.8, 52.0) in the pembrolizumab group versus 33.1% (95% CI: 25.8, 41.1) in the SOC group (Table 28).
- More participants achieved a complete response in the pembrolizumab group than in the SOC group (11.1% vs 3.9%) (Table 29).

Table 28 Analysis of best overall response by central imaging vendor per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI*)	Difference in % vs. SOC	
				Estimate (95% CI)†	p-Value‡
Pembrolizumab	153	67	43.8 (35.8,52.0)	10.7 (-0.2,21.3)	0.0275
SOC	154	51	33.1 (25.8,41.1)		

Only confirmed responses are included.
* Based on binomial exact confidence interval method.
† Based on Miettinen & Nurminen method.
‡ One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 19FEB2020.

Table 29 Summary of best overall response by central imaging vendor per RECIST 1.1 (ITT population)

Response Evaluation	Pembrolizumab (N=153)			SOC (N=154)		
	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	17	11.1	(6.6, 17.2)	6	3.9	(1.4, 8.3)
Partial Response (PR)	50	32.7	(25.3, 40.7)	45	29.2	(22.2, 37.1)
Objective Response (CR+PR)	**67**	**43.8**	**(35.8, 52.0)**	**51**	**33.1**	**(25.8, 41.1)**
Stable Disease (SD)	32	20.9	(14.8, 28.2)	65	42.2	(34.3, 50.4)
Disease Control (CR+PR+SD)	**99**	**64.7**	**(56.6, 72.3)**	**116**	**75.3**	**(67.7, 81.9)**
Progressive Disease (PD)	45	29.4	(22.3, 37.3)	19	12.3	(7.6, 18.6)
Not Evaluable	3	2.0	(0.4, 5.6)	2	1.3	(0.2, 4.6)
No Assessment	6	3.9	(1.5, 8.3)	17	11.0	(6.6, 17.1)

Only confirmed responses are included.
† Based on binomial exact confidence interval method.
No Assessment: subject had no post-baseline imaging.
Database Cutoff Date: 19FEB2020.

Time to response and duration of response

For the pembrolizumab group and SOC group:

- Median time to response was similar (2.2 months vs 2.1 months) (Table 30).
- Median response duration was not reached (range: 2.3+-41.4+ months) in the

pembrolizumab group and was 10.6 months (range: 2.8-37.5+ months) in the SOC group (Table 30).

- The proportion of participants with a DOR ≥12 months (85.1% vs 43.8%) and ≥24 months (82.6% vs 35.3%) was >2-fold higher in the pembrolizumab group than in the SOC group (Table 30).
- In the pembrolizumab group, the plateau in the KM curve after 24 months suggests that participants were still responding after discontinuing treatment after the maximum 24 months of pembrolizumab treatment per protocol (Table 31 and Figure 11).

Table 30 Summary of time to response and duration of response in subjects with confirmed response by central imaging vendor per RECIST 1.1 (ITT population)

	Pembrolizumab (N=153)	SOC (N=154)
Number of subjects with response[†]	67	51
Time to Response (months)		
Mean (SD)	4.0 (3.7)	3.6 (4.1)
Median (Range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)
Response Duration[‡] (months)		
Median (Range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	61 (96.9)	43 (87.9)
≥9 months	55 (91.9)	27 (59.9)
≥12 months	50 (85.1)	19 (43.8)
≥18 months	45 (85.1)	11 (35.3)
≥24 months	29 (82.6)	9 (35.3)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 19FEB2020.

Table 31 Summary of response outcome in subjects with confirmed response by central imaging vendor per RECIST 1.1 (ITT population)

	Pembrolizumab (N=153)	SOC (N=154)
Number of Subjects with Response[†]	67	51
Subjects Who Progressed or Died[‡] (%)	**13 (19.4)**	**32 (62.7)**
Range of DOR (months)	3.3 to 27.0	2.8 to 28.8
Censored Subjects (%)	**54 (80.6)**	**19 (37.3)**
Subjects who received oncologic surgery with curative intent	8 (11.9)	2 (3.9)

	Pembrolizumab (N=153)	SOC (N=154)
Subjects who missed 2 or more consecutive disease assessments	3 (4.5)	1 (2.0)
Subjects who started new anti-cancer treatment	1 (1.5)	6 (11.8)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	4 (6.0)	1 (2.0)
Ongoing response[§]	38 (56.7)	9 (17.6)
≥6 months	38 (56.7)	9 (17.6)
≥9 months	38 (56.7)	8 (15.7)
≥12 months	38 (56.7)	8 (15.7)
≥18 months	34 (50.7)	8 (15.7)
≥24 months	24 (35.8)	6 (11.8)
Range of DOR (months)	15.7+ to 41.4+	6.2+ to 37.5+

[†] Includes subjects with a confirmed complete response or partial response.

[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

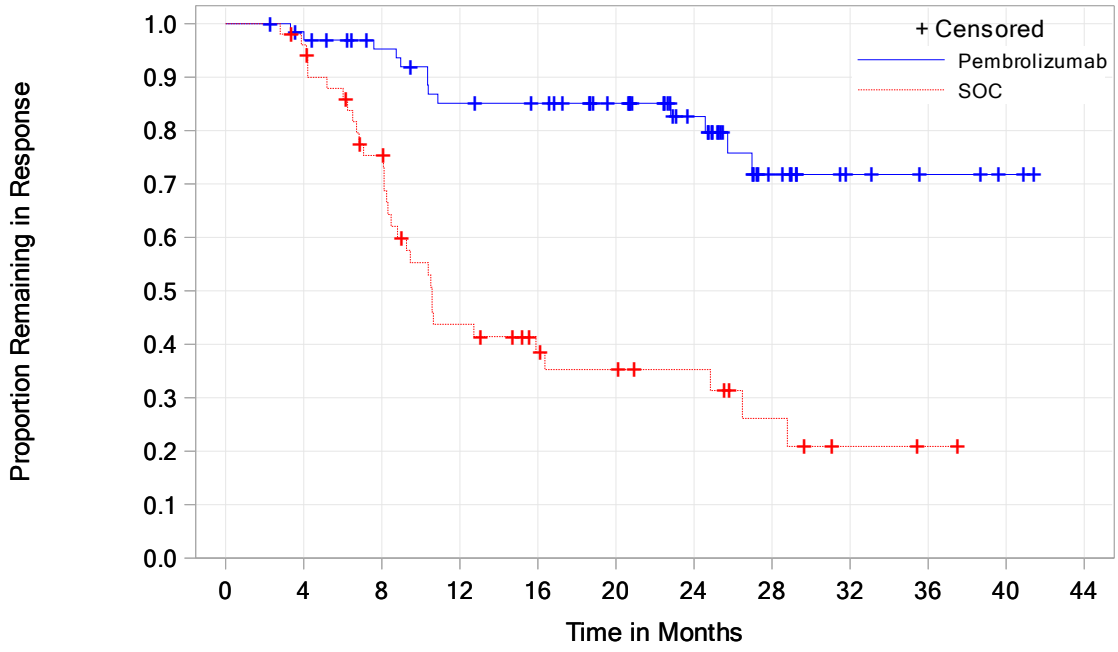
[§] Includes subjects who are alive, have not progressed, have not received oncologic surgery with curative intent, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

Database Cutoff Date: 19FEB2020.

Figure 11 Kaplan-Meier estimates of duration of response in subjects with confirmed response by central imaging vendor per RECIST 1.1 (ITT population)



Number of subjects at risk

Pembrolizumab	67	64	57	50	48	41	29	13	6	4	2	0
SOC	51	48	35	19	13	11	9	5	2	1	0	0

Progression-free survival 2

Progression-free survival 2 (PFS2) results are provided in Appendix L.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-C29

EORTC QLQ-C30 and EORTC QLQ-C29 results are provided in Appendix L.

EQ-5D

For the EQ-5D utility score, the mean change from baseline to Week 18 showed improvement (LS mean = 0.04 points [95% CI: 0.00, 0.08]) in the pembrolizumab group, and a decline (LS mean = -0.01 points [95% CI: -0.05, 0.02]) in the SOC group, although the difference was not clinically meaningful (difference in LS means = 0.05; 95% CI: 0.00, 0.10; two-sided nominal p=0.0311, not adjusted for multiplicity) (Table 32).

Baseline EQ-5D VAS and utility scores were similar between treatment groups. At prespecified Week 18, the mean change from baseline in the EQ-5D VAS score showed

improvement (LS mean = 4.50 points [95% CI: 1.16, 7.83]) in the pembrolizumab group, and a decline (LS mean = -2.88 points [95% CI: -6.46, 0.69]) in the SOC group. The difference in LS means between pembrolizumab and the SOC group at Week 18 was 7.38 points (95% CI: 2.82, 11.93; two-sided nominal p=0.0016, not adjusted for multiplicity) (Table 33).

EQ-5D Utility Score

Table 32 Analysis of change from baseline in EQ-5D Utility Score at Week 18 (FAS population)

	Baseline		Week 18		Change from Baseline at Week 18		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembrolizumab	142	0.77 (0.195)	102	0.84 (0.175)	151	0.04 (0.00, 0.08)	
SOC	133	0.75 (0.197)	82	0.77 (0.199)	141	-0.01 (-0.05, 0.02)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC						0.05 (0.00, 0.10)	0.0311

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction as covariates.

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided test.

Database Cutoff Date: 19FEB2020.

EQ-5D VAS

Table 33 Analysis of change from baseline in EQ-5D VAS at Week 18 (FAS population)

	Baseline		Week 18		Change from Baseline at Week 18		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]	
Pembrolizumab	142	70.12 (18.862)	102	76.86 (17.916)	151	4.50 (1.16, 7.83)	
SOC	133	70.83 (19.788)	82	70.76 (18.198)	141	-2.88 (-6.46, 0.69)	
Pairwise Comparison						Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. SOC						7.38 (2.82, 11.93)	0.0016

	Baseline		Week 18		Change from Baseline at Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction as covariates.

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided test.

Database Cutoff Date: 19FEB2020.

B.2.7 Subgroup analysis

To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the two primary endpoints (OS and PFS) are estimated and plotted within each category of the following classification variables:

- Age category (≤70 years vs. >70 years).
- Geographic region (Asia vs. Western Europe/North America vs. Rest of World).
- Hepatic or pulmonary metastases vs other metastases.
- Recurrent vs newly diagnosed stage IV CRC.
- BRAF wild-type vs. BRAF V600E.
- Site of primary tumour (right vs. left).
- Surgical vs non-surgical subjects, where surgical patients are those who have surgery with curative intent.

The results of the subgroup analyses are shown in section B.2.6 in Figure 5 and Figure 10.

Additionally, results from the KEYNOTE-177 study are presented for the subpopulation of patients excluding those who were chosen to receive to a bevacizumab-containing regimen prior to randomisation, for brevity this population is described as the population excluding patients who received bevacizumab, ITT-minus-bevacizumab, or "ITT-bevacizumab" population in this submission. The chemotherapy regimen to be given to any patient if they were randomised to the SOC arm was chosen before randomisation occurred, as part of the study protocol as described in section B.2.3. Data are presented for this specific subpopulation as KEYNOTE-177 study is a global study that included a high proportion of patients who were treated with bevacizumab-containing regimens in the SOC arm, however bevacizumab is not reimbursed for this indication in the NHS and so is not used in standard clinical practice in the UK. In order to make the data presentation more logical and documents easier to navigate, the data for this subpopulation is shown in Appendix F for safety results, Appendix L for clinical efficacy results, and Appendix M for NMA results.

B.2.8 Meta-analysis

Pooling of study data via pair-wise meta-analysis was not performed because the KEYNOTE-177 trial is the only trial that compared pembrolizumab to comparators in the population of interest.

B.2.9 Indirect and mixed treatment comparisons

Full details of the methodology for the network meta-analyses (NMAs) used are provided in Appendix D. The same SLR used to identify and select relevant studies with direct clinical evidence (described in section B.2.1) was used to identify studies with data that could be used as inputs in the NMAs, the inclusion criteria for this SLR is summarised in Table 34.

Table 34 PICOS criteria to identify trials for the SLR

Criteria	Inclusion criteria	Exclusion criteria
Population	• Previously untreated adult patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC	• Patients who have received prior systemic therapy for stage IV CRC. Subjects may have received prior adjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to randomisation • Patients under age 18 years
Interventions	• FOLFOX or mFOLFOX6 • FOLFOX or mFOLFOX6 + cetuximab • FOLFIRI + cetuximab • FOLFIRI • Capecitabine + oxaliplatin (XELOX/CAPOX) • Capecitabine • Panitumumab + FOLFOX or mFOLFOX6 (RAS wild-type patients) • Panitumumab + FOLFIRI (RAS wild-type patients)	
Comparators	• Placebo or best supportive care • Any intervention of interest • Any treatment that facilitates an indirect comparison	N/A
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Duration of response (DOR) • Surgical conversion rate • Time to second objective disease progression (PFS2) • Objective response rate (ORR) • Drug-related adverse events (AE) ≥10% • Grade 3-5 AE (all, drug-related) • Discontinuation due to AE (DAE) • Serious AE (SAE)	N/A

Criteria	Inclusion criteria	Exclusion criteria
	• Patient reported outcomes (PRO) (e.g. EQ-5D, EORTC QLQ-C30, EORTC QLQ-Cr29)	
Time	• No time restriction	N/A
Study design	• Randomised clinical trials • Controlled clinical trials • Non-randomised clinical trials, including single arm prospective interventional trials	• Prospective and retrospective cohort studies • Case-control studies • Cross-sectional studies • Case reports and case series
Other	• Only studies published in English	

Pembrolizumab versus relevant comparators (using the KEYNOTE-177 ITT population)

Overall survival

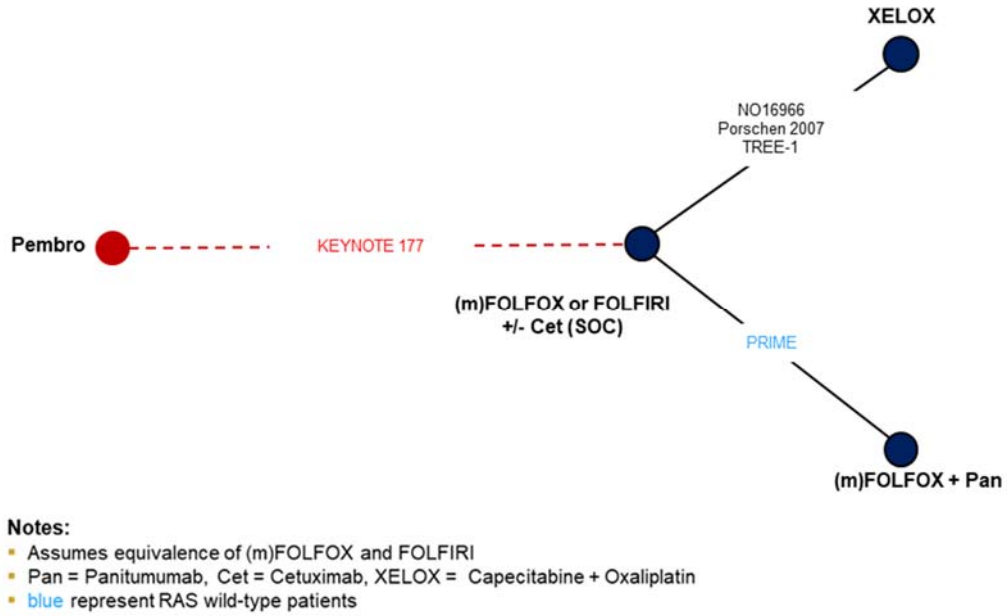
OS was reported in all 5 trials eligible for inclusion in the base case analysis; these evaluated four interventions (pembrolizumab, CAPOX, mFOLFOX + panitumumab and SOC). While the SLR sought to identify studies meeting the inclusion criteria that would allow a comparison versus FOLFIRI + panitumumab (Table 34), no such studies were found. The networks of evidence for both constant and time-varying HR analyses are shown in Figure 12.

In order to allow estimated relative treatment effects to vary over time, an analysis was done using extracted KM curves. The best-fitting time-varying HR models are determined by the lowest DIC as seen in Table 35. Employing fixed-effects, the best-fitting model (as determined by the lowest DIC) was the 2nd order FP model with p1=0, p2=1. The HRs for competing interventions of interest versus. SOC for the best-fitting model are presented in Figure 13 and was accompanied by HRs at selected time points (Table 36) and by basic parameter estimates shown in Table 37. The results show that pembrolizumab is associated with statistically significantly better OS than CAPOX and SOC from month 12 and better than panitumumab + FOLFOX from month 24.

Analyses were also performed that adjusted for treatment crossover (post-study switch-over of control arm patients to immune checkpoint inhibitor) via the 2-stage method, these are shown in Figure 14, Table 38, Table 39, and Table 40. These results show that pembrolizumab is associated with statistically significantly better OS than CAPOX and SOC from month 8 and better than panitumumab + FOLFOX from month 12.

Network of evidence for indirect treatment comparison

Figure 12 Network of evidence for overall survival



Note: XELOX = CAPOX

Time-varying hazards ratios analysis - no adjustment for treatment crossover

Model fit estimates for fixed-effects network meta-analysis with parametric survival models

Table 35 Model fit estimates for fixed-effects network meta-analysis with parametric survival models for overall survival; ITT population

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=1, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=1, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			

Network meta-analysis results using the best fitting model

Figure 13 Estimated hazard ratios of overall-free survival; treatment hazard ratio over time relative to pembrolizumab (2nd order FP model; p1=0, p2=1); fixed effects analysis, ITT population

Table 36 Time-varying hazard ratios at select follow-up times for competing interventions versus pembrolizumab (2nd order FP model (p1=0 p2=1)); fixed effects analysis, ITT population

Months	HR versus. Pembrolizumab (95% CrI)		
	CAPOX	Panitumumab + FOLFOX	SOC
4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]

Table 37 Basic parameter estimates of 2nd order FP model (p1=0, p2=1); fixed effects analysis, ITT population; pembrolizumab as reference treatment

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Pembrolizumab	Reference		Reference		
Panitumumab + FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAPOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time-varying hazards ratios analysis - treatment crossover adjusted for using the 2-stage method

Model fit estimates for fixed-effects network meta-analysis with parametric survival models

Table 38 Model fit estimates for fixed-effects network meta-analysis with parametric survival models for overall survival; Crossover adjusted (2-stage model)

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
2nd order FP with p1=1, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
2nd order FP with p1=1, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]

Network meta-analysis results using the best fitting model

Figure 14 Estimated hazard ratios of overall-free survival; treatment hazard ratio over time relative to Pembrolizumab (2nd order FP model; p1=0, p2=1); Crossover adjusted (2-stage model)

Table 39 Time-varying hazard ratios at select follow-up times for competing interventions versus Pembrolizumab (2nd order FP model (p1=0 p2=1)); Crossover adjusted (2-stage model)

Months	HR versus. Pembrolizumab (95% CrI)		
	CAPOX	Panitumumab + FOLFOX	SOC
4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]

Table 40 Basic parameter estimates of 2nd order FP model (p1=0, p2=1); Crossover adjusted (2-stage model); Pembrolizumab as reference treatment

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Pembrolizumab	Reference		Reference		
Panitumumab + FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAPOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

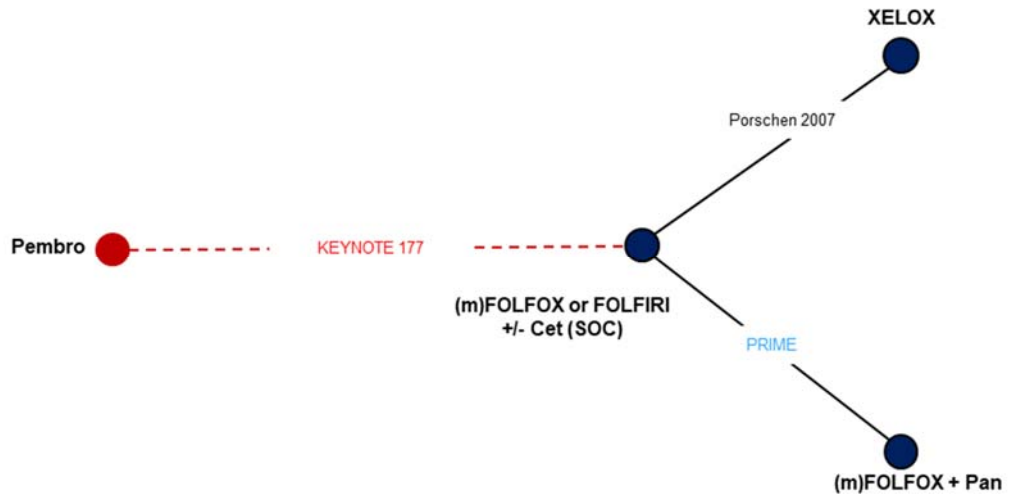
Progression-free survival

PFS was reported in 3 trials eligible for inclusion in the base case analysis; these evaluated 4 interventions (pembrolizumab, CAPOX, mFOLFOX + panitumumab, and SOC). The network of evidence for both constant and time-varying HR analyses are shown in Figure 17.

In order to allow estimated relative treatment effects to vary over time, an analysis was done using extracted KM curves. The best-fitting time-varying HR models are determined by the lowest DIC as seen in Table 41. Employing fixed-effects, the best-fitting model (as determined by the lowest DIC) was the 2nd order FP model with p1=0, p2=1. The HRs for competing interventions of interest versus SOC for the best-fitting model was presented in and are accompanied by HRs at selected time points (Figure 16 and Table 42) and by basic parameter estimates shown in Table 43. These results show that pembrolizumab is associated with statistically significantly better PFS than CAPOX from month 4 and better than SOC and panitumumab + FOLFOX from month 8.

Network of evidence for indirect treatment comparison

Figure 15 Network of evidence for progression-free survival



Note: XELOX = CAPOX

Time-varying hazards ratios analysis

Model fit estimates for fixed-effects network meta-analysis with parametric survival model

Table 41 Model fit estimates for fixed-effects network meta-analysis with parametric survival models for progression-free survival; ITT population

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=1, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			
2nd order FP with p1=1, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)			

Network meta-analysis results using the best fitting model

Figure 16 Estimated hazard ratios of progression-free survival; treatment hazard ratio over time relative to pembrolizumab (2nd order FP model; p1=0, p2=0); ITT population

Table 42 Time-varying hazard ratios at select follow-up times for competing interventions versus pembrolizumab (2nd order FP model (p1=0 p2=0)); progression-free survival; ITT population

Months	HR versus. Pembrolizumab (95% CrI)		
	CAPOX	Panitumumab + FOLFOX	SOC
4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]

Table 43 Basic parameter estimates of 2nd order FP model (p1=0, p2=0); progression-free survival; ITT population; pembrolizumab as reference treatment

	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Pembrolizumab	Reference		Reference		
Panitumumab + FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAPOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Uncertainties in the indirect and mixed treatment comparisons

Given the limited evidence base identified in the SLR and following the comprehensive feasibility assessment for NMA (as detailed in Appendix D), some key assumptions needed to be made in order to build the NMA network and conduct these analyses:

1. Applicability of treatment effects estimates in mCRC patients to MSI-H/dMMR m CRC patients: Of the trials identified in the SLR and included in the NMAs, only the KEYNOTE-177 study was conducted in MSI-H/dMMR patients or reported outcomes for a subset of MSI-H/dMMR patients (described in greater detail in Appendix D). Consequently, it was not possible to conduct NMAs using data purely from MSI-H/dMMR patients.

   It is unknown whether the assumption that treatment effects estimates in mCRC patients are the same as in MSI-H/dMMR mCRC holds since there are currently few clinical studies evaluating efficacy and safety of treatments in MSI-H/dMMR patients and general mCRC patients. Indeed, published meta-analyses to date suggest there may be unfavourable prognosis for the MSI-H/dMMR patients, though the extent of treatment effect modification is unclear for treatments other than pembrolizumab (20, 33). In order to construct a network and make requested comparisons to SOC regimens, the assumption that relative treatment effects do not differ between MSI-H/dMMR mCRC patients and general mCRC patients needed to be made. It should be noted that by using this assumption, the results of the NMAs are likely to be conservative/underestimate the relative effectiveness of pembrolizumab versus comparator regimens (this is discussed in more detail in section B.2.13).

2. Equivalence of FOLFOX to FOLFIRI: Colucci and colleagues and the GERCOR study both compared FOLFOX to FOLFIRI in a trial setting; the regimens were found to be non-differentiable in terms of efficacy and safety (34, 35). Additional large scale

cross-sectional studies and cost-effective analyses also showed the similarity between FOLFOX and FOLIRI in terms of survival, cost and benefits (22, 36, 37).

3. Equivalence of different FOLFOX regimens: FOLFOX4 and mFOLFOX6 are the two most widely used FOLFOX regimens, where mFOLFOX6 is generally preferred by physicians because of its convenience and improved safety profile (38, 39). While no clinical trial has directly compared FOLFOX4 with mFOLFOX6, several studies have concluded the similarity between these two regimens (40, 41).

4. Lack of effect of adding cetuximab to FOLFOX/FOLFIRI: Results for KEYNOTE-177 were not available for just patients receiving FOLFOX/FOLFIRI; these were combined with the patients receiving FOLFOX/FOLFIRI + cetuximab to form the SOC arm. The addition of cetuximab to FOLFIRI or FOLFOX was studied in CRYSTAL and OPUS (42, 43). There was evidence of an advantage in terms of PFS in unselected and KRAS wildtype patients in CRYSTAL trial receiving cetuximab. In OPUS, there was no difference in response rate or PFS between patients receiving cetuximab+FOLFOX4 vs FOLFOX4 alone, but an advantage in KRAS wildtype patients. Therefore, caution should be taken in interpreting results that include cetuximab in the SOC arm, particularly for KRAS wildtype patients.

5. Lack of effect modification in KRAS patients for interventions other than panitumumab: A systematic review found that while KRAS was an effect modifier for patients receiving anti-EGFR treatment, there was no evidence of effect modification on chemotherapy regimens (44). Within KEYNOTE-177, however, KRAS wildtype patients on pembrolizumab had significantly improved PFS vs SOC (HR 0.44, 95% CI 0.29-0.67), while KRAS mutant patients on pembrolizumab showed evidence of worse PFS than those on SOC (HR 1.19, 95% CI 0.68-2.07). This indicates that conclusions concerning KRAS patients should be regarded with caution.

Additionally, sensitivity analyses have been performed to explore the effect of several factors on the results of the NMAs (the details and results of these sensitivity analyses are shown in Appendix M):

- Using only data from the KEYNOTE-177 study from those patients who did not receive bevacizumab: As noted previously, the KEYNOTE-177 study was a global study and included a large proportion of patients who were treated with bevacizumab in the comparator arm. As bevacizumab is not reimbursed for use in this indication on the NHS, sensitivity analyses have been conducted to explore the effect excluding those patients

who were chosen to receive a bevacizumab-containing regimen prior to randomisation. The chemotherapy regimen to be given to any patient if they were randomised to the SOC arm was chosen before randomisation occurred, as part of the study protocol as described in Document B section B.2.3. It should be noted that analyses using this population are less robust than those performed using the whole KEYNOTE-177 population due to the much smaller sample size (i.e. 99 patients compared to 307 patients in the total population).

- Random effects analyses for overall survival: For the analyses of overall survival, three different studies assessed the comparison of SOC versus CAPOX in the comparison network (NO16966, Porschen 2007, and TREE-1, as shown in Figure 12), which raises the possibility that the observed estimates of treatment effect for this particular comparison in the network can vary across studies because of real differences in the treatment effect in each study as well as sampling variability, which is a factor that would be taken into account of in random effects analysis but not in fixed effects analysis.
- Hazard ratios assuming time-constant hazards for both OS and PFS: Both constant and time-varying hazard ratio analyses were performed because some of the Kaplan-Meier curves crossed, which indicates that the proportional hazards assumption may have been violated. Additionally, within-trial violations of the proportional hazards assumption for OS were found in TREE-1 (which assessed CAPOX versus FOLFOX) by conducting the Grambsch and Therneau test based on the weighted residuals and Schoenfeld residuals (shown in Appendix D at the of section D1.1). Visual assessment (curves are non-parallel) and p-values ($p < 0.05$) of the Grambsch and Therneau test for proportional hazards in TREE-1 indicated these interventions violated the proportional hazards assumption. Visual assessment of the Schoenfeld residuals was also assessed, which showed non-flat lines that were not centred on 0, indicating the proportional hazards' assumption for these interventions in TREE-1, were violated. Based on violations of the proportional hazards assumption for these interventions, it may be inferred that violations of the proportional hazards assumption will still hold in the NMA. Similar observations are made for PFS (also shown in Appendix D at the of section D1.1).
- Time-varying HR NMA analyses using the Weibull model instead of the best-fitting fractional polynomial model: Results using the simpler 1st-order Weibull model are also presented in addition to the more complex and better fitting 2nd-order fractional polynomial model. This set of sensitivity analyses were conducted to assess whether the better fitting 2nd-order fractional polynomial models "over-fit" the data. The results from the 1st-order

Weibull models were chosen to be presented instead of the 1st-order Gompertz models as the Weibull models consistently fit better than the Gompertz models in terms of DIC.

- Different adjustments for treatment crossover (post-study switch-over of control arm patients to immune checkpoint inhibitor) for the analyses of overall survival. Network meta-analyses have been conducted using OS results from the KEYNOTE-177 trial that had been adjusted for treatment switching via the RPSFT and IPCW methods as well via the 2-stage method.

Additionally, NMA results presented with SOC as the reference treatment are shown in Appendix M as these results are used in the cost-effectiveness model.

B.2.10 Adverse reactions

A summary of the adverse events (AEs) data from the KEYNOTE-177 study are provided in this section. Full details of the adverse events from this study are provided in Appendix F.

Pembrolizumab versus SOC (ITT population) data from the KEYNOTE-177 study

Summary of adverse events

The median duration of exposure was longer in the pembrolizumab group (11.1 months) compared with the SOC group (5.7 months) (Table 18). A greater proportion of participants in the pembrolizumab group were on therapy after 12 months when compared with the SOC group (47.7% vs 22.4%) (Table 19). The longer duration of exposure in the pembrolizumab group resulted in a longer time frame for collection of AEs relative to the SOC group, which should be considered in interpreting the results of the safety analyses.

Overall, pembrolizumab treatment was generally well-tolerated when compared to SOC treatment. In particular, participants in the pembrolizumab group had a lower frequency of drug-related AEs (79.7% vs 98.6%), Grade 3 to 5 AEs (56.2% vs 77.6%), drug-related Grade 3 to 5 AEs (21.6% vs 65.7%), serious adverse events (SAEs) (40.5% vs 52.4%), and drug-related SAEs (16.3% vs 28.7%) (Table 44). In the pembrolizumab group and the SOC group, 6 participants (3.9%) and 7 participants (4.9%) experienced an AE resulting in death. The pembrolizumab group had a similar proportion of participants who experienced an AE resulting in treatment discontinuation (13.7% vs 11.9%).

When adjusted for exposure, the rates of drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, and drug-related SAEs remained lower in the pembrolizumab group when compared with the SOC group (Table 45).

The results of analysis of between-treatment comparisons in adverse events sorted by the risk difference between the pembrolizumab and SOC arms is summarised in Figure 17.

Table 44 Adverse Event Summary, (ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	153		143	
with one or more adverse events	149	(97.4)	142	(99.3)
with no adverse event	4	(2.6)	1	(0.7)
with drug-related[†] adverse events	122	(79.7)	141	(98.6)
with toxicity grade 3-5 adverse events	86	(56.2)	111	(77.6)
with toxicity grade 3-5 drug-related adverse events	33	(21.6)	94	(65.7)
with serious adverse events	62	(40.5)	75	(52.4)
with serious drug-related adverse events	25	(16.3)	41	(28.7)
who died	6	(3.9)	7	(4.9)
who died due to a drug-related adverse event	0	(0.0)	1	(0.7)
discontinued[‡] drug due to an adverse event	21	(13.7)	17	(11.9)
discontinued[‡] drug due to a drug-related adverse event	15	(9.8)	8	(5.6)
discontinued[‡] drug due to a serious adverse event	12	(7.8)	13	(9.1)
discontinued[‡] drug due to a serious drug-related adverse event	7	(4.6)	5	(3.5)

[†] Determined by the investigator to be related to the drug.
[‡] All study medications withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 19FEB2020.

Table 45 Exposure-Adjusted Adverse Event Summary, (Including Multiple Occurrences of Events), (ASaT Population)

	Event Count and Rate (Events/100 person-months)[†]			
	Pembrolizumab		SOC	
Number of Subjects exposed	153		143	
Total exposure[‡] in person-months	2176.02		1319.39	
Total events (rate)				
adverse events	2,298	(105.6)	3,308	(250.7)
drug-related[§] adverse events	671	(30.8)	2,021	(153.2)
toxicity grade 3-5 adverse events	227	(10.4)	380	(28.8)
toxicity grade 3-5 drug-related adverse events	50	(2.3)	219	(16.6)
serious adverse events	115	(5.3)	148	(11.2)
serious drug-related adverse events	30	(1.4)	55	(4.2)
adverse events leading to death	6	(0.3)	7	(0.5)
drug-related adverse events leading to death	0	(0.0)	1	(0.1)
adverse events resulting in drug discontinuation[*]	21	(1.0)	18	(1.4)

	Event Count and Rate (Events/100 person-months)[†]			
	Pembrolizumab		SOC	
drug-related adverse events resulting in drug discontinuation[*]	15	(0.7)	9	(0.7)
serious adverse events resulting in drug discontinuation[*]	12	(0.6)	13	(1.0)
serious drug-related adverse events resulting in drug discontinuation[*]	7	(0.3)	5	(0.4)

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

[‡] Drug exposure is calculated as min(last dose date+30, Cutoff Date) – first dose date +1, and converted to months.

[§] Determined by the investigator to be related to the drug.

[*] All study medications withdrawn.

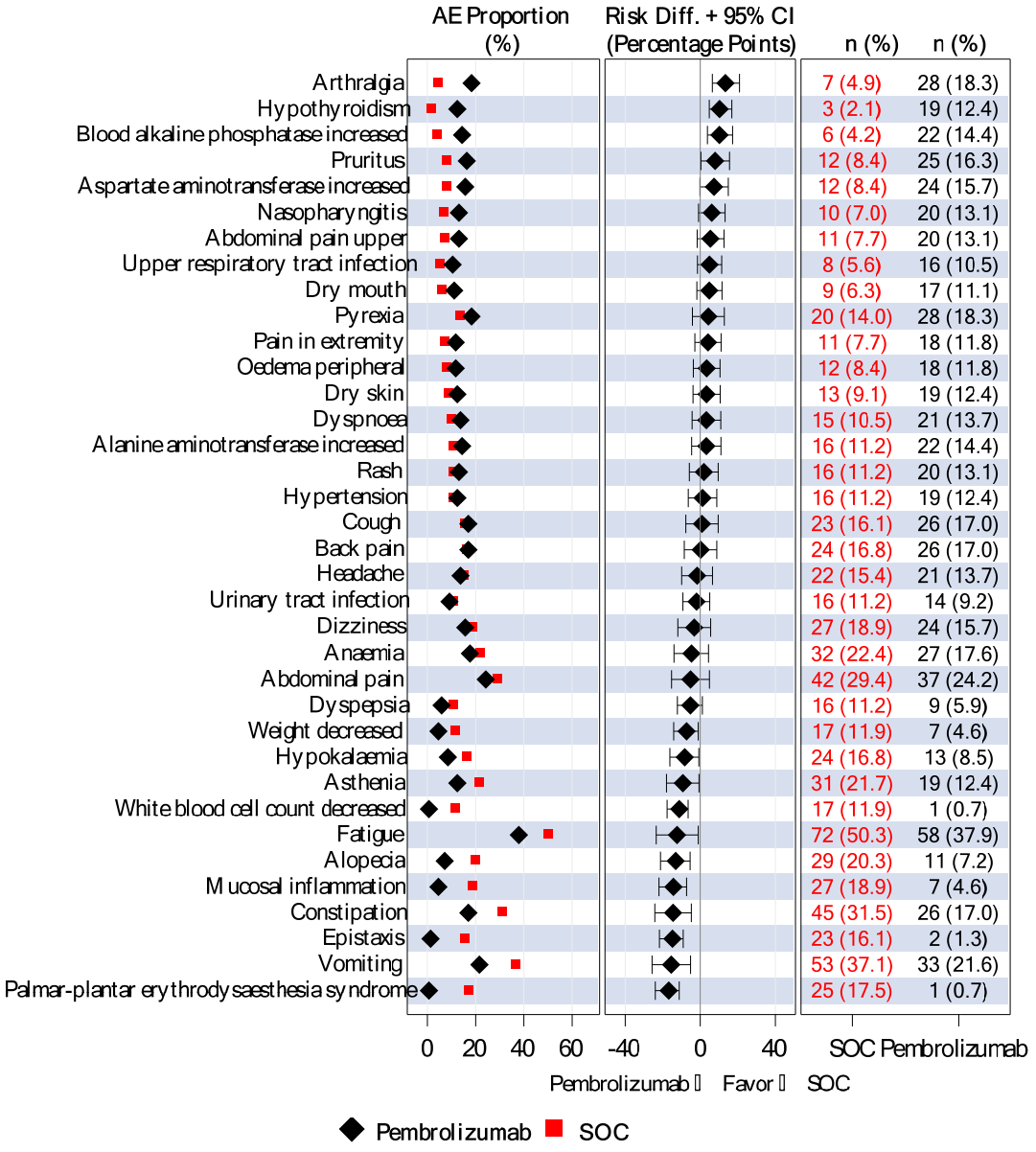
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

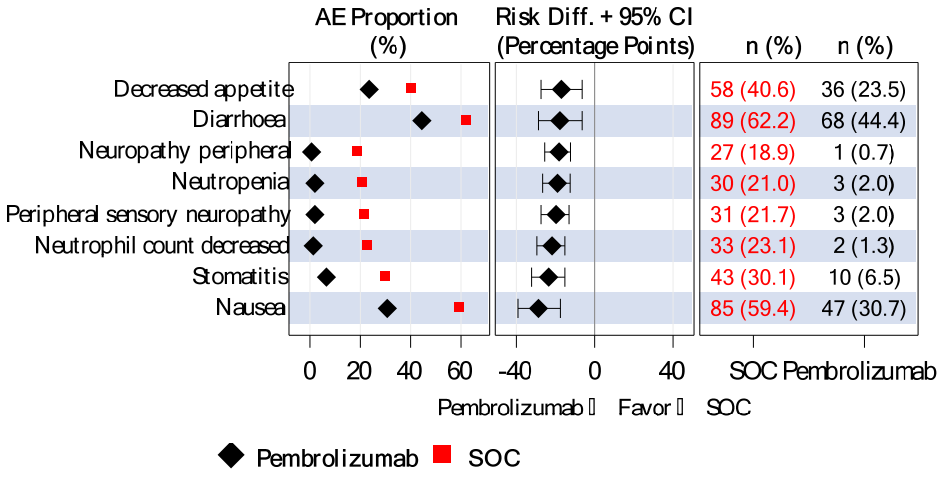
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 19FEB2020.

Figure 17 Between-Treatment Comparisons in Adverse Events, (Incidence >= 10% in One or More Treatment Groups), Sorted by Risk Difference, (ASaT Population), Pembrolizumab (N=153) vs. SOC (N=143)





Summary of adverse events of special interest

The longer duration of exposure in the pembrolizumab group resulted in a longer time frame for an adverse event of special interest (AEOSI) to develop and be collected in the pembrolizumab group relative to the SOC group, which should be considered when interpreting AEOSI safety analyses (Table 18 and Table 19).

The pembrolizumab group had a higher incidence of participants who experienced an AEOSI when compared with the SOC group (30.7% vs 12.6%) (Table 46). Fourteen (9.2%) participants and 3 (2.1%) participants experienced a Grade 3 to 5 AEOSI in the pembrolizumab and SOC groups, respectively. Serious AEOSIs were 10.5% and 0.7% in the pembrolizumab and SOC groups, respectively (Table 46). Furthermore (and detailed in Appendix F):

- The most common AEOSI categories (≥2% incidence) in the pembrolizumab group were hypothyroidism, hyperthyroidism, colitis, pneumonitis, adrenal insufficiency, hepatitis, and infusion reactions. Most of these AEOSI events were Grade 1 or 2 in severity.
- Incidence of hypothyroidism was higher in the pembrolizumab group (19 participants, 12.4%) versus the SOC group (3 participants, 2.1%). In the pembrolizumab group, all hypothyroidism AEOSIs were Grade 1 or 2 in severity. These participants were managed with standard treatments, including hormone replacement therapy, or monitored by symptoms and/or laboratory parameters. In the pembrolizumab group, 5 of the 19 participants with hypothyroidism AEOSIs had resolved events, and none had events resulting in treatment discontinuation or treatment interruption. No participants received concomitant corticosteroids for hypothyroidism events.

- Incidence of colitis AEOSIs was higher in the pembrolizumab group versus the SOC group (10 participants [6.5%] vs 0%). In the pembrolizumab group, half of the participants with colitis had Grade 1 or 2 events, 3 had Grade 3 events, and 2 participants experienced Grade 4 colitis events. Five participants reported colitis events as SAEs (also considered to be drug-related) and 2 discontinued treatment due to a serious colitis AEOSI. All serious colitis AEOSIs were reported as resolved. Four participants experienced colitis AEOSIs resulting in treatment discontinuation, and 4 participants experienced a PT of colitis that resulted in treatment interruption. Out of the 10 participants with colitis events, 8 were treated with systemic corticosteroids. As of the data cut-off date, 9 of 10 participants with colitis AEOSIs had resolved events. One participant with a Grade 1 event had an unresolved event; however, this participant experienced disease progression resulting in the participant's death.
- Of the 65 total AEOSI episodes in the pembrolizumab group, 23.1% were initially treated with high-dose corticosteroids.
- In the pembrolizumab group, 42.6% of the participants with AEOSIs had resolved AEOSIs, and 4.3% of participants had resolving AEOSIs.
- The incidences of participants with AEOSIs leading to the discontinuation of pembrolizumab were generally low (6.5 %), suggesting most AEOSIs were manageable with systemic corticosteroids, supportive care, and dose interruption. There were no fatal AEOSIs in the study.
- No new immune-mediated events causally associated with pembrolizumab were identified in the study.

Table 46 Adverse Event Summary, AEOSI, (ASaT Population)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	153		143	
with one or more adverse events	47	(30.7)	18	(12.6)
with no adverse event	106	(69.3)	125	(87.4)
with drug-related[†] adverse events	42	(27.5)	15	(10.5)
with toxicity grade 3-5 adverse events	14	(9.2)	3	(2.1)
with toxicity grade 3-5 drug-related adverse events	12	(7.8)	3	(2.1)
with serious adverse events	16	(10.5)	1	(0.7)
with serious drug-related adverse events	14	(9.2)	1	(0.7)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued[‡] drug due to an adverse event	10	(6.5)	0	(0.0)
discontinued[‡] drug due to a drug-related adverse event	10	(6.5)	0	(0.0)
discontinued[‡] drug due to a serious adverse event	6	(3.9)	0	(0.0)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
discontinued‡ drug due to a serious drug-related adverse event	6	(3.9)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ All study medications withdrawn.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 19FEB2020.

B.2.11 Ongoing studies

For the KEYNOTE-177 study, longer-term data from the full analysis (FA) is anticipated to become available in [redacted].

There are no ongoing studies of pembrolizumab in addition to the KEYNOTE-177 study that will provide additional evidence in the next 12 months for the indication being appraised.

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. As evident by clinical and safety data presented, pembrolizumab offers a durable and well tolerated treatment option for patients with MSI-H/dMMR mCRC.

Currently, first line-treatment options for MSI-H/dMMR mCRC in routine UK clinical practice is limited to chemotherapy regimens (FOLFOX, FOLFIRI, and CAPOX) which are associated with significantly poorer efficacy in terms of overall and progression-free survival compared to treatment with pembrolizumab (as shown in section B.2.9 and Appendix M) along with significantly worse adverse events rates compared to pembrolizumab (as shown in section B.2.10 and Appendix F).

Patients who have RAS wild-type MSI-H/dMMR mCRC may be treated with panitumumab in combination with chemotherapy (FOLFOX or FOLFIRI) and patients who have EGFR expressing and RAS wild-type MSI-H/dMMR mCRC may be treated with cetuximab in combination with chemotherapy (FOLFOX or FOLFIRI). The results from the NMAs (as shown in section B.2.9) show that treatment with pembrolizumab also results in significantly superior survival outcomes compared to panitumumab in combination with chemotherapy.

MSI-H/dMMR mCRC is a highly symptomatic disease that can exert a considerably negative effect on patients' health-related quality of life, it is therefore notable that patients treated with pembrolizumab exhibited improving health-related quality of life scores over 45 weeks of follow-up.

These facts therefore show that pembrolizumab offers a significant step-change in benefit for patients with MSI-H/dMMR mCRC in the UK.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Clinical effectiveness

The KEYNOTE-177 study is a phase III randomised controlled trial that is the first global study to demonstrate significant and meaningful benefit of pembrolizumab in participants with MSI-H/dMMR mCRC over globally accepted standard of care (SOC) chemotherapies including mFOLFOX6 or FOLFIRI or respective combinations with bevacizumab or cetuximab.

The efficacy results of the KEYNOTE-177 study at IA2 demonstrated pembrolizumab provides statistically significant and clinically meaningful improvement in PFS in participants with MSI-H/dMMR CRC relative to SOC. The HR for PFS was 0.60 (p=0.0002) in favour of pembrolizumab, representing a 40% reduction in the risk of disease progression or death. Median PFS in the pembrolizumab group was double the median PFS in the SOC group (16.5 months vs 8.2 months). The PFS rate for pembrolizumab remained higher than the PFS rate for SOC at 12 and 24 months. The Kaplan-Meier curve for PFS suggests a durable clinical benefit. With regards to OS, the success criterion for statistical significance was not met when compared to the p-value boundary of 0.0053; however, a trend toward improved survival for pembrolizumab was observed.

Furthermore, the results of the NMAs showed that pembrolizumab is associated with statistically significantly better PFS than CAPOX from month 4 and better PFS than panitumumab + FOLFOX from month 8. The NMAs showed that pembrolizumab is associated with statistically significantly better OS than CAPOX [redacted] and better OS than panitumumab + FOLFOX [redacted], once the analysis of OS was adjusted for subsequent anti-PD-1/PD-L1 therapy use in the SOC group of the KETNOTE-177 trial using the simplified 2-stage model, the results show that pembrolizumab is associated with statistically significantly better OS than CAPOX [redacted] and better than panitumumab + FOLFOX [redacted].

While use of panitumumab in combination with chemotherapy in this indication is restricted in UK clinical practice to patients with RAS wild-type disease, and the KEYNOTE-177 study is not restricted to RAS-wild type patients, the NMA results comparing pembrolizumab to panitumumab in combination with chemotherapy are very likely to be a conservative estimate of pembrolizumab's effectiveness versus that of panitumumab in combination with chemotherapy, this is because:

1. The mechanism of action of pembrolizumab (blocking the interaction of PD-1 and its ligands PD-L1 and PD-L2) acts on a cellular pathway that is independent of the RAS signalling pathway, and so the action and efficacy of pembrolizumab would not be affected if the patient was either RAS-wildtype or RAS-mutant. There is no evidence that RAS wildtype/mutant status affect the efficacy of pembrolizumab and consequently, in all the indications for which pembrolizumab has regulatory approval (described in section B.1.2 Table 2), in no licenced indication is pembrolizumab restricted to patients who either RAS-wildtype or RAS-mutant.

2. The comparison between pembrolizumab and panitumumab in combination with chemotherapy in the NMA is driven by the KEYNOTE-177 study and the PRIME study. The PRIME study was restricted to patients who were RAS-wildtype, and not restricted to patients who were MSI-H/dMMR (the relevance/effect of this particular factor is described in more detail later on in this section), and so the results of that are from a population in which panitumumab has optimal efficacy. Therefore, the indirect comparison of pembrolizumab versus panitumumab in combination with chemotherapy driven by the KEYNOTE-177 and PRIME studies represents the best-case scenario for panitumumab (with regard to the RAS status of patients) and consequently a representative/conservative scenario from the perspective of pembrolizumab in the comparison.

3. The SOC arm of the KEYNOTE-177 consists not only of patients treated with FOLFOX or FOLFIRI, but also of patients treated with cetuximab or bevacizumab in combination with these. The addition of either cetuximab or bevacizumab to standard chemotherapies (i.e. FOLFOX or FOLFIRI) is very likely to be associated with superior clinical efficacy. Therefore, the pembrolizumab versus SOC results from the KEYNOTE-177 would represent an underestimate of the relative efficacy of pembrolizumab compared to a pembrolizumab versus FOLFOX/FOLFIRI comparison. Consequently, the use of the pembrolizumab versus SOC data from the KEYNOTE-177 study with the panitumumab + FOLFOX/FOLFIRI versus

FOLFOX/FOLFIRI data from the PRIME study represents a worse-case scenario for pembrolizumab and the results of this indirect comparison would underestimate the relative effectiveness of pembrolizumab versus panitumumab in combination with chemotherapy.

It was not possible to compare, either directly or indirectly, pembrolizumab to cetuximab in combination with chemotherapy (FOLFOX or FOLFIRI) in the EGFR-expressing and RAS-wildtype population due to the small number of patients who were treated with cetuximab in the KEYNOTE-177 study. However, as clinical expert advice has indicated that cetuximab in combination with chemotherapy in the EGFR-expressing and RAS-wildtype population is no more efficacious than panitumumab in combination with chemotherapy in the RAS-wildtype population in this indication, the NMA results for the comparison of pembrolizumab versus panitumumab in combination with chemotherapy can be considered a reasonable proxy for the comparison of pembrolizumab versus cetuximab in combination with chemotherapy.

It was not possible to compare pembrolizumab, either directly or indirectly, to CAPOX or panitumumab in combination with chemotherapy specifically in the MSI-H/dMMR population due to the lack of published clinical trials for these treatment regimens in this specific population. However, as the efficacy or these regimens relative to FOLFOX/FOLFIRI are unlikely to be superior in the MSI-H/dMMR mCRC population than in the overall mCRC population, the results of the NMAs presented in section B.2.9 which are driven by studies of these comparator regimens in the overall mCRC population plus the study of pembrolizumab in the MSI-H/dMMR population is very unlikely to underestimate the relative efficacy of these comparator regimens versus pembrolizumab in the MSI-H/dMMR population and consequently the NMA results are unlikely to be overestimates of the relative efficacy of pembrolizumab.

Safety profile

The results of the KEYNOTE-177 study show that pembrolizumab had a favourable adverse event profile that was generally well-tolerated compared to SOC, with a low rate of treatment discontinuation, and had a safety profile that was generally consistent with the established safety profile of pembrolizumab.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See section 3.1 of the user guide for full details of the information required in appendix G.

A systematic literature review was undertaken in April 2020 to identify relevant cost-effectiveness studies from the published literature. The target population in this submission is patients with untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. However, the scope of the review was also broadened to patients with untreated metastatic colorectal cancer, in order to identify all relevant data that could inform the development and population of the model. Full details of the SLR strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

No cost-effectiveness study meeting the relevant inclusion criteria to this submission was identified, indicating that a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with the relevant comparators. However, other publications in the broader colorectal cancer indication were identified (22). The approach to modelling within this publication was used to inform our approach.

Patient population

The patient population included in the economic evaluation consisted of patients with stage IV MSI-H/dMMR CRC who had received no prior systemic chemotherapy treatment. This is in line with the proposed licensed indication and with the final NICE scope (45).

The main body of clinical evidence for pembrolizumab compared to SoC was derived from the KEYNOTE-177 (KN177) study. However, as stated in Table 9, within the SoC arm is a group of patients who received a bevacizumab containing treatment regimen which is currently not reimbursed in the UK. As a result, the model was designed to perform analyses based on efficacy data for:

- all patients included in KN177 study, this is designated as the “all patients” population within the model; or

- the group of patients within KN177 who received only treatment regimens not containing bevacizumab (control arm) or would have received a treatment regimen not containing bevacizumab had they been randomised to the control arm (intervention arm). This is designated as the “all patients excluding bevacizumab population” within the model.

The patient characteristics for both populations based on KN177 trial are presented in Table 47, below.

Table 47: Baseline characteristics of the population in the cost-effectiveness model

	All patients N=307	All patients excl. bevacizumab N=99	Source
Average patient age (years)	61.2	63.2	KN177
Mean body surface area (m^2)	1.81	1.78	
Mean weight (kg)	71.14	68.67	
Proportion female	50.2%	50.5%	
Proportion ECOG 1	48.2%	56.6%	
Proportion Mutation Status			
BRAF/KRAS/NRAS all wild type	22.5%	35.4%	
KRAS/NRAS mutant and BRAF V600E not mutant	23.1%	11.1%	
BRAF V600E mutant and KRAS/NRAS not mutant	24.1%	22.2%	
BRAF V600E and KRAS/NRAS mutant	1.0%	2.0%	
Other	29.3%	29.3%	

The choice of therapy in the SoC arm in KN177 trial was left to the investigator. The population within the expected indication for pembrolizumab (decision problem population) encompasses the entire ITT population. Investigators provided patients with the therapy they saw as most effective for that patient considering their ability to tolerate therapy. There is published evidence demonstrating improvements in time to progression and survival with the addition of bevacizumab to FOLFOX and FOLFIRI (46, 47). This means where access is available to all treatments that either those who are frailer or considered more suitable due to mutation status

for cetuximab instead are more likely to receive therapy without bevacizumab; this can be seen in the differences in outcomes for SoC in the population excluding bevacizumab along with some differences in baseline characteristics (Appendix L).

The base case for this submission is the ITT "all patients" population, with a subgroup analysis presenting the all patients excluding bevacizumab population. This subgroup analysis has several limitations that should be considered when interpreting the results:

- Sample size is considerably reduced – this increases uncertainty and also precludes conduct of some of the preferred analyses (e.g. use of the 2-stage method to correct for crossover) as can be seen in Table 125.
- Imbalances in baseline characteristics between the pembrolizumab and SoC arm in the "all patients excluding bevacizumab" population as seen in Table 125.
- Patients in the pembrolizumab arm of the All patients-bevacizumab population have a substantially worse ECOG status and more left-sided cancers than patients in the SoC arm (Table 125)

Model structure

In order to accommodate the appropriate treatments for the disease pathway as well as incorporate the trial data to minimise uncertainty, a de-novo five health state transition model was built. We noted that previous oncology evaluations have employed the use of partition survival models, as such, extensive validation was done using an alternative partition survival model, the results of which are presented in Appendix J.

Due to the nature of disease progression in Stage IV MSI-H/dMMR mCRC and routine treatment, the economic model had to capture all possible health states. Therefore, in consultation with medical advisors, health economists as well as aligning with the approach used in TA439, a cost effectiveness model comprising of two distinct structures was developed to estimate health outcomes and costs for pembrolizumab and comparator regimens in the target patient population. The model structures included were as follows:

- A three-health state partitioned survival model
- A five-health state semi-Markov transition model

Partitioned Survival Model

There are three mutually exclusive health states in the model:

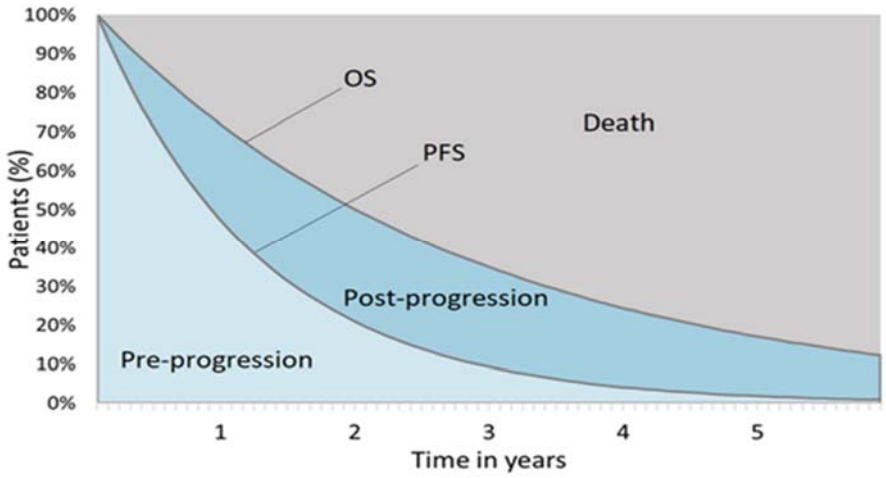
- Progression free, which is the starting health state, with patients staying in this state until disease progression or death
- Progressed disease, which encompasses patients alive after progression and before death
- Death, which is an absorbing health state

In the partitioned survival model, the proportion of patients within each health state at each point in time is based directly on each treatment's progression free survival (PFS) and overall survival (OS) estimates. In this model, the following formulae are used:

- Proportion of patients in the "progression free" health state = PFS
- Proportion of patients in the "progressed disease" health state = OS-PFS
- Proportion of patients in the "death" health state = 1-OS

An illustration of the model diagram is presented in Figure 18.

Figure 18: Three-health state partitioned survival model diagram

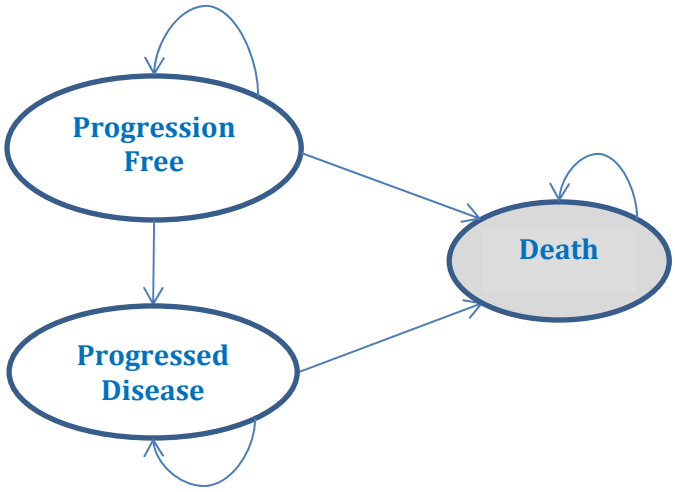


In the cost-effectiveness model, progression is defined by the primary censoring rule in KN177 trial, i.e. assessment by independent radiologist's review per the Response Evaluation Criteria in Solid Tumors [RECIST] V1.1.

Patients enter the model in the progression free health state. At the end of each weekly cycle, patients may remain in the state, transition to the progressed disease health state or to death; patients who are in the progressed disease state may remain in that state or die at the end of each cycle. Patients cannot transition to an improved health state (i.e. from progressed disease to progression free).

The transition diagram of the partition survival model is presented in Figure 19. Detailed explanation of the partitioned survival modelling technique can be found in Appendix N.

Figure 19: Transition Diagram for the Cohort Simulation



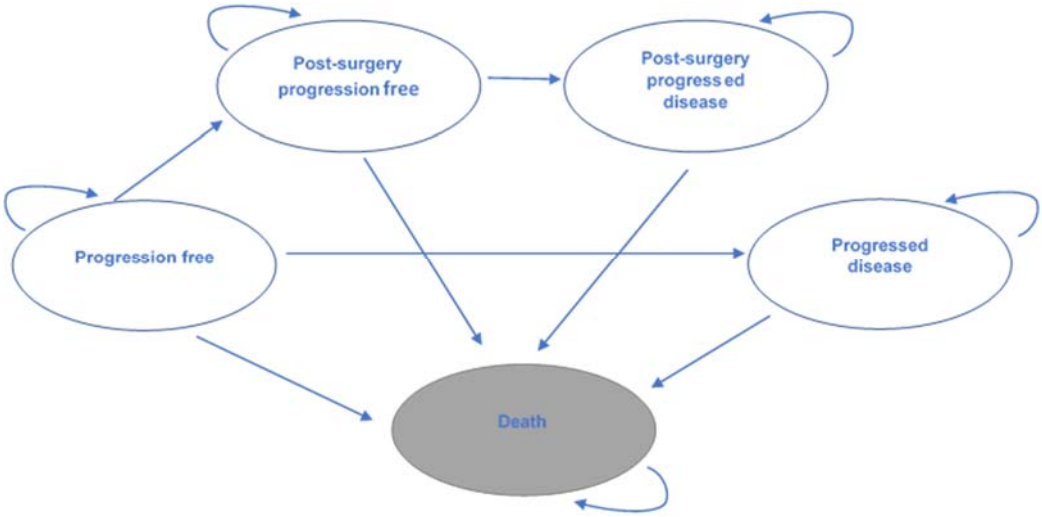
State Transition Model

In the state transition model, all patients enter the model in the "progression free" health state. Starting from that health state, the following transitions are allowed:

- Patients in the "progression free" health state can remain in that health state or move to the "progressed disease", "post-surgery progression free" or "death" health state
- Patients in the "progressed disease" health state can remain in that health state or move to the "death" health state
- Patients in the "post-surgery progression free" health state can remain in that health state or move to the "post-surgery progressed disease" or "death" health state
- Patients in the "post-surgery progressed disease" health state can remain in that health state or move to the "death" health state
- Patients in the "death" health state remain in that health state (absorbing health state)

The transition diagram for this simulation model is presented in Figure 20.

Figure 20: Five-health state semi-Markov state transition model diagram



In the state transition model, the transitions between the "post-surgery progression free" health state, the "post-surgery progressed disease" health state and the "death" health state are not modelled explicitly. Instead, for patients undergoing curative intent surgery, a partitioned survival model approach was used. In other words, patients who undergo curative intent surgery are distributed over the "post-surgery progression free", "post-surgery progressed disease" and "death" health states based on post-surgery PFS and OS data.

For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative costs and cumulative QALYs over the modelled time horizon. Costs and QALYs are discounted with an annual rate of 3.5% in line with NICE reference case (48). The economic perspective is that of the UK National Health Service (NHS) and Personal Social Services (PSS).

Base Case Model Selection

The following have been taken into account for the selection of the most appropriate model structure:

1. **Extent of KN177 crossover:** Of the 154 patients randomised to the SoC arm of KN177, 113 patients progressed and of these 91 (80.5% of those who progressed) crossed over to pembrolizumab or received another anti-PD1/PD-L1 therapy. Due to the large extent of crossover, the results of all crossover-adjustment analyses that have been performed (RPSFTM analyses, two-stage analyses and IPCW analyses)

are associated with substantial uncertainty. Unlike the partitioned survival model which relies extensively on the use of crossover-adjusted OS data, the state transition model largely relies on data collected prior to crossover (time to progression [TTP] and progression-free survival [PFS] data).

2. **KN177 OS data maturity:** At the end of follow up in KN177, OS in the "all patients" population was 60.6% for pembrolizumab and 49.2% for SoC. As a result, OS extrapolations for both pembrolizumab and SoC vary widely. As OS is the main driver of cost-effectiveness in the partitioned survival model, the results of this model are associated with a degree of uncertainty. The TTP data from KN177 – the main driver of cost effectiveness in the state transition model are substantially more mature. Due to this, the results of the state transition model are likely to be associated with less uncertainty.

3. **Model structure in previous NICE submission:** The most recent NICE technology appraisal in first-line Stage IV CRC (TA439), made use of a seven-health state semi-Markov state transition model. For reference, the only structural difference between the TA439 model and our state transition model is that we chose not to explicitly model 3rd-line best supportive care (BSC) in order to use KN177 data only for patients not undergoing surgery. Also, in TA439, 2nd-line PFS and 3rd-line OS were based on data from literature sources rather than trial data for the treatments of interest. Given the paucity of data for the specific patient population and the availability of said data from KN177, the choice of using trial data over literature sources within our analysis was considered a more robust option.

Based on the considerations above, the state transition model was concluded to be the most appropriate choice to use in this evaluation.

Table 48: Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**NICE [TA439]**	**Chosen values**	**Justification**
Time horizon	30	40	Lifetime horizon for the defined population (NICE reference case)
Treatment waning effect?	None	None	Any treatment waning effect is reflected in the extrapolation of OS
Source of utilities	Literature sources (49, 50)	Utility values collected in KN177 trial using the EQ-5D-3L questionnaire	Consistent with NICE reference case
Source of costs	NICE TA176, eMIT 2015, BNF 2015, NHS reference costs schedule 2013-2014	NICE TA439, NHS reference costs schedule 2018-19, eMIT 2018, PSSRU and published literature, BNF	Resource use was based on previous HTAs in colorectal cancer (TA439 and published literature). Unit costs were taken from recognised national databases
Key: KN177, KEYNOTE-177; EQ-5D, NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Service; PSSRU, Personal Social Services Research Unit.			

Intervention technology and comparators

The intervention (i.e. pembrolizumab) was modelled as per the anticipated licensed dosing regimen. As a monotherapy administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]. It is also expected that the monotherapy licence will include an option to administer pembrolizumab at a fixed dose of 400mg over 30 minutes every 6 weeks [Q6W] which is associated with improved symptom control, improves patient quality of life due to reduced hospital visits, increases capacity within hospital due to reduced patient visits to hospital for infusions.

In KN177, patients were to continue pembrolizumab until progressive disease, unacceptable adverse events or intercurrent illness preventing further administration of treatment, the subject has a confirmed positive serum pregnancy test or a maximum of 35 cycles of uninterrupted treatment with pembrolizumab.

In line with the comparators assessed in KN177, the primary comparator in the model is SoC. Patient numbers in KN177 did not allow for analyses for pembrolizumab vs. the individual treatment regimens comprising SoC.

In this arm, physician's choice of six possible chemotherapy regimens is given:

Table 49: Distribution of patients across SoC arm in KN177

Treatment	All patients (n = 154)	All patients excluding bevacizumab (n = 47)
mFOLFOX6	14 (9.1%)	14 (29.8%)
FOLFIRI	17 (11.0%)	17 (36.2%)
mFOLFOX6 + cetuximab	5 (3.2%)	5 (10.6%)
FOLFIRI + cetuximab	11 (7.1%)	11 (23.4%)
mFOLFOX6 + bevacizumab	67 (43.5%)	0%
FOLFIRI + bevacizumab	40 (26.0%)	0%

This was deemed to be a pragmatic approach that would allow comparisons of pembrolizumab with the most commonly used chemotherapy options in the UK. Clinical experts have suggested that these treatments are likely to be the same as those used in clinical practice in England (except for bevacizumab which is not reimbursed in the UK).

The distributions of patients across SoC arm in KN177 for the "all patients" and "all patients excluding bevacizumab" populations are given in Table 49. As bevacizumab is currently not recommended for CRC in the UK, in the base case analysis, the bevacizumab-containing regimens are costed as the corresponding cetuximab-containing regimens. However, the model offers the option to evaluate the impact of costing the bevacizumab-containing regimens as such in a scenario analysis.

The following comparators were also assessed as per the NICE final scope with efficacy estimates derived from a network meta-analysis and indirect treatment comparison (45). Further details are available in Section B 2.8 and 2.9:

- CAPOX (oxaliplatin + capecitabine)
- mFOLFOX6 + panitumumab

The following treatments that were included in the NICE final scope for the appraisal of pembrolizumab in Stage IV MSI-H/dMMR CRC but excluded in the model are:

- Tegafur + uracil (in combination with folinic acid) as this is no longer available in the UK (22).

- Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable). Clinical experts confirmed in UK clinical practice this is reserved for patient who get heart toxicity with the fluorouracil due to dihydropyrimidine dehydrogenase (DPD) deficiency. The dose of folinic acid is therefore reduced to mitigate the toxic effect. As such, raltitrexed is very rarely used.

- Capecitabine as this is only used in elderly and frail patients who have an ECOG status of > 1. The subject inclusion criteria for KN177 states they must have an ECOG performance status of 0 or 1.

- FOLFIRI + panitumumab, the final scope referred to FOLFOX or FOLFIRI in combination with panitumumab. The clinical SLR aimed to identify studies which would allow a comparison versus FOLFIRI + panitumumab, however, no such study was found. According to TA439 and clinical expert opinion, the clinical efficacy between FOLFOX and FOLFIRI is considered equivalent the FOLFOX + panitumumab combination was assessed. As well, whilst marginal the FOLFIRI component of the regimen is the more costly of the two chemotherapy options in combination with panitumumab (£39.85 for FOLFIRI versus £35.51 versus FOLFOX), concluding the choice of comparator used is the more conservative option.

B.3.3 Clinical parameters and variables

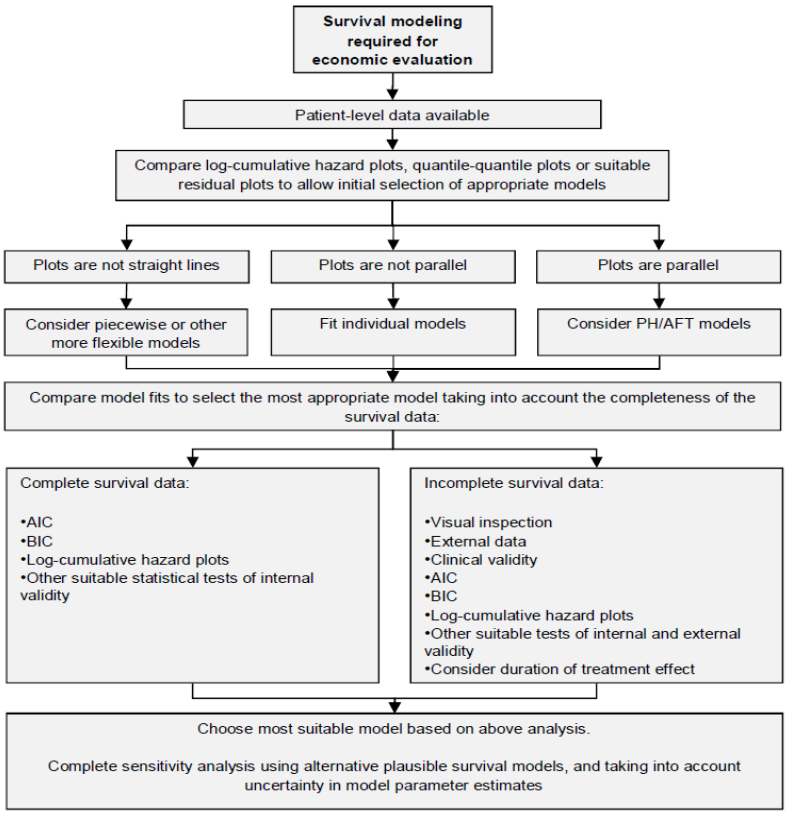
Method of Modelling Effectiveness

The clinical effectiveness parameters for pembrolizumab in the cost-effectiveness model were estimated from the KN177 patient-level data on OS, PFS and adverse event rates. Clinical effectiveness estimates for non-trial comparators were applied using the hazard ratios from the network meta-analysis (please see section B.2.9).

The follow-up period in KN177 was shorter than the time horizon of the economic model. Therefore, extrapolation of the OS and PFS was required.

Parametric models were fitted to the KN177 Kaplan–Meier (KM) data. The survival curve fitting was carried out in line with the NICE Decision Support Unit (DSU) guidelines outlined in Technical Support Document 14 (51, 52)(52). In summary, the steps that were followed are presented in Figure 21 below.

Figure 21: Survival Model Selection Process Algorithm (adapted from TSD 14)



AFT: Accelerated failure time; AIC: Akaike information criterion; BIC: Bayesian information criterion; PH: Proportional hazards Source

State Transition Model

Transition probabilities were estimated based on survival analysis of individual patient-level data from KN177.

Overview of State transition Model Health States

Transition probabilities between the PF and the PD health state were obtained from the KN177 TTP data excluding patients who underwent surgery with curative intent (TTPXS), as these patients were modelled as a separate health state.

For transition probabilities between the PF health state and the post-surgery progression free health state, these were informed by the rates of surgery with curative intent observed in KN177. Based on assumptions made in TA439, all surgeries were assumed to take place 12 weeks after the start of treatment. The impact of this simplification on the results will be minimal due to the proportions of patients who undergo surgery being small and similar between both treatment ams.

Transition probabilities between the PF health state and the 'death' health state were informed by the difference between KN177 PFS data excluding patients who underwent surgery with curative intent and KN177 TTP data excluding patients who underwent surgery with curative intent.

Transition probabilities between the PD health state and the death health state were informed by KN177 post-progression survival data excluding patients who underwent surgery with curative intent. A Visual Basic® for Applications (VBA) macro was used to ensure that patients in the PD health state are assigned the correct probabilities for transition to the 'death' health state irrespective of in which cycle they enter the PD health state (that is, patients who enter the PD health state in a cycle greater than 1 should still be assigned the transition probability based on the post-progression survival excluding surgery data at t=0 weeks and t=1 week at entry). The VBA macro implements the usual calculations for tunnel states but is computationally more efficient than programming these into front-end Excel®.

No transition probabilities were calculated for the transitions between the 'post-surgery progression free' health state, the 'post-surgery progressed disease' health state and the 'death' health state. Instead, for patients undergoing surgery with curative intent, a partitioned survival model approach was used, meaning that patients who underwent surgery were distributed over the 'post-surgery progression free', 'post-surgery progressed disease' and 'death' health states based on post-surgery PFS and OS data directly. The post-surgery PFS and OS data were obtained from the literature as the number of patients who underwent surgery with curative intent within KN177 were small and follow-up in the trial was relatively short (53, 54). This was assumed to be the same for pembrolizumab and SoC.

Modelling Time to Progression excluding Patients who underwent surgery (TTPXS)

For parametric survival modelling, due to TTPXS data from KN177 not being fully mature, parametric survival models (PSMs) had to be fitted to the data to extrapolate TTPXS over time.

Statistical testing for proportionality of hazards and visual assessment of the Kaplan–Meier data indicated that TTPXS hazards for pembrolizumab and SoC were not proportional, therefore, only independent survival models were fit to the pembrolizumab and SoC KN177 TTPXS data (Figure 22 and Figure 23).

Figure 22: Cumulative hazards plots for TTP (All Patients)

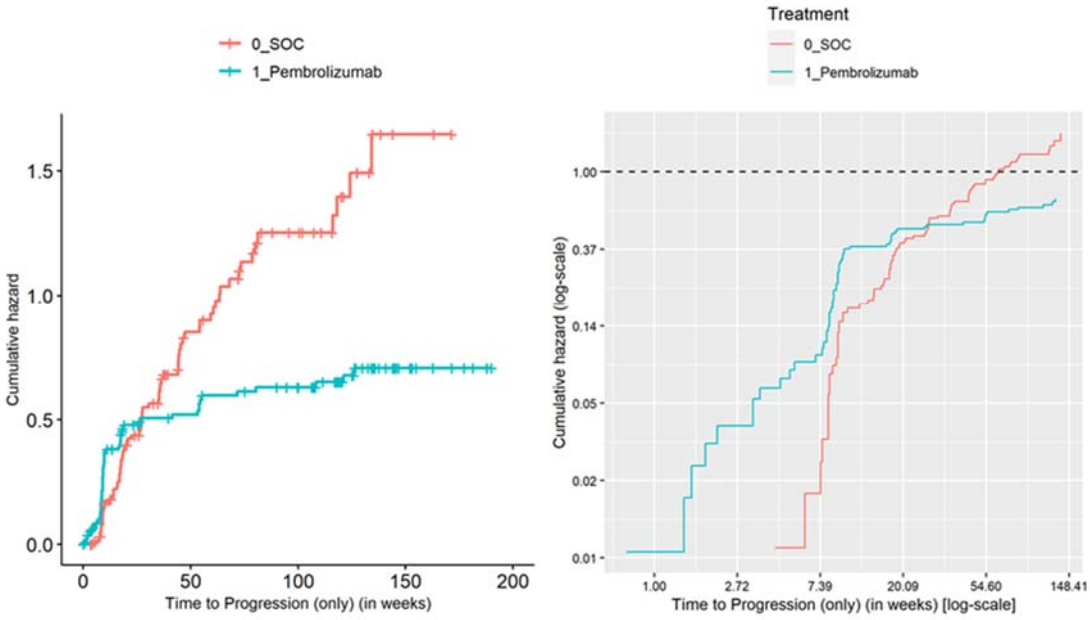
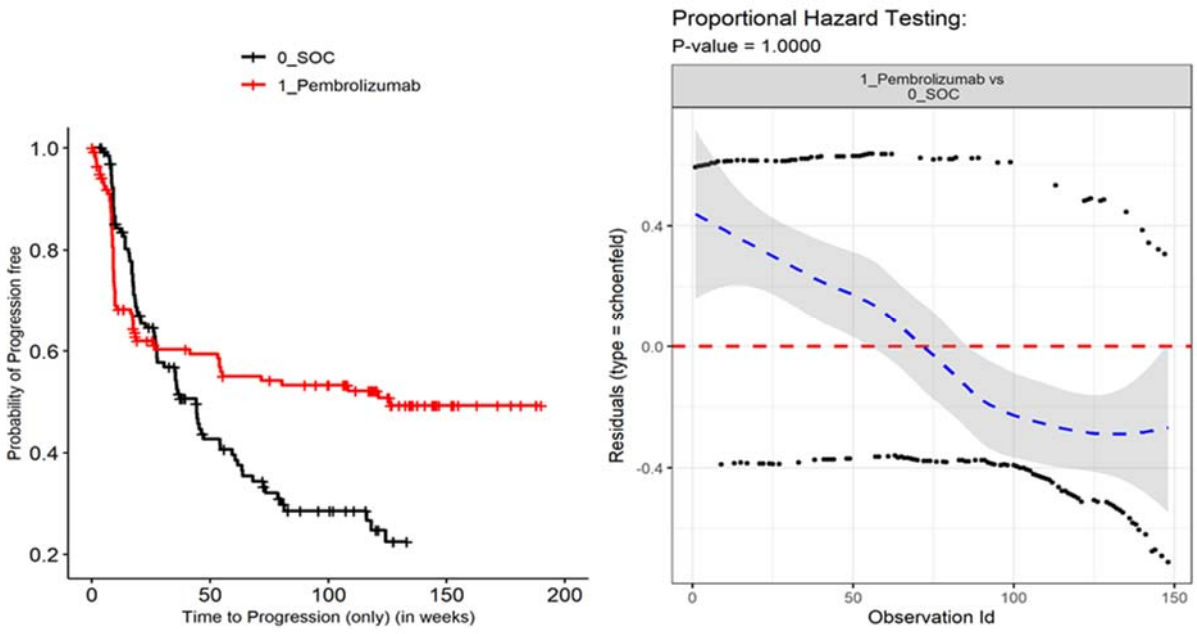


Figure 23: Pembrolizumab versus SoC TTPXS Kaplan–Meier data and Schoenfeld residual plot



The cumulative hazard plot demonstrates the change in hazard is not constant over time. This suggests that a piecewise model is more appropriate than a single parametric curves. Both one-piece and two-piece models were fitted to the data. Two-piece models were fit from two distinct cut-off points: 10 weeks and 20 weeks. These cut-off points were chosen because

after 10 weeks and 20 weeks most patients would have had their first and second on-study imaging assessment, respectively (performed every 9 weeks). To assess the most appropriate choice, visual inspection and clinical plausibility were utilised.

Figure 24: One Piece Parametric Fit

Figure 25: Two-piece (10 weeks) Parametric Fit

Figure 26: Two-piece (20 weeks) Parametric Fit

Referring to the figures above (Figure 24, Figure 25 and Figure 26), the two-piece at 20 weeks more closely followed the TTPXS Kaplan Meier data.

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The statistical goodness of fit for each parametric distribution are presented in Table 50, showing good fit across both arms with Exponential, Gompertz and Log-logistic.

Table 50: Summary of goodness-of-fit qualities of TTPXS survival models at 20-week cut-off point – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	191.79	194.10	1	484.08	486.49	2
Weibull	193.65	198.28	5	484.50	489.31	5
Gompertz	192.96	197.59	3	482.51	487.32	3
Log-logistic	193.40	198.03	4	482.40	487.22	1
Log-normal	192.62	197.25	2	483.55	488.37	4
Generalised Gamma	194.10	201.05	6	484.88	492.10	6

As the modelled period is much longer than the data, the external validity was considered most important for parametric curve selection. Furthermore, as shown in Figure 26 all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period to yield substantially different long-term extrapolations. Hence the base-case TTPXS curve selection was based primarily on the clinical plausibility of long-term predictions. Input from clinical experts suggested the exponential curve was the most clinically plausible estimation.

For comparators not included in the SoC arm (CAPOX and FOLFOX + panitumumab), there was no reported TTP data from the literature searches. As such, TTPXS for CAPOX and FOLFOX + panitumumab are based on the PFS hazard ratios of these versus SoC resulting from the NMA.

Modelling Progression free survival excluding patients who undergo surgery (PFSXS)

As was the case in TTPXS, the PFSXS data from KN177 were not fully mature. Statistical testing for proportionality of hazards and visual assessment of the Kaplan-Meier data indicated that PFSXS hazards for pembrolizumab and SoC were not proportional, therefore only

independent survival models were fit to the pembrolizumab and SoC KN177 PFSXS data (Figure 27 and Figure 28).

Figure 27: Cumulative hazards plots for PFSXS (All Patients)

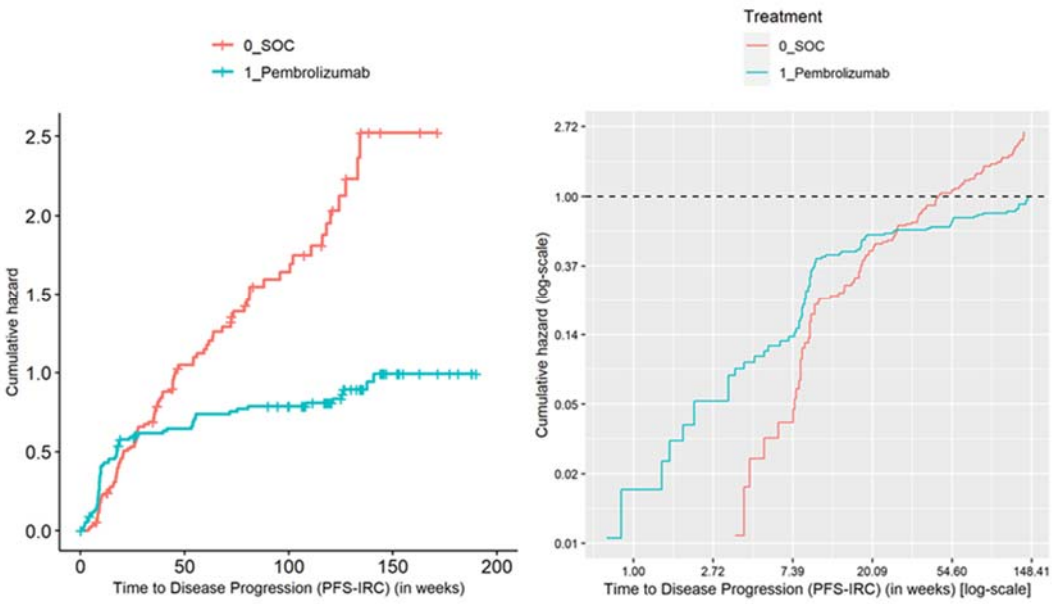
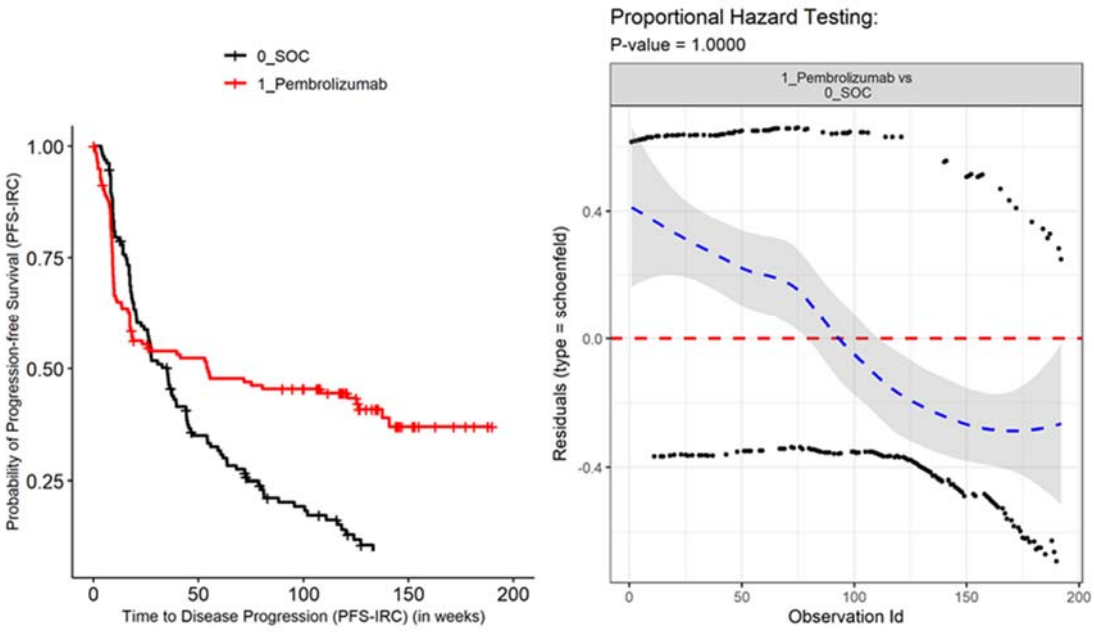


Figure 28: Pembrolizumab versus SoC PFSXS Kaplan–Meier data and Schoenfeld residual plot



As was the case for TTPXS, one- and two-piece were used to fit the PSM and visual inspection was utilised to estimate the closest fit to the Kaplan Meier data.

Similar to TTPXS, the two-piece at 20 weeks showed the closest fit of all six parametric extrapolations to the Kaplan Meier (Figure 29, Figure 30 and Figure 31).

Figure 29: One-piece Parametric Fit

Figure 30: Two-piece (10 weeks) Parametric Fit

Figure 31: Two-piece (20 weeks) Parametric Fit

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The statistical goodness of fit for each parametric distribution are presented in Table 51. Across both arms, the best fit was shown to be the Exponential extrapolation.

Table 51: Summary of goodness-of-fit qualities of PFSXS survival models at 20-week cut-off point – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	276.75	279.07	1	655.25	657.66	1
Weibull	278.69	283.32	5	655.51	660.32	2
Gompertz	278.64	283.27	4	656.31	661.12	3
Log-logistic	278.61	283.25	3	659.38	664.20	5
Log-normal	278.40	283.03	2	665.91	670.72	6
Generalised Gamma	280.38	287.33	6	657.44	664.66	4

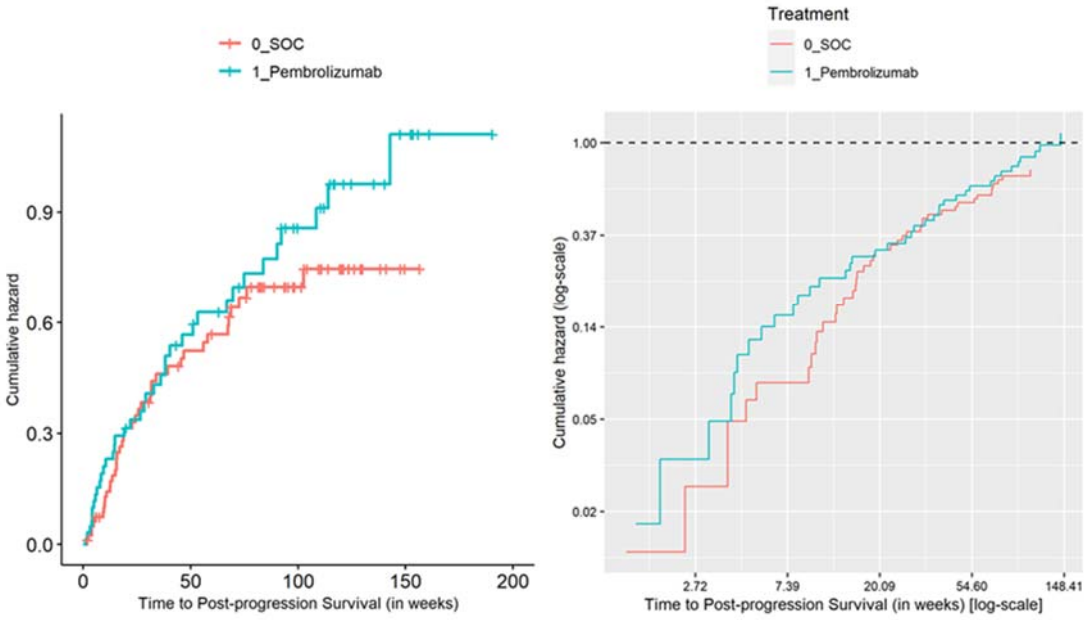
External validity was considered most important for parametric curve selection. As Figure 31 shows, all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period to yield different long-term extrapolations. As a result, the PFSXS curve selection was primarily based on clinical plausibility of long-term predictions and the exponential curve was the most appropriate choice.

Similar to TTPXS, for comparators not included in the SoC arm (CAPOX and FOLFOX + panitumumab), PFSXS are based on the hazard ratios applied to SoC PFSXS derived from the NMA.

Modelling Post-progression Survival excluding Patients who undergo surgery (PostPSXS)

Due to the immaturity of KN177 PostPSXS data, PSMs had to be fit to the data to extrapolate PostPSXS over time. As a result of the log-cumulative hazard plots (Figure 32) for the PostPSXS data being relatively linear over time and the assumption of the same model being used for both treatment arms, one-piece models were fit to the data.

Figure 32: Cumulative Hazard Plots for PostPSXS (All patients)



Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The statistical goodness of fit for each parametric distribution are presented in Table 52 showing good fit across both arms with Lognormal, Generalised Gamma and Log-logistic.

Table 52: Summary of goodness-of-fit qualities of PostPSXS survival models – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	436.67	438.82	6	482.38	484.83	6
Weibull	432.28	436.57	5	478.42	483.31	5
Gompertz	430.88	435.17	4	469.60	474.48	1
Log-logistic	430.37	434.66	2	474.45	479.33	4
Log-normal	428.51	432.80	1	471.62	476.51	2
Generalised Gamma	429.68	436.11	3	470.29	477.62	3

Visual inspection combined with external validity was used for parametric curve selection. As seen in Figure 33, all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period yielding different long-term extrapolations. Hence the base-case curve selection was based on external validation from a ten-year multicenter follow-up study of patients diagnosed with dMMR/MSI-H CRC (55).

Figure 33 below shows a superimposed curve of the Tougeron results alongside all six parametric curves, the graph shows the extrapolation to closely follow the Tougeron *et al*. results is the Weibull curve. As a result, this was selected for the base case analysis with a scenario analysis looking at the Lognormal curve which had the best statistical fit for pembrolizumab and the second-best fit for SoC.

The state transition model assumes the post-progression from the pembrolizumab arm data to equal that in the SoC arm. This is to overcome the bias of the post-progression data in the SoC arm generated by cross-over within the trial (PD-L1s are not recommended as a second-line treatment for Stage IV CRC in England and a large proportion of patients who progressed in the SoC arm of KN177 received a PD-L1 as a subsequent therapy). This is likely to be a conservative assumption as pembrolizumab might also be effective post-progression.

Figure 33: One-piece Parametric Fit

Modelling Surgery Rates and Post-surgery Progression-free and Overall Survival

The proportions of patients undergoing surgery with curative intent for both treatment arms was obtained from KN177. For pembrolizumab and the SoC arm, the proportions were 9.2% and 8.4%, respectively, for the 'all patients population' and 15.4% and 10.6%, respectively, for the 'all patients excluding bevacizumab population'.

Literature sources were used to inform post-surgery PFS and OS. Adam et al. and Cucchetti et al., both observational studies on PFS and OS after surgery with curative intent in Stage IV CRC patients were identified (53, 54). Observed Post-surgery PFS and OS for Adam et al. and Cucchetti et al. are seen in Figure 34 and Figure 35 respectively.

Figure 34: Observed Post-surgery PFS and OS observed in Adam et al. (2004)

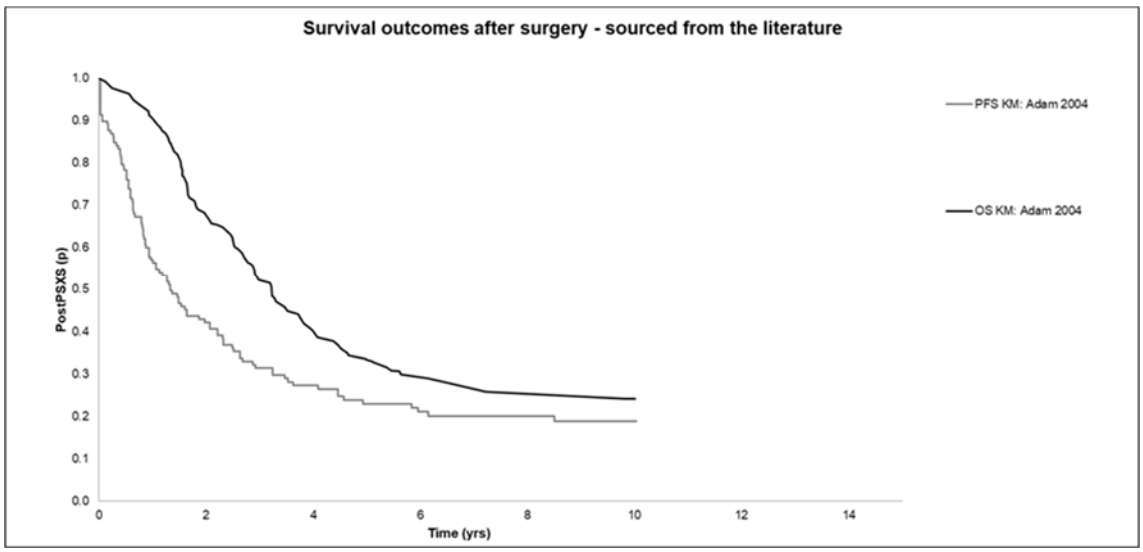
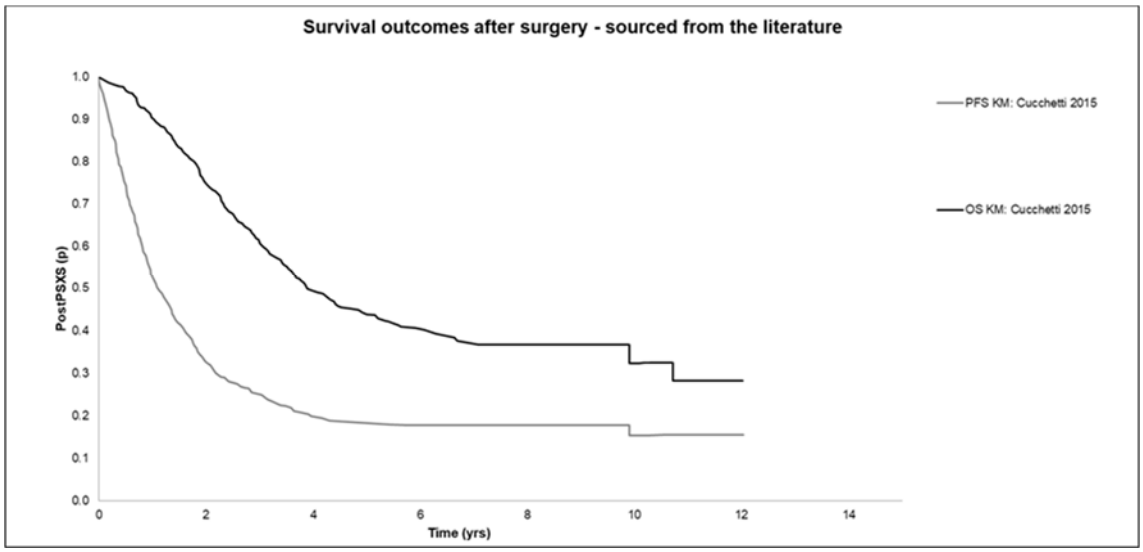


Figure 35: Observed Post-surgery PFS and OS observed in Cuchetti et al. (2015)



The choice of literature source to use for the base case came down to three criteria:

- Sample size
- Type of study
- Time of study

Cucchetti et al. was the most recent publication; 2015 and a study date between 2001 and 2012. The Adam et al. study on the other hand ran from 1988 to 1999, within which time clinical practice and patient demographics could have changed substantially. The sample size in the Cucchetti et al. study and the Adam et al. study were 1,012 and 138 respectively. The smaller the sample size the greater the risk of failing to demonstrate a treatment difference when one is present i.e. type II error thereby a preference towards larger sample sizes. Finally, the Cucchetti et al. and Adam et al. studyt were multicenter and single centre respectively. The advantages of a multicenter observational study is it presents a practical means of accruing sufficient subjects to satisfy the objective criteria within a reasonable time frame. It also provides a better basis for the subsequent generalization of findings; this is because there is an increased possibility of recruiting subjects from a broader population as well as delivering treatment regimens in a broader range of clinical settings, presenting an experimental situation more typical of future use. Based on the above criteria, the Cucchetti et al. study was chosen as the base case data source for post-surgery PFS and OS.

PSMs were fit to the data from Cucchetti et al. to extrapolate PFS and OS over time. Even though the assumption is some patients who undergo surgery with curative intent will most likely be cured, the decision was made to only fit one-piece PSMs to the data. This is because the impact of post-surgery PFS and OS on incremental results is likely to be minor due to the proportions of patient who undergo surgery being small and similar between the pembrolizumab and the SoC arms. Additionally, given the proportion of patients who undergo surgery with curative intent is slightly higher for pembrolizumab than the SoC arm, this is likely to be a conservative assumption.

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution. The statistical goodness of fit for each parametric distribution are presented in Table 53 and the graph with all six parametric curves are shown in Figure 36 and Figure 37 for OS and PFS respectively.

Figure 36: One-piece parametric Fit to Post-surgery OS observed in Cucchetti et al. (2015)

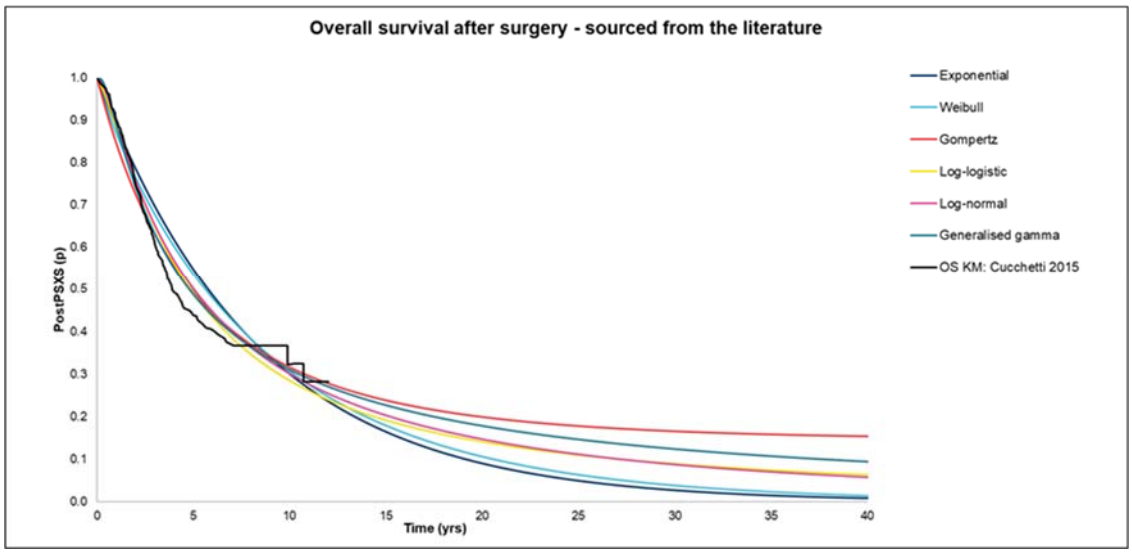


Figure 37: One-piece parametric Fit to Post-surgery PFS observed in Cucchetti et al. (2015)

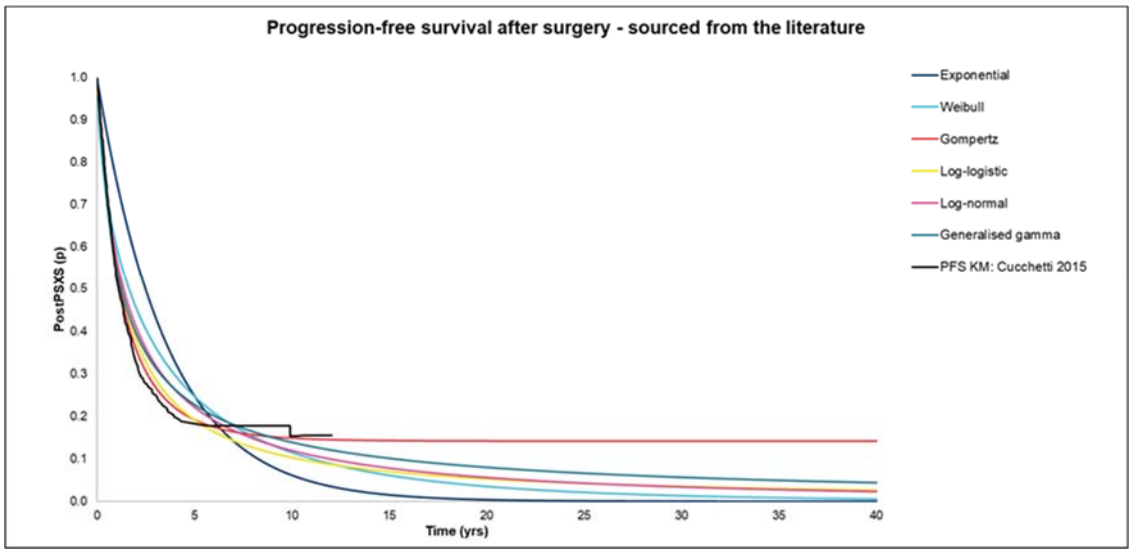


Table 53: Summary of goodness-of-fit qualities of Post-surgery survival models – PFS and OS

Fitted Function	OS		Statistical Rank	PFS		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	4521.80	4526.72	6	3868.07	3872.99	6
Weibull	4517.44	4527.27	5	3498.18	3508.02	5
Gompertz	4460.14	4469.98	4	3179.42	3189.26	1
Log-logistic	4423.09	4432.93	3	3267.54	3277.38	2
Log-normal	4402.51	4412.35	2	3290.23	3300.07	4

Generalised Gamma	4386.44	4401.20	1	3262.75	3277.50	3

According to the AIC and BIC values for both OS and PFS, the Generalised gamma model provided the best statistical fit to the data. However, on visual inspection the Gompertz parametric curve most closely fit the Cucchetti et al. data and was therefore selected as the base case. Also, the time point where the Gompertz extrapolation flattens (that is, where not further patients are diagnosed with progressed disease after undergoing surgery with curative intent) is very much in line with the 6.48 years after which patients alive without tumour recurrence can be considered cured with 99% certainty as concluded in Cucchetti et al study.

Modelling Comparators not included in KN177 Trial SoC Arm

NMAs assuming proportional hazards (PH NMAs) and NMAs using fractional polynomials (FP NMAs) were performed for PFS for pembrolizumab and SoC versus CAPOX and FOLFOX + panitumumab. Details on the selection of NMA results included in the model are described in Appendix M.

There are limitations to the NMA (section B.2.9.) which should be considered when interpreting the results, namely:

- Key differences in patient characteristics and trial design between KN177 and the other trials in the network
- Applicability of treatment effect estimates in mCRC patients to MSI-H/dMMR mCRC patients
- Assumed equivalence of FOLFOX and FOLFIRI regimens
- Assumed equivalence of different FOLFOX regimens
- Assumed lack of effect of adding cetuximab to FOLFOX/FOLFIRI
- Assumed lack of effect modification in KRAS patients for interventions other than panitumumab

Given the above (and lack of face validity of some of the comparisons that come from the NMA) the results of the NMA should be interpreted with caution and should be viewed only as exploratory analyses.

The HRs for PFSXS in the state transition model were informed by the HRs for PFS resulting from the NMAs. Hence, we assumed that relative efficacy in terms of PFS is the same in the total populations and the populations excluding patients who undergo surgery. The HRs for TTPXS in the state transition model were also informed by the HRs for PFS resulting from the

NMA. Hence, we also assumed that relative efficacy in terms of preventing pre-progression mortality is the same as relative efficacy in terms of preventing progression. As only few patients undergo surgery with curative intent (KN177: pembrolizumab arm: 9.2%, SoC arm: 8.4%) and because only few patients with Stage IV MSI-H/dMMR CRC die before progressing (KN177: pembrolizumab arm: 8.6%, SoC arm: 8.5%) we consider this assumption appropriate. Also, as PFSXS and TTPXS were not available for CAPOX or FOLFOX + panitumumab, was considered necessary to make these assumptions.

In our base case analysis, we used the FP NMA rather than the PH NMA results for PFS as the PFSXS and TTPXS data for pembrolizumab and SoC did not meet the proportional hazards assumption and there were violations to proportional hazards observed in the other trials (TREE-1 and NO16966). Also, this is consistent with the base case analysis in TA439 which used independent PSMs fit to the intervention and comparator data.

All HRs for PFS at selected follow-up times are significantly lower for pembrolizumab than SoC. The HRs for panitumumab + FOLFOX are lower than for SoC, which was to be expected as panitumumab + FOLFOX is a targeted therapy and not all patients in the SoC arm of KN177 received targeted therapy. Most of the HRs for CAPOX are also lower than for SoC. This is surprising as CAPOX is not a targeted therapy and a large proportion of patients in the SoC arm of KN177 did receive a targeted therapy. Hence, the incremental effectiveness and cost effectiveness results for pembrolizumab versus CAPOX resulting from the model are considered conservative.

KN177 data for SoC was used as a reference when implementing the NMA results, as they are the most mature dataset for projection.

Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients in any treatment arm. In the base case, AE costs per patient is applied as a one-off cost in the first cycle of the model for each treatment arm. This was consistent with the methods used in previous oncology submissions and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting (56, 57).

To calculate AEs, the number of times an AE was experienced in KN177 was multiplied by the number of patients who experienced that particular AE with the average number of times the AE was experienced per patient experiencing the AE. From these numbers weekly rates were calculated by dividing by the total time on treatment in KN177 (153 patients times a median time on treatment of 57.7 weeks for pembrolizumab and 143 patients times a mean

time on treatment of 34.8 weeks for SoC). AE data for non-trial comparators were obtained from the published literature used in the NMA. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 54. This was consistent with the methods used in previous oncology submissions and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting (56, 57).

Table 54: AEs incidence - grade ≥3, 5%+ incidence

Adverse event (Grade 3+)	Patients experiencing the adverse event (%)		Times the adverse event is experienced (n)		Adverse event rate (n/week)	
	Pembro	SoC	Pembro	SoC	Pembro	SoC
Any AE	56.2%	77.6%	2.64	3.42	0.0264	0.0782
Anaemia	5.2%	10.5%	1.00	1.07	0.0009	0.0033
Neutropenia	0.0%	15.4%	1.00	1.27	0.0000	0.0058
Febrile neutropenia	0.7%	4.9%	1.00	1.00	0.0001	0.0014
Diarrhoea	5.9%	11.2%	1.00	1.19	0.0010	0.0039
Abdominal pain	5.2%	5.6%	1.25	1.13	0.0012	0.0019
Nausea	2.6%	4.2%	1.00	1.00	0.0005	0.0012
Vomiting	1.3%	4.9%	1.00	1.14	0.0002	0.0016
Small intestinal obstruction	1.3%	3.5%	1.00	1.80	0.0002	0.0019
Stomatitis	0.0%	4.2%	1.00	1.00	0.0000	0.0012
Fatigue	3.9%	9.1%	1.00	1.08	0.0007	0.0029
Asthenia	2.0%	4.2%	1.00	1.00	0.0003	0.0012
Pneumonia	3.3%	2.1%	1.00	1.00	0.0006	0.0006
Neutrophil count decreased	0.0%	16.8%	1.00	1.42	0.0000	0.0070
Gamma-glutamyltransferase increased	4.6%	0.7%	1.00	1.00	0.0008	0.0002
White blood cell count decreased	0.0%	4.2%	1.00	1.17	0.0000	0.0014
Hyponatraemia	5.2%	2.8%	1.00	1.25	0.0009	0.0010
Hypokalaemia	1.3%	6.3%	1.00	1.33	0.0002	0.0025
Decreased appetite	0.0%	4.9%	1.00	1.00	0.0000	0.0014
Dehydration	1.3%	3.5%	1.00	1.60	0.0002	0.0016
Pulmonary embolism	2.0%	3.5%	1.00	1.00	0.0003	0.0010
Hypertension	7.2%	4.9%	1.09	1.86	0.0014	0.0027
Embolism	0.0%	4.9%	1.00	1.00	0.0000	0.0014

Adverse event (Grade 3+)	Patients experiencing the adverse event (%)		Times the adverse event is experienced (n)		Adverse event rate (n/week)	
	Pembro	SoC	Pembro	SoC	Pembro	SoC
Key: n, number; Pembro, pembrolizumab; SoC, standard of care. Source: KN177.						

An NMA was performed on Grade 3+ adverse events in the ITT population. The NMA-generated odds ratios of Grade 3+ AEs for pembrolizumab and SoC versus CAPOX and panitumumab + FOLFOX are presented in Table 55.

Table 55: Odds ratios estimated from fixed-effects network meta-analysis of Grade 3+ adverse events (All patients)

Odds ratio (fixed effects)			
SoC	1.29 (1.02, 1.62)	0.44 (0.30, 0.63)	2.73 (1.63, 4.58)
0.78 (0.62, 0.98)	**CAPOX**	0.34 (0.22, 0.53)	2.12 (1.20, 3.79)
2.29 (1.59, 3.36)	2.95 (1.90, 4.63)	**Panitumumab + FOLFOX**	6.26 (3.32, 11.84)
0.37 (0.22, 0.61)	0.47 (0.26, 0.83)	0.16 (0.08, 0.30)	**Pembrolizumab**
Key: CrI, credible interval; ITT, intention-to-treat; SoC, standard of care. Notes: Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment; all bolded values are statistically meaningful at the 0.05 significance level; deviance information criterion: 11.45; deviance: 5.44.			

Odds ratios were applied to the weekly SoC rates to calculate the weekly rates for CAPOXand FOLFOX + panitumumab.

The calculated rates are presented in Table 56. We chose to use KN177 data for SoC as a reference when implementing the NMA results to be consistent with the way the efficacy NMA results were implemented.

Table 56: Grade 3+ adverse event weekly incidence of NMA treatments

Adverse event (Grade 3+)	Adverse event rate (n/week)	
	CAPOX	mFOLFOX6 + panitumumab
Any AE	0.0621	0.1627
Anaemia	0.0026	0.0075
Neutropenia	0.0045	0.0131
Febrile neutropenia	0.0011	0.0033
Diarrhoea	0.0031	0.0089

Abdominal pain	0.0015	0.0043
Nausea	0.0010	0.0028
Vomiting	0.0013	0.0038
Small intestinal obstruction	0.0014	0.0042
Stomatitis	0.0010	0.0028
Fatigue	0.0023	0.0066
Asthenia	0.0010	0.0028
Pneumonia	0.0005	0.0014
Neutrophil count decreased	0.0055	0.0159
Gamma-glutamyltransferase increased	0.0002	0.0005
White blood cell count decreased	0.0011	0.0033
Hyponatraemia	0.0008	0.0024
Hypokalaemia	0.0019	0.0056
Decreased appetite	0.0011	0.0033
Dehydration	0.0013	0.0038
Pulmonary embolism	0.0008	0.0024
Hypertension	0.0021	0.0061
Embolism	0.0011	0.0033
Key: NMA, network meta-analysis.		

Subsequent treatment

Subsequent treatment in KN177 is not in line with what would be expected in UK clinical practice. Table 57 presents the subsequent treatments distributions and durations as observed in KN177 for both the All patients and All patients excluding bevacizumab populations.

Table 57: Subsequent treatment distribution as per KN177

Subsequent treatment	All patients			All patients excluding bevacizumab		
	% received by pembrolizumab patients	% received by SoC patients	Mean treatment duration (weeks)	% received by pembrolizumab patients	% received by SoC patients	Mean treatment duration (weeks)
No second line treatment	46.3%	16.8%	NA	55.6%	25.6%	NA
mFOLFOX6	13.2%	6.9%	20.16	10.3%	18.6%	22.76
FOLFIRI	10.0%	8.2%	20.16	18.0%	18.6%	22.76
mFOLFOX6 + cetuximab	1.6%	0.0%	20.16	2.9%	0.0%	22.76
FOLFIRI + cetuximab	1.3%	0.0%	20.16	5.1%	0.0%	22.76

mFOLFOX6 + bevacizumab	15.6%	30.9%	20.16	2.9%	18.6%	22.76
FOLFIRI + bevacizumab	11.9%	37.1%	20.16	5.1%	18.6%	22.76
Key: ITT, intention to treat; ITT-bev, intention to treat excluding bevacizumab patients; NA, not applicable; SoC, standard of care. Source: KN177						

In the base case subsequent treatment distribution in line with the current clinical practice in England. This was obtained through interviewing 50 UK oncology consultants to determine the current treatment landscape within the UK. Table 58 below shows the breakdown of subsequent treatment based on the responses of 50 UK consultant oncologists.

Table 58: Subsequent treatment distribution as per Clinician Feedback

Subsequent treatment	All patients			All patients - bevacizumab		
	% received by pembrolizumab patients	% received by SoC patients	Mean treatment duration (weeks)	% received by pembrolizumab patients	% received by SoC patients	Mean treatment duration (weeks)
No second line treatment	46.3%	46.3%	NA	55.6%	55.6%	NA
mFOLFOX6	0.0%	0.0%	20.16	0.0%	0.0%	22.76
FOLFIRI	37.6%	37.6%	20.16	31.1%	31.1%	22.76
mFOLFOX6 + cetuximab	0.0%	0.0%	20.16	0.0%	0.0%	22.76
FOLFIRI + cetuximab	16.1%	16.1%	20.16	13.3%	13.3%	22.76
mFOLFOX6 + bevacizumab	0.0%	0.0%	20.16	0.0%	0.0%	22.76
FOLFIRI + bevacizumab	0.0%	0.0%	20.16	0.0%	0.0%	22.76
Key: ITT, intention to treat; ITT-bev, intention to treat excluding bevacizumab patients; NA, not applicable; SoC, standard of care. Source: KN177						

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

Health-related quality-of-life (HRQoL) was evaluated in the KN177 trial using the EuroQoL EQ-5D-3L. The estimated utilities were used in the cost-effectiveness model as evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case (48).

In KN177, the EQ-5D questionnaire was administered at treatment cycle 1, 2, 3, 4, 5, 7 up to a year or End of Treatment, whichever occurred first and at the 30-day post-treatment discontinuation follow-up visit. The EQ-5D analysis below is based on the PRO Full Analysis Set (PRO FAS) population. UK preference-based scores were used for all patients analysed from the KN177 clinical trial.

When estimating utilities, two approaches were considered:

Estimation of utilities based on time-to-death

This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy, in advanced melanoma patients and in patients with urothelial cancer (56-61).

Based on KEYNOTE-177 EQ-5D data, time to death was categorized into the following groups:

- 360 or more days to death
- 180 to 360 days to death
- 30 to 180 days to death
- Under 30 days to death.

Time to death approach is considered as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit. However, this analysis was not considered robust enough to be included in the model due to the very low observation numbers for patients especially in the category closest to death. This can be viewed in Table 59.

Table 59: EQ-5D health utility scores by time-to-death

Time from EQ-5D Assessment Date to Death (days)	Pembrolizumab (N=46)					SOC (N=61)					Pooled (N=107)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
≥360															
[180, 360)															
[30, 180)															
<30															

n† = Number of subjects with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cutoff date: 19Feb2020

Estimation of utilities based upon whether or not patients have progressive disease.

Another approach, more commonly seen in previous oncology economic modelling literature, is to define health states based on time relative to disease progression. This approach generates results to fit the economic model by health state, there is a practical issue with the KEYNOTE-177 trial-based utility, where the utility data was collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, the utility data for post-progression is very limited as it is usually collected right after progression, thus missing the utility data as patients' HRQoL deteriorates when getting closer to death. This leads to an overestimation of the utility in the post-progression state.

Following this approach, the date of progression was determined from the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) using blinded independent central review (BICR).

- To estimate utilities for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
- Utilities for the progressive state were based on the EQ-5D scores collected at all visits after the progression date.

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab and SoC arms), and pooled for both arms. In addition, 95% confidence intervals were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested.

The utility values based on progression status is presented in Table 60.

Table 60: EQ-5D health utility scores by progression status

	Pembrolizumab (n= 141)					SoC (n = 137)					Pooled (n = 278)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression free	[redacted]														
Progression free no AE	[redacted]														
Progression free AE	[redacted]														
Progressed	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

SE = standard error

SoC = standard of care.

EQ-5D score during baseline is not included

Database cut-off date: 19Feb2020

Mapping

Not applicable as HRQoL was derived from the KN177 EQ-5D data.

Health-related quality-of-life studies

Please see Appendix H for a list of the studies identified through the SLR. No suitable studies were identified as part of the SLR that reported utility data in the population under review.

Adverse reactions

Grade 3+ AEs occurring in at least 5% of patients treated with pembrolizumab or any of the comparators are considered in the cost-effectiveness analysis. The utility impact of AEs associated with subsequent therapies is not included in the economic model.

In the base case, disutilities associated with AEs are calculated based upon KN177 trial data as this was considered the most relevant source of information. This is calculated by taking the difference between the progression-free health state utility values for with and without Grade 3+ AEs, then adjusting for the duration of adverse events. These inputs and calculations are presented in Table 61.

Table 61: One-off QALY losses due to adverse events

Treatment	One-off QALY loss
	KN177 data (base case)
Pembrolizumab	0.032
SoC	0.044
CAPOX	0.035
mFOLFOX6 + panitumumab	0.092

Key: QALY, quality-adjusted life year; SoC, standard of care.

Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values used in the base case analysis using the state transition model are shown in Table 62. The utilities for the "progression free" health state were informed by the "progression free no AE utility data". Different values are used for pembrolizumab and SoC as a statistically significant difference was seen between treatment arms in KN177. The higher utility values for pembrolizumab might be a consequence of pembrolizumab administration being less burdensome tin comparison to SoC administration. Where pembrolizumab is administered three-weekly on a single day, the SoC treatments are administered bi-weekly over the course of three days. For the "progressed disease" health state, the pooled

"progressed" utility was used as no statistically significant difference between treatments arms was observed here. The utilities for the "post-surgery progression free" and "post-surgery progressed disease" health states were assumed equal to the utilities for the "progression free" and "progressed disease" health states, respectively. This is a conservative assumption.

For the comparators not included in the KN177 trial, CAPOX and mFOLFOX6 + panitumumab, treatment-specific health state utility values were not available. Therefore, it was assumed that the health state utility values for these treatments would be equal to SoC. This assumption is plausible as both treatments are similar to those included in the SoC treatment arm of KN177.

Table 62: State Transition Model- Base case Analysis Utility Values

Health state	Pembrolizumab		SoC		CAPOX		mFOLFOX6 + panitumumab	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Progression free	0.852	0.008	0.800	0.012	0.800	0.012	0.800	0.012
Progressed disease	0.730	0.016	0.730	0.016	0.730	0.016	0.730	0.016
Post-surgery progression free	0.852	0.008	0.852	0.008	0.852	0.008	0.852	0.008
Post-surgery progressed disease	0.750	0.020	0.750	0.020	0.750	0.020	0.750	0.020
One-off QALY loss due to AEs	0.032	NA	0.044	NA	0.035	NA	0.092	NA
Key: SE, standard error; SoC, standard of care.								

The utility values used in the partitioned survival model are shown in Table 63 below.

Table 63: Partitioned Survival Model Analysis Utility Values

Health state	Pembrolizumab		SoC		CAPOX		mFOLFOX6 + panitumumab	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Pre-progression	0.852	0.008	0.800	0.012	0.800	0.012	0.800	0.012
Post-progression	0.730	0.016	0.730	0.016	0.730	0.016	0.730	0.016

One-off QALY loss due to AEs	0.032	NA	0.044	NA	0.035	NA	0.092	NA
Key: SE, standard error; SoC, standard of care.								

B.3.5 Cost and healthcare resource use identification, measurement and valuation

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below.

Input from clinical experts

The costing approach adopted in this submission was previously validated with clinical experts in previous HTA submissions of pembrolizumab (56, 57).

Intervention and comparators' costs and resource use

Intervention

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks (Q3W) (see Appendix A). As a monotherapy, it is anticipated that pembrolizumab can also be administered at a 400mg fixed dose every six weeks (Q6W). The list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. [redacted]

Comparators

For each of the comparators, dosing is administered based on patients' body surface area (BSA) or body weight. For the high cost comparators, namely, panitumumab, cetuximab and bevacizumab, vial wastage is not considered, that is, vial sharing is assumed. To implement this assumption, the minimum cost per mg is multiplied by the total dose per administration to calculate the total drug cost per administration.

Missed doses and dose reductions

The model includes the option to account for missed doses and dose reductions for pembrolizumab and SoC which were included based upon the relative dose intensity (RDI) of each treatment. The RDIs were sourced from the KN177 trial and are presented in Table 64 for both populations of interest. For treatments outside of KN177, drug costs were not adjusted based on missed doses and dose reductions. In the base case the impact of missed doses was considered for both pembrolizumab and SoC in order to fully match the costs modelled within the trial to the efficacy based upon the doses received.

Table 64: Relative dose intensity values as per KN177

RDI	All patients		All patients-bevacizumab	
	Mean	SD	Mean	SD
Pembrolizumab	96.5%	8.1%	95.6%	7.2%
SoC	88.6%	12.0%	88.6%	11.3%

Key: ITT, intention to treat; ITT-bev, intention to treat excluding bevacizumab patients; RDI, relative dose intensity; SD, standard deviation; SoC, standard of care.

Source: KN177

The cost of drugs and dosing schedule used in the model can be found in Table 65 and Table 66 below.

Table 65: Drug Acquisition Cost

Treatment	Formulation per vial/cap (pack size)	Unit cost (£)	Source
Pembrolizumab	1 x 50 mg vial	£1,315.00	MIMS 2020
	1 x 100 mg vial	£2,630.00	
Fluorouracil	1 x 1000 mg vial	£1.29	eMIT 2018
	1 x 2500 mg vial	£3.59	
	1 x 2500 mg vial	£5.16	
	1 x 500 mg vial	£1.36	
	1 x 5000 mg vial	£7.76	
Leucovorin	1 x 100 mg vial	£2.71	eMIT 2018
	1 x 300 mg vial	£7.90	
	1 x 500 mg vial	£2.52	
Oxaliplatin	1 x 50 mg vial	£3.81	eMIT 2018
	1 x 100 mg vial	£6.44	
	1 x 200 mg vial	£19.90	
Irinotecan	1 x 100 mg vial	£4.65	eMIT 2018
	1 x 300 mg vial	£11.23	

Treatment	Formulation per vial/cap (pack size)	Unit cost (£)	Source
	1 x 40 mg vial	£3.19	
	1 x 500 mg vial	£17.33	
Cetuximab	1 x 100 mg vial	£178.10	MIMS 2020
	1 x 500 mg vial	£890.50	
Bevacizumab	1 x 100 mg vial	£242.66	MIMS 2020
	1 x 400 mg vial	£924.40	
Panitumumab	1 x 100 mg vial	£379.29	eMIT 2018
	1 x 400 mg vial	£1,517.16	
Capecitabine	60 x 150 mg tablets	£3.97	eMIT 2018
	120 x 500 mg tablets	£21.76	
Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities.			

Table 66:Dosing Schedules included in the Model

Treatment	Drug	Dosing per administration (mg, mg/kg or mg/m²)		Dose per adminstration (mg)	Dosing frequency
KN177 individual SoC treatments					
Pembrolizumab	Pembrolizumab	200	mg	200	Once every 3 weeks
mFOLFOX6	Fluorouracil bolus	400	mg/m²	724	once every 2 weeks
	Fluorouracil infusion	2400	mg/m²	4,344	
	Leucovorin	400	mg/m²	724	
	Oxaliplatin	85	mg/m²	154	
FOLFIRI	Irinotecan	180	mg/m²	326	once every 2 weeks
	Fluorouracil bolus	400	mg/m²	724	
	Fluorouracil infusion	2400	mg/m²	4,344	
	Leucovorin	400	mg/m²	724	
mFOLFOX6 + cetuximab	Fluorouracil bolus	400	mg/m²	724	once every 2 weeks
	Fluorouracil infusion	2400	mg/m²	4,344	
	Leucovorin	400	mg/m²	724	
	Oxaliplatin	85	mg/m²	154	
	Cetuximab	400	mg/m²	724	first infusion (over 2 hours)
	Cetuximab	250	mg/m²	453	weekly (over 1 hour)
FOLFIRI + cetuximab	Irinotecan	180	mg/m²	326	once every 2 weeks
	Fluorouracil bolus	400	mg/m²	724	
	Fluorouracil infusion	2400	mg/m²	4,344	
	Leucovorin	400	mg/m²	724	
	Cetuximab - first	400	mg/m²	724	first infusion (over 2 hours)
	Cetuximab - subsequent	250	mg/m²	453	weekly (over 1 hour)
mFOLFOX6 + bevacizumab	Fluorouracil bolus	400	mg/m²	724	once every 2 weeks
	Fluorouracil infusion	2400	mg/m²	4,344	

	Leucovorin	400	mg/m²	724	
	Oxaliplatin	85	mg/m²	154	
	Bevacizumab	5	mg/kg	356	
FOLFIRI + bevacizumab	Irinotecan	180	mg/m²	326	once every 2 weeks
	Fluorouracil bolus	400	mg/m²	724	
	Fluorouracil infusion	2400	mg/m²	4,344	
	Leucovorin	400	mg/m²	724	
	Bevacizumab	5	mg/kg	356	
Other comparators					
mFOLFOX6 + panitumumab	Fluorouracil bolus	400	mg/m²	724	once every 2 weeks
	Fluorouracil infusion	600	mg/m²	1,086	
	Leucovorin	200	mg/m²	362	
	Oxaliplatin	85	mg/m²	154	
	Panitumumab	6	mg/kg	427	

Treatment duration

As per the licensed indication, patients treated with pembrolizumab are expected to be treated until disease progression or unacceptable toxicity. In line with the KN177 protocol, a stopping rule has been implemented in the model whereby patients do not receive therapy beyond 35 treatment cycles. To estimate the duration of treatment of pembrolizumab, time on treatment (ToT) data from KN177 was used to reflect both early discontinuations caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression.

Figure 38: Time on Treatment (ToT) Data for Pembrolizumab

Standard of Care (SoC) Comparators

The SoC regimen were assumed to be administered until disease progression or death. The time on treatment for the SoC regimen is shown in Figure 39.

Figure 39: Time on Treatment (ToT) Data for SoC Arm

NMA Comparators

The time on treatment duration for CAPOX and mFOLFOX6 + panitumumab are assumed to be equal to the PFS curve in the absence of alternative data. PFS was estimated as outlined in Section 3.3 using the output of the NMA described in Section 2.9.

Administration Costs

Drug administration costs include the cost of therapy infusions required at each treatment administration. Costs ere sourced from NHS reference costs 2018-2019 (62). Administration costs are applied such that drug administration occurs to the time on treatment curve for each intervention. For the base case it is assumed that oral treatments have no administration costs, however, there is an option to assign a cost for oral treatments. The relevant administration modes and corresponding costs by treatment are outlined in Table 67.

The time required for the administration of pembrolizumab is 30 minutes, the Health Resource Groups (HRG) code for SB12Z: *Deliver Simple Parenteral Chemotherapy at First Attendance* based on the latest NHS reference costs 2017-2018 was used to reflect administration costs for pembrolizumab. The assumption had been previously agreed with NHS England and used in previous NICE submissions for pembrolizumab (56, 57, 63).

Table 67: Administration costs

Treatment	Type of administration required	NHS reference cost code	Setting	Unit cost
Pembrolizumab	Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£254.14
mFOLFOX6	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	SB14Z	Daycase and reg day/night	£385.28
FOLFIRI	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	SB14Z	Daycase and reg day/night	£385.28
CAPOX	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	SB14Z	Daycase and reg day/night	£385.28
Cetuximab	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	SB14Z	Daycase and reg day/night	£385.28
Panitumumab	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	SB14Z	Daycase and reg day/night	£385.28
Source for costs: NHS Reference Costs 2018/19				

Health-state unit costs and resource use

A comprehensive literature search was conducted in April 2020, to identify costs and resource use in the treatment of and on-going management of MSI-H/dMMR CRC as well as the broader colorectal cancer disease area. Please see Appendix I for details of the search strategy and literature identified. TA439 was the main source of resource utilisation as it is the only recent submission in a similar indication and no other suitable sources were found during the literature search.

Patients incur disease management costs whilst in different health states over time. In the partitioned survival model, this means patients receive different costs for pre-progression and post-progression, and for the state transition model, costs are further split by post-surgery pre- and post-progression. These costs are based on the frequency of certain services per month based on TA439. Table 68 shows the frequency of each resource use and the calculated usage per month as presented in TA439. Unit costs were multiplied by the frequency of each resource to generate the total disease management cost per month which is then in turn

transformed to the weekly cost. It was assumed that patients incurred the same disease monitoring use regardless of treatment.

Table 68: Disease Management Unit Costs and Frequency

Resource	Reported Cost (£)	Transformed cost (£) [if applicable]	Reference	Description	Partitioned survival and state transition models				State transition model only			
					Pre-progression		Post-progression		Post-surgery pre-progression		Post-surgery post-progression	
					Description	Usage per month	Description	Usage per month	Description	Usage per month	Description	Usage per month
Consultant outpatient appointment	£187	n/a	NHS reference costs 2018/19	Service code: 370, Medical Oncology, Outpatient Attendance	one every 2 weeks	2.17	none	0	one every 4 months	0.25	none	0
Tumour marker test	£13	£14	NICE IPG135, 2015/2016 prices	Unit cost as per TA439, inflated from 2015 prices	one at month 1 then one every 4 months	0.25	none	0	one every 3 months	0.33	none	0
Liver function test	£27	£29	NICE IPG135, 2015/2016 prices	Unit cost as per TA439, inflated from 2015 prices	one at month 1 then one every 4 months	1.25	none	0	one every 3 months	0.33	none	0
CT scan	£116	n/a	NHS reference costs 2018/19	RD26Z: Computerised Tomography Scan of Three Areas, with Contrast, Outpatient	one every 3 months	0.33	none	0	one every 3 months	0.33	none	0
MRI scan	£206	n/a	NHS reference costs 2018/19	RD05Z: Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast, Outpatient	two during time on treatment period*	0.25	none	0	none	0	none	0
Best supportive care	1,667€	£1,600	Färkkilä (2015), cost reported as 2010 EUR	Monthly cost as per TA439, converted to GPB and inflated from 2015 prices	none	0	cost per month	1	none	0	cost per month	1
Colonoscopy	£520	n/a	NHS reference costs 2018/19	FE32Z: Diagnostic Colonoscopy, 19 years and over	none	0	none	0	one after 1 year then one every 3 years	0.03	none	0
Reference [description]	[redacted]				TA439 [First- and second-line pre-progression]		TA439 [Third-line post-progression]		TA439 [Post-successful resection pre-progression]		TA439 [Post-successful resection post-progression]	

For cost of surgery, the unit cost with curative intent was £10,106 at 2013/14 prices, which was sourced from TA439. This captures the average cost for liver resection (weighted for proportion which are open and laparoscopic). This was inflated to 2018/19 prices; £10,919.

The proportion of patients who go on to have surgery differs depending on the active treatment. Data were available from KN177 to inform these proportions for pembrolizumab and SoC. We assumed that the surgery rates of NMA comparators (CAPOX and mFOLFOX6 + panitumumab) patients were equal to SoC patients. Table 69 presents the proportions who receive surgery with curative intent and the calculated surgery costs used in the economic analysis, for both the ITT and ex-bevacizumab populations.

It should be noted that in both KN177 and clinical practice, patients may receive more than one surgery with curative intent. In TA439, it was given that the mean number of surgeries required per patient undergoing surgery was 1.6 surgeries. To account for this, the costs of one surgery were multiplied by 1.6.

Table 69: Surgery costs

Treatment	All Patients		All patients excluding bevacizumab	
	Surgery rate	Calculated surgery costs (£)	Surgery rate	Calculated surgery costs (£)
Pembrolizumab	9.2%	£1,598.59	15.4%	£2,687.74
SoC	8.4%	£1,474.77	10.6%	£1,858.54
XELOX	8.4%*	£1,474.77	10.6%*	£1,858.54
mFOLFOX6 + panitumumab	8.4%*	£1,474.77	10.6%*	£1,858.54

Key: SoC, standard of care.

*Assumed same as SoC.

Application of surgical cost differs depending on the modelling methodology. For the partitioned survival model, the total surgery cost is applied as a one-off cost whereas for the state-transition model, the proportion of patients who enter the 'post-surgery' health state per model cycle are assigned the surgery unit cost.

Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

The costs of managing AEs are derived from the NHS Reference costs 201-2019, with previous NICE submissions for pembrolizumab used as a guide for the appropriate HRG code(64, 65)s. The costs of treating each AE and the associated HRG code and descriptions are provided in Table 70.

Table 70: Unit costs of adverse events

Adverse event (Grade 3+)	Unit cost	Reference	Description [assumption]
Anaemia	£799.00	Crathorne et al. (2013)	TA323, Erythropoiesis-stimulating agents for treating cancer treatment induced anaemia [as per TA439]
Neutropenia*	£93.32	NHS reference costs 2018/19	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions [assumed that 10% of patient require hospital treatment, each requiring two episodes during chemotherapy]
Febrile neutropenia*	£3,171.57	NICE DSU 2007	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2017-2018 prices using the Hospital & community health services (HCHS) index
Diarrhoea*	£823.95	NHS reference costs 2018/19	Assumed that a typical patient will have two hospital admissions, corresponding to FD10M-Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode, each costing £412
Abdominal pain	£157.00	NHS reference costs 2018/19	Service code: 191, Pain Management [as per TA439]
Nausea*	£823.95	NHS reference costs 2018/19	Assumed that a typical patient will have two hospital admissions, corresponding to FD10M-Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode, each costing £412

Adverse event (Grade 3+)	Unit cost	Reference	Description [assumption]
Vomiting*	£823.95	NHS reference costs 2018/19	Assumed that a typical patient will have two hospital admissions, corresponding to FD10M-Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode, each costing £412
Small intestinal obstruction	£13,257.50	NHS reference costs 2018/19	Weighted average of FF20A:C, Complex Small Intestine Procedures, HRG
Stomatitis	£2,111.18	NHS reference costs 2018/19	Weighted average of CB02A:F, Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, Elective Inpatient [as per TA439]
Fatigue*	£3,320.57	NHS reference costs 2018/19	Assume equal to fatigue (Brown et al. 2013) WA17X code, no longer in use. Code used WH14C Other or Unspecified Neoplasm, without Interventions, with CC Score 2+
Asthenia*	£3,320.57	NHS reference costs 2018/19	WH14C Other or Unspecified Neoplasm, without Interventions, with CC Score 2+ [assumed equal to fatigue]
Pneumonia	£1,770.38	NHS reference costs 2018/19	Weighted average of DZ11K:DZ11V, Lobar, Atypical or Viral Pneumonia, with Multiple Interventions/with Single Intervention/without Interventions, HRG
Neutrophil count decreased*	£93.32	NHS reference costs 2018/19	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions [assumed same as neutropenia]
Gamma-glutamyltransferase increased*	£499.01	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay
White blood cell count decreased*	£93.32	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay
Hyponatraemia*	£740.92	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay

Adverse event (Grade 3+)	Unit cost	Reference	Description [assumption]
Hypokalaemia*	£740.92	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay
Decreased appetite*	£532.32	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay
Dehydration*	£740.92	NHS reference costs 2018/19	Total HRG KC05G-H Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ Non-elective short stay
Pulmonary embolism	£1,396.87	NHS reference costs 2018/19	Weighted average of DZ09J:Q, Pulmonary Embolus with Interventions, HRG
Hypertension	£598.58	NHS reference costs 2018/19	EB04Z, Hypertension, HRG
Embolism	£1,396.87	NHS reference costs 2018/19	Weighted average of DZ09J:Q, Pulmonary Embolus with Interventions, HRG
Key: SE, standard error. *Indicates AEs that were not included in TA439.			

Miscellaneous unit costs and resource use

Subsequent Treatment Costs

The economic model possesses two options regarding the choice of subsequent therapies: trial-based distribution of subsequent treatments (as per KN177 trial), or real-world distributions of subsequent treatments expected in UK clinical practice (as per clincal feedback). The trial-based distribution of subsequent therapies was used in the base-case analysis, with the real-world distribution of subsequent therapies explored in scenario analysis. In the economic model, upon disease progression patients were assumed to incur the costs of subsequent therapies. The proportions are presented in Table 57 and Table 58.

Terminal Care Cost

The model includes the option to apply a one-off, end-of-life cost of £5,156.50. This was applied to patients at the point of dying to reflect the cost of terminal care. The end-of-life cost was calculated based on the average cost derived from the Round et al. (2015) modelling study, which estimated the cost of cancer care during the final phases of life (66). The study presented the end-of-life cost from health, social, charity or informal care services for

colorectal, lung or prostate cancer individually in England and Wales. These care costs were uplifted to 2018–2019 costs using indices from PSSRU.

In the base case and in line with TA439, this cost is not applied in order to avoid double-counting costs. The resource value used for progressed disease from Färkkilä (2015) already takes palliative care costs into account.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

An overview of the key base case inputs is provided in Table 71. The full list of variables used in the cost-effectiveness analysis is presented in Appendix O.

Table 71: Overview of base case inputs

Input	Base case input			
Model settings				
Time horizon	40 years making this a lifetime horizon			
Parametric functions for modelling transitions from recurrence-free state	Time to progression	PFS	Post-progression survival	Surgery
	Exponential	Exponential	Weibull	Gompertz
Source of surgery survival outcomes	Cucchetti 2015			
Utility				
Health State Utility value source	KN177			
Apply age-related disutility?	Yes			
Treatment in subsequent therapy				
Source of subsequent therapy market shares	KN177			
Drug and Administration Costs				
Use of vial sharing	Yes			

Assumptions

Table 72 summarises the assumptions used in the economic model.

Table 72: List of assumptions used in the economic model

Assumption	Justification
Use KM data for the first 20 weeks from KN177 trial to model PFS and TTP for pembrolizumab and SoC, then extrapolate	Based on the shape of the survival curves, 2-phases piecewise approach was considered appropriate. Given the data maturity and hazards over time, 20 weeks was considered an appropriate point to begin the extrapolation.
Use KM data from KN177 trial to model Post progression survival for pembrolizumab and SoC, then extrapolate	Due to the data being relatively linear over time and the same model being used for both treatment arms, one-piece model was considered appropriate for extrapolation
The incidence of AEs from KN177 assumed to reflect that observed in practice	Assumption based on the results of the KN177 trial for the indication under consideration. The same method and criteria were applied in previous NICE appraisals of pembrolizumab (TA357, 366, 428, 519)
Utilities were adjusted by UK general population utility where utility deceases with age	Based on the Ara and Brazier study suggesting the impact of age on HRQoL
Pembrolizumab will be administered for a maximum of 35 cycles.	This assumption is in line with KN177 clinical trial
For SoC regimens, vial sharing is assumed.	This is the assumption is a conservative estimate
No use of pembrolizumab as a subsequent therapy despite its use in KN177.	Pembrolizumab is not currently recommended as a subsequent therapy for this indication in the UK, Therefore, a cross-over adjustment was conducted to remove its effect on the overall survival curve and its cost was not included in the economic model.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

In the base case analysis, the estimated mean overall survival was 6.51 years with pembrolizumab and 3.79 years with SoC. Patients treated with pembrolizumab accrued 4.01 QALYs compared to 2.37among patients in the SoC cohort. Table 73 presents the base case cost-effectiveness results for pembrolizumab versus SoC, incorporating the discount of the CAA. The results show pembrolizumab to be cost-effective compared to SoC when considering a willingness to pay threshold of £30,000 per QALY.

Table 73: Base-case Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	14,659	1.64	8,925
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Additional Analyses- NMA-related Comparators

Additional analyses considering the NMA-related comparators showed an estimated mean overall survival of 6.51 years with pembrolizumab versus 3.76 with CAPOX and 4.04 with FOLFOX + panitumumab. Patients treated with pembrolizumab accrued 4.01 QALYs compared to 2.35 and 2.50 versus CAPOX and FOLFOX + panitumumab respectively.

Table 74 and Table 75 below present the cost-effectiveness results for pembrolizumab, incorporating the discount of the CAA compared to CAPOX and FOLFOX + panitumumab.

Table 74: Base-case Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£53,469	1.66	£32,111
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 75: Base-case Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-£35,802	1.51	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Fully incremental ICERs are shown in Table 76. CAPOX was the least costly alternative and dominates FOLFOX + panitumumab which was found to be the least effective.

Table 76: Incremental Analysis Results

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	38,809	0.02	1,719,531
Pembrolizumab	[redacted]	[redacted]	[redacted]	14,659	1.64	8,925
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	35,802	-1.51	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix O.

The pairwise and incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for pembrolizumab is presented in Table 77 and Table 78 and the corresponding scatterplots and cost-effectiveness acceptability curves (CEAC) are presented in Figure 40 to Figure 43.

Table 77: Probabilistic Pairwise Results

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	19,476	1.64	11,868
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 78: Probabilistic Sensitivity Results- Incremental Analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	38,615	0.01	2,585,304
Pembrolizumab	[redacted]	[redacted]	[redacted]	19,453	1.63	11,892
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	31,564	-1.50	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Figure 40: CEAC for Pembrolizumab vs. SoC, CAPOX and FOLFOX + panitumumab

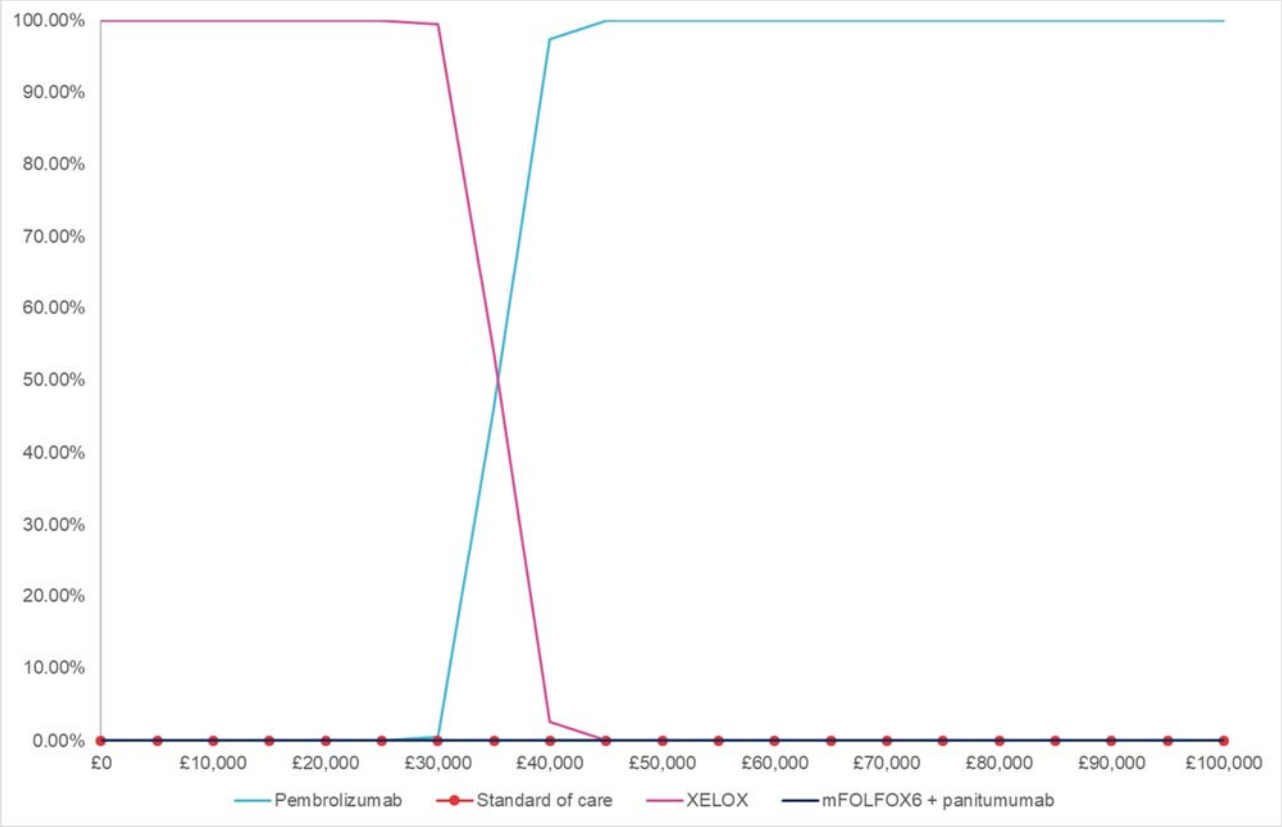


Figure 41: Scatterplot for Pembrolizumab vs. SoC

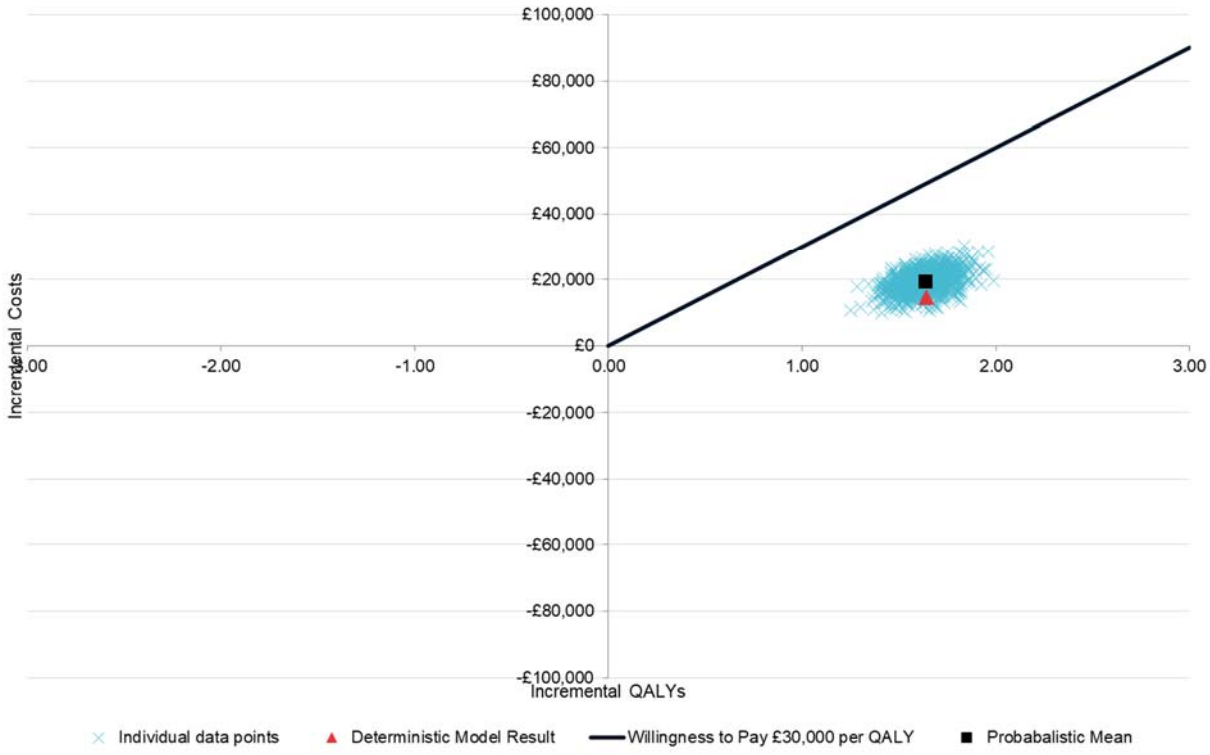


Figure 42: Scatterplot for Pembrolizumab vs. CAPOX

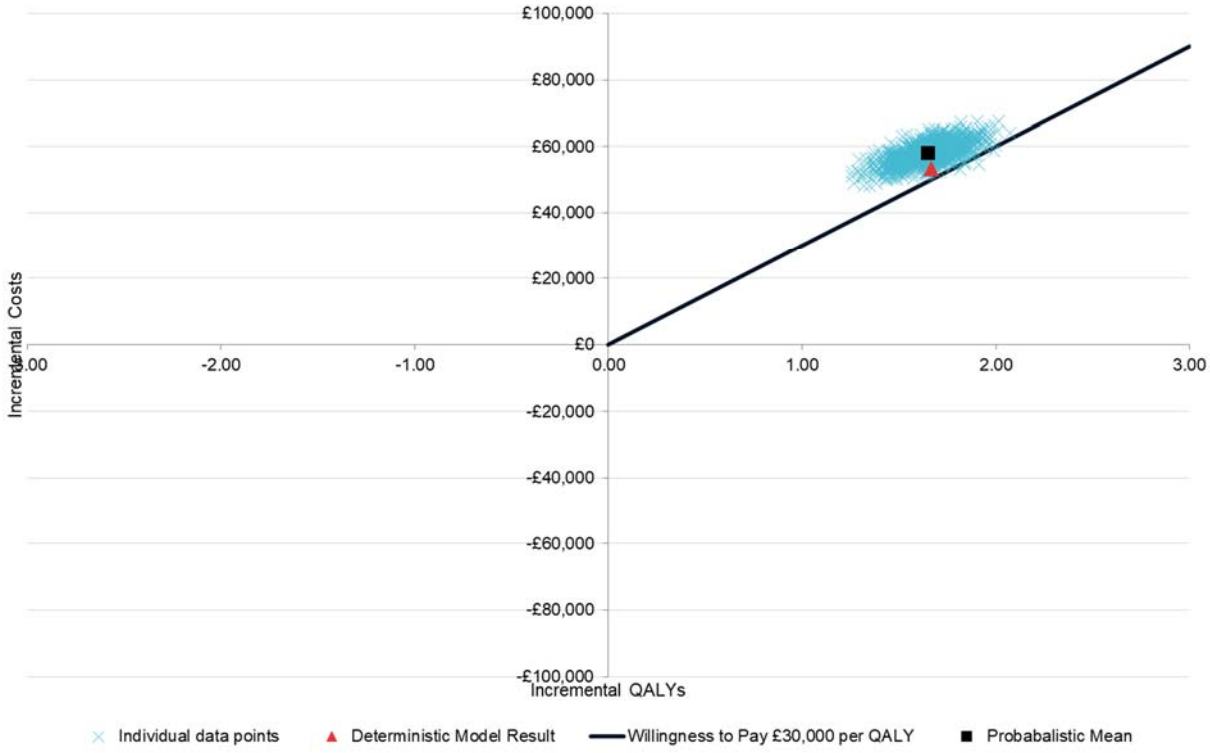
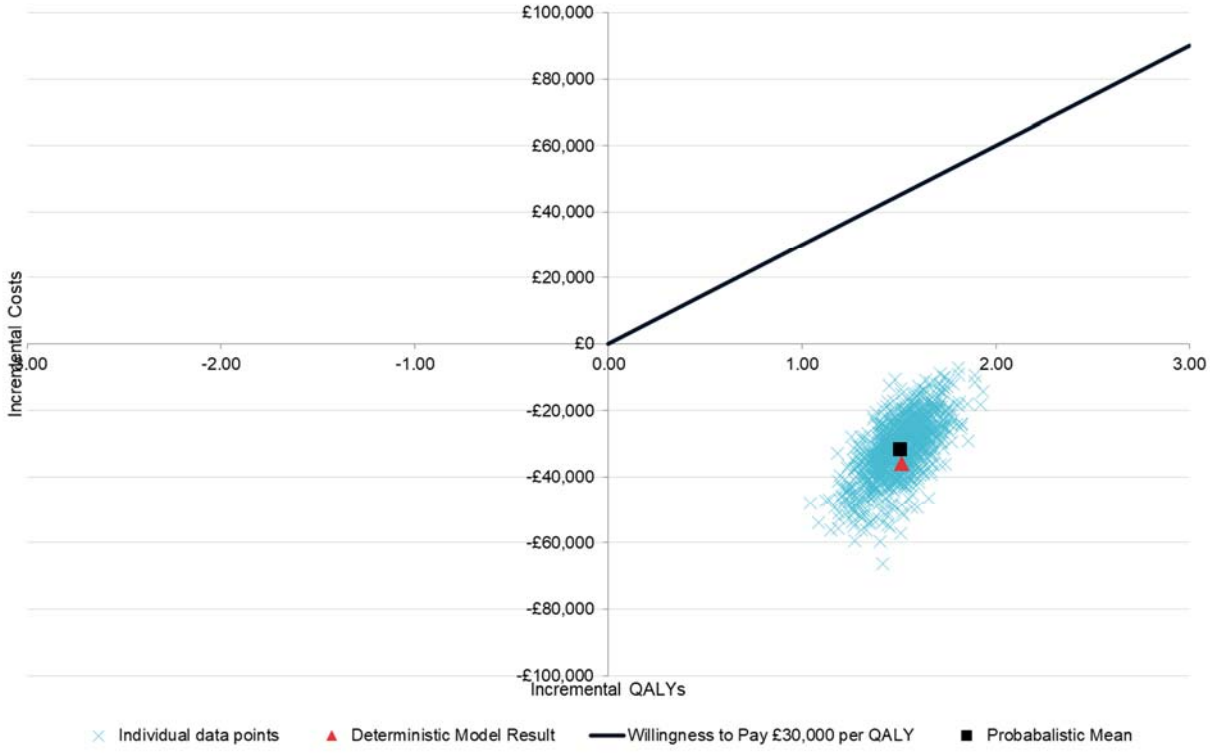


Figure 43: Scatterplot Pembrolizumab vs. FOLFOX + panitumumab



Deterministic sensitivity analysis

Extensive sensitivity analyses were conducted to explore the uncertainty associated with the estimates of cost-effectiveness. One-way deterministic sensitivity analysis (DSA) was conducted using the parameters outlined in Appendix O, and the associated lower and upper bound. The tornado diagrams of these one-way DSA are presented in Figure 44 to Figure 46 the full table of results are presented in Appendix O.

Figure 44: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. SoC

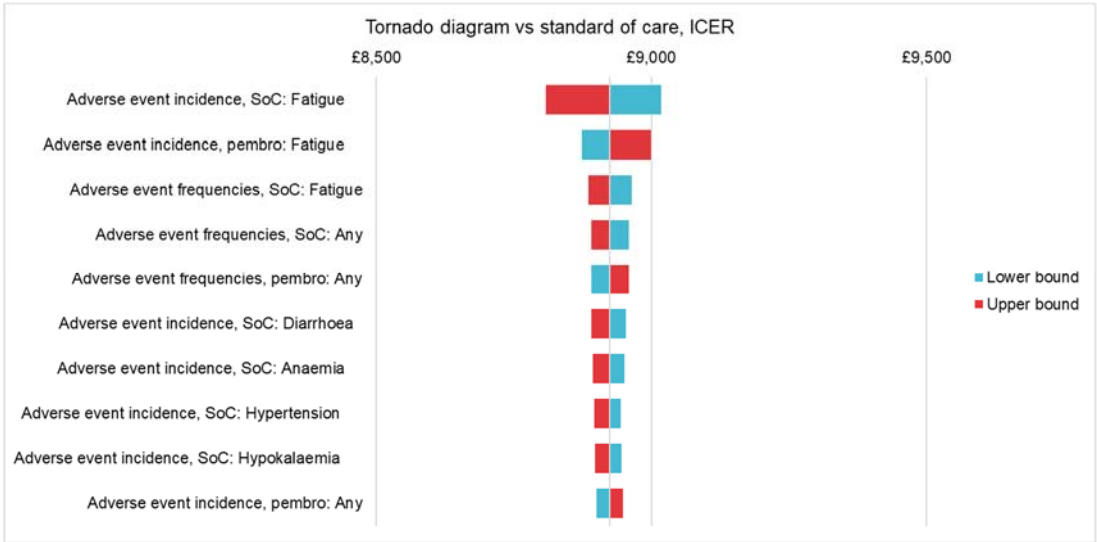


Figure 45: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. CAPOX

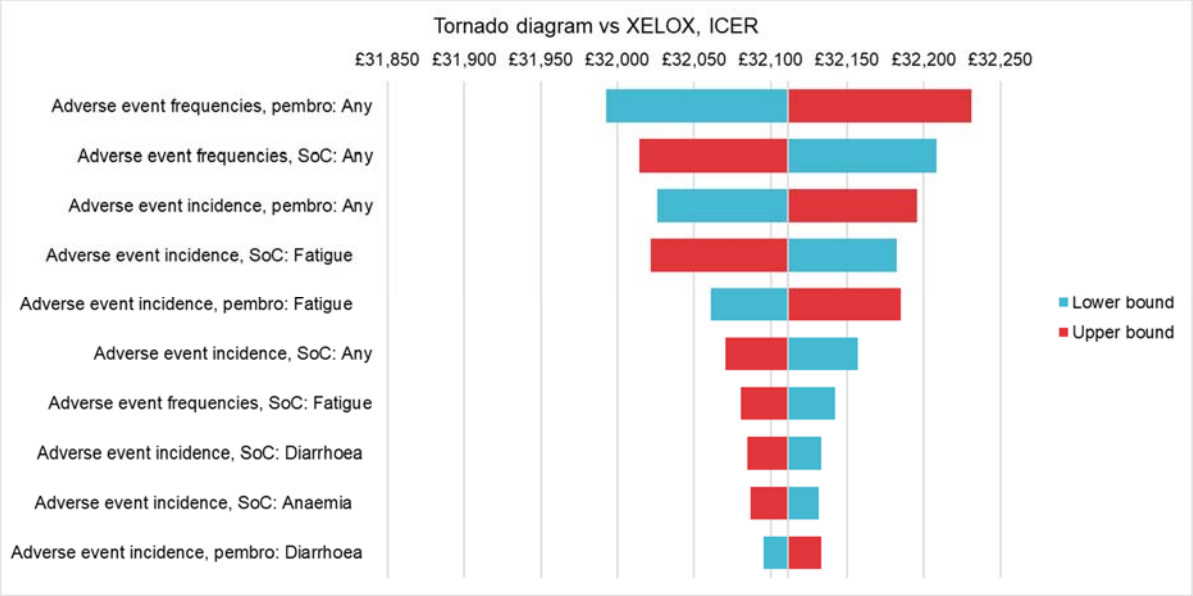
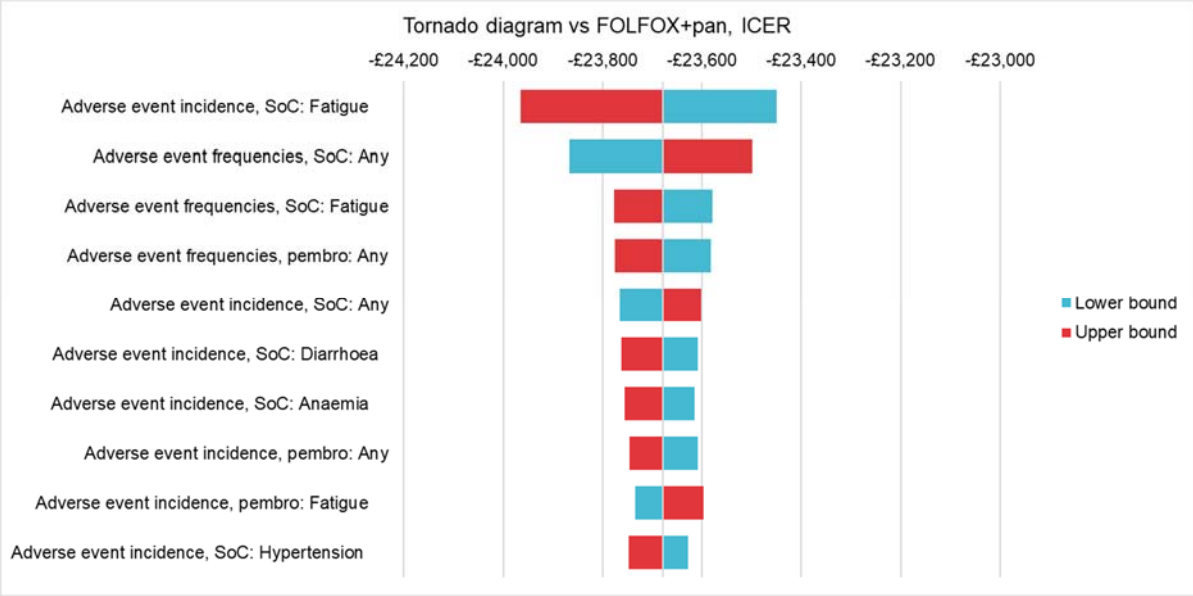


Figure 46: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. FOLFOX + panitumumab



Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions.

The parameters explored are summarised below.

Table 79: Scenario Analyses Settings

Model settings	Base case settings	Scenario analysis
Time horizon	40 years	30 years
NMA results used	FP NMA	PH NMA
Time to progression and Progression free survival (pembro & SoC)	Two-piece cut-off 20 weeks, exponential	Two-piece cut-off 10 weeks, weibull
Post progression survival (pembro & SoC)	One-piece, Weibull	One-piece, lognormal
Source used for surgery survival outcomes	Cucchetti 2015	Adams 2004
Surgery parametric survival model: PFS and OS	Gompertz	Generalised gamma
Consider wastage	No - Vial sharing assumed	Yes

The scenario analysis results are all presented in the tables below.

Table 80: Scenarios Analysis Results: Pembrolizumab vs. SoC

Pembrolizumab monotherapy vs SoC	Pembrolizumab		SoC		ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs		
Pembrolizumab Monotherapy Versus SoC base case	[redacted]	[redacted]	[redacted]	[redacted]	£8,925	-
Time horizon- 30 years	[redacted]	[redacted]	[redacted]	[redacted]	£8,828	-£97
PH NMA results used	[redacted]	[redacted]	[redacted]	[redacted]	£8,925	£0
Time to progression and Progression free survival (pembro & SoC) Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£8,468	-£457
Post progression survival (pembro & SoC) Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	£8,189	-£735
Source used for surgery survival outcomes- Adams 2004	[redacted]	[redacted]	[redacted]	[redacted]	£8,829	-£96
Surgery parametric survival model: PFS and OS- Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£8,943	£18
Consider wastage	[redacted]	[redacted]	[redacted]	[redacted]	£7,465	-£1,460

Table 81: Scenarios Analysis Results: Pembrolizumab vs. CAPOX

Pembrolizumab monotherapy vs CAPOX	Pembrolizumab		CAPOX		ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs		
Pembrolizumab Monotherapy Versus CAPOX base case	[redacted]	[redacted]	[redacted]	[redacted]	£32,111	-
Time horizon- 30 years	[redacted]	[redacted]	[redacted]	[redacted]	£32,142	£30
PH NMA results used	[redacted]	[redacted]	[redacted]	[redacted]	£31,564	-£547
Time to progression and Progression free survival (pembro & SoC) Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£30,578	-£1,533
Post progression survival (pembro & SoC) Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	£32,288	£176
Source used for surgery survival outcomes- Adams 2004	[redacted]	[redacted]	[redacted]	[redacted]	£32,127	£16
Surgery parametric survival model: PFS and OS- Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£32,136	£24
Consider wastage	[redacted]	[redacted]	[redacted]	[redacted]	£32,091	-£20

Table 82: Scenarios Analysis Results: Pembrolizumab vs. FOLFOX + panitumumab

Pembrolizumab monotherapy vs FOLFOX + panitumumab	Pembrolizumab		FOLOFX + panitumumab		ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs		
Pembrolizumab Monotherapy Versus FOLFOX + panitumumab base case	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-
Time horizon- 30 years	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
PH NMA results used	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
Time to progression and Progression free survival (pembro & SoC) Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
Post progression survival (pembro & SoC) Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
Source used for surgery survival outcomes- Adams 2004	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
Surgery parametric survival model: PFS and OS- Genera;ised gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA
Consider wastage	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	NA

The results show that pembrolizumab remains a cost-effectiveness treatment option versus the SoC regimen and FOLFOX + panitumumab in the vast majority of scenarios explored. Whilst marginal, the results show in all scenarios pembrolizumab is marginally above the cost-effectiveness threshold versus CAPOX. The results are robust to changes in the time horizon, estimation of treatment costs, surgery outcomes and alternative parametric distributions.

Summary of sensitivity analyses results

We have conducted extensive sensitivity analyses to understand the key determinants of the cost-effectiveness of pembrolizumab for Stage IV MSI-H/dMMR CRC. The results demonstrate that the model is robust to the vast majority of scenarios explored, with pembrolizumab remaining a cost-effective treatment option for patients with Stage IV MSI-H/dMMR CRC.

B.3.9 Subgroup analysis

No subgroup analysis has been indicated.

B.3.10 Validation

Validation of cost-effectiveness analysis

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab for the treatment of patients with MSI-H/dMMR mCRC. The economic evaluation reflects patients assessed in KN177 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab for the target population specified above was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Model Functionality

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developers to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications.

Health economists not involved in the development of the model reviewed the model for coding errors, inconsistencies, and the plausibility of inputs and results. The model has also been subjected to a checklist of known modelling errors, and the assumptions have been questioned. Moreover, the model has been reviewed from a technical and methodological perspective by a health economist external to the company that built the model.

Model outputs have been compared against observed trial results.

For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J1.1.

External validity

Overall survival data obtained from a large cohort of patients receiving treatment for Stage IV MSI-H/dMMR CRC in France between 2007 and 2017 as reported in Tougeron et al. was used to select the most appropriate PSMs to extrapolate PostPSXS data for the state transition model and OS for the partitioned survival model. Moreover, OS as modelled in the base case analysis using the state transition model is well aligned with OS as observed in patients receiving first-line treatment in Tougeron et al.

B.3.11 Interpretation and conclusions of economic evidence

The population included in the economic evaluation was consistent with the population eligible for pembrolizumab as per the anticipated licence. As mentioned previously, clinical efficacy estimates from the KN177 trial, which assessed patients in line with the anticipated licenced indication, were used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab in the patient population under consideration.

Generalisability of the analysis to clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KN177 is reflective of UK patients with stage IV MSI-H/dMMR CRC, and a proportion of the choice of comparator matches the current UK standard of care.

- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions for pembrolizumab and colorectal cancer, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab.

- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

Strengths and weaknesses of the evaluation

The analysis performed makes use of the best available evidence to inform the model. Head-to-head data from the KN177 trial comparing pembrolizumab to a variety of SoC, which represent the majority of current UK clinical practice, were used in the economic evaluation. OS, PFS and ToT data for pembrolizumab from KN177 trial informed inputs within the model. For the comparators not included in the trial, a network meta-analysis was conducted. However, the SoC arm of KN177 trial contained a significant proportion of patients (70%) given the bevacuzimab containing regimens which are not approved for use for this indication in the UK. To account for this bevacuzimab containing regimens were assumed to have equal efficacy to cetuximab containing regimens. This is a conservative assumption, as literature sources show MSI-H/dMMMR CRC patients have a significantly better OS when treated with bevacuzimab versus cetuximab (67).

There was a high level of cross-over (> 80%) of patients who progressed on the SoC arm to a subsequent PD-L1 inhibitor. However, as stated during the model selection process, this is limited by the use of a state transition model as this modelling methodology largely relies on data collected prior to crossover (time to progression [TTP] and progression-free survival [PFS] data).

Regardless of the limitations, there was consistency and stability of cost-effectiveness results to wide-ranging scenario analyses. In the majority of analyses conducted, pembrolizumab continues to show cost effectiveness versus the comparators for patients with stage IV MSI-H/dMMR CRC.

The results presented here support the conclusion that, within the context of innovative therapies, pembrolizumab is a cost-effective therapeutic option for the treatment of patients with Stage IV MSI-H/dMMR mCRC.

B.4 References

1. NICE. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer [TA61]: National Institute for Health and Care Excellence; 2003 [updated 27-MAY-2003. Available from: https://www.nice.org.uk/Guidance/TA61.
2. NICE. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer ID794 - Committee papers Multiple Technology Appraisal [Internet]. 2015. Available from: https://www.nice.org.uk/guidance/ta439/documents/committee-papers.
3. Alex B, Stephen F, Iris N, Alexander H, Jonathan K, Michael M, et al. Colorectal cancer - Oxford Textbook of Oncology. Oxford, UK: Oxford University Press; 2017.
4. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103.
5. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
6. CRUK. Bowel cancer statistics: Cancer Research UK; 2018 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer.
7. Macrae F. Colorectal cancer: Epidemiology, risk factors, and protective factors: UpToDate; 2020 [updated 06-JUL-2020. Available from: https://www.uptodate.com/contents/colorectal-cancer-epidemiology-risk-factors-and-protective-factors.
8. ONS. Cancer registration statistics, England. Datasets [Internet]. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.
9. ONS. Cancer registration statistics, England: 20172019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017.
10. AJCC. AJCC Cancer Staging Manual - 7th Edition2009. Available from: https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%207th%20Ed%20Cancer%20Staging%20Manual.pdf.
11. Dukes CE. The classification of cancer of the rectum. The Journal of Pathology and Bacteriology. 1932;35(3):323-32.
12. BCUK. Staging and grading2019. Available from: https://www.bowelcanceruk.org.uk/about-bowel-cancer/diagnosis/staging-and-grading/.
13. Duineveld LA, van Asselt KM, Bemelman WA, Smits AB, Tanis PJ, van Weert HC, et al. Symptomatic and Asymptomatic Colon Cancer Recurrence: A Multicenter Cohort Study. Ann Fam Med. 2016;14(3):215-20.
14. CRUK. Survival - Bowel Cancer: Cancer Research UK; 2018 [updated 13-SEP-2018. Available from: https://www.cancerresearchuk.org/about-cancer/bowel-cancer/survival.
15. Gologan A, Sepulveda AR. Microsatellite instability and DNA mismatch repair deficiency testing in hereditary and sporadic gastrointestinal cancers. Clin Lab Med. 2005;25(1):179-96.
16. Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015;5(1):16-8.
17. Fujiyoshi K, Yamamoto G, Takenoya T, Takahashi A, Arai Y, Yamada M, et al. Metastatic Pattern of Stage IV Colorectal Cancer with High-Frequency Microsatellite Instability as a Prognostic Factor. Anticancer Res. 2017;37(1):239-47.

18. NICE. Molecular testing strategies for Lynch syndrome in people with colorectal cancer [DG27]: National Institute for Health and Care Excellence; 2017 [updated 22-FEB-2017. Available from: https://www.nice.org.uk/guidance/dg27.
19. Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Cascinu S. The evolving role of microsatellite instability in colorectal cancer: A review. Cancer Treat Rev. 2016;51:19-26.
20. Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014;20(20):5322-30.
21. NICE. Colorectal cancer [NG151]: National Institute for Health and Care Excellence; 2020 [updated 29-JAN-2020. Available from: https://www.nice.org.uk/guidance/ng151.
22. NICE. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer [TA439]: National Institute for Health and Care Excellence; 2017 [updated 25-SEP-2017. Available from: https://www.nice.org.uk/guidance/ta439.
23. NICE. NICE Pathways - Managing metastatic colorectal cancer - First-line biological therapy: National Institute for Health and Care Excellence; 2020 [Available from: https://pathways.nice.org.uk/pathways/colorectal-cancer/managing-metastatic-colorectal-cancer#content=view-node%3Anodes-first-line-biological-therapy.
24. NICE. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer [TA212]: National Institute for Health and Care Excellence; 2010 [updated 15-DEC-2010. Available from: https://www.nice.org.uk/guidance/TA212.
25. NICE. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer [TA118]: National Institute for Health and Care Excellence; 2012 [updated 01-JAN-2012. Available from: https://www.nice.org.uk/guidance/TA118.
26. NCCN. NCCN Guidelines For Patients - Colon Cancer2018 04-SEP-2020. Available from: https://www.nccn.org/patients/guidelines/content/PDF/colon-patient.pdf.
27. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386-422.
28. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol. 2018;23(1):1-34.
29. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in Statistics - Theory and Methods. 1991;20(8):2609-31.
30. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.
31. Maurer W, Bretz F. Multiple Testing in Group Sequential Trials Using Graphical Approaches. Statistics in Biopharmaceutical Research. 2013;5(4):311-20.
32. NICEDSU. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching2014. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf.
33. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372(26):2509-20.
34. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005;23(22):4866-75.
35. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37.

36. Neugut AI, Lin A, Raab GT, Hillyer GC, Keller D, O'Neil DS, et al. FOLFOX and FOLFIRI Use in Stage IV Colon Cancer: Analysis of SEER-Medicare Data. Clin Colorectal Cancer. 2019;18(2):133-40.
37. Tumeh JW, Shenoy PJ, Moore SG, Kauh J, Flowers C. A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer. Am J Clin Oncol. 2009;32(1):49-55.
38. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2011;29(1):11-6.
39. Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA. 2012;307(13):1383-93.
40. Shimizu T, Satoh T, Tamura K, Ozaki T, Okamoto I, Fukuoka M, et al. Oxaliplatin/fluorouracil/leucovorin (FOLFOX4 and modified FOLFOX6) in patients with refractory or advanced colorectal cancer: post-approval Japanese population experience. Int J Clin Oncol. 2007;12(3):218-23.
41. Goldstein D, Mitchell P, Michael M, Beale P, Friedlander M, Zalcberg J, et al. Australian experience of a modified schedule of FOLFOX with high activity and tolerability and improved convenience in untreated metastatic colorectal cancer patients. Br J Cancer. 2005;92(5):832-7.
42. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408-17.
43. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27(5):663-71.
44. Adelstein BA, Dobbins TA, Harris CA, Marschner IC, Ward RL. A systematic review and meta-analysis of KRAS status as the determinant of response to anti-EGFR antibodies and the impact of partner chemotherapy in metastatic colorectal cancer. Eur J Cancer. 2011;47(9):1343-54.
45. NICE. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency - Final scope2020. Available from: https://www.nice.org.uk/guidance/gid-ta10420/documents/final-scope.
46. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42.
47. Hedrick E, Kozloff M, Hainsworth J, Badarinath S, Cohn A, Flynn P, et al. Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE). Journal of Clinical Oncology. 2006;24(18_suppl):3536-.
48. NICE. Guide to the methods of technology appraisal [PMG9]2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.
49. Bennett L, Zhao Z, Barber B, Zhou X, Peeters M, Zhang J, et al. Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. Br J Cancer. 2011;105(10):1495-502.
50. Wang J, Zhao Z, Sherrill B, Peeters M, Wiezorek J, Barber B. PCN86 A Q-TWIST ANALYSIS COMPARING PANITUMUMAB PLUS BEST SUPPORTIVE CARE (BSC) WITH BSC ALONE IN PATIENTS WITH WILD-TYPE KRAS METASTATIC COLORECTAL CANCER. Value in Health. 2011;14(3):A170.
51. 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.
52. NICEDSU. NICE DSU Technical Support Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level

data2013. Available from: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/.
53. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240(4):644-57; discussion 57-8.
54. Cucchetti A, Ferrero A, Cescon M, Donadon M, Russolillo N, Ercolani G, et al. Cure model survival analysis after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2015;22(6):1908-14.
55. Tougeron D, Sueur B, Zaanan A, de la Fouchardiere C, Sefrioui D, Lecomte T, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: An AGEO retrospective multicenter study. Int J Cancer. 2020;147(1):285-96.
56. NICE. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840] [TA428] - Committee Papers. Single Technology Appraisal [Internet]. 2016. Available from: https://www.nice.org.uk/guidance/ta428/documents/committee-papers.
57. NICE. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019] [TA519] - Committee Papers. Single Technology Appraisal [Internet]. 2017. Available from: https://www.nice.org.uk/guidance/ta519/documents/committee-papers.
58. Batty A, Winn B, Pericleous L, Rowen D, Lee D, Nikoglou T. A Comparison of General Population and Patient Utility Values for Advanced Melanoma. Annals of Oncology. 2012;23:ix372.
59. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12:140.
60. Huang MP, J.; Liao, J.;. A trial-based EuroQoL EQ-5D health utility analysis in patients with previously treated advanced NSCLC. Value in Health. 2016;19(7):A744.
61. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
62. NHS. 2018/19 National Cost Collection data. National Cost Collection for the NHS [Internet]. 2019. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819.
63. NICE. Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140] - Committee papers. Single Technology Appraisal [Internet]. 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10181/documents/committee-papers.
64. NICE. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [TA490]: National Institute for Health and Care Excellence; 2017 [updated 22-NOV-2017. Available from: https://www.nice.org.uk/guidance/ta490.
65. NICE. Cetuximab for treating recurrent and/or metastatic head and neck cancer; Rapid reconsideration of TA172 2nd appraisal committee meeting. 2017 01-FEB-2017.
66. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.
67. Innocenti F, Ou FS, Qu X, Zemla TJ, Niedzwiecki D, Tam R, et al. Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome. J Clin Oncol. 2019;37(14):1217-27.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID1498 Pembrolizumab ERG clarification questions v1.0 for PM [CIC]	1.0	Yes	21/10/2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

KEYNOTE-177: Trial conduct

A1. Figure 1 of the company submission indicates that progressive disease was assessed by irRECIST in the pembrolizumab arm, but centrally verified by RECIST 1.1 in the standard care (SC) group. Please:

a) outline how irRECIST differs from RECIST 1.1;

b) provide absolute numbers for events as assessed per irRECIST in the pembrolizumab group for the intention to treat (ITT) population, and the subgroups requested in A8 and A9;

c) Page 27 of the company submission reports that irRECIST has been used in an exploratory analysis of progression-free survival (PFS). Please provide the results of the exploratory analysis for PFS for the ITT population from KEYNOTE-177.

Please note that the primary objective of KEYNOTE-177 states "To compare Progression-Free Survival (PFS) per RECIST 1.1 by central imaging vendor". Section

4.2.4.1 *Efficacy Endpoints* of the KEYNOTE-177 study protocol (shown on page 780 of 2727 of the KEYNOTE-177 clinical study report) states that "RECIST 1.1, as assessed by the central imaging vendor, will be used to determine the dates of progression as this methodology is accepted by regulatory authorities."

The site may confirm progression with irRECIST as listed in Figure 1 if desired to do so. Figure 8 of the KEYNOTE-177 study protocol (shown on page 828 of 2727 of the KEYNOTE-177 Clinical Study Report) notes that after central verification of progression is confirmed a "Clinically stable subject on pembrolizumab may remain on pembrolizumab at the discretion of Investigator." In the case where the investigator has elected to keep the patient on pembrolizumab therapy, repeat tumour imaging will be performed at ≥4 weeks. Patients who have confirmed progressive disease by irRECIST will be discontinued from the trial (unless subject experiences clinically meaningful benefit per Investigator after marketing authorisation holder consultation) and if progressive disease is not confirmed, patients may remain on study drug at Investigators discretion and be followed by irRECIST. Evaluation of tumour response by RECIST 1.1 per the central imaging vendor is the basis for efficacy assessment in this study; however, irRECIST was used to make treatment decisions beyond progression by RECIST 1.1.

A1.a):

RECIST 1.1 and irRECIST provide the same response assessment until progressive disease. Per irRECIST (detailed in Section 7.1.4.6 of the KEYNOTE-177 study protocol, shown in page 826 of 2727 of the KEYNOTE-177 Clinical Study Report), disease progression on patients treated with pembrolizumab should be confirmed locally by the site at least 4 weeks after central verification of site assessed first radiologic evidence of PD in clinically stable patients. Patients who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.4.6 of the KEYNOTE-177 study protocol (shown in page 826 of 2727 of the KEYNOTE-177 Clinical Study Report). Patients who obtain a confirmation scan do not need to undergo the next scheduled tumour imaging if it is <4 weeks later; tumour imaging may resume at the subsequent scheduled imaging time point if clinically stable. Patients with confirmed disease progression, as assessed by the site,

will discontinue study medication. Exceptions are detailed in Section 7.1.4.6 of the KEYNOTE-177 study protocol (shown in page 826 of 2727 of the KEYNOTE-177 Clinical Study Report).

A1.b):

At the time of this interim analysis 2, there were [redacted] patients in the pembrolizumab arm who actually have irRECIST imaging. Two patients developed a response after progressive disease per irRECIST. A summary of irRECIST 1.1 imaging, for the overall ITT population and by RAS subgroups is presented in Table 1 below.

Table 1 Summary of irRECIST 1.1 imaging, overall population and by RAS subgroups (ITT population), KEYNOTE-177 study

	Pembrolizumab	SOC
	n	n
Overall KRAS and NRAS Wild type KRAS or NRAS Mutant	[redacted]	[redacted]
Database Cutoff Date: 19FEB2020.		

A1.c):

Progression-free survival per irRECIST by central imaging vendor is an exploratory objective of the KEYNOTE-177 study and was not analysed at the second interim analysis. This exploratory analysis will be performed at the time of the final analysis and the results will be become available at that time.

A2. Table 10 of the company submission outlining KEYNOTE-177 patient characteristics states that oncologic surgery with curative intent, "*occurred after subject randomisation and before initiation of new anti-cancer therapy, crossover treatment and second course treatment*". This description does not align with the assumption made in the economic analysis that all surgeries took place 12 weeks after the start of treatment. Please clarify the potential disparity and provide the mean and median time to surgery (with accompanying measures of variance) with curative intent in each treatment group.

The estimated mean and median time from randomisation date to surgery with curative intent (with accompanying measures of variance) in each treatment group is presented in Table 2. The unit of time used is weeks. Median time to surgery with curative intent was not reached for both treatment groups.

Table 2 Estimated median and mean of time to surgery (intention-to-treat population), KEYNOTE-177 study

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab	153	14 (9.2)	Not Reached	(-, -)	99.462	2.176	(95.198, 103.726)
SOC	154	13 (8.4)	Not Reached	(-, -)	61.684	1.394	(58.952, 64.415)

Estimated median and mean of Time to Surgery is from product-limit (Kaplan-Meier) method
Time to Surgery is defined as the time from the randomization date to curative surgery date
Number of Events is defined as number of subjects who had a curative surgery received before initiation of new anti-cancer therapy, crossover treatment and second course treatment
Database Cutoff Date: 19Feb2020

The assumption made in the economic analysis that all surgeries took place 12 weeks after the start of treatment is a simplification based on the assumptions made in TA439 which is reflective of clinical opinion in the UK.

A3. Table 10 of the company submission reports that 14 and 13 people underwent surgery in the pembrolizumab and standard of care (SoC) groups, respectively. However, different numbers are reported in table 14.2-14 of the Clinical Study Report (8 for pembrolizumab and 2 for SoC). Please clarify this potential discrepancy.

Table 10 of the company submission reports that 14 and 13 patients underwent surgery in the pembrolizumab and standard of care (SoC) groups, respectively, across the overall ITT population (N=307; 153 vs. 154). Table 14.2-14 of the Clinical Study Report presents the summary of response outcome in subjects with confirmed response by central imaging vendor per RECIST 1.1 (N=118; 67 vs. 51); i.e., this analysis includes only patients with a confirmed complete response or partial response, so does not include all ITT patients. Out of the subset of patients with confirmed response, there were 10 patients who underwent surgery with curative intent (8 in the pembrolizumab arm and 2 in the SoC arm).

A4. Please clarify the difference between clinical progression and progressive disease as referred to in Table 15 of the company submission.

Progressive disease is an objective measurement based on RECIST 1.1 criteria. Clinical progression is non-objective and based on physician assessment to stop treatment or study without objective measurement of progressive disease.

KEYNOTE-177: Clinical effectiveness results

A5. Please clarify how median OS in the standard of care (SoC) arm from KEYNOTE-177 has been calculated given that, according to Table 20 of the company submission, fewer than 50% of people in that group have died (44.8% [69/154]).

As indicated in the footnote at the bottom of Table 20 of the submission, the median OS (95% CI) are calculated from product-limit (Kaplan-Meier) method for censored data for survival time. In the standard of care (SoC) arm, 44.8% [69/154] of patients had event (i.e., died), and 55.2% [85/154] did not have event (i.e., survive), and the median 34.8 indicates that 50% of patients survive up to 34.8 months.

A6. Please provide details on the censoring of patients in the ITT population of KEYNOTE-177. Please provide a table detailing the number at risk in each treatment arm, the number of patients censored and the number with an event (death) for the time points listed in Figure 4 of the company submission for each of:

a. OS (considering the Kaplan–Meier plot in Figure 4 of the company submission)

b. PFS (considering the Kaplan–Meier plot in Figure 9 of the company submission)

Summary of event and censoring for OS and PFS by time points listed in Kaplan-Meier plots of the company submission is presented in Table 3 and Table 4, respectively.

Table 3 Summary of event and censoring for overall survival (ITT population), KEYNOTE-177 study

	Pembrolizumab (N=153)			SOC (N=154)		
Time in Months	Number at Risk	Number Censored	Number with Event	Number at Risk	Number Censored	Number with Event
0	153	0	19	154	4	13
4	134	0	11	137	0	16
8	123	0	4	121	1	10
12	119	0	7	110	1	10
16	112	0	5	99	0	4
20	107	1	3	95	2	7
24	103	26	2	86	19	3
28	75	22	3	64	21	4
32	50	21	2	39	19	2
36	27	11	0	18	8	0
40	16	11	0	10	7	0
44	5	5	0	3	3	0
48	0	0	0	0	0	0
Database Cutoff Date: 19FEB2020.						

Table 4 Summary of event and censoring for progression-free survival (primary analysis) by central imaging vendor per RECIST 1.1 (ITT population), KEYNOTE-177 study

	Pembrolizumab (N=153)			SOC (N=154)		
Time in Months	Number at Risk	Number Censored	Number with Event	Number at Risk	Number Censored	Number with Event
0	153	2	55	154	14	40
4	96	9	10	100	6	26
8	77	3	2	68	6	19
12	72	2	6	43	1	9
16	64	1	3	33	4	7
20	60	5	0	22	0	4
24	55	16	2	18	3	4
28	37	14	3	11	3	4
32	20	12	1	4	1	0
36	7	2	0	3	3	0
40	5	5	0	0	0	0
44	0	0	0	0	0	0

Time in Months	Pembrolizumab (N=153)			SOC (N=154)		
	Number at Risk	Number Censored	Number with Event	Number at Risk	Number Censored	Number with Event
48	0	0	0	0	0	0
Database Cutoff Date: 19FEB2020.						

Population

A7. Please clarify, by treatment arm, how many people had unresectable disease at baseline in KEYNOTE-177.

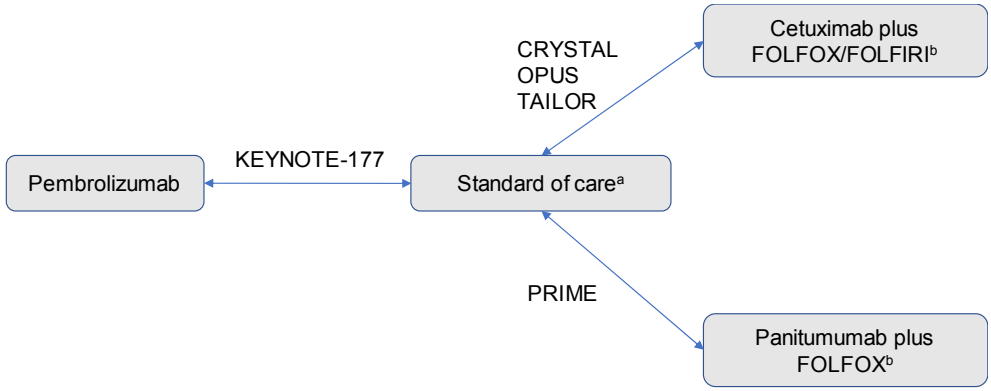
No unresectable patients were included in the KEYNOTE-N177 study.

Network meta-analysis (NMA)

A8. Priority question: The ERG considers that the company's NMA does not reflect the NICE final scope and outlines three populations of interest for the cost-effectiveness analysis:

- **Population A: All patients (ITT population)**
- **Population B: patients with RAS wildtype**
- **Population C: patients without RAS wildtype**

The ERG has produced the below network for people with RAS-wildtype colorectal cancer. Included studies are based on those in technology appraisal (TA) 439 or identified in the company's systematic literature review as evaluating people with RAS-wildtype.



[a] Standard of care is defined as FOLFOX or FOLFIRI, with or without bevacizumab.
[b] RCTs specified are those identified and analysed in TA439 and the company's literature review. Assumes equivalence of FOLFOX/FOLFIRI in combination with cetuximab.

a. please validate the ERG's study selection.

b. to align with the final NICE scope, please carry out the NMA depicted in the network for people with RAS-wildtype. As proportional hazards do not hold for some studies, please use the fractional polynomial (FP) method to generate relative estimates of effect for pembrolizumab versus the listed comparators of interest for: a) PFS, b) OS and c) OS adjusted for crossover to pembrolizumab treatment in the SoC group.

For KEYNOTE-177, please use the subgroup of people from the pembrolizumab and SoC groups who were designated as having wildtype RAS genes, irrespective of mutation status of BRAF ([redacted] people as indicated in figures 5 and 10 of the company submission).

c. As a scenario, please explore use of the lower bound of the post-progression treatment acceleration factor for adjusted OS with the two-stage approach to account for cross-over.

d. For pembrolizumab and SoC, by treatment arm, please also provide:

- **baseline characteristics;**
- **absolute event rates and number of people in the analyses for PFS and OS;**
- **median and mean (with accompanying measures of variance) PFS and OS;**

- **KM plots for: a) PFS and b) OS and (c) OS adjusted for subsequent treatment in the SoC group, indicating number at risk, censored, and events for both treatment arms. Please provide plots the equivalent of Figure 2A and Figure 2E combined as presented in the paper by Morris *et al*.[1] (i.e. including a table of patients at risk and a shaded area around the KM curves to indicate the 95% confidence intervals);**
- **hazard ratio (HR) and 95% confidence interval (95% CI) for pembrolizumab versus SoC for a) PFS, b) OS and c) OS adjusted for subsequent treatment in the SoC group.**

e. For each fractional polynomial analyses, please report:

- **relevant beta values;**
- **the number of iterations used as "burn-ins";**
- **the number of iterations run for data collection;**
- **the priors implemented in the code;**
- **the curves for each comparator produced from the fractional polynomial analysis;**
- **the appropriate measures of assessment of best curve fit.**

The ERG's proposed indirect treatment comparison network shown in the figure above as part of question A8.a shows pembrolizumab being compared to cetuximab + FOLFOX/FOLFIRI via "standard of care", which would not be appropriate as the "standard of care" arm of the KEYNOTE-177 contains cetuximab + FOLFOX/FOLFIRI as one of its treatment regimens.

It would be inappropriate to perform these analyses for the subgroup of patients with RAS-wildtype colorectal cancer, and the results of such analyses would be inappropriate for use in decision making, for the following reasons:

- These analyses would be considerably under-powered and consequently very likely to produce false-negative results. As described in the submission in Section B.2.4, *Sample size and power calculations*, 190 OS events and 209 PFS events are required for the KEYNOTE-177 study to be appropriately powered for the analyses of these two outcomes. However, as shown in Figures

38 and 39 in Appendix E of the submission, there were only [redacted] OS events and only [redacted] PFS events in the RAS-wildtype and RAS-mutant subgroups respectively at the second interim analysis of the KEYNOTE-177 study.

- Randomisation would be broken for treatment comparisons in these subgroups, as described in the submission in Section B.2.3, *Trial design*, no stratification of randomisation based on age, sex, or other characteristics were used in the KEYNOTE-177 study. There are also differences in the patient baseline characteristics between treatment arms for these subgroups (shown in Table 5 for RAS-wildtype patients and in Table 6 for RAS-mutant patients), which could confound the results of these analyses making them unreliable.

Table 5 Baseline characteristics (ITT population with KRAS/NRAS wild type), KEYNOTE-177 study

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	75		76		151	
Gender						
Male	[redacted]		[redacted]		[redacted]	
Female	[redacted]		[redacted]		[redacted]	
Age (Years)						
<65	[redacted]		[redacted]		[redacted]	
>=65	[redacted]		[redacted]		[redacted]	
	[redacted]		[redacted]		[redacted]	
Subjects with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)						
<=70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
ASIAN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BLACK OR AFRICAN AMERICAN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHITE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
HISPANIC OR LATINO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOT HISPANIC OR LATINO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOT REPORTED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Western Europe/North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Site of Primary Tumor*						
Right	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Left	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastases Location						
Hepatic or pulmonary	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosed stage						
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Newly diagnosed stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Systemic Therapy						
Adjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant and adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mutation Status**						
BRAF/KRAS/NRAS all wild type	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
BRAF V600E mutant and KRAS/NRAS not mutant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSI-High Status#						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oncologic Surgery with Curative Intent##						
Received surgery with curative-intent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Did not receive surgery with curative-intent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* If there were primary tumors in both left side and right side, the subject would be categorized into Other

** When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other

MSI status by PCR test or IHC test at local site laboratory

Oncologic surgery that was with curative intent and occurred after subject randomization and before initiation of new anti-cancer therapy, crossover treatment and second course treatment

(Database Cutoff Date: 19Feb2020).

Table 6 Baseline characteristics (ITT population with KRAS/NRAS mutant), KEYNOTE-177 study

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)						
<65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)						
<=70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
ASIAN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BLACK OR AFRICAN AMERICAN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHITE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
HISPANIC OR LATINO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOT HISPANIC OR LATINO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NOT REPORTED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Western Europe/North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Site of Primary Tumor*						
Right	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Left	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastases Location						
Hepatic or pulmonary	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosed stage						
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Newly diagnosed stage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Systemic Therapy						
Adjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant and adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
		[redacted]		[redacted]		[redacted]
Mutation Status**						
KRAS/NRAS mutant and BRAF V600E not mutant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF V600E and KRAS/NRAS mutant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSI-High Status#						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oncologic Surgery with Curative Intent##						
Received surgery with curative-intent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oncologic Surgery with Curative Intent##						
Did not receive surgery with curative-intent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* If there were primary tumors in both left side and right side, the subject would be categorized into Other

** When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other

MSI status by PCR test or IHC test at local site laboratory

Oncologic surgery that was with curative intent and occurred after subject randomization and before initiation of new anti-cancer therapy, crossover treatment and second course treatment

(Database Cutoff Date: 19Feb2020).

- It should also be noted that KRAS/NRAS wildtype/mutation status was not available for 27% of patients in KEYNOTE-177. As shown in Figures 38 and 39 in Appendix E of the submission, information on RAS-wildtype or RAS-mutant status was only available in 225 of the 307 patients randomised in the KEYNOTE-177 study.

It is also worth noting that subgroup analyses for the subgroup of patients with RAS-wildtype colorectal cancer are not necessary for the purposes of this appraisal, as the results from the analyses in the overall population would be reasonable and appropriate proxies for what would be observed in RAS-wildtype patients (i.e. would be more appropriate for use in decision making for the purposes of this appraisal than

results obtained from the under-powered and confounded RAS-wildtype subgroup analyses proposed in question A8):

- In the indirect treatment comparison networks presented as part of the submission, only panitumumab + FOLFOX is a comparator where RAS status is a treatment effect modifier and its use in the NHS is restricted to RAS-wildtype patients. As described in section B.2.9, *Uncertainties in the indirect and mixed treatment comparisons*, and in section B.2.13 of the submission, the results of analyses using the ITT population from KEYNOTE-177 are conservative with respect to the relative efficacy of pembrolizumab to panitumumab + FOLFOX (i.e. the results are very likely to be underestimates of the relative efficacy of pembrolizumab versus panitumumab + FOLFOX, in both RAS-wildtype and overall populations).

A9. Priority question: Based on results from studies evaluating FOLFOX versus FOLFIRI,[2] CAPOX versus FOLFOX,[3-6] and clinical expert opinion, the ERG is assuming equal clinical effectiveness of the three regimens. Please estimate the comparative treatment effectiveness in those without RAS-wildtype from KEYNOTE-177 (N=[redacted]). For SoC, please include those who received FOLFOX or FOLFIRI, with or without bevacizumab.

a. **Please provide the information requested in A8d for pembrolizumab versus SoC in people without RAS-wildtype.**

Similar to the case for the subgroup of patients with RAS-wildtype colorectal cancer, it would also be inappropriate to perform these analyses for the subgroup of patients with RAS-mutant colorectal cancer, and the results of such analyses would be inappropriate for use in decision making, for the same reasons as described in the response to question A8.

A10. For each of the fractional polynomial analyses provided in the company submission, please clarify:

- the number of iterations used as “burn-ins”;
- the number of iterations run for data collection;
- the priors implemented in the code.

The number of iterations used as “burn-ins” was 20,000 and the number of iterations run for data collection was 40,000. Normal non-informative priors were used with a mean of 0 and a variance of 10,000. For the first order fractional polynomials, these were implemented as follows:

$$\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\0\end{pmatrix},\begin{pmatrix}10^4 & 0\\ 0 & 10^4\end{pmatrix}\right)$$

$$\begin{pmatrix}d_{0Ak}\\ d_{1Ak}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\0\end{pmatrix},\begin{pmatrix}10^4 & 0\\ 0 & 10^4\end{pmatrix}\right)$$

Corresponding BUGS code:

```
for (j in 1:Ns){                          # Loop through studies
mu[j,1:2] ~ dmnorm(mean[1:2],prec[,])     # vague priors for all trial baselines
}

d[1,1]<-0                                 # alpha_0 treatment effect is zero for reference treatment
d[1,2]<-0                                 # alpha_1 treatment effect is zero for reference treatment

for (k in 2:Ntx){                         # Loop through treatments
d[k,1:2] ~ dmnorm(mean2[1:2],prec2[,])    # vague priors for treatment effects
}
```

For the second order fractional polynomials, these were implemented as follows:

$$\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\0\\0\end{pmatrix},\begin{pmatrix}10^4 & 0 & 0\\ 0 & 10^4 & 0\\ 0 & 0 & 10^4\end{pmatrix}\right)$$

$$\begin{pmatrix}d_{0Ak}\\ d_{1Ak}\\ d_{2Ak}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\0\\0\end{pmatrix},\begin{pmatrix}10^4 & 0 & 0\\ 0 & 10^4 & 0\\ 0 & 0 & 10^4\end{pmatrix}\right)$$

Corresponding BUGS code:

```
for (j in 1:Ns){                                  # Loop through studies
mu[j,1:3] ~ dmnorm(mean[1:3],prec[,])    # vague priors for all trial baselines
}

d[1,1]<-0                                         # alpha_0 treatment effect is zero for reference treatment
d[1,2]<-0                                         # alpha_1 treatment effect is zero for reference treatment
d[1,3]<-0                                         # alpha_2 treatment effect is zero for reference treatment

for (k in 2:Ntx){                                 # Loop through treatments
d[k,1:3] ~ dmnorm(mean2[1:3],prec2[,])  # vague priors for treatment effects
}
```

Section B: Clarification on cost-effectiveness data

Please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating any revised base case assumptions are provided. For any scenarios requested in Section B, please implement as user selectable options in the economic model.

Scenarios requested by the ERG may be summarized in tables split by population and comparator (akin to Tables 80-82 in the company submission).

Overall approach to cost-effectiveness analysis

B1. Priority question: As per question A8, the ERG considers that the company's NMA does not reflect the NICE final scope. Furthermore, the ERG's clinical experts do not consider surgery with curative intent to be an important outcome in the cost-effectiveness analysis. This is due to the small proportions of patients in each arm of KEYNOTE-177 who had surgery and the assumption of equal clinical outcomes for patients regardless of treatment regimen.

For simplicity, the ERG prefers the use of a three-health state structure for the economic analysis (progression-free, progressed disease and death). However, the partitioned survival model (PSM) employs OS data that is immature. The ERG therefore focuses on the company's state-transition model structure, but with the post-surgery health states, costs and utilities removed.

a. **Please provide cost-effectiveness analyses for populations A, B and C following the general approach outlined in Table 1 to Table 3 below, using a three health-state state-transition model. Please ensure that all other parameters are appropriately aligned for the population in the model, where not listed in the tables below.**

b. **Please conduct survival analysis as outlined in the company submission (and presented in Figure 17) for populations A, B and C, presenting model fit assessment plots and statistics and final model selection.**

All scenarios requested in the remainder of Section B should be explored for the analyses for population A, B and C. The response to question B1 can be provided as an addendum.

Table 1. Cost-effectiveness analysis approach – Population A (all patients – ITT population)

	Pembrolizumab	**SoC (FOLFOX/ FOLFIRI)**	**CAPOX**
Source of clinical data	As per company base case	As per company base case	Equal to FOLFOX/FOLFIRI
PFS (excl. surgery patients)	As per company base case	As per company base case	Equal to FOLFOX/FOLFIRI
Time to progression (TTP) (excl. surgery patients)	As per company base case	As per company base case	Equal to FOLFOX/FOLFIRI
Post progression survival (PPS) (excl. surgery patients)	As per company base case	As per company base case	Equal to FOLFOX/FOLFIRI
Time to treatment discontinuation (TTD)	As per company base case	As per company base case	TTD = PFS TTD = TTD SoC as a scenario
Treatment Costs	As per company base-case	As bevacizumab-containing regimens are not approved in the UK, costs should only reflect FOLFOX and FOLFIRI.	To only reflect CAPOX as per the company base-case
Utilities	As per company base-case	As per company base-case	As per company base-case
Adverse events	As per company base case	As per company base case	As per company base case

Table 2. Cost-effectiveness analysis approach – Population B (RAS wild-type)

	Pembrolizumab	Cetuximab + FOLFOX or FOLFIRI	Panitumumab + FOLFOX or FOLFIRI	SoC (FOLFOX/ FOLFIRI)	CAPOX
Source of clinical data	KEYNOTE-177 - RAS wildtype subgroup (excl. surgery patients)	ERG FP NMA (question A8)	ERG FP NMA (question A8)	KEYNOTE-177 - RAS wildtype subgroup (excl. surgery patients)	Equal to FOLFOX/ FOLFIRI
Baseline to apply per cycle time varying HRs	-	KEYNOTE-177 SoC - RAS wild-type	KEYNOTE-177 SoC - RAS wild-type	-	-
PFS (excl. surgery patients)	KEYNOTE-177 - RAS wildtype subgroup	ERG FP NMA (question A8) - time varying HR	ERG FP NMA (question A8) - time varying HR	KEYNOTE-177 - RAS wildtype subgroup	Equal to FOLFOX/ FOLFIRI
TTP (excl. surgery patients)	KEYNOTE-177 - RAS wildtype subgroup	ERG FP NMA (question A8) – PFS time varying HR	ERG FP NMA (question A8) – PFS time varying HR	KEYNOTE-177 - RAS wildtype subgroup	Equal to FOLFOX/ FOLFIRI
PPS (excl. surgery patients)	KEYNOTE-177 - RAS wildtype subgroup	Equal to pembrolizumab (as per company base case assumption)	Equal to pembrolizumab (as per company base case assumption)	Equal to pembrolizumab (as per company base case assumption)	Equal to FOLFOX/ FOLFIRI
TTD	KEYNOTE-177 - RAS wildtype subgroup	TTD = PFS TTD = TTD SoC (RAS wild-type) as a scenario	TTD = PFS TTD = TTD SoC (RAS wild-type) as a scenario	KEYNOTE-177 - RAS wildtype subgroup	TTD = PFS TTD = TTD SoC (RAS wild-type) as a scenario
Treatment Costs	As per company base-case	To reflect only cetuximab + FOLFOX or FOLFIRI	To reflect only panitumumab + FOLFOX or FOLFIRI as per company base case	As bevacizumab-containing regimens are not approved in the UK, costs should only reflect FOLFOX and FOLFIRI.	To reflect only CAPOX as per company base case
Utilities	As per company base-case	As per company base-case	- As per company base-case - Results from question B3 as a scenario	- As per company base-case - Results from question B3 as a scenario	As per company base-case
Adverse events	As per company base case	Update fixed effects NMA to include cetuximab	As per company base case	As per company base case	As per company base case

Table 3. Cost-effectiveness analysis approach – Population C (non-RAS wild-type)

	Pembrolizumab	SoC (FOLFOX/ FOLFIRI)	CAPOX
Source of clinical data	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	Equal to FOLFOX/FOLFIRI

PFS (excl. surgery patients)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	Equal to FOLFOX/FOLFIRI
TTP (excl. surgery patients)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	Equal to FOLFOX/FOLFIRI
PPS (excl. surgery patients)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	Equal to pembrolizumab (as per company base case assumption)	Equal to FOLFOX/FOLFIRI
TTD	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	KEYNOTE-177 – non-RAS-wild type subgroup (question A9)	TTD = PFS TTD = TTD SoC (non-RAS wild type) as a scenario
Treatment Costs	As per company base-case	As bevacizumab-containing regimens are not approved in the UK, costs should only reflect FOLFOX and FOLFIRI.	To reflect only CAPOX as per company base case
Utilities	As per company base-case	- As per company base-case - Results from question B3 as a scenario	- As per company base-case - Results from question B3 as a scenario
Adverse events	As per company base case	As per company base case	As per company base case

In line with the responses ‘A8’ and ‘A9’ MSD has not performed any analyses on the RAS and non-RAS wild type subgroups.

As per the ERG request the cost effectiveness model (CEM) was modified to implement the changes requested. Within the CEM modification a three-health state, state transition model was used. All surgery rates have been set to 0% and TTP, PFS and PPS data including patients who had undergone surgery was utilised. MSD believe this was the more appropriate methodology as opposed to completely excluding all surgery patients. However, MSD did not adjust for FOLFOX/FOLFIRI in which efficacy is based on KN177 SoC and costs are based on FOLFOX/FOLFIRI only (not combinations with cetuximab/ bevacizumab). cetuximab- and bevacizumab-containing regimens are more effective than FOLFOX/FOLFIRI alone and many patients in KN177 received these therapies as such we feel this modification would be overly conservative at it would take into account the efficacy of the eGFR therapies but not the costs associated with them. All results will be generated from the three-health state, state transition model.

In the modified base case analysis, the estimated mean overall survival was 6.92 years with pembrolizumab and 3.78 years with SoC. Patients treated with pembrolizumab accrued 4.24 QALYs compared to 2.38 among patients in the SoC cohort. Table 7 presents the base case cost-effectiveness results for pembrolizumab versus SoC, incorporating the discount of the CAA. The results show pembrolizumab to be cost-effective compared to SoC when considering a willingness to pay threshold of £30,000 per QALY.

Table 7: Modified Base-case Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	13,497	1.86	7,250
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Additional analyses considering the NMA-related comparators showed an estimated mean overall survival of 6.92 years with pembrolizumab versus 3.78 with CAPOX and 4.10 with FOLFOX + panitumumab. Patients treated with pembrolizumab accrued 4.25 QALYs compared to 2.39 and 2.56 versus CAPOX and FOLFOX + panitumumab respectively.

Table 8 and

Table ***9*** below present the cost-effectiveness results for pembrolizumab, incorporating the discount of the CAA compared to CAPOX and FOLFOX + panitumumab.

Table 8: Base-case Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.85	27,480
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 9: Base-case Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,317	1.68	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Fully incremental ICERs are shown in Table 10. CAPOX was the least costly alternative and dominates FOLFOX + panitumumab which was found to be the least effective.

Table 10: Incremental Analysis Results

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.86	27,343
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	48,317	-1.68	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Modelling Time to Progression (TTP)

Both one-piece and two-piece models were fitted to the data. Two-piece models were fit from two distinct cut-off points: 10 weeks and 20 weeks.

Figure 1: One Piece Parametric Fit

Figure 2: Two-piece (10 weeks) Parametric Fit

Figure 3: Two-piece (20 weeks) Parametric Fit

Referring to the figures above (Figure 1, Figure 2 and Figure 3), the two-piece at 20 weeks more closely followed the TTP Kaplan Meier data.

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The statistical goodness of fit for each parametric distribution are presented in Table 11, showing good fit across both arms with Exponential, Gompertz and Log-logistic.

Table 11: Summary of goodness-of-fit qualities of TTP survival models at 20-week cut-off point – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	192.94	195.39	1	486.54	489.05	3
Weibull	194.88	199.79	5	487.33	492.35	5
Gompertz	194.34	199.25	3	485.49	490.51	2
Log-logistic	194.65	199.56	4	485.29	490.31	1
Log-normal	193.87	198.78	2	486.50	491.52	4
Generalised Gamma	195.42	202.78	6	487.76	495.29	6

Furthermore, as shown in Figure 3 all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period to yield substantially different long-term extrapolations. Hence the base-case TTP curve selection was based primarily on the clinical plausibility of long-term predictions.

Modelling Progression free survival

Both one-piece and two-piece models were fitted to the data. Two-piece models were fit from two distinct cut-off points: 10 weeks and 20 weeks.

Figure 4: One-piece Parametric Fit

Figure 5: Two-piece (10 weeks) Parametric Fit

Figure 6: Two-piece (20 weeks) Parametric Fit

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The statistical goodness of fit for each parametric distribution are presented in Table 12. Across both arms, the best fit was shown to be the Exponential extrapolation.

Table 12: Summary of goodness-of-fit qualities of PFS survival models at 20-week cut-off point – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	307.17	309.63	1	691.20	693.73	1
Weibull	309.15	314.08	5	691.47	696.53	2
Gompertz	309.06	314.00	4	692.40	697.47	3
Log-logistic	309.01	313.95	3	695.19	700.25	5
Log-normal	308.77	313.70	2	701.81	706.87	6
Generalised Gamma	310.75	318.15	6	693.35	700.95	4

As Figure 6 shows, all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period to yield different long-term extrapolations. As a result, the PFS curve selection was also based on clinical plausibility of long-term predictions and the exponential curve was the most appropriate choice.

Modelling Post-progression Survival

As was the case in the original submission, statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution. The statistical goodness of fit for each parametric distribution are presented in Table 13 showing good fit across both arms with Lognormal, Generalised Gamma and Log-logistic.

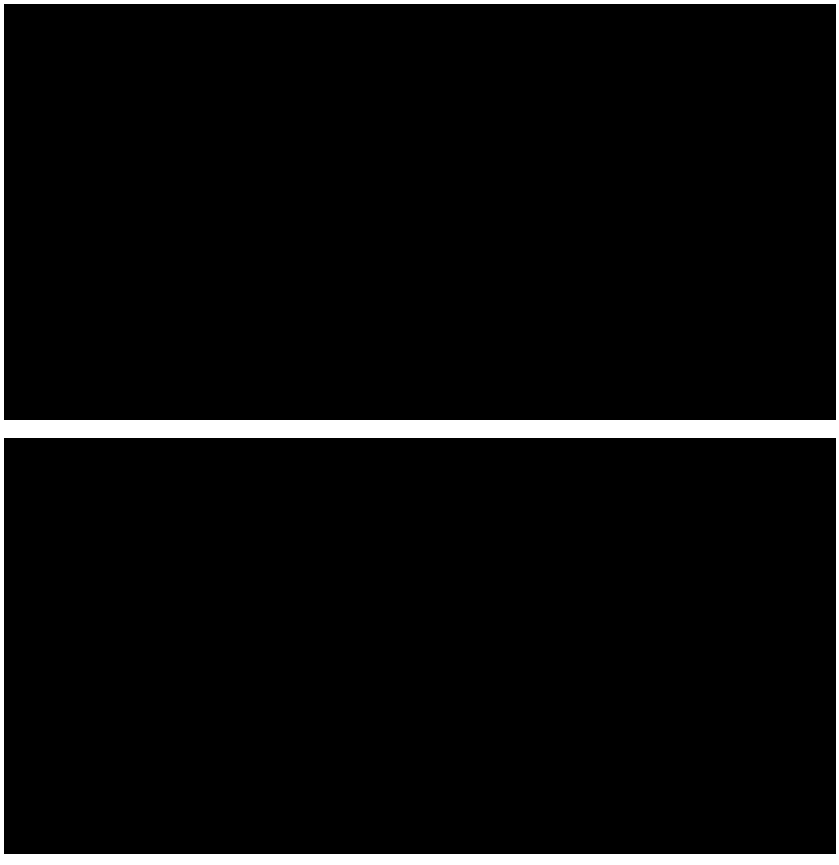
Table 13: Summary of goodness-of-fit qualities of PPS survival models – pembrolizumab and SoC

Fitted Function	Pembrolizumab		Statistical Rank	SoC		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	441.83	444.00	6	484.80	487.26	6

Weibull	436.73	441.08	5	480.44	485.34	5
Gompertz	434.99	439.34	4	471.14	476.05	1
Log-logistic	434.70	439.05	2	476.43	481.34	4
Log-normal	432.76	437.11	1	473.54	478.44	2
Generalised Gamma	433.69	440.21	3	471.99	479.35	3

Visual inspection combined with external validity was used for parametric curve selection. As seen in Figure 7, all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period yielding different long-term extrapolations. Hence the base-case curve selection was based on external validation from a ten-year multicenter follow-up study of patients diagnosed with dMMR/MSI-H CRC (Tougeron et al. 2020 [https://doi.org/10.1002/ijc.32879]). Figure 7 below shows a superimposed curve of the Tougeron results alongside all six parametric curves, the graph shows the extrapolation to closely follow the Tougeron et al. results is the Weibull curve. As a result, this was selected for the base case analysis.

Figure 7: One-piece Parametric Fit



Survival modelling

B2. Priority question: Please describe what is meant by one-piece and two-piece models for the extrapolation of clinical data? Based on information in Table 72, two-piece models use KM data up to the cut-off point and then extrapolated using standard parametric distributions (sometimes defined as hybrid models) rather than single parametric distributions for each defined time period (as described in DSU TSD 14). In addition, one-piece models seem to be single standard parametric curves used for the entire time horizon.

Yes, the description above is correct. The economic model was used to estimate the outcomes of treatment over a 40-year time horizon in the base case scenario. Health state occupancy was determined using a piecewise modelling approach, comprising of Kaplan Meier (KM) curves for progression-free survival (PFS), Time to Progression (TTP) until a cut-off point and thereafter, parametric survival curves fitted to the clinical trial data. Cut-off points of 20 weeks for PFS and TTP were used and extrapolated beyond this time point using the exponential curve in the base case analysis. The extrapolation choice was because this gave the best fit as depicted by the AIC and BIC criteria and it is the standard model to use in a piecewise approach (Latimer et al. 2013 [NICE Decision Support Unit Technical Support Document 14]). In addition, the piecewise parametric extrapolation provided a closer visual fit than a one-piece parametric extrapolation.

For Post progression survival a single parametric curve was used to estimate the outcomes of treatment over the 40-year time horizon. One-piece models were estimated by taking consideration of the KM data. This was used due to immature trial data. As per the DSU TSD 14 document, parametric distributions were fitted to the observed KM data from week 0.

B3. Please justify why the one-piece exponential distribution was selected for the extrapolation of time on treatment for SoC, as no reason is provided in the company submission.

The choice of the one-piece model is because the data for time on treatment (ToT) are relatively mature with a relatively smooth curve. Due to the maturity of the Kaplan-

Meier data, selection of the parametric curve was based on statistical fit as can be seen in Table 14 below, the exponential curve showed the best statistical fit. A graphical representation of the parametric curves can be seen in Figure 8 below.

Table 14: Summary of goodness-of-fit Statistics (ToT)

Fitted Function	SoC		Statistical Rank
	AIC	BIC	
Exponential	1269.44	1272.40	1
Weibull	1271.43	1277.35	5
Gompertz	1269.76	1275.69	2
Log-logistic	1269.91	1275.84	3
Log-normal	1282.95	1288.87	6
Generalised Gamma	1270.90	1279.79	4

Figure 8: Time on Treatment (ToT) Data for SoC Arm

Health-related quality of life

B4. Priority question: Please provide the results of tests for statistical significance to determine whether or not treatment specific utility values are used for specific health states in the model.

MSD would like to clarify the statement "In addition, 95% confidence intervals were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested". The misunderstanding comes from the latter part of the sentence referring to the statistical significance being tested. the intended meaning of the statement is that the utility values in pre-progression health state were identified as statistically significantly different between treatment arms

since the 95% confidence intervals do not overlap; allowing the use of different utilities between both arms.

B5. Priority question: In TA439, the ERG stated that utilities for patients based on RAS-wild type were preferred but data were unavailable. As utility data from KEYNOTE-177 are available and RAS wildtype status for patients is known, please provide utility values for the RAS wildtype and the non-RAS wildtype subgroups and explore these as a scenario analysis for population B and C.

As stated previously MSD does not believe an analysis looking at this subgroup is robust. Due to reasons specified in response 'A8' and 'A9'we believe results from such an analysis will not be informative due to limitations stated in response 'A8' and 'A9'.

B6. Priority question: Please provide a scenario where health state utilities based on the pooled estimates in Table 60 of the company submission are used in the model.

a) **Please provide an alternative scenario where the pooled progression-free AE utility value is applied only in the first cycle, after which the progression-free no AE utility value is implemented.**

The ability to implement health state utilities based on pooled estimates was included in the CEM. Control selections to implement this scenario are (controls: "con_HSUV.pembro", "con_HSUV.pembro.pp", "con_HSUV.SoC", "con_HSUV.SoC.pp"). Results based on these changes in the modified CEM are as follows:

In the scenario analysis, the estimated mean overall survival was 6.92 years with pembrolizumab and 3.78 years with SoC. Patients treated with pembrolizumab accrued 4.16 QALYs compared to 2.42 among patients in the SoC cohort. Table 15 presents the scenario analysis cost-effectiveness results for pembrolizumab versus SoC, incorporating the discount of the CAA. The results show pembrolizumab to be cost-effective compared to SoC when considering a willingness to pay threshold of £30,000 per QALY.

Table 15: Pooled Utilites Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	13,497	1.73	7,762
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

When considering the NMA-related comparators, results showed an estimated mean overall survival of 6.92 years with pembrolizumab versus 3.78 with CAPOX and 4.10 with FOLFOX + panitumumab. Patients treated with pembrolizumab accrued 4.16 QALYs compared to 2.43 and 2.60 versus CAPOX and FOLFOX + panitumumab respectively.

The tables below present the cost-effectiveness results for pembrolizumab, incorporating the discount of the CAA compared to CAPOX and FOLFOX + panitumumab.

Table 16: Pooled Utilites Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.72	29,432
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 17: Pooled Utilites Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,317	1.55	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Fully incremental ICERs are shown in Table 18. CAPOX was the least costly alternative and dominates FOLFOX + panitumumab which was found to be the least effective.

Table 18: Incremental Analysis Results (pooled Utilities)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.73	29,275
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	48,317	-1.55	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

When pooled progression-free AE utility value is applied only in the first cycle, the results are as follows:

Table 19: 1st Cycle Pooled Utilities Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	13,497	1.77	7,615
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 20: 1st Cycle Pooled Utilities Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.76	28,869
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 21: 1st Cycle Pooled Utilities Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,317	1.58	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 22: Incremental Analysis Results (1st Cycle Pooled Utilities Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.77	28,718
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	48,317	-1.58	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

As is shown in the tables above pembrolizumab remains a cost-effective option in all scenarios versus the treatment regimes in use.

B7. Priority question: Please provide a scenario implementing the pooled time-to-death health state utilities in the model.

As stated in the original submission (page 128), MSD does not believe the use of time-to-death utilities is robust enough for decision making. This is due to the very low observation numbers for patients especially in the category closest to death.

B8. Page 134 of the company submission states that the utility impact of adverse events (AEs) is not included in the model. However, in the controls tab of the model,

cell D106, ‘Include adverse events disutilities’ is set to “yes”. Please confirm which is correct?

MSD would like to clarify the statement in the aforementioned page. The sentence currently reads “the utility impact of AEs associated with subsequent therapies is not included in the economic model”. Within the model adverse disutilities are implemented but only to the first line treatments and not subsequent treatments.

B9. Priority question: Table 4 presents a comparison of utility values used in the model as listed in the company submission and applied in the model. Please review the table and clarify which utility values should be used in the company's base case analysis for the state-transition model. Please amend either the text or the model as necessary.

Table 4. Utility values – company submission vs. economic model

	Presented in company submission				Applied in model			
Health state	**Pembrolizumab**	**SoC**	**CAPOX**	**mFOLFOX 6 + panitumumab**	**Pembrolizumab**	**SoC**	**CAPOX**	**mFOLFOX 6 + panitumumab**
Progression-free	**0.852** – progression-free no AE (Table 60 of company submission)	**0.80** - progression-free no AE (Table 60 of company submission)			**0.843** - progression-free (Table 60 of company submission)	**0.787** - progression-free (Table 60 of company submission)		
AEs (disutility)	**0.032** – Table 61 of company submission	**0.044** – Table 61 of company submission	**0.035** – Table 61 of company submission	**0.092** – Table 61 of company submission	**0.032**	**0.032**	**0.025**	**0.066**

MSD apologise for the confusion caused. The utility to be used in the base case analysis are the ones included in the model:

Base case values				
Health State	**Pembrolizumab**	**SoC**	**CAPOX**	**mFOLFOX6 + panitumumab**
Progression-free	0.843	0.787		
AEs (disutility)	0.032	0.032	0.025	0.066

Costs and resource use

B10. Priority question: In KEYNOTE-177, patients who stopped pembrolizumab with locally confirmed complete response (CR), or stable disease (SD) or better at the end of the Initial Treatment Phase may be treated with up to 17 administrations of pembrolizumab in a Second Course Treatment Phase. However, in the economic model, a stopping rule of 35 treatment cycles has been implemented.

a) **Please complete the table below.**

b) **Please clarify why the second course treatment phase was not included in the stopping rule?**

c) **Please provide a scenario where the second course of treatment with pembrolizumab (17 cycles) is included in the treatment stopping rule.**

d) **The summary of product characteristics states that treatment with pembrolizumab can be continued until disease progression or unacceptable toxicity. To test the sensitivity of the model, please provide a scenario where pembrolizumab TTD is equal to PFS.**

Measure	**Cycles of pembrolizumab (including the second course of treatment)**
Mean (standard deviation)	19.29 (14.39)
Median (range)	16.00 (1.00 – 50.00)
Number of people receiving up to 35 cycles	150

Number of people receiving between 36 and 52 cycles	3
Number of people receiving more than 52 cycles	0

b) In line with previous pembrolizumab NICE submissions such as Pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer [ID1140] the second course treatment phase is excluded from the analyses. Please note, 4 patients received a second course of treatment and as such the impact to the results is expected to be negligible.

Though Keynote 177 protocol states that treatment should continue until disease progression or unacceptable toxicity, the maximum possible treatment duration with pembrolizumab monotherapy was 35 cycles. Implementing a 2-year stopping rule is consistent with other NICE technology appraisal guidance such as untreated NSCLC (TA531 and TA557).

c) However, as requested by the ERG an option has been included within the CEM to consider the cost of retreatment, the results of which can be found below. To implement this change, the drug acquisition and administration costs for pembrolizumab were multiplied by 1 + the proportion of patients on pembrolizumab who received retreatment in KN177. This is a simplification that results in a very conservative estimate of pembrolizumab's ICER as the mean duration of retreatment is shorter than the mean duration of initial treatment (29.5 vs. 57.7 weeks) and as retreatment costs are incurred later than the initial treatment costs and should ideally have been more heavily discounted. In addition, retreatment can last a maximum of 17 cycles whilst the initial treatment is for 35 cycles, this means that this modification is likely to include twice the cost that is expected.

Table 23: Pembrolizumab Retreatment Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	14,848	1.86	7,976
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 24: Pembrolizumab Retreatment Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	52,253	1.85	28,210
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 25: Pembrolizumab Retreatment Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-46,965	1.68	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 26: Incremental Analysis Results (Pembrolizumab Retreatment Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	14,848	1.86	28,069
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	46,965	-1.68	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

d) MSD believes that ToT data are more appropriate to be used in the cost-effectiveness model as treatment discontinuation can occur for reasons other than progressed disease such as adverse events, withdrawal and physician's

decision. This is demonstrated by the graph below which was generated to show PFS versus TTD. Observed in the graph is a slight difference towards the tail between PFS and ToT.

Figure 9: Pembrolizumab PFS vs. ToT

B11. Priority question: Page 146 of the company submission states that subsequent treatment proportions from KEYNOTE-177 are used for the base case, however in the economic model, proportions from clinical expert feedback are used (tab "Subsequent treatment costs", cells G13:G20 and G26:G33). Please confirm which is correct?

a) Please provide the alternative to the base-case selection as a scenario analysis.

MSD can confirm subsequent treatment proportions from clinical feedback were used in the base case analysis. Results for the scenario analysis using KN177 subsequent treatment proportions are as follows:

Table 27: KN177 Subsequent Treatment Proportion Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	8,316	1.86	4,467

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 28: KN177 Subsequent Treatment Proportion Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	45,721	1.85	24,683
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 29: KN177 Subsequent Treatment Proportion Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-53,422	1.68	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 30: Incremental Analysis Results (KN177 Subsequent Treatment Proportion Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	45,721	1.86	24,560
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	53,422	-1.68	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

As the results show, pembrolizumab still remains a cost-effective option compared to the current therapy choices when the subsequent treatment proportions from the trial are used.

B12. Priority question: The ERG's clinical experts advised that in clinical practice, pembrolizumab would be given at 400mg once every 6 weeks. Please

provide a scenario analysis implementing the 400mg once every 6 weeks treatment regimen for pembrolizumab.

The results of the 6-weekly dosing of pembrolizumab can be found in the tables below. Like all other scenario analyses, pembrolizumab remains a cost-effective treatment option.

Table 31: 6-Weekly Dosing Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	12,970	1.86	6,967
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 32: 6-Weekly Dosing Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,375	1.85	27,196
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 33: 6-Weekly Dosing Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,843	1.68	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 34: Incremental Analysis Results (6-Weekly Dosing Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	0.02	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,375	1.86	27,061
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	48,843	-1.68	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B13. The ERG's clinical experts advised that liver function tests and consultant outpatient appointments (pre-progression) would occur once every treatment cycle. Please provide a scenario analysis where the above resources are incorporated into the assumptions presented in Table 68 of the company submission.

The functionality has been included in the CEM. Within the control sheet if "con_RU" is set to "Yes" the resource use estimates suggested by the ERG are used. The results of which are as shown below. The results suggest pembrolizumab remains a cost-effective option in this scenario.

Table 35: Health State Resource Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	7,516	1.86	4,037
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 36: Health State Resource Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	46,823	1.85	25,278
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 37: Health State Resource Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-54,301	1.68	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 38: Incremental Analysis Results (Health State Resource Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	39,307	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	46,823	1.86	25,152
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	54,301	-1.68	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B14. The dosing schedule for mFOLFOX6 + panitumumab in Table 66 of the company submission does not match the data in the economic model (tab "Drug acquisition costs" cells D18:D22 and F18:F22). Furthermore, Table 66 does not present the dosing schedule for CAPOX, but it is provided in the model. Please clarify the dosing schedules for mFOLFOX6+panitumumab and CAPOX.

Treatment	Drug	Dosing per administration (mg, mg/kg or mg/m²)		Dose per adminstration (mg)	Dosing frequency
CAPOX	Oxaliplatin	130	mg/m²	235	once every 3 weeks
	Capecitabine	1000	mg/m²	1810	Twice daily for first two weeks, then 1 week off
mFOLFOX6 + panitumumab	Fluorouracil bolus	400	mg/m²	724	once every 2 weeks
	Fluorouracil infusion	2400	mg/m²	1,086	
	Leucovorin	300	mg/m²	362	
	Oxaliplatin	85	mg/m²	154	
	Panitumumab	6	mg/kg	427	

Model functionality and sensitivity analyses

B15. Priority question: In the company submission, costs of adverse events are included in the model only in the first cycle. However, in the one-way sensitivity analysis, the top 10 key drivers of the model for each comparator are adverse event parameters.

a) Please explain why adverse event parameters are a key driver of cost-effectiveness for pembrolizumab as opposed to utility values or costs that are applied per cycle for the lifetime of the model?

MSD believes this was due to an error in the VBA code not capturing all parameters. This has now been amended with an updated tornado diagram shown in section b.

b) Please provide the one-way sensitivity analysis where adverse event incidence and frequencies are excluded.

Figure 10: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. SoC

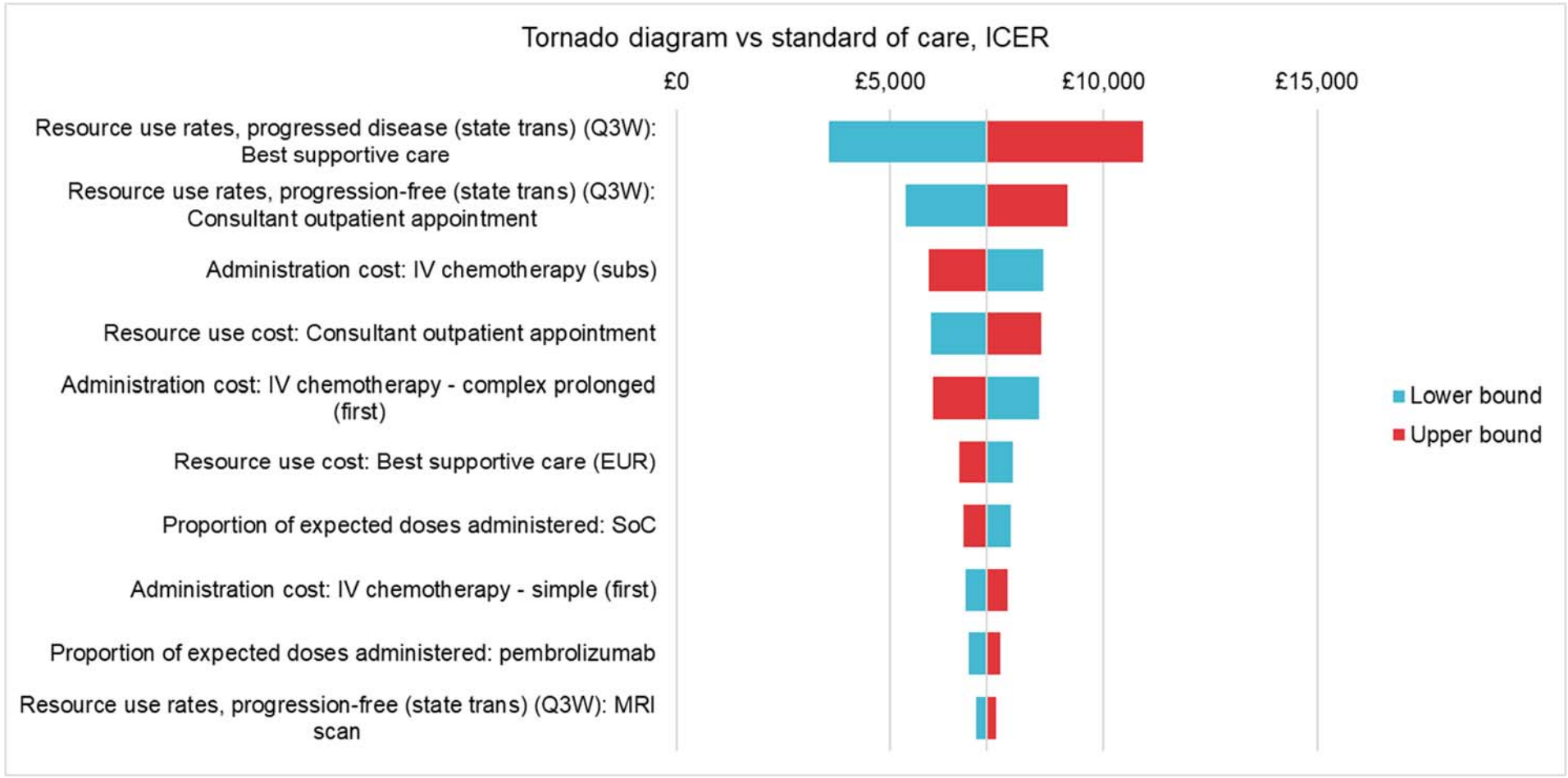


Figure 11: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. CAPOX

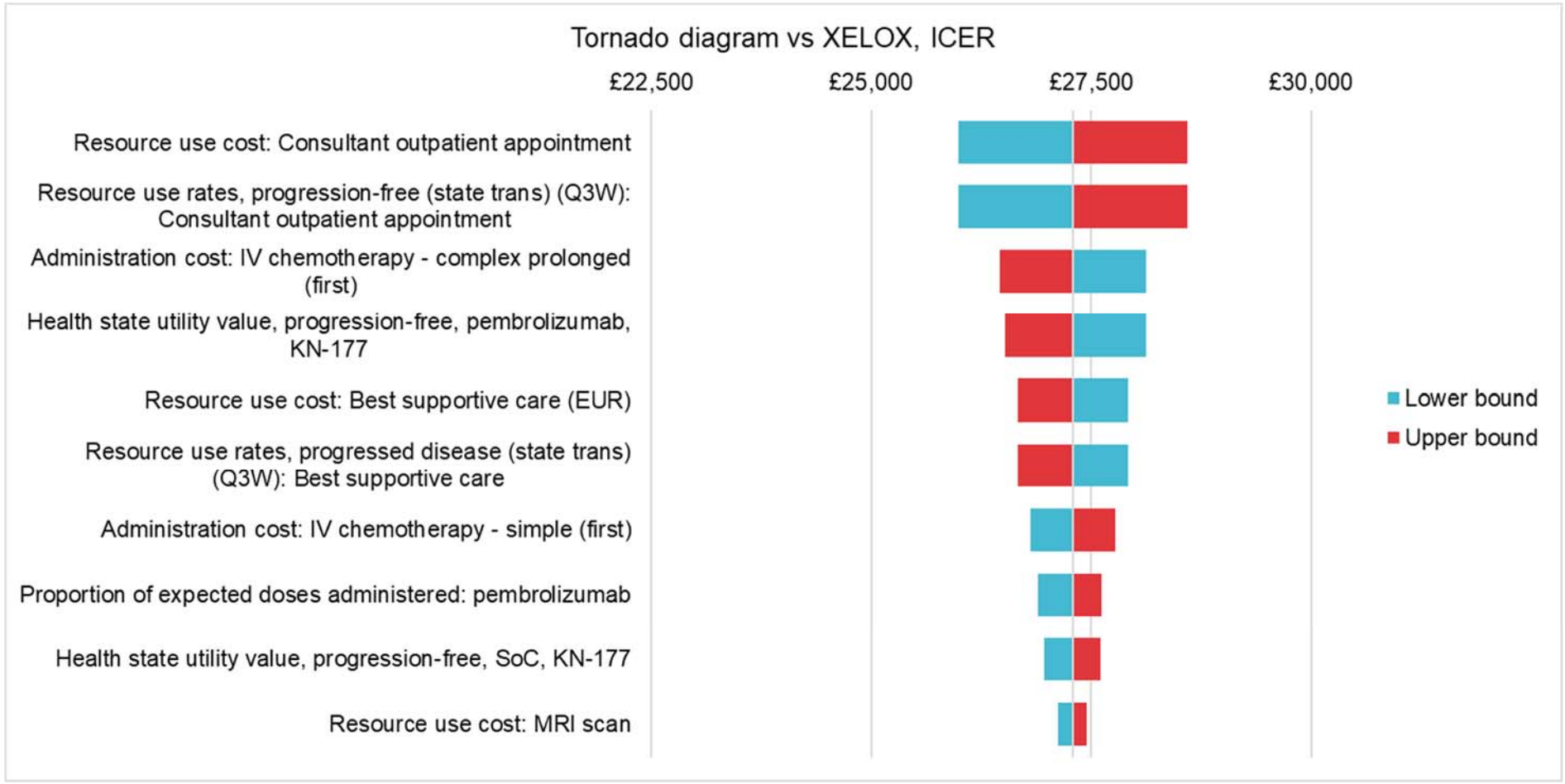
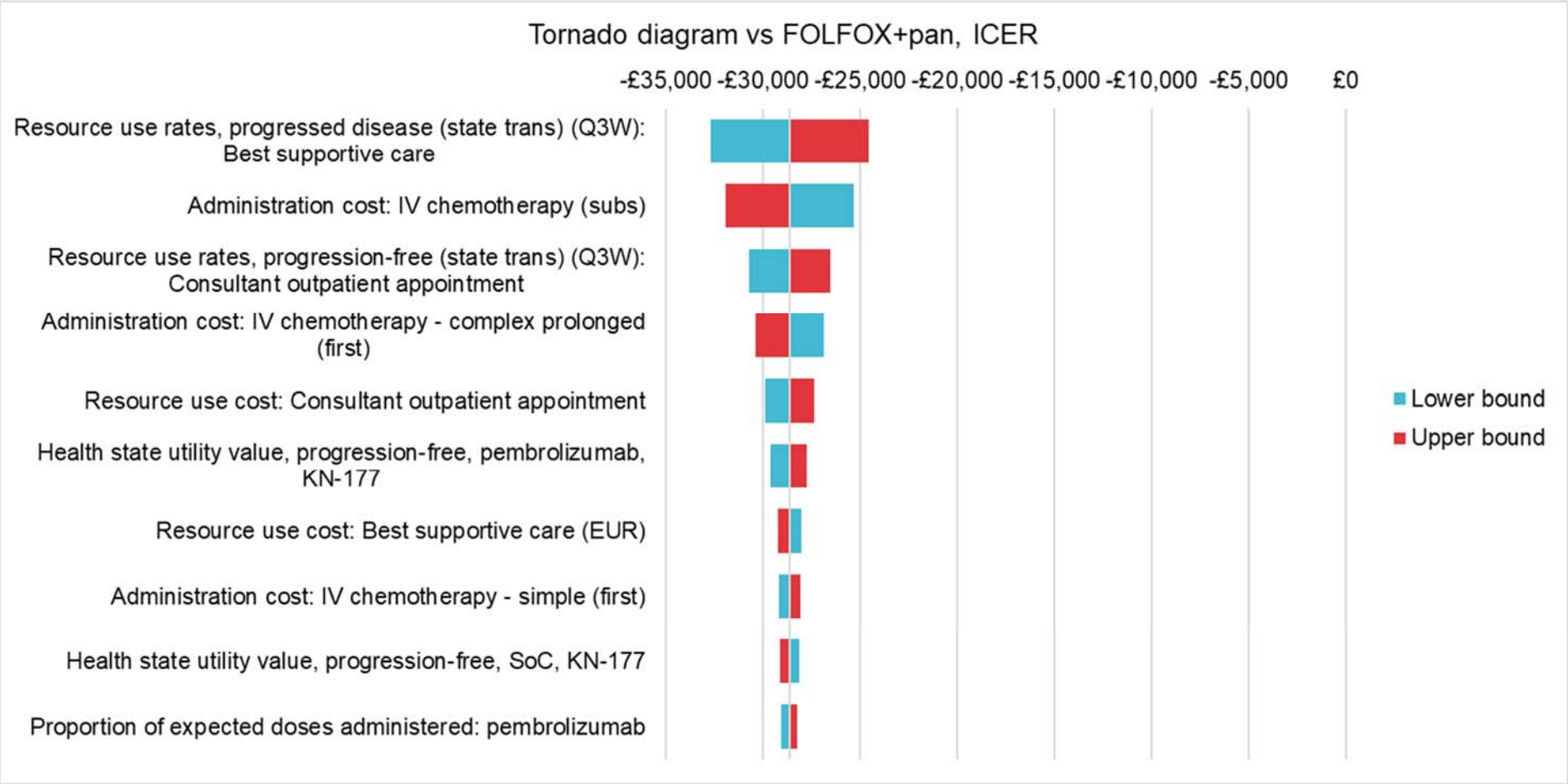


Figure 12: Tornado diagram presenting one-way DSA results: Pembrolizumab vs. FOLFOX + panitumumab



B16. Please add functionality to the economic model to allow alternative fractional polynomial models to be explored and provide scenario analyses based on different plausible FP model fits.

This has now been included in the CEM, the results of which are shown in the tables below. The scenario analyses results are in line with other scenarios showing pembrolizumab to be cost-effective when compared to the current treatment regimen.

Table 39: Alternative FP NMA Scenario Analysis Results versus SoC

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizuamb	[redacted]	[redacted]	[redacted]	13,497	1.86	7,250
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 40: Alternative FP NMA Scenario Analysis Results versus CAPOX

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.85	27,480
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 41: Alternative FP NMA Scenario Analysis Results versus FOLFOX + panitumumab

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-45,829	1.71	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 42: Incremental Analysis Results (Alternative FP NMA Scenario Scenario Analysis)

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	37,405	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,902	1.86	27,343
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	45,829	-1.71	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B17. Please clarify how the plots presented in Figure 42 and Figure 43 of the company submission were obtained using the economic model.

The PSA and scatterplots have been updated in line with the revised CEM. The scatterplots in the figures below are a representation of incremental costs versus incremental QALYs for each of the comparisons. To create the quadrant layout of the scatterplot in the figures mentioned, the graphs from the CEM were formatted at the x and y axis to include negative figures to enable the plot to be viewed as a quadrant. The line represents the willingness to pay threshold of £30,000. The simulation results show that versus Soc, CAPOX and FOLFOX + panitumumab, pembrolizumab falls on or below the willingness-to-pay threshold of £30,000.

Figure 13: Scatterplot for Pembrolizumab vs. SoC

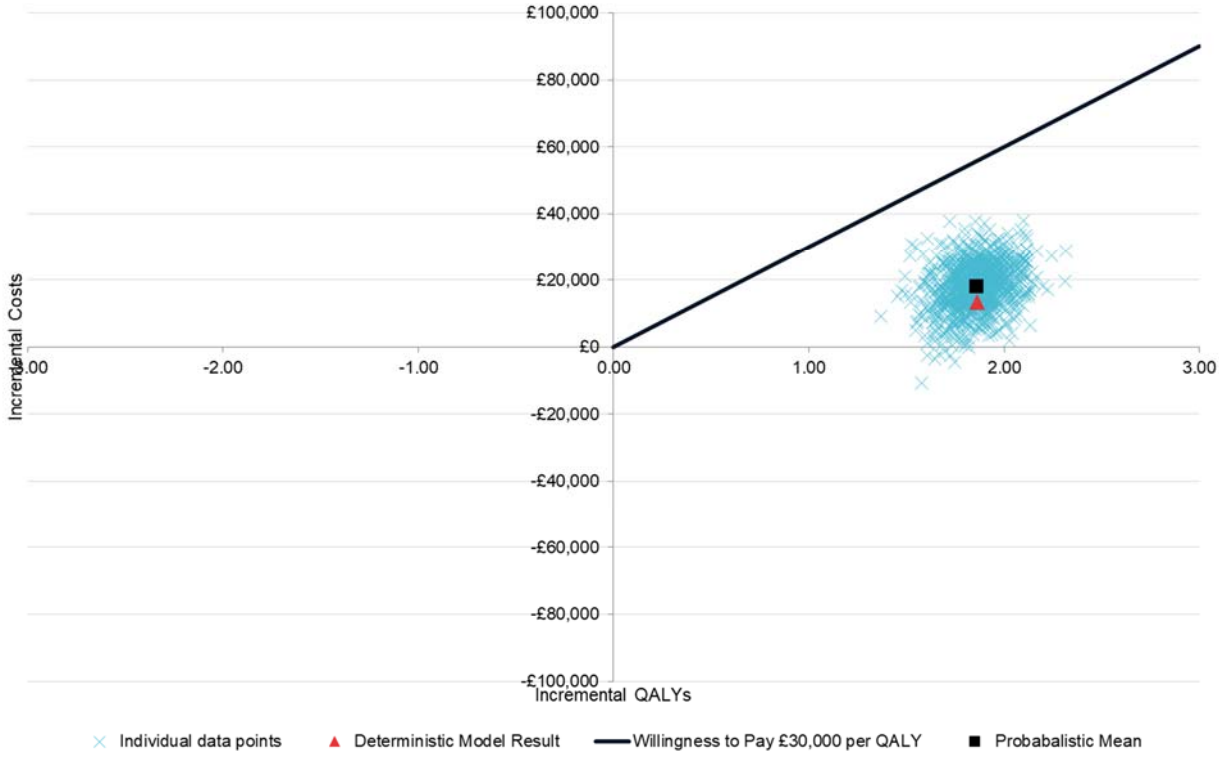


Figure 14: Scatterplot for Pembrolizumab vs. CAPOX

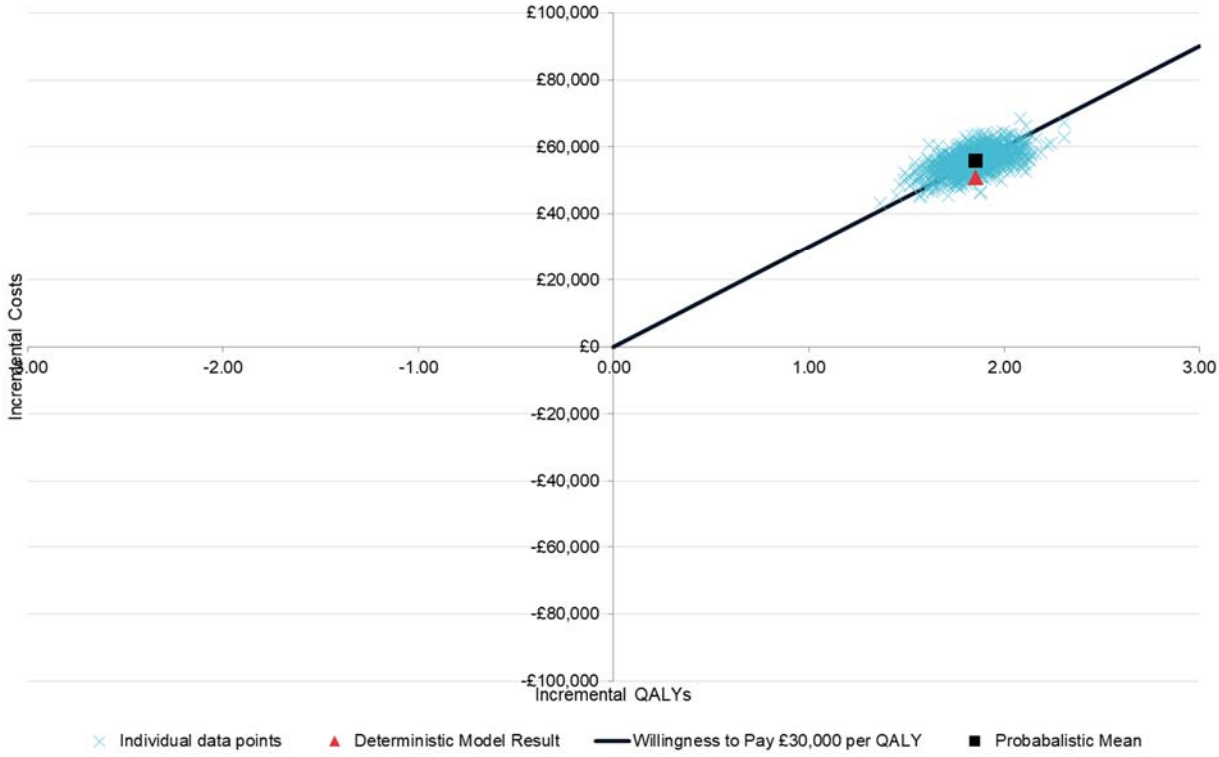
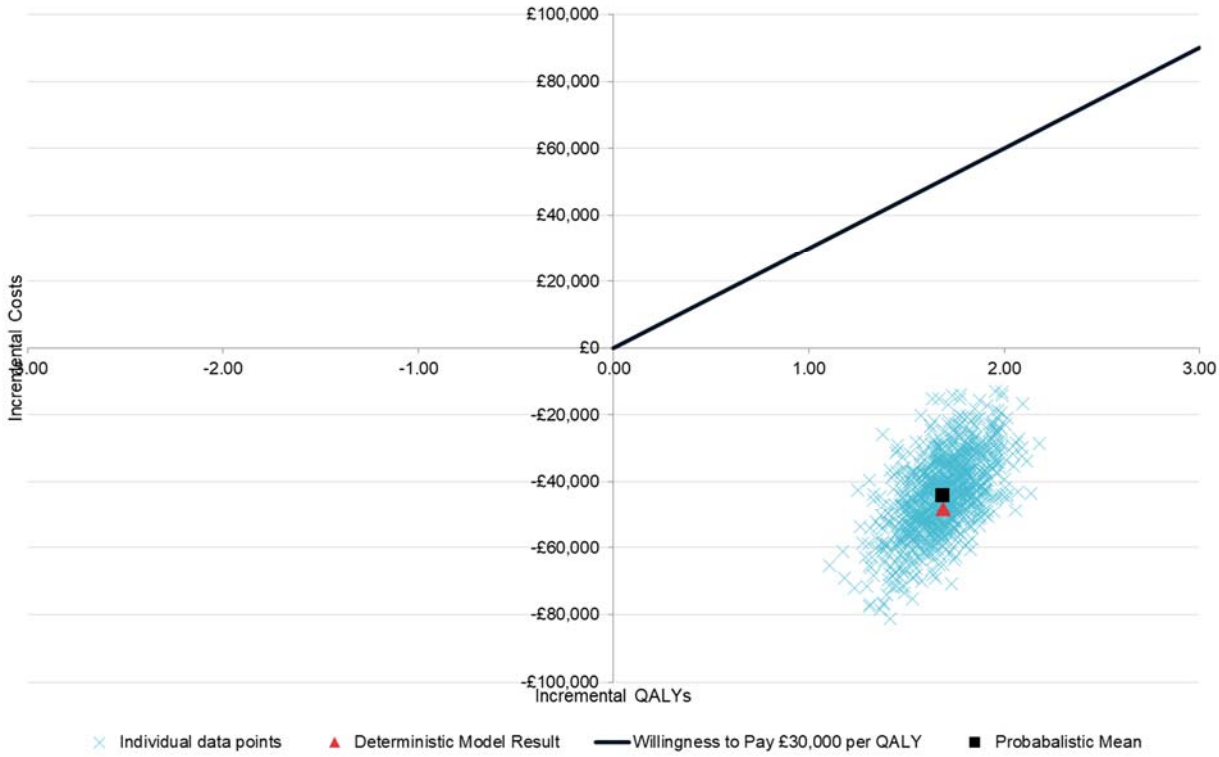


Figure 15: Scatterplot Pembrolizumab vs. FOLFOX + panitumumab



Section C: Textual clarification and additional points

Clinical data

C1. Please clarify how many people from the UK were included in the pembrolizumab and standard care groups in the ITT population of KEYNOTE-177.

Number of patients by country and treatment groups is presented in Table 43. A total of 20 patients (10 in each treatment group) were randomised from the UK.

Table 43 Patient characteristics - distribution of countries (ITT Population), KEYNOTE-177 study

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	153		154		307	
Country						
Australia	7	(4.6)	6	(3.9)	13	(4.2)
Belgium	3	(2.0)	1	(0.6)	4	(1.3)
Brazil	8	(5.2)	4	(2.6)	12	(3.9)
Canada	4	(2.6)	2	(1.3)	6	(2.0)
Denmark	9	(5.9)	13	(8.4)	22	(7.2)
Finland	3	(2.0)	2	(1.3)	5	(1.6)
France	17	(11.1)	19	(12.3)	36	(11.7)
Germany	3	(2.0)	3	(1.9)	6	(2.0)
Ireland	2	(1.3)	2	(1.3)	4	(1.3)
Israel	4	(2.6)	4	(2.6)	8	(2.6)
Italy	0	(0.0)	2	(1.3)	2	(0.7)
Japan	12	(7.8)	10	(6.5)	22	(7.2)
Korea, Republic of	6	(3.9)	8	(5.2)	14	(4.6)
Netherlands	6	(3.9)	8	(5.2)	14	(4.6)
Norway	4	(2.6)	5	(3.2)	9	(2.9)
Singapore	1	(0.7)	4	(2.6)	5	(1.6)
South Africa	3	(2.0)	1	(0.6)	4	(1.3)
Spain	17	(11.1)	12	(7.8)	29	(9.4)
Sweden	1	(0.7)	3	(1.9)	4	(1.3)
Switzerland	3	(2.0)	3	(1.9)	6	(2.0)
Taiwan	3	(2.0)	4	(2.6)	7	(2.3)
United Kingdom	10	(6.5)	10	(6.5)	20	(6.5)
United States	27	(17.6)	28	(18.2)	55	(17.9)
Database Cutoff Date: 19FEB2020.						

C2. For Table 20 of the company submission, please clarify whether the 95% confidence intervals accompanying the median OS should actually be interquartile ranges.

The 95% confidence intervals accompanying the median OS are calculated based on the sign test (Brookmeyer, R. and Crowley, J. [1982], "A Confidence Interval for the Median Survival Time," Biometrics, 38, 29–41. doi:10.2307/2530286), so are the limits of the median survival times from the Kaplan-Meier method and not interquartile ranges.

C3. Please clarify which application should be used to open the files with the *.dig extension, which were supplied as part of the fractional polynomial analysis.

Kaplan-Meier curves were extracted in terms of the proportion of patients who had an event over time using DigitizeIt® (https://www.digitizeit.de/) in addition to the number of patients at risk over time. The software can be downloaded from the website in order to view the extracted data in the .dig files.

Cost-effectiveness analysis

C4. Priority question: Please provide details of the NMA used to generate odds ratios for adverse events (described on page 127 of the company submission). Please report:

- **the dataset used in the NMA;**
- **the number of iterations used as "burn-ins";**
- **the number of iterations run for data collection;**
- **the priors implemented in the code;**

- **the appropriate measures of assessment to demonstrate why the fixed effects model was selected.**

The dataset used for the NMA of adverse events is presented in Table 44. The number of iterations used as "burn-ins" was 40,000 and the number of iterations run for data collection was 80,000.

Table 44 Dataset used to conduct network meta-analysis of adverse events

Study	Reference	Intervention	Ref, N	Int, N	Grade ≥3 AEs (reference)		Grade ≥3 AEs (intervention)	
					N	%	N	%
KEYNOTE-177[a]	SOC	Pembrolizumab	143	153	111	77.6	86	56.2
NO16966	FOLFOX-4 + Placebo/FOLFOX-4	XELOX + Placebo/XELOX	648	655	506	78.1	468	71.5
PRIME	FOLFOX	Panitumumab + FOLFOX	327	322	227	69.4	270	83.9
TREE-1	FOLFOX	XELOX	99	48	59	59.6	35	72.9

Normal non-informative priors were used with a mean of 0 and a variance of 10,000, with BUGS code set up as follows:

```
for(i in 1:ns){                          # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001)T(-7,7)            # vague priors for all trial baselines
}
d[1]<-0                                  # treatment effect is zero for reference treatment
beta[1]<-0                               # covariate effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001)T(-7,7)   # vague prior for treatment effect
beta[k]<-B                               # common covariate effect
}
B ~ dnorm(0,.0001)T(-7,7)                # vague prior for covariate effect
```

The random effects model had a slightly lower DIC relative to the fixed effects model ([redacted] versus [redacted]); however, as almost all connections in the safety network were only described by a single trial, stable estimates of between-study heterogeneity could not be obtained. This resulted in credible intervals that were not meaningful i.e. values at or very close to zero for the lower bound and implausibly high values for the upper bound (up to [redacted]), therefore the results of fixed-effects analyses were preferred.

References

1. Morris TP, Jarvis CI, Cragg W, Phillips PPJ, Choodari-Oskooei B, Sydes MR. Proposals on Kaplan-Meier plots in medical research and a survey of stakeholder views: KMunicate. *BMJ Open* 2019; **9**: e030215.
2. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; **23**: 4866-75.
3. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011; **105**: 58-64.
4. Porschen R, Arkenau HT, Kubicka S, Greil R, Seufferlein T, Freier W, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin Oncol* 2007; **25**: 4217-23.
5. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008; **26**: 3523-9.
6. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. *Int J Cancer* 2011; **128**: 682-90.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID1498 Pembrolizumab Additional ERG clarification question	1	No	20/10/2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Fractional polynomial Network Meta-Analysis

A1. The ERG have reviewed the files supplied in response to the request for data implemented in the fractional polynomial (FP) network meta-analysis (NMA), including digitised plots, Excel spreadsheets and BUGS code. However, it could not locate the single dataset that would be run in the BUGS code. There are insufficient data in some of the supplied Excel spreadsheets NRISK tab (e.g. PRIME Douillard 2014 KRAS wt Panitumumab) to allow the ERG to construct the dataset used by the company.

To ensure that the ERG's validation has maximum chance of reproducing that run by the company:

a. Please complete the table below to provide the data as analysed/incorporated in the FP. The ERG is focusing on progression free survival and so only requires the dataset for the FP depicted in Figure 15 of the company submission.

b. Please indicate the number attributed to each study and each treatment as a separate key. For example, 1 = KEYNOTE-177 for study, and 1 = pembrolizumab for treatment.

The data used in the FP NMA of PFS is provided in the table below, along with the key index used to indicate study name and treatment name.

Key index:

- Study number:
  - 1 = KEYNOTE-177 (not including patients treated with bevacizumab-containing regimens, i.e. “ITT-bevacizumab” population),
  - 2 = Porschen_2007,
  - 3 = PRIME
- Treatment and comparator number:
  - 1 = SOC (mFOLFOX or FOLFIRI with or without Cetuximab),
  - 2 = Pembrolizumab,
  - 3 = SOC (FOLFOX),
  - 4 = XELOX,
  - 5 = SOC (FOLFOX4),
  - 6 = Panitumumab + FOLFOX4

Study number	Number of events		Number at risk		Treatment		Comparator		Time interval	
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										
1										

Study number	Number of events	Number at risk	Treatment	Comparator	Time interval
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	0	231	3	4	1
2	11	228	3	4	1
2	13	214	3	4	1
2	14	198	3	4	1

Study number	Number of events	Number at risk	Treatment	Comparator	Time interval
2	10	181	3	4	1
2	13	168	3	4	1
2	12	152	3	4	1
2	24	134	3	4	1
2	13	106	3	4	1
2	12	89	3	4	1
2	9	75	3	4	1
2	8	64	3	4	1
2	7	54	3	4	1
2	7	46	3	4	1
2	8	37	3	4	1
2	2	28	3	4	1
2	2	23	3	4	1
2	2	19	3	4	1
2	2	15	3	4	1
2	0	13	3	4	1
2	0	12	3	4	1
2	1	12	3	4	1
2	2	10	3	4	1
2	0	8	3	4	1
2	0	8	3	4	1
2	1	7	3	4	1
2	0	5	3	4	1
2	1	4	3	4	19
2	2	239	4	3	1
2	10	235	4	3	1
2	17	222	4	3	1
2	14	201	4	3	1
2	18	185	4	3	1
2	24	164	4	3	1
2	14	133	4	3	1
2	18	109	4	3	1
2	9	84	4	3	1
2	11	66	4	3	1
2	12	55	4	3	1
2	6	42	4	3	1
2	3	35	4	3	1
2	6	31	4	3	1
2	3	24	4	3	1
2	1	21	4	3	1
2	0	19	4	3	1
2	3	18	4	3	1
2	0	15	4	3	1
2	1	14	4	3	1
2	1	12	4	3	1
2	0	10	4	3	1
2	0	8	4	3	1
2	0	7	4	3	1
2	0	7	4	3	1
2	1	7	4	3	1

Study number	Number of events	Number at risk	Treatment	Comparator	Time interval
2	0	5	4	3	1
2	0	5	4	3	1
2	1	5	4	3	18
3	3	331	5	6	1
3	18	328	5	6	1
3	17	310	5	6	1
3	33	293	5	6	1
3	5	260	5	6	1
3	38	255	5	6	1
3	11	217	5	6	1
3	36	206	5	6	1
3	5	170	5	6	1
3	25	165	5	6	1
3	11	140	5	6	1
3	21	129	5	6	1
3	9	108	5	6	1
3	15	99	5	6	1
3	4	84	5	6	1
3	8	80	5	6	1
3	10	72	5	6	1
3	5	62	5	6	1
3	7	57	5	6	1
3	1	50	5	6	1
3	7	49	5	6	1
3	4	42	5	6	1
3	1	38	5	6	1
3	4	37	5	6	1
3	1	33	5	6	1
3	0	32	5	6	1
3	1	32	5	6	1
3	5	31	5	6	1
3	1	26	5	6	1
3	0	25	5	6	1
3	3	25	5	6	1
3	3	22	5	6	1
3	0	19	5	6	1
3	0	19	5	6	1
3	2	19	5	6	1
3	0	17	5	6	1
3	0	17	5	6	1
3	3	17	5	6	1
3	6	325	6	5	1
3	15	319	6	5	1
3	9	304	6	5	1
3	26	295	6	5	1
3	9	269	6	5	1
3	31	260	6	5	1
3	10	229	6	5	1
3	20	219	6	5	1
3	10	199	6	5	1

Study number	Number of events	Number at risk	Treatment	Comparator	Time interval
3	27	189	6	5	1
3	11	162	6	5	1
3	10	151	6	5	1
3	12	141	6	5	1
3	12	129	6	5	1
3	10	117	6	5	1
3	12	107	6	5	1
3	6	95	6	5	1
3	7	89	6	5	1
3	7	82	6	5	1
3	1	75	6	5	1
3	3	74	6	5	1
3	6	71	6	5	1
3	2	65	6	5	1
3	5	63	6	5	1
3	2	58	6	5	1
3	5	56	6	5	1
3	0	51	6	5	1
3	7	51	6	5	1
3	4	44	6	5	1
3	4	40	6	5	1
3	4	36	6	5	1
3	4	32	6	5	1
3	5	28	6	5	1
3	0	23	6	5	1
3	3	23	6	5	1
3	1	20	6	5	1
3	0	19	6	5	1
3	1	19	6	5	1
3	0	18	6	5	1
3	0	18	6	5	1

Responses to the clarification questions sent on 24-NOV-2020 with regard to the company submission for pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

1.

The data set used for the time varying hazard 2nd order fractional polynomial NMA of PFS for the full study ITT population from KEYNOTE-177. Please include data appropriate for use in OpenBUGS i.e. to include the data inputs variables:
s[] r[] z[] a[] time[] dt[]
Where s = study number, r = number of events, z = number at risk, a = treatment, time = time, and dt = time interval

The data used in the FP PFS NMA analysis is provided in the table below, along with the indexes used to indicate study and treatment. All time and time intervals are in months.

Indexes:

- Study number: 1 = KEYNOTE-177 (ITT), 2 = Porschen_2007, 3 = PRIME
- Treatment: 1 = SOC, 2 = XELOX, 3 = Panitumumab + FOLFOX4, 4 = Pembrolizumab

s	r	z	a	time	dt
1	3	154	1	1	1
1	13	148	1	2	1
1	14	132	1	3	1
1	11	114	1	4	1
1	14	100	1	5	1
1	2	85	1	6	1
1	9	81	1	7	1
1	1	70	1	8	1
1	9	68	1	9	1
1	2	58	1	10	1
1	8	55	1	11	1
1	1	45	1	12	1
1	2	43	1	13	1
1	2	41	1	14	1
1	3	38	1	15	1
1	1	35	1	16	1
1	4	33	1	17	1
1	0	29	1	18	1
1	4	28	1	19	1
1	0	23	1	20	1
1	1	22	1	21	1
1	0	21	1	22	1
1	1	21	1	23	1
1	2	20	1	24	1
1	0	18	1	25	1
1	1	18	1	26	1
1	1	16	1	27	1

s	r	z	a	time	dt
1	2	14	1	28	1
1	1	11	1	29	1
1	1	10	1	30	1
1	2	8	1	39	9
1	12	153	4	1	1
1	16	141	4	2	1
1	22	125	4	3	1
1	9	103	4	4	1
1	4	94	4	5	1
1	2	88	4	6	1
1	1	83	4	7	1
1	0	80	4	8	1
1	0	77	4	9	1
1	2	77	4	10	1
1	0	74	4	11	1
1	0	73	4	12	1
1	6	72	4	13	1
1	0	66	4	14	1
1	0	65	4	15	1
1	0	64	4	16	1
1	1	64	4	17	1
1	1	63	4	18	1
1	1	62	4	19	1
1	0	60	4	20	1
1	0	60	4	21	1
1	0	60	4	22	1
1	0	58	4	23	1
1	0	57	4	24	1
1	1	55	4	25	1
1	0	52	4	26	1
1	0	47	4	27	1
1	1	44	4	28	1
1	2	38	4	29	1
1	0	33	4	30	1
1	0	29	4	31	1
1	1	26	4	32	1
1	1	20	4	43	11
2	0	231	1	1	1
2	11	228	1	2	1
2	13	214	1	3	1
2	14	198	1	4	1
2	10	181	1	5	1
2	13	168	1	6	1
2	12	152	1	7	1
2	24	134	1	8	1
2	13	106	1	9	1
2	12	89	1	10	1
2	9	75	1	11	1

s	r	z	a	time	dt
2	8	64	1	12	1
2	7	54	1	13	1
2	7	46	1	14	1
2	8	37	1	15	1
2	2	28	1	16	1
2	2	23	1	17	1
2	2	19	1	18	1
2	2	15	1	19	1
2	0	13	1	20	1
2	0	12	1	21	1
2	1	12	1	22	1
2	2	10	1	23	1
2	0	8	1	24	1
2	0	8	1	25	1
2	1	7	1	26	1
2	0	5	1	27	1
2	1	4	1	46	19
2	2	239	2	1	1
2	10	235	2	2	1
2	17	222	2	3	1
2	14	201	2	4	1
2	18	185	2	5	1
2	24	164	2	6	1
2	14	133	2	7	1
2	18	109	2	8	1
2	9	84	2	9	1
2	11	66	2	10	1
2	12	55	2	11	1
2	6	42	2	12	1
2	3	35	2	13	1
2	6	31	2	14	1
2	3	24	2	15	1
2	1	21	2	16	1
2	0	19	2	17	1
2	3	18	2	18	1
2	0	15	2	19	1
2	1	14	2	20	1
2	1	12	2	21	1
2	0	10	2	22	1
2	0	8	2	23	1
2	0	7	2	24	1
2	0	7	2	25	1
2	1	7	2	26	1
2	0	5	2	27	1
2	0	5	2	28	1
2	1	5	2	46	18
3	3	331	1	1	1
3	18	328	1	2	1

s	r	z	a	time	dt
3	17	310	1	3	1
3	33	293	1	4	1
3	5	260	1	5	1
3	38	255	1	6	1
3	11	217	1	7	1
3	36	206	1	8	1
3	5	170	1	9	1
3	25	165	1	10	1
3	11	140	1	11	1
3	21	129	1	12	1
3	9	108	1	13	1
3	15	99	1	14	1
3	4	84	1	15	1
3	8	80	1	16	1
3	10	72	1	17	1
3	5	62	1	18	1
3	7	57	1	19	1
3	1	50	1	20	1
3	7	49	1	21	1
3	4	42	1	22	1
3	1	38	1	23	1
3	4	37	1	24	1
3	1	33	1	25	1
3	0	32	1	26	1
3	1	32	1	27	1
3	5	31	1	28	1
3	1	26	1	29	1
3	0	25	1	30	1
3	3	25	1	31	1
3	3	22	1	32	1
3	0	19	1	33	1
3	0	19	1	34	1
3	2	19	1	35	1
3	0	17	1	36	1
3	0	17	1	37	1
3	3	17	1	38	1
3	6	325	3	1	1
3	15	319	3	2	1
3	9	304	3	3	1
3	26	295	3	4	1
3	9	269	3	5	1
3	31	260	3	6	1
3	10	229	3	7	1
3	20	219	3	8	1
3	10	199	3	9	1
3	27	189	3	10	1
3	11	162	3	11	1
3	10	151	3	12	1

s	r	z	a	time	dt
3	12	141	3	13	1
3	12	129	3	14	1
3	10	117	3	15	1
3	12	107	3	16	1
3	6	95	3	17	1
3	7	89	3	18	1
3	7	82	3	19	1
3	1	75	3	20	1
3	3	74	3	21	1
3	6	71	3	22	1
3	2	65	3	23	1
3	5	63	3	24	1
3	2	58	3	25	1
3	5	56	3	26	1
3	0	51	3	27	1
3	7	51	3	28	1
3	4	44	3	29	1
3	4	40	3	30	1
3	4	36	3	31	1
3	4	32	3	32	1
3	5	28	3	33	1
3	0	23	3	34	1
3	3	23	3	35	1
3	1	20	3	36	1
3	0	19	3	37	1
3	1	19	3	38	1
3	0	18	3	39	1
3	0	18	3	40	1

2.

The initial values and data structure as implemented in the above analysis using the following format:

#Initial values
list(d = structure(.Data = c(NA,NA,NA,-0.5,-1,-1,-0.5,-1,-1,-0.5,-1,-1), .Dim = c(4,3)), mu = structure(.Data = c(-2,-1,-1,-2,-1,-1,-2,-1,-1), .Dim = c(3,3)))

#Data
list(mean=c(0,0,0), prec2 = structure(.Data = c(0.0001, 0, 0, 0, 0.0001, 0, 0, 0, 0.0001), .Dim = c(3,3)), P1=0, P2=1, Ns=3, Ntx=4, N=196, maxt=40)

In our analysis, all initial values were randomly selected within JAGS, and therefore we cannot provide the requested information in the above structure. (Note: Compared to OpenBUGS and WinBUGS, JAGS is more robust to initial value selection).

3.

The mean values and associated 95% credible intervals for beta1, beta2 and beta3 in the company analysis of PFS using the company preferred values of P1 and P2 (P1=0 and P2=1) for the full study ITT population from KEYNOTE-177.

Correction: The preferred values of P1 and P2 for the PFS analysis using full study ITT population from KEYNOTE-177 should be P1 = 0 and P2 = 0, as shown in Table 41 of the company submission.

The mean values and associated 95% credible internals for beta1, beta2, and beta3 for each intervention are summarized in the table below. Beta[i,j] indicates Beta i for treatment j, where j = 1 represents SOC, j = 2 represents XELOX, j = 3 represents Panitumumab + FOLFOX4, j = 4 represents Pembrolizumab.

	Mean	X50.[Median]	X2.5.	X97.5.
[redacted]				

4.

Please can the company confirm that they have run the NMA with sufficient iterations to converge on the posterior distribution (e.g. using the Brooks-Gelman-Rubin diagnostic statistic).

The number of iterations used as "burn-ins" was 20,000 (2 chains) and the number of iterations run for data collection was 40,000 (2 chains). According to the density and Gelman plots (shown in the *MCMC_Diag_Consistency_Model.pdf* file provided along with this response document), the number of iterations were deemed sufficient to converge on the posterior distribution.

5.

Please can the company inform the ERG which parameters need to be monitored in the code to generate the values for d0 and d1 as provided in Table 43 for PFS in the company submission.

The BUGS (used in JAGS) code used for the 2nd order FP model is presented below. Please monitor "d[k,0]" and "d[k,1]" to generate the values for d0 and d1. In addition, please be note that due to the limited data, we assumed d2 = 0 (treatment only has an effect on Beta1 and Beta 2) and therefore only d0 and d1 are provided below.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Bowel Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UK's leading bowel cancer charity. We are determined to save lives and improve the quality of life of everyone affected by bowel cancer by championing early diagnosis and access to best treatment and care. We support and fund targeted research, provide expert information and support to patients and their families, educate the public and professionals about the disease and campaign for early diagnosis and access to best treatment and care. The majority of our income is generated from individual, corporate and trust fundraisers. A small proportion (£78,048) is given by a handful of pharmaceutical companies in support of training for nurses, patient information and international activity in bowel cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information provided was gathered from a survey of people diagnosed with advanced bowel cancer with high microsatellite instability or mismatch repair deficiency carried out by Bowel Cancer UK. We posted the survey on social media and our patient online forum for one week, and asked our Medical Advisory Board members to share it with relevant patients. In addition we have used experiences from existing case studies gathered from patients diagnosed with advanced bowel cancer. The patients are a mixture of those treated with immunotherapy - nivolumab with ipilimumab, nivolumab only and pembrolizumab, as well as patients who have broader experience of a range of treatments for their metastatic bowel cancer.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of bowel cancer is life changing and can affect almost every aspect of daily life, not only for the individual diagnosed but also for their family and loved ones. This is even more acute for those diagnosed at the metastatic stages of the disease, when it is harder to treat and the chance of survival is low. Patients experience numerous difficulties and challenges across the pathway, from initial diagnosis, to treatment and care. In particular, these relate to the impact and reality of an incurable bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on quality of life. Patients used words like **'devastating', 'tough', 'a battle', stressful' and 'difficult'** to describe their overall experience living with advanced bowel cancer. Our community told us:

	"It is extremely difficult, challenging, with pain on various levels; physical, emotional, psychological, and spiritual. It impacts work, relationships, social life." *"Living with cancer is both a physical and mental condition that requires support from professional experts and family to help one through the unknown and difficult journey ahead. It greatly affects your thought process and daily outlook on life leading to anxiety and depression."* *"Chemo was tough but in some ways it has been harder afterwards. During chemo I felt like something was being done to combat the cancer. I am back at work and struggling. Very tired. But trying to stay positive."* *"There is a level of anxiety especially when scan or blood test results are due."* Patients undergoing treatments for metastatic bowel cancer experience a range of side effects, which significantly affect their quality of life – both physically and emotionally. Bowel Cancer UK has heard from a number of metastatic bowel cancer patients who are experiencing painful side effects while going through treatment with cetuximab and panitumumab as first line treatment. Prolonged use of these drugs causes a number of skin toxicities and side effects including: **Extremely painful red skin rashes and fissures; Dry and peeling skin across hands, feet and face; Cystic, painful acne-like spots; Severe paronychia; Loss of eye lashes and eye soreness; Nausea; Diarrhoea; Reduced appetite**. Patients have also emphasised the **psychological impact** continued treatment has had. Many patients have described how their side effects have left them feeling **debilitated**, **isolated** and **self-conscious**. Unfortunately, often patients do not get access to the treatment and support to alleviate these side effects. *"In December 2017, treatment was commenced with chemotherapy (FOLFIRI) and a biological targeted therapy - panitumumab. Despite a rocky start with severe side effects of diarrhoea, abdominal pains, fatigue, severe neutropenia and skin rash, 6 cycles were completed with a dose titration. A CT scan concluded a phenomenal response with marked regression of multiple tumours in the liver."* *"I started treatment in October 2019. I had Folfox and Panitumumab….My skin was incredibly dry and despite the constant use of moisturiser, I was like a walking Head and Shoulders advert……I became incredibly sensible to extremes of temperature. I was tired, almost constantly exhausted.* *I was covered in spots, all over my scalp and face. It spread to my chest and back. I would wake up each morning with blood on my pillows and throughout my treatment it got worse. Some days I was literally peeling my face off my pillow…. As time progressed this got me more and more depressed. I know it is horrible but I had to comb through my beard trying to gently remove the dried blood and puss. It was painful and made me feel embarrassed.*

	I also lost a lot of the feeling in my hands and feet, which still has yet to return….My memory has been badly affected. I struggle with names and lose track of what I have been saying, as well as struggle to concentrate."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Survival rates for metastatic bowel cancer are poor, with less than one in ten people surviving more than five years. These patients deserve access to the best quality treatment and care. For some patients these drugs can be lifesaving, while for others they can prolong life, resulting in more time to spend with loved ones. Therefore, it is essential patients gain timely access to the treatments that their clinicians feel could benefit them. However, current treatment options approved for use on the NHS for metastatic bowel cancer are extremely limited. The impact of this on patients in terms of both survival and psychologically is detrimental, with many patients unable to access a treatment that could prolong their life and give them the best possible outcome. This also has financial implications for patients and their families, with many resorting to fundraising or borrowing money to fund treatments privately. For patients and their families, this inequity of access causes unnecessary stress, worry and anxiety when they are already struggling to come to terms with being diagnosed with bowel cancer. Limiting access in this way means that patients may miss out on treatments that could extend their life. The majority of patients felt that treatment options available on the NHS were 'limited' or 'inadequate' for those with metastatic bowel cancer, especially so for those with high microsatellite instability or mismatch repair deficiency. "*In the context of the latest breakthrough science and research I believe a lot of the treatment options are outdated… these aren't always best options for the patient. The side effects from chemotherapy are devastating*." *"The bowel cancer with mismatch repair deficiency which I suffered meant only limited drugs were available to actively combat the disease as immunotherapy is not currently approved by NICE. I received chemotherapy treatment (Avastin) which unfortunately didn't work…the cancer increased. I then received Nivolumab (the costs were covered by my medical provider). The improvement following the immunotherapy were apparent within a couple of months."* *"My treatment (Nivolumab with ipilimumab) was fabulous however I feel treatment options for those with bowel cancer are limited and the most effective treatments need to be made more widely available."* *"Poor, colon cancer second biggest killer, early onset colorectal cancer rising rapidly, most current treatments are 20 to 30 years old, folfiri, folfox! And existing treatments don't seem to work very well."*

	"Very limited. Early phase trials often only have a 5-10% chance or doing anything. Lack of scanners and leading edge technologies leaves UK trailing along way behind European countries." *"Current treatments as in chemotherapy are barbaric! Tolerable but barbaric."* *"They are inadequate for a whole patient population with lynch syndrome/ MSI high genetics."*
8. Is there an unmet need for patients with this condition?	Bowel Cancer UK believe that there is an unmet need for this specific patient population and all of our responders of the survey feedback a similar view. There are currently extremely limited treatment options available for people diagnosed with metastatic bowel cancer with high microsatellite instability or mismatch repair deficiency. As such, patients described a range of issues across the pathway relating to diagnosis, treatment and care. *"Metastatic Bowel cancer patients vary in nature (lynch syndrome, MSI high etc), yet they are all treated the same, and are given the same treatment lines as they were from decades ago. This being so regardless of the advancements in drug development such as immunotherapy. Therefore those with genetic certain genetic bowel cancers are at a disadvantage, whereby the chemo offered most likely won't work."* *"Yes, 5% of metastatic cancer patients are MSI high but only a very small fraction of this number are offered immunotherapy with checkpoint inhibitors."* *"Bowel cancer is the poor relation compared to other cancers."* *"This patient population have unique genetic profile which needs a personalised approach. These newer immunotherapy treatments are a lifesaver, yet are tragically unavailable on the NHS."* *"Yes, the majority of NHS patients cannot afford to pay for this treatment, once a patient has had chemotherapy treatment and not had any beneficial response to it there doesn't seem to be any other treatment available."* *"I don't know anyone with my condition, or who is on immunotherapy, so felt quite isolated in those terms."* *"Absolutely. Diagnostic equipment is lagging and new treatments/technologies are not available."*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients have told us that immunotherapies and medicines that are personalised offer patients greater **hope**, **additional treatment choice, extended life** and **less debilitating side effects** of medicines that may not work for their genetic profile. The **absence of side effects** like vomiting, diarrhea and fatigue means patients have a **better quality of life**. Another benefit is the **speed** and **duration** of the treatment. A pembrolizumab infusion can be over within 30 minutes and the cycles are every 3 weeks. Whereas chemo involves a 48 hour pump in addition to a few hours in the hospital, every 2 weeks. This means **fewer hospital visits**, **reduction in travel time and cost**. One patient said*: "These drugs are lifesaving and life enriching. I was a terminal patient, after a year of chemotherapy failed to control my cancer diagnosed in 2014. Because of my lynch syndrome/ MSI high, I was a good candidate for immunotherapy. The NHS rejected my individuals funding requested, and as a last resort I crowdfunded £200,000 for pembrolizumab. I began pembro in June 2016 until May 2017. I have not had any treatment since, and I am 'No evidence of disease'. I have reached 6 years since my stage 4 bowel cancer diagnosis. This goes against the expectancy guides on the NHS. How many other people can have an enriched life with these new treatments? It's tragic that money, and lack of access, is the reason why this patient population die when incredible treatment is out there."* *Another patient said about Pembrolizumab: "Given me more time to be alive. My cancer has been kept under control. I'm able to sleep well, and wake up with hope. Prior to receiving immunotherapy, my cancer progressed whilst on the chemo. They were growing and showing signs of spreading into other organs.* *After 4 cycles of immunotherapy, my tumours reduced significantly. I went on to have 16 cycles over a 1-year period and each scan showed a continued response. With the tumours under control**, I've been able to get back to everyday things such as driving, going for walks unassisted, spending time with family and friends, attending sporting events**."* *Other comments include: "These treatments target the cancer differently, with some **incredible results** in comparison to the traditional chemotherapy that's routinely offered on the NHS. The side effects are less intrusive, and the treatment is administered in a considerably shorter time period. Chemo can be plugged in for over 48 hours, immunotherapy can be all done within an hour."* *"The huge benefit to the patient's quality and extended life. The cost and time saving benefits for the NHS"*

	*"Advantages: quicker intravenous applications, longer intervals between treatments, next to nothing in terms of side effects. I can work and interact with others as normal (unlike chemotherapy). Most importantly**… I live**, and the disease is currently dormant!"*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients raised some disadvantages of the treatment, including the **cost** and **lack of access** for most people, as well as **questions about its effectiveness** and the fact there is some evidence of **longer-term effects** that can result from the treatment including **ulcerative colitis** and **rheumatoid arthritis**. *"The cost and lack of access. Not enough doctors are aware of Lynch Syndrome, and how immunotherapy is targeted for this profile."* *"Some evidence of longer term issues e.g. adrenal gland issues, colitis."* *"The length of time it worked for me."* *"Very expensive. Still unpredictable in terms of the response. A few people have had hyper progression"* *"There will always be potential side-effects/toxicities, but these are less can be more condensed than chemo and much more tolerable in my experience."* *"I have not experienced any disadvantages - the immunotherapy eased my pain, successfully treated the cancer and enabled me to return to full time work."*

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients described those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people as groups that would benefit most from this treatment for the reasons outlined below. *"MSI high patients will benefit disproportionately more as MSI high tumours have a higher level of mutational load which results in higher levels of immune activity at the tumour site and a greater likelihood of positive response to checkpoint inhibitor immunotherapy."* *"Lynch syndrome patients, and those cancers that have an MSI high profile. The treatment targets these cancers differently, by stimulating the T cells, to activate the immune system, which has overtime been unable to keep up with the cancer burden."* *"MSI high patients like me. Other patient groups as per testing currently going on...In family hereditary disease suffers such as Lynch Syndrome patients and their children."*
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are no obvious equality issues, under the 2010 Equality Act, however as long as this drug is not available on the NHS there will be an inequality as to who can access (or afford) it. Equal access for these drugs was of upmost importance to our community. *"Lack of equal access is a major issue with this treatment currently as only certain hospitals run clinical trials and some work more closely with manufacturers, such as BMS, than others. For the unlucky ones who do not have access to this treatment through the NHS there is a huge financial burden to be paid in order to access this treatment via the private sector."* *"Socio economic criteria aren't covered by the equality act, however the poorest in society won't be able to pay for these drugs privately."* *"They are available on the NHS for lung and skin cancers, but I had to spend my life savings and crowd fund to access my immunotherapy for colon cancer. Which seems to have worked!"* *"All cancer patients should be treated equally and have access to any appropriate treatment."*

	"No doctors ever suggested or recommended this course of treatment to me. I discovered it. I pursued it. I was extremely lucky to have the ability and drive in order to do this. That speaks of a huge inequality. Being one of a handful on this treatment for bowel cancer."
Other issues	
13. Are there any other issues that you would like the committee to consider?	None
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- 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 approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life.
- Patients told us that this treatment offers them greater hope, added months and years of life, additional treatment choice and fewer side effects than chemotherapy, giving them better quality of life.
- Patients felt those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people would benefit most from this treatment.

- All patients should have access to personalised, tailored treatment that is right for them. If outcomes for people with metastatic bowel cancer are to improve, a one-size fits all approach to treating people with the disease will not work.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

BMJ TAG

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 129039T.

Title:	Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steven J Edwards, Director of Health Technology Assessment, BMJ-TAG, London Samantha Barton, Principal Health Technology Assessment Analyst, BMJ-TAG, London Tracey Jhita, Health Economics Manager, BMJ-TAG, London Victoria Wakefield, Principal Health Technology Assessment Analyst, BMJ-TAG, London Sarah Roberts, Senior Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	03/12/2020
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 129039T.
Declared competing interests of the authors	Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The ERG would like to thank Professor Tim Maughan (Professor of Clinical Oncology, University of Oxford) and Dr Fiona Lofts (Consultant Medical Oncologist, St George's University Hospital) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Barton S, Jhita T, Wakefield V and Roberts S. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency: A Single Technology Appraisal. BMJ Technology Assessment Group, 2020.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Sarah Roberts	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BICR	Blinded independent central review
CAPOX/XELOX	Capecitabine plus oxaliplatin
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical Study Report
DIC	Deviance information criterion
dMMR	Mismatched repair deficiency
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
FOLFIRI	Folinic acid plus fluorouracil plus irinotecan
FOLFOX	Folinic acid plus fluorouracil plus oxaliplatin
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry

IPD	Individual patient data
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intention to treat
KM	Kaplan–Meier
LYG	Life years gained
mCRC	Metastatic colorectal cancer
MMR	Mismatched repair
MSI-H	High microsatellite instability
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PPS	Post-progression survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model

Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALYs	Quality-adjusted life years
QoL	Quality of life
RAS	KRAS and NRAS (the RAS genes)
RCT(s)	Randomised controlled trial(s)
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single Technology Appraisal
STM	State-transition model
ToT	Time on treatment
TSD	Technical support document
TTP	Time to progression

1 Executive summary

Below is a summary of aspects of the submitted evidence identified by the Evidence Review Group (ERG) as potentially important considerations in decision making. The ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) are also reported. Supplementary details on the clinical condition, technology under assessment, evidence submitted, and discussion of non-key issues are available in the main body of the ERG report.

1.1 Overview of the ERG's key issues

Table 1 presents a summary of the ERG's key issues on the evidence submitted on the clinical and cost effectiveness of pembrolizumab.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	KEYNOTE-177 is the only RCT reporting data for first-line treatment of MSI-H/dMMR mCRC and includes a comparator of physician's choice	1.3, 2.3.1, 2.3.3, 3.3.1, 3.5.1
2	Subgroup analyses based on RAS mutation status	1.4, 2.3.3.2, 3.3.1, 3.4, 3.5, 4.2.2, 4.2.3, 4.2.5.1
3	Treatment regimen and resource use for pembrolizumab	1.4, 4.2.3, 4.2.8.9
4	Duration of treatment with pembrolizumab	1.4, 4.2.8.9
5	Treatment costs for standard of care	1.4, 4.2.8.9
6	Time on treatment for non-KEYNOTE-177 comparators	1.4, 4.2.8.9

Abbreviations: dMMR, mismatched repair deficiency; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; RCT, randomised controlled trial.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are around the appropriate subgroups for the analyses based on RAS mutation status and associated comparators and the cost assumptions used in the economic model.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival; OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival (PFS).

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared with currently available treatments in the NHS.
- Reducing the frequency of treatment cycles compared to currently available treatments in the NHS.
- Reducing the resource use associated with delivering treatment.
- Inclusion of a cap on number of treatment cycles (maximum of 35 treatment cycles).

The modelling assumptions that have the greatest effect on the ICER are:

- The use of post-progression survival (PPS) for all arms of the model directly impacts OS, as any gain in PFS directly equates to a gain in the estimated OS.
- Treatment regimen of 400mg once every six weeks and consultant oncologist appointments aligned to treatment cycle.
- Treatment costs for standard of care (SoC) based on mFOLFOX6 and FOLFIRI.
- Time on treatment for non-KEYNOTE-177 comparators equal to time on treatment for standard of care in KEYNOTE-177.

1.3 The decision problem: summary of the ERG's key issues

Table 2 presents the ERG's key issue with the internal and external validity of the evidence derived from KEYNOTE-177 in the context of the decision problem. Issue 1 is also applicable to the section on the ERG's issues with the evidence on clinical effectiveness.

Table 2. Issue 1: Direct head-to-head evidence is not available for comparators listed in final scope issued by NICE

Report section	2.3.3, 3.3
Description of issue and why the ERG has identified it as important	At the time of writing, KEYNOTE-177 is the only RCT enrolling specifically those with locally confirmed MSI-H/dMMR Stage IV CRC and for which data are available in the first-line setting. The comparator group in KEYNOTE-177 was SoC, which was physician's choice from one of (treatment chosen before randomisation): • mFOLFOX6, with or without bevacizumab (52.5%); • FOLFIRI, with or without bevacizumab (36.4%); • Cetuximab with either mFOLFOX6 or FOLFIRI (11.2%).

	Thus, no RCT is available in those with MSI-H/dMMR mCRC to provide head-to-head data, without breaking randomisation, for pembrolizumab versus individual comparators of interest listed in the final scope issued by NICE, including subgroup analysis based on RAS wild-type. Additionally, bevacizumab is not an available treatment option for first-line mCRC in England. Lack of direct comparative data for individual interventions means that caveats that need to be considered when interpreting available estimates of effect, which could lead to concerns in the robustness of the estimates.
What alternative approach has the ERG suggested?	For comparison with CAPOX, FOLFIRI and FOLFOX, the ERG considers the SoC group in totality from KEYNOTE-177 provides the most robust estimate of comparative treatment effectiveness for pembrolizumab, and likely underestimates the true effect of pembrolizumab, because SoC included bevacizumab and cetuximab-combination regimens. To provide more robust estimates of PFS for pembrolizumab versus cetuximab- and panitumumab- combination treatments in those with RAS wild-type mCRC, the ERG proposes that an NMA based on RAS wild-type would be more appropriate than the company's NMA in all patients.
What is the expected effect on the cost-effectiveness estimates?	Please see Issue 2 (Table 3) for a detailed description of the potential impact of carrying out the FP NMA in the subgroup of those with RAS wild-type.
What additional evidence or analyses might help to resolve this key issue?	As noted above, the ERG proposes an NMA in those with RAS wild-type and including relevant comparators listed in the NICE final scope.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CS, company submission; dMMR, mismatched repair deficiency; ERG, Evidence Review Group; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; FP, fractional polynomial; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability; NICE, National Institute of Health and Care Excellence; NMA, network meta-analysis; PFS, progression-free survival.

1.4 The clinical and cost effectiveness evidence: summary of the ERG's key issues

Issue 1 relating to the decision problem is also of relevance to this section. Table 3 to Table 7 presents the ERG's key issues with the company's cost-effectiveness analysis. All cost-effectiveness analyses presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted]%.

Table 3. Issue 2: Subgroup analyses by RAS mutation status

Report section	2.3.3.2, 3.3.1, 3.4, 3.5, 4.2.2, 4.2.3, 4.2.5.1
Description of issue and why the ERG has identified it as important	The final scope issued by NICE specifies that panitumumab-combination regimens are a first-line treatment option for those with RAS wild-type mCRC, together with cetuximab plus FOLRIRI or FOLFOX for EGFR-expressing RAS wild-type. In the CS, the company provided an FP NMA that omitted cetuximab-combination treatment and was based on all patients. The company's rationale for not including cetuximab plus FOLFIRI or FOLFOX in the NMA was that cetuximab-based treatment formed part of

	SoC, and the six regimens comprising SoC were considered as a single group for the purposes of the NMA Subgroup analysis from KEYNOTE-177 indicates that the beneficial effect of pembrolizumab in PFS noted for the ITT population is maintained versus SoC for those with RAS wild-type. However, RAS status was not determined for all those enrolled in KEYNOTE-177 and was not necessarily a factor in choice of treatment in SoC, thus, some allocated to SoC might not have received the optimum intervention according to clinical practice in England. The ERG considers an FP NMA based on those with RAS wild-type in KEYNOTE-177 versus comparators relevant to clinical practice in England could substantiate the estimate of PFS observed for pembrolizumab in KEYNOTE-177 for all patients. *Post hoc* subgroup analyses of PFS based on those identified as having RAS mutations generated a markedly different result from other subgroups, with a change in direction of effect to favour SoC, albeit that the difference between pembrolizumab and SoC was not statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). However, the ERG notes that the 95% CIs for estimates of PFS for RAS wild-type and non-RAS wild-type do not overlap and, as such, considers the results in the two subgroups unlikely to have arisen due to random chance. The company base case population in the economic model is the ITT population of KEYNOTE-177 with all estimates of clinical efficacy for all comparators based on this population. The ERG was concerned that subgroup analyses by RAS mutation status were not fully explored.
What alternative approach has the ERG suggested?	To carry out the FP NMA based on IPD data for those from KEYNOTE-177 identified as RAS wild-type and to produce a network including cetuximab- and panitumumab-combination regimens for PFS. The ERG appreciates that the same bias in the company's FP NMA based on "all patients" will be present in the ERG's proposed NMA, due to the different mCRC populations included in the network. However, by focusing on the RAS wild-type population, the clinical heterogeneity will be minimised as much as possible. For the RAS wild-type subgroup, the ITT cost-effectiveness analysis presented by the company may provide conservative approximations for the comparisons against mFOLFOX6/FOLFIRI, CAPOX and panitumumab combination treatment, based on a comparison of HRs from KEYNOTE-177 for pembrolizumab versus SoC for each population (ITT HR = 0.60 versus RAS wildtype HR = 0.44). However, currently there is no explicit comparison of pembrolizumab versus cetuximab combination treatment as it is blended with the SoC analysis. To provide an estimation of the cost effectiveness of pembrolizumab versus cetuximab combination treatment, the ERG considers that a simplified analysis assuming clinical equivalence between cetuximab combination treatment and panitumumab combination treatment may not be unreasonable. TA439 reports that NMA provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was more effective than panitumumab plus FOLFOX at increasing PFS or OS.
What is the expected effect on the cost-effectiveness estimates?	For the illustrative analysis for pembrolizumab versus cetuximab combination treatment, the ERG estimated that pembrolizumab is the dominant treatment.

	For the non-RAS wild-type subgroup analysis, as the direction of effect favours SoC, the ERG predicts that pembrolizumab is less effective and more costly that SoC and as such would be dominated by the comparator.
What additional evidence or analyses might help to resolve this key issue?	Given the importance of RAS mutation status, not only in terms of relative treatment effectiveness but also for directing treatment choice for patients in the NHS, during the clarification stage the ERG requested the company to provide cost-effectiveness analyses for RAS wild-type and non RAS wild-type subgroups from KEYNOTE-177 and update the FP NMA to generate relative estimates of treatment effect for pembrolizumab versus the listed comparators in the NICE final scope for the relevant subgroups. The company declined to provide the requested analyses. The ERG reiterates that the preferred approach is for the company to: • Produce relative estimates of treatment effectiveness for patients with and without RAS wildtype mCRC from KEYNOTE-177 using the recommended ERG FP NMA outlined in the ERG's clarification questions; • Implement the results of the subgroup treatment effectiveness analyses in the economic model to produce cost-effectiveness estimates by relevant comparator for the RAS wild-type and non-RAS wild-type subgroups.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; CS, company submission; EGFR, epidermal growth factor receptor; ERG, evidence review group; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; FP, fractional polynomial; HR, hazard ratio; ITT, intention-to-treat; mCRC, metastatic colorectal cancer; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Table 4. Issue 3: Treatment regimen and resource use for pembrolizumab

Report section	4.2.3 and 4.2.8.9
Description of issue and why the ERG has identified it as important	In KEYNOTE-177, the treatment regimen for pembrolizumab was 200mg once every three weeks, but the company stated that it can also be administered at a 400mg dose once every six weeks. The ERG's clinical experts advised that in clinical practice, they would prefer to administer pembrolizumab using the 400mg dose once every six weeks for patient convenience and also to reduce NHS resource use. As such, a less frequent treatment regimen requires less frequent consultant oncologist appointments, which is a primary driver of the cost-effectiveness analysis.
What alternative approach has the ERG suggested?	To reflect how pembrolizumab would be used in UK clinical practice, the ERG considers the treatment regimen of 400mg once every six weeks and consultant oncologist appointments aligned to treatment cycle is appropriate.
What is the expected effect on the cost-effectiveness estimates?	The company base case ICERs after the clarification stage reduced from £7,250 to £535 for the comparison with SoC and from £27,474 to £20,736 for the comparison with CAPOX, but pembrolizumab still dominates panitumumab combination treatment under this scenario
What additional evidence or analyses might help to resolve this key issue?	The company expects that the monotherapy marketing authorisation will include an option to administer pembrolizumab at a 400mg dose once every six weeks. As such, confirmation of the treatment regimen for pembrolizumab will be available when the marketing authorisation is approved.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; mg, milligram; SoC, standard of care.

Table 5. Issue 4: Duration of treatment with pembrolizumab

Report section	4.2.8.9
Description of issue and why the ERG has identified it as important	In KEYNOTE-177, treatment with pembrolizumab was restricted to 35-cycles, which has been implemented in the cost-effectiveness analysis. However, the draft SmPC states that it can be given until disease progression or unacceptable toxicity.
What alternative approach has the ERG suggested?	The ERG performed an illustrative scenario, which assumes time on treatment is equal to PFS for pembrolizumab and removed the 35-cycle stopping rule.
What is the expected effect on the cost-effectiveness estimates?	The company base case ICERs after the clarification stage increased from £7,250 to £73,809 for the comparison with SoC and from £27,474 to £94,262 for the comparison with CAPOX, and from dominant to £44,777 for the comparison with panitumumab combination treatment.
What additional evidence or analyses might help to resolve this key issue?	As clinical efficacy for pembrolizumab in the economic model is based on a maximum of 35-cycles of treatment, it is unknown what the impact on PFS would be if treatment was given until progression.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; SmPC, summary of product characteristics; SoC, standard of care.

Commented [ED1]: MA granted so removed CIC marking.

Commented [ED2]: Removed CIC marking

Table 6. Issue 5: Treatment costs for standard of care

Report section	4.2.8.9
Description of issue and why the ERG has identified it as important	In KEYNOTE-177 approximately 70% of patients received bevacizumab combination treatment, which is not recommend in the NHS. The company assumed that costs for patients who received bevacizumab combination treatment would be reflective of cetuximab combination treatment. However, cetuximab combination treatment is only recommend in the NHS for patients with RAS-wildtype mCRC. As such, the ERG considers that costs for standard of care are inflated compared to what would be incurred in the NHS.
What alternative approach has the ERG suggested?	For the ITT and RAS wildtype analysis, which focuses only on the comparison with FOLFOX and FOLFIRI (SoC), the ERG ran a scenario where treatment costs for standard of care are based only on FOLFOX and FOLFIRI treatments.
What is the expected effect on the cost-effectiveness estimates?	The company base case ICER after the clarification stage increased from £7,250 to £21,636 for the comparison with SoC.
What additional evidence or analyses might help to resolve this key issue?	As a large proportion of the direct evidence for pembrolizumab versus standard from KEYNTOTE-177 is based on patients in the comparator arm receiving treatment with bevacizumab, the uncertainty of the clinical efficacy of pembrolizumab versus FOLFOX and FOLFIRI is unresolvable. Furthermore, the ERG considers it is important to highlight that SoC treatment costs for the company base case are higher than may be incurred in NHS. However, the ERG considers that the bias in the ITT analysis and the ERG's treatment cost scenario favours SoC and as such provides a conservative estimate of the ICER.

Abbreviations: ERG, evidence review group; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; ICER, incremental cost-effectiveness ratio; ITT, intention-to treat; mCRC, metastatic colorectal cancer; SoC, standard of care.

Table 7. Issue 6: Time on treatment for non-KEYNOTE-177 comparators

Report section	4.2.8.9
Description of issue and why the ERG has identified it as important	In the base case analysis, the company assumed time on treatment to be equal to estimated progression-free survival for CAPOX and panitumumab combination treatment, in the absence of alternative data. However, mean time on treatment for CAPOX and panitumumab combination treatment is substantially longer compared with pembrolizumab and SoC, which results in inflated treatment costs. In TA439, mean treatment duration for panitumumab combination treatment was estimated to be approximately nine months, which is shorter than the company's estimated mean treatment duration of 18.5 months based on time on treatment equal to progression-free survival.
What alternative approach has the ERG suggested?	The ERG considers that a more appropriate assumption for time on treatment for non-KEYNOTE-177 comparators is to assume it is equal to KEYNOTE-177 time on treatment for SoC. Mean time on treatment for SoC was estimated to be approximately [redacted] months, which is closer to the estimates in TA439 for panitumumab combination treatment. Furthermore, given the company assume clinical outcomes for CAPOX are equal to SoC, it is not unreasonable to assume time on treatment is equal to time on treatment for SoC.
What is the expected effect on the cost-effectiveness estimates?	The scenario had a negligible impact on the ICER for CAPOX (increased from £27,474 to £29,205) but changed the ICER for panitumumab combination treatment from being dominant to £3,158.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that its scenario sufficiently explores the uncertainty around time on treatment for comparators not evaluated in KEYNOTE-177. Furthermore, mean estimates of time on treatment for panitumumab from TA439 were accepted by the committee and as such could be considered appropriate for use in the ERG's preferred analysis.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; SoC, standard of care.

1.5 Summary of ERG's preferred assumptions and resulting ICER

Table 8 to Table 11 presents the results of the ERG's preferred assumptions, as well as the ERG preferred ICER for pembrolizumab compared with SoC and CAPOX for the ITT/ RAS wild-type population proxy analysis and panitumumab and cetuximab combination treatment for the RAS wild-type population analysis. The ERG could not produce probabilistic sensitivity analysis (PSA) ICERs for its base case as the PSA takes several hours to run and due to paucity of time and complexity of the model, some scenarios could not be integrated with the PSA.

Table 8. ERG's preferred assumptions - pembrolizumab vs SoC (ITT and RAS wild-type proxy analysis)

Scenario	Incremental costs	Incremental QALYs	ICER - change from company base case (£/QALY)
Company base case [after clarification]	13,497	1.86	7,250
Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks	996	1.86	535
Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS	13,171	1.89	6,966
Removal of AE disutility	13,497	1.86	7,251
FOLFOX/FOLFIRI costs for SoC	40,278	1.86	21,636
Removal of second-line cetuximab combination treatment	13,911	1.86	7,473
ERG's preferred base case [combination of all scenarios]	**27,541**	**1.89**	**14,569**

Abbreviations: AE, adverse events; ERG, evidence review group; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PFS, progression-free survival; QALYs, quality-adjusted life-years; TTP, time to progression; SoC, standard of care.

Table 9. ERG's preferred assumptions - pembrolizumab vs CAPOX (ITT and RAS wild-type proxy analysis)

Scenario	Incremental costs	Incremental QALYs	ICER - change from company base case (£/QALY)
Company base case [after clarification]	50,968	1.86	27,474
Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks	38,468	1.86	20,736
Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS	50,307	1.71	29,819
Removal of AE disutility	50,968	1.86	27,383
ToT for comparator is equal to ToT for standard of care	54,180	1.86	29,205
Removal of second-line cetuximab combination treatment	51,383	1.86	27,697

ERG's preferred base case [combination of all scenarios]	**41,443**	**1.89**	**21,923**

Abbreviations: AE, adverse events; CAPOX, capecitabine plus oxaliplatin; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PFS, progression-free survival; QALYs, quality-adjusted life-years; ToT, Time on treatment; TTP, time to progression.

Table 10. ERG's preferred assumptions - pembrolizumab vs panitumumab combination treatment (RAS wild-type proxy analysis)

Scenario	Incremental costs	Incremental QALYs	ICER - change from company base case (£/QALY)
Company base case [after clarification]	-48,317	1.69	Dominant
Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks	-60,817	1.69	Dominant
Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS	-56,167	1.68	Dominant
Removal of AE disutility	-48,317	1.65	Dominant
ToT for comparator is equal to ToT for standard of care	5,330	1.69	3,158
Removal of second-line cetuximab combination treatment	-47,946	1.69	Dominant
ERG's preferred base case [combination of all scenarios]	**-7,675**	**1.65**	**Dominant**

Abbreviations: AE, adverse events; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life-years; ToT, Time on treatment; TTP, time to progression; SoC, standard of care.

Table 11. ERG's preferred assumptions - pembrolizumab vs cetuximab combination treatment (RAS wild-type proxy analysis)

Scenario	Incremental costs	Incremental QALYs	ICER - change from company base case (£/QALY)
Company base case [after clarification]	-	-	-
Cetuximab combination treatment is clinical equivalent to panitumumab combination treatment	-49,510	1.69	Dominant

Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks	-62,011	1.69	Dominant
Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS	-57,446	1.68	Dominant
Removal of AE disutility	-49,510	1.65	Dominant
ToT for comparator is equal to ToT for standard of care	4,814	1.69	2,852
Removal of second-line cetuximab combination treatment	-49,140	1.69	Dominant
ERG's preferred base case [combination of all scenarios]	**-8,191**	**1.65**	**Dominant**

Abbreviations: AE, adverse events; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life-years; ToT, Time on treatment; TTP, time to progression; SoC, standard of care.

For further details of the exploratory and sensitivity analyses done by the ERG, see Section 1326.2 and 6.3.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of pembrolizumab (Keytruda®; Merck Sharp & Dohme Limited) as a regimen for adults with untreated metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).[1]

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- pembrolizumab, including its mode of action, dose and method of administration (Section B.1.2);
- mCRC with MSI-H or dMMR, including prevalence, prognosis, staging and disease management (Section B.1.3).

Based on advice from its clinical experts, the Evidence Review Group (ERG) considers the CS to present an accurate overview of the aetiology and diagnosis of mCRC that is MSI-H or dMMR, and the management of mCRC.

Direct evidence submitted in support of the clinical effectiveness of pembrolizumab in the population of interest to this STA is derived from one randomised controlled trial (RCT), KEYNOTE-177.[2] The company notes that KEYNOTE-177 is the first RCT focussing on those with untreated mCRC that is determined to be MSI-H or dMMR. To aid understanding of some points raised in the ERG's critique of the submitted evidence in the context of the decision problem, the ERG provides a summary of aspects of mCRC not covered in detail in the CS and that potentially affect response to treatment and prognosis, together with how presence of MSI-H or dMMR impacts on course of disease.

2.2.1 Colorectal cancer

Colorectal cancer (also known as bowel cancer) starts in either the colon or the rectum. The colon is about 5 feet long and is part of the beginning of the large bowel. By contrast, the rectum, which is located towards the end of the large bowel, is only 5 to 6 inches in length.[3] About two thirds of CRCs develop in the colon, with the remainder arising in the rectum.[4] Despite the difference in anatomical location of tumours, the two cancers have similar features, giving rise to cancers of the colon and rectum being grouped together.[3, 5] Although cancers of the colon and rectum have similar features,

types of symptom experienced by a person with CRC depend on whether their primary tumour is located on the left or the right side of the large intestine.[4, 5] Right-sided tumours are more frequently associated with weight loss and anaemia, whereas those located on the left side of the colon or rectum often lead to colicky pain, rectal bleeding, and bowel obstruction.

Stage of disease at presentation is the strongest prognostic factor for clinical outcomes in CRC.[6] However, tumour position, in terms of left or right side, impacts on disease progression, overall survival (OS) and response to treatment.[3] Compared with tumours on the left, tumours on the right are more likely to be at an advanced stage of disease at presentation and, therefore, have a poorer prognosis.[3] Additionally, right and left tumours differ in their molecular characteristics and histology.[3] Mutations in the MMR pathway are more commonly identified in tumours located on the right of the colon or rectum, whereas those on the left typically have more anomalies in genes involved in chromosomal instability, such as KRAS and p53. Positioning of tumour is reported to influence response to treatment,[3] with left-sided CRC tumours tending to show better response to adjuvant chemotherapy (e.g., 5-fluorouracil-based treatment) and to targeted therapy (e.g., inhibitors of epidermal growth factor receptor [EGFR]). By contrast, right-sided CRCs do not respond well to conventional chemotherapies, and are reported to have a better outcome with immunotherapies (e.g., pembrolizumab).[3]

2.2.2 Microsatellite instability, mismatch repair, and other genetic anomalies involved in development of colorectal cancer

Colorectal cancer is a heterogenous disease. Although disease stage remains the key determinant of prognosis, there is variability in clinical outcomes for the same disease stage.[7, 8] Various genetic anomalies have been identified as having a role in development of CRC, with differences in mutations across patients likely contributing to heterogeneity in clinical outcomes. Two molecular pathways involved in CRC are the MSI and the chromosomal instability (CIN) pathways.[3, 7-9] Most CRCs develop via the CIN pathway, whereas 12–15% arise from the MSI pathway that is, in turn, a consequence of dMMR.[7, 8]

Genomic stability is maintained through the DNA MMR system, which repairs errors in insertions, deletions, and base–base mismatches introduced into microsatellites during DNA replication and combination.[7, 8] Microsatellites are short, tandemly-repeated sequences (1–6 base pairs) occurring throughout the genome. As a result of their repeated structure, microsatellites are prone to mutation. Presence of microsatellites with a sequence not occurring in germline DNA indicates presence of MSI and a dMMR system, and, therefore, microsatellites are a marker of dMMR.[7, 8] The

DNA MMR system comprises four MMR genes and their encoded proteins (MLH1, MSH2, MSH6, PMS2).[7, 8] Inactivation of MLH1 and MSH2 accounts for over 90% of dMMR CRCs. Deficiency of MMR results in the production of a truncated, non-functional protein or the loss of a protein, which causes MSI. Therefore, dMMR is frequently assessed by testing for loss of an MMR protein with immunohistochemistry or for MSI using a polymerase chain reaction (PCR)-based assay. The ERG's clinical experts commented that, mostly, tests for MSI and MMR status give the same result, that is both generate a positive or negative status. However, on occasion, a person could be identified as microsatellite stable but dMMR, and, therefore, evaluating MMR proteins could be the preferred technique.

Tumours arising from a dMMR pathway have distinct features, such as origin in the right side of the colon or rectum and poorly differentiated morphology.[9] In early-stage CRC, dMMR tumours are associated with a favourable prognosis.[9] Prevalence of dMMR is low in mCRC (3.5%), which supports the proposal that dMMR tumours have a lower potential to metastasise. However, when dMMR tumours are present in mCRC, they are associated with a considerably worse outcome than those with a functional MMR system.[9] An analysis of individual patient data (IPD) from participants of four RCTs evaluating first-line treatment in mCRC found that median progression-free survival (PFS) and OS were significantly worse for those with dMMR compared with MMR tumors:[9]

- PFS:
    - 6.2 months for dMMR versus 7.6 months for MMR;
    - hazard ratio (HR) 1.33, 95% CI (confidence interval) 1.12 to 1.5;
    - p=0.001;
- OS:
    - 13.6 months for dMMR versus 16.8 months for MMR;
    - HR 1.35, 95% CI: 1.13: to 1.61;
    - p=0.001.

Other genetic anomalies involved in pathways leading to the development of CRC, and that are now targets for treatment, are those affecting proteins acting in the Ras-Raf-mitogen-activated protein kinase (MAPK) signalling pathway.[10] One such gene is BRAF, which is a modulator of the MAPK signalling pathway. BRAF mutations are present in 10% of CRC, and carriers of BRAF mutations exhibit discrete clinical characteristics and outcomes. A specific mutation, $BRAF^{v600E}$, accounts for approximately 90% of all BRAF mutations seen in CRC. Additionally, $BRAF^{v600E}$ is strongly associated with MSI. In sporadic CRCs, BRAF mutation is seen in approximately 60% of MSI-H tumours and only

5–10% of microsatellite stable tumours.[10] People with BRAF mutant CRC have low response rates to conventional therapies and poor OS. Analysis of individual patient data (IPD) from the study mentioned earlier found that median PFS and OS were significantly worse for those with BRAF mutation (includes both dMMR and MMR) compared with those with BRAF wild-type:[9]

- PFS:
    - 6.2 months for BRAF mutant versus 7.7 months for BRAF wild-type;
    - HR 1.34, 95% CI: 1.17 to 1.54;
    - p<0.001;
- OS:
    - 11.4 months for BRAF mutant versus 17.2 months for BRAF wild-type;
    - HR 1.91, 95% CI 1.66 to 2.19;
    - p<0.001.

Other genes involved in the MAPK signalling pathway are the RAS genes, KRAS and NRAS.[10] Mutations in KRAS and NRAS are present in 50% of CRCs. KRAS/NRAS mutations lead to activation of the MAPK signalling pathway downstream of EGFR, rendering these tumours resistant to anti-EGFR therapies, such as cetuximab and panitumumab.[11]

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the NICE, together with their rationale for any deviation from the final scope (Table 12).[1] The company highlights that the submission differs from the final scope primarily in terms of the comparators of interest to the decision problem. The key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow.

Table 12. Summary of decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	Adults with mCRC with MSI-H or dMMR.	Adults with mCRC with MSI-H or dMMR.	N/A	Evidence derived from KEYNOTE-177[2] is aligned with the population specified in the final scope (more detailed description available in Section 2.3.1). The ERG notes that the anticipated marketing authorisation for pembrolizumab could be interpreted as encompassing first-line treatment of adults with unresectable CRC (not metastatic) that is MSI-H or dMMR, a population that is not covered in the final scope issued by NICE (more detailed discussion available in Section 2.3.1).
Intervention	Pembrolizumab	Pembrolizumab	N/A	The ERG notes two factors associated with pembrolizumab treatment that could impact on the estimates of cost effectiveness (discussed in greater detail in the Section 2.3.2 and Section 0): • choice of dosing regimen: o fixed dose of 200 mg over 30 minutes every 3 weeks; o fixed dose of 400 mg over 30 minutes every 6 weeks.

				• number of cycles of pembrolizumab administered.
Comparator(s)	**For all patients** • FOLFOX • FOLFIRI • CAPOX • Capecitabine • Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) **For patients with RAS wild-type mCRC** • Panitumumab in combination with FOLFOX or FOLFIRI **For patients with EGFR expressing, RAS wild-type mCRC** • Cetuximab in combination with FOLFOX or FOLFIRI	**For all patients** • FOLFOX • FOLFIRI • CAPOX **For patients with RAS wild-type mCRC** • Panitumumab in combination with FOLFOX or FOLFIRI **For patients with EGFR expressing, RAS wild-type mCRC** • Cetuximab in combination with FOLFOX or FOLFIRI	• Tegafur with uracil (in combination with folinic acid) is not a relevant comparator for this appraisal as this regimen is no longer available as it was discontinued in the UK.[12, 13] • Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) is not a relevant comparator for this appraisal as this is only very rarely used in UK clinical practice. • Capecitabine is not a relevant comparator for this appraisal as it is used in elderly and frail patients who have a poor performance status (i.e. ECOG performance status score of ≥2).	The ERG's clinical experts agree with the company, and the company's rationale for each treatment, that tegafur with uracil, raltitrexed, and capecitabine are not relevant comparators for pembrolizumab in the first-line treatment of MSI-H/dMMR mCRC. No RCT is available that provides direct comparison of pembrolizumab versus any of the individual comparators specified in the final scope issued by NICE (discussed in more detail in Section 2.3.3). The comparator to pembrolizumab in KEYNOTE-177 was SoC as chosen by the investigator, with choice of treatment for each participant prespecified before randomisation. Options for SoC (total of six) were: • mFOLFOX6, with or without bevacizumab; • FOLFIRI, with or without bevacizumab; • Cetuximab with either mFOLFOX6 or FOLFIRI. The ERG notes that bevacizumab is not an available treatment option for

				first-line mCRC in England (discussed in more detail in Section 2.3.3). Data for pembrolizumab versus CAPOX in MSI-H/dMMR mCRC are derived from network meta-analysis. Comparisons of pembrolizumab versus cetuximab and panitumumab, both of which are combined with FOLFOX or FOLFIRI, were not fully explored in the CS (more detail provided in Section 2.3.3).
Outcomes	The outcome measures to be considered include: • overall survival; • progression-free survival; • response rates; • adverse effects of treatment; • health-related quality of life.	The outcome measures to be considered include: • overall survival; • progression-free survival; • response rates; • adverse effects of treatment; • health-related quality of life.	N/A	Data are available for all outcomes listed in the NICE scope; the ERG notes OS data are immature.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			The ERG notes that the economic model does not include costs associated with diagnostic testing for MSI status in people with mCRC as assessment of MSI or dMMR is standard clinical practice for all patients with CRC, as per recommendations in DG27.[14]

	The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.			
Subgroups to be considered	If the evidence allows the subgroup of people with RAS wild-type colorectal cancer will be considered.			The ERG considers that the company did not fully explore comparators of interest for the population of RAS wild-type mCRC. The company presented an NMA for all patients and that included panitumumab-based therapy and CAPOX. Given that the company has access to IPD for those with RAS wild-type from KEYNOTE-177, to align with the NICE scope, the ERG requested that the company carries out an NMA derived from IPD for those with RAS-wildtype from KEYNOTE-177 and versus the comparators specified above.

Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			

Abbreviations: CAPOX; capecitabine plus oxaliplatin; CS, company submission; dMMR, mismatched repair deficiency; ECOG; Eastern Cooperative Oncology Group; ERG, Evidence Review Group; FOLFIRI; folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; MMR, mismatched repair; N/A, not applicable; SoC, standard of care.

2.3.1 Population

KEYNOTE-177 enrolled those with locally confirmed MSI-H/dMMR Stage IV CRC.[2] Participants were also required to have measurable disease at baseline as per RECIST 1.1 criteria, and as determined by the local site investigator and/or radiology assessment. Those enrolled could have recurrent or newly diagnosed mCRC. Receipt of prior systemic therapy for Stage IV CRC rendered a person ineligible for recruitment to KEYNOTE-177: previous adjuvant chemotherapy for CRC was permitted, as long as treatment had been completed at least 6 months prior to randomisation.

The ERG's clinical experts consider the characteristics of the population enrolled in KEYNOTE-177 to be representative of those in England likely to be eligible for treatment with pembrolizumab: a more detailed discussion of baseline characteristics is available in Section 3.2.

The final scope issued by NICE indicates a subgroup of interest to be those with RAS wild-type mCRC.[1] Subgroup analyses reported within the CS indicate that, in those with RAS wild-type, pembrolizumab is associated with a statistically significant improvement in PFS compared with standard of care (SoC; HR 0.44, 95% CI: 0.29 to 0.67). However, in those with mutation of KRAS or NRAS, the direction of effect favours SoC, albeit that the difference between treatments does not reach statistical significance (HR 1.19, 95% CI: 0.68 to 2.07). The ERG notes that the 95% CIs for the two subgroups do not overlap.

Estimates of PFS and OS for pembrolizumab versus the regimens specified by NICE in the final scope as being comparators of interest for RAS wild-type are not available within the CS (detailed in Section 2.3.3). The ERG appreciates that subgroup analyses are hypothesis generating. However, to substantiate the effect of pembrolizumab, the ERG considered it beneficial for the company to generate estimates of PFS and OS for RAS wild-type and relevant comparators as set out in the final scope, together with assessment of those without RAS-wild-type. As part of the clarification process, the ERG requested that the company carry out network meta-analyses (NMA) based on individual patient data (IPD) for KEYNOTE-177 in those with and without RAS wild-type (NMA discussed in more detail in Section 3.5). The ERG appreciates that, because all studies evaluating comparator regimens involve participants with mCRC and data are not available for the subgroup of MSI-H or dMMR mCRC, bias is present in the NMA. The potential direction of any bias, and its impact on the estimate of relative clinical effectiveness, are discussed in Section 3.5.

To summarise, the ERG considers three populations to be relevant to the decision problem:

- Population A: all participants (ITT population);
- Population B: subgroup of participants with RAS wild-type;
- Population C: subgroup of participants without RAS wild-type.

The ERG considers that the wording of the anticipated marketing authorisation for pembrolizumab could be interpreted as incorporating those with unresectable MSI-H or dMMR CRC that has not metastasised. The ERG's clinical experts commented that unresectable could be applied to either the primary colorectal tumour (with or without metastases) or any metastases. The ERG notes that the inclusion criteria for KEYNOTE-177 specified classification of CRC as Stage IV, which, by definition, denotes presence of metastases. Text in the Clinical Study Report for KEYNOTE-177 states that, "[redacted]".[2] As part of the clarification process, the company indicated that no person [redacted] was enrolled to KEYNOTE-177.

2.3.2 Intervention

In December 2020, the Committee for Medicinal Products for Human Use adopted a positive opinion on the use of pembrolizumab as a monotherapy for the first-line treatment of unresectable or metastatic MSI-H or dMMR CRC in adults.[15]

In KEYNOTE-177, pembrolizumab was given at a fixed dose of 200 mg infused over 30 minutes, with treatment occurring every 3 weeks (Q3W). The company anticipates that the marketing authorisation for pembrolizumab will include an option to administer pembrolizumab at a fixed dose of 400 mg infused over 30 minutes on a 6-weekly cycle (Q6W). The ERG's clinical experts commented that they would expect the two dosing schedules for pembrolizumab to be of equivalent clinical effectiveness. The ERG's experts agreed with the company's proposals that the reduction in number of hospital visits required for the Q6W schedule would lead to improvements in patients' quality of life and to increased capacity within hospitals, should this schedule become an option. The choice of Q3W or Q6W would be based on patient preference and the treating clinician's opinion.

The impact on the cost effectiveness of following the Q6W dosing schedule for pembrolizumab is assessed in Section 4.2.8.

Considering the recommended number of cycles of pembrolizumab, the ERG notes that wording of guidance on how long to continue pembrolizumab for MSI-H/dMMR mCRC differs between the CS, the CSR[2] and the draft Summary of Product Characteristics (SmPC).[16] The draft SmPC advises that, "*patients should be treated with KEYTRUDA [pembrolizumab] until disease progression or unacceptable toxicity*", with no restriction mentioned for number of treatment cycles. The SmPC also states, "*It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed*."

Commented [ED3]: MA granted: removed CIC marking.

In the CS, in Section B.3.2 (page 101), for the purposes of the economic model the company has applied a maximum number of 35 cycles of pembrolizumab, based on treatment administration in KEYNOTE-177, which is reported as, "*patients were to continue pembrolizumab until progressive disease, unacceptable adverse events or intercurrent illness preventing further administration of treatment, the subject has a confirmed positive serum pregnancy test or a maximum of 35 cycles of uninterrupted treatment with pembrolizumab*". Wording in Section B.2.3 of the CS (page 18) suggests that all participants receiving pembrolizumab can enter a Second Course Treatment Phase during which they could receive up to 17 additional cycles: "*pembrolizumab arm patients received up to 35 administrations of pembrolizumab (approximately 2 years) in the Initial Treatment Phase. Patients who stopped pembrolizumab with locally confirmed complete response (CR), or stable disease (SD) or better at the end of the Initial Treatment Phase may be treated in a Second Course Treatment Phase with up to 17 administrations of pembrolizumab*".

Additional detail provided in the CSR[2] for KEYNOTE-177 clarifies that participants allocated to the pembrolizumab group who stopped treatment after achieving stable disease or better and **subsequently progressed** could be eligible for an additional 17 cycles of pembrolizumab. Key criteria for re-treatment with pembrolizumab in KEYNOTE-177 are (additional criteria are available in the CSR):

- [redacted]

[redacted]

The ERG's clinical experts fed back that their preference would be to continue pembrolizumab until disease progression. The number of cycles of pembrolizumab administered has implications for cost effectiveness analyses. As part of the clarification process, the ERG requested a breakdown of the number of people receiving 35 cycles during the Initial Treatment Phase, and the proportion given the additional 17 cycles in the Second Course of Treatment Phase. The potential impact on cost effectiveness of pembrolizumab is discussed in Section 4.2.8.

2.3.3 Comparators

Based on advice from clinical experts, the ERG agrees with the company that the comparators listed below are the most relevant to the decision problem;

- **For all patients:**
  - FOLFOX;
  - FOLFIRI;
  - CAPOX.
- **For patients with RAS wild-type mCRC:**
  - Panitumumab in combination with FOLFOX or FOLFIRI.

- **For patients with EGFR expressing, RAS wild-type mCRC:**
    - Cetuximab in combination with FOLFOX or FOLFIRI.

2.3.3.1 *All patients*

No RCT is available in those with MSI-H/dMMR mCRC to provide head-to-head data, without breaking randomisation, for pembrolizumab versus individual comparators of interest listed in the final scope issued by NICE (Table 12). Data for pembrolizumab versus FOLFOX and FOLFIRI could be derived from KEYNOTE-177 through subgroup analyses of participants receiving these treatment options in the SoC group. However, estimates of clinical treatment effect would be associated with the inherent uncertainty arising from *ad hoc* subgroup analyses. Additionally, in KEYNOTE-177, FOLFOX and FOLFIRI could be given either alone or in combination with bevacizumab, which, as the company comments, is not available as a treatment option in the NHS in England. In KEYNOTE-177, 70% of those in the SoC group received FOLFOX or FOLFIRI with bevacizumab (Table 13), and, thus, the sample size to inform the subgroup analyses for FOLFOX or FOLFIRI alone is small, which would add to the uncertainty associated with the analyses. In the CS, the company provides analyses for KEYNOTE-177 that excludes participants receiving bevacizumab-containing regimens, and cautions that the results are less robust than analyses based on the full trial population. The inclusion of cetuximab-based treatment is discussed below.

CAPOX was not a treatment option in SoC for KEYNOTE-177. To generate an estimate of effect for pembrolizumab versus CAPOX, the company carried out an NMA in all patients, with the network also including panitumumab-based treatment. Studies evaluating CAPOX were in adults with mCRC, and the RCT assessing panitumumab focused on RAS wild-type mCRC. Thus, there is considerable clinical heterogeneity between the population enrolled in KEYNOTE-177 and those of other studies informing the network. The extent of bias across all studies in the network is difficult to quantify.

Taken together, and given that no RCT, other than KEYNOTE-177, reports data for solely those with untreated MSI-H/dMMR mCRC, the ERG considers the SoC group in totality from KEYNOTE-177 provides the most robust estimate of comparative treatment effectiveness for pembrolizumab versus FOLFOX, FOLFIRI and CAPOX in the specified group of all patients with MSI-H/dMMR mCRC. In reaching its conclusion, based on data available from published RCTs (details available in Section 3.3), the ERG has assumed that:

- FOLFOX, FOLFIRI and CAPOX are of comparable clinical effectiveness as first-line treatments in mCRC;[17-21]
- combining bevacizumab with FOLFOX, FOLFIRI or CAPOX improves PFS compared with the standard regimen alone in the first-line treatment of mCRC.[22, 23]

When using SoC as a proxy for FOLFOX, FOLFIRI or CAPOX alone, the ERG's assumption that bevacizumab-containing regimens are more clinically effective than FOLFOX or FOLFIRI alone introduces bias that favours SoC and therefore underestimates the likely true estimate of PFS and OS for pembrolizumab versus FOLFOX, FOLFIRI or CAPOX in those with untreated MSI-H/dMMR mCRC. Thus, the ERG considers using the ITT population to provide a conservative estimate of the clinical effectiveness of pembrolizumab. The ERG's clinical experts have fed back that the ERG's assumptions are appropriate for this STA.

Table 13. Proportion of people receiving treatment options available in the standard of care group (reproduced from the CS, Table 16, page 43)

	Standard of care group (N = 143)	
Treatment option	**Number receiving treatment**	**Percentage**
FOLFIRI	16	11.2
mFOLFOX6	11	7.7
FOLFIRI + bevacizumab	36	25.2
mFOLFOX6 + bevacizumab	64	44.8
FOLFIRI + cetuximab	11	7.7
mFOLFOX6 + cetuximab	5	3.5

Abbreviations: CS, company submission; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin.

2.3.3.2 *RAS wild-type*

The ERG considers that the company did not fully explore comparators of interest for the population of RAS wild-type mCRC. The company presented an NMA for all patients that included panitumumab-containing regimens as a comparator, but not cetuximab-based treatment with the rationale that cetuximab combination treatment was an option in the SoC group of KEYNOTE-177.

Subgroup analyses from KEYNOTE-177 in those with RAS wild-type indicated that pembrolizumab is associated with a statistically significant improvement in PFS compared with SoC (HR 0.44, 95% CI: 0.29 to 0.67). Given that RCTs are available evaluating panitumumab and cetuximab-based therapies as first-line treatments in RAS wild-type mCRC, the ERG considers it would be beneficial to carry out an NMA derived from IPD for those with RAS wild-type from KEYNOTE-177 to substantiate the estimate of effect for pembrolizumab noted in KEYNOTE-177 but versus relevant comparators set out in the final scope (Table 12).[24-27] Again, the ERG acknowledges that the NMA evaluating treatments in RAS wild-type is associated with bias that is difficult to quantify because the impact of MSI-H or dMMR is not accounted for in trials other than KEYNOTE-177. The ERG also highlights that its clinical experts commented that MSI-H/dMMR mCRC is distinct from that of RAS wild-type mCRC. Moreover, based on mode of action of pembrolizumab, pembrolizumab is likely to have benefit in MSI-H/dMMR mCRC, irrespective of RAS wild-type status.

The ERG notes the distinction between panitumumab and cetuximab in their marketing authorisations.[11] Cetuximab-based treatment is indicated for EGFR-expressing RAS wild-type mCRC and in combination with FOLFOX as a first-line treatment. By contrast, in the same setting, panitumumab is indicated for RAS wild-type mCRC, with no specification for EGFR expression, in combination with FOLFOX or FOLFIRI. Both cetuximab and panitumumab elicit their effect by binding to the EGFR, thereby preventing ligand binding and disrupting the MAPK signalling pathway (described in Section 2.2.2). Thus, the ERG considers that cetuximab and panitumumab can be included in the same NMA.

2.3.3.3 *Without RAS wild-type*

As noted in Section 2.3.1, subgroup analyses from KEYNOTE-177 indicated that, in those with mutation of KRAS or NRAS, for PFS, the direction of effect favours SoC, albeit that the difference between treatments does not reach statistical significance (HR 1.19, 95% CI: 0.68 to 2.07). Thus, for completeness, the ERG requested subgroup analysis from KEYNOTE-177 in those without RAS wild-type for pembrolizumab versus FOLFOX or FOLFIRI, with or without bevacizumab, from the SoC group, which would equate to FOLFOX, FOLFIRI, and CAPOX.

3 Clinical effectiveness

3.1 Critique of the methods review

The company undertook a broad systematic literature review (SLR) to capture studies of various designs on the efficacy and safety of pembrolizumab in metastatic colorectal cancer (mCRC) that was categorised as high microsatellite instability (MSI-H) or mismatch repair deficient (dMMR). The company carried out their SLR in accordance with guidance from the National Institute for Health and Care Excellence (NICE). Full methods and results of the SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the Evidence Review Group's (ERG's) critique of the appropriateness of the methods adopted, is presented in Table 14.

The purpose of the SLR was to identify all relevant studies that could inform the comparison of pembrolizumab with other interventions for untreated MSI-H or dMMR mCRC. The company commented that the initial literature searches and inclusion criteria were designed for a project aimed at a global market, which therefore included interventions not relevant to UK clinical practice. To identify studies relevant to the NICE final scope, the company retrieved a subset of records from their searches focusing on interventions specified by NICE.

As noted earlier, KEYNOTE-177 is the first randomised controlled trial (RCT) evaluating clinical effectiveness of interventions in untreated mCRC that is MSI-H or dMMR, with a comparator group formed of multiple treatments considered to be standard of care (SoC) for mCRC. The company anticipated that the number of studies involving MSI-H or dMMR mCRC would be small. Thus, during the abstract-screening phase, citations meeting all other criteria, but not mentioning MSI or dMMR were included. During the first pass of full-text screening, studies fully matching the target population (or reporting outcomes for a relevant subset) were included, and publications meeting all other criteria but failing to report on MSI-H or dMMR mCRC were excluded but flagged.

As discussed in Section 2.3.3, options available in SoC in KEYNOTE-177 included treatments not available in UK clinical practice. Additionally, CAPOX and panitumumab in combination with FOLFOX or FOLFIRI were not treatment choices in the SoC group, and estimates of clinical effectiveness for pembrolizumab versus the two regimens are derived from a network meta-analysis (NMA). To identify studies to inform the NMA, the company rescreened the flagged studies excluded at an earlier stage. The ERG considers the company's methodological approach to retrieving studies to be

appropriate, but considers that cetuximab with FOLFOX or FOLFIRI should also be included in the NMA (discussed in more detail in Section 1.1.1).

Thirteen studies reported across 31 publications were identified for inclusion in the SLR (CS, Appendix D, Table 9). Of the 13 studies, three involved MSI-H/dMMR mCRC, with only one publication – KEYNOTE-177 – providing direct evidence on the comparative clinical effectiveness of pembrolizumab; the two remaining studies were retrospective analyses of response to treatment (not pembrolizumab) in a subgroup of people with MSI-H mCRC.

Through a non-systematic search of Google Scholar, the ERG identified a systematic review (preprint) of RCTs of systemic first-line treatments for mCRC, which the ERG used as a source to cross-reference the studies included by the company.[28] The ERG notes that the company excluded one RCT comparing CAPOX versus FOLFOX (Ducreux *et al.* 2011[19]; N = 316), with the reason for exclusion given as "wrong study type", that the ERG considers meets criteria for inclusion in the SLR. However, as discussed in Section 2.3.3, for the ITT population, the ERG has assumed equivalent clinical effectiveness for FOLFOX, FOLFIRI and CAPOX, a decision that was directly informed by Ducreux *et al*. 2011 (more detailed discussion available in Section 3.5).

Overall, the ERG considers the company's SLR to be of reasonable quality and likely to have retrieved all studies relevant to pembrolizumab, despite limiting inclusion to English-language publications.

Table 14. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D.1.1.	**The ERG considers the sources and dates searched appropriate.** Databases searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials. Additional sources: Trial registry (clinicaltrials.gov), conference proceedings (ASCO and ESMO). Latest search update: 28 April 2020
Literature searches	Appendix D.1.1. Tables 1–6	**The ERG is satisfied that searches have identified all evidence relevant to the decision problem.** Search strategies combined comprehensive terms for the population (colorectal cancer) and interventions, medical subject headings, and study design filters. Terms for MSI-H or dMMR were not included, and

		studies in MSI-H or dMMR mCRC were identified through screening of abstracts and full texts. The ERG considers the company's approach to be appropriate.
Inclusion criteria	Appendix D.1.1. Tables 7 and 8	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Inclusion criteria for listed interventions of interest were considerably broader than the NICE final scope. The company highlighted that the literature review was carried out for a global project, which therefore included interventions not relevant to UK clinical practice. The company presented a revised set of inclusion criteria for interventions tailored to the requirements for their submission to NICE. Lists of studies excluded at full-text appraisal, together with reasons for exclusion, are provided. The ERG notes that one RCT excluded during the screening stage could have informed the company's NMA of pembrolizumab versus CAPOX (discussed in the text above). The ERG considers that the omission of the RCT was an oversight and not related to the inclusion criteria. Limited to English-language publications.
Screening and data extraction	Appendix D.1.1	**The ERG considers the methods for screening and data extraction to be robust.** Independent duplicate screening and data extraction by two reviewers against predefined criteria, with a third reviewer consulted when consensus could not be reached; screening results summarised in a PRISMA diagram.
Tool for quality assessment of included study or studies	Appendix D.1.3. Tables 23–26	**The ERG agrees with the quality assessment tool used for KEYNOTE-177 and other RCTs informing the NMA.** The ERG notes that it is unclear if quality assessment was done by one or two reviewers and, if so, whether the assessments were done independently. Detailed reasons were presented in support of the judgement of level of bias for each aspect of trial design covered in the assessment tool.

Abbreviations: ASCO, American Society of Clinical Oncology; CS, company submission; dMMR, mismatch repair deficient; ERG, Evidence Review Group; ESMO, European Society for Medical Oncology; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The ERG reiterates that, for those with MSI-H/dMMR mCRC, it considers the ITT population from KEYNOTE-177 to provide the most robust estimate of comparative clinical effectiveness of pembrolizumab versus FOLFOX, FOLFIRI and CAPOX.[2]

In subsequent sections, the ERG focuses on aspects of trial design, conduct and external validity of KEYNOTE-177 that are of importance to this Single Technology Appraisal (STA). The ERG's critique of the design, conduct and internal validity of KEYNOTE-177 is summarised in Table 15. The ERG agrees with the company's assessment of KEYNOTE-177 as being at overall low risk of bias for analysis of the primary outcome, progression-free survival (PFS), based on the full trial population. The ERG notes that the results for KEYNOTE-177 have been made public through conference abstracts but, at the time of writing, areyet to be published in full in a peer-reviewed journal.

Table 15. Summary of ERG's critique of the design and conduct of KEYNOTE-177,[2] the trial evaluating the technology of interest to the decision problem

Aspect of trial design or conduct	Section of CS providing details on trial characteristic	ERG's critique
Trial conduct		
Randomisation	B.2.3 (page 18)	**Appropriate** Randomisation carried out centrally using an IVRS/IWRS. People randomised 1:1 to pembrolizumab versus SoC. No randomisation strata.
Concealment of treatment allocation	B.2.3 (page 18)	**Appropriate** Treatment allocation concealed through use of IVRS/IWRS at randomisation. For SoC group, treating clinician was required to select treatment from options available before randomisation.
Eligibility criteria	B.2.3 (page 19)	Adults aged ≥18 years with locally confirmed MSI-H or dMMR stage IV CRC. Disease must be measurable at baseline based on RECIST 1.1 as determined by the local site Investigator/radiology assessment. People must also have had a life expectancy of at least 3 months, and an ECOG performance status of 0 or 1 within 10 days prior to treatment initiation.
Baseline characteristics	B.2.3 (page 28)	Baseline characteristics were well balanced between the pembrolizumab and SoC groups in the ITT population. Baseline characteristics from KEYNOTE-177 are available in Appendix 9.1 (Table 67) of the ERG report. The ERG notes that all enrolled in KEYNOTE-177 were classified as MSI-H, which was determined by either PCR or immunohistochemistry. As outlined in Section 2.2.2, immunohistochemistry is used to analyse presence of dMMR rather than MSI-H, but MSI-H and dMMR are synonymous.

Masking appropriate	B.2.3 (page 18)	**Open label design.** However, primary analyses for disease progression-related outcomes (e.g., PFS and ORR) were based on assessment by an independent central imaging vendor who was masked to treatment allocation.
No difference between groups in treatments given, other than intervention versus control	B.2.3 (page 26)	No evidence to suggest a difference between groups in treatments given additional to allocated intervention. A proportion of people, primarily in the SoC group, went on to receive pembrolizumab on disease progression, which likely confounds analysis of long-term outcomes, such as OS (discussed in greater detail in Section 3.2.1).
Dropouts (high drop out and any unexpected imbalance between groups)	B.2.4, Table 15, page 43 Appendix D.1.2 (Figure 37, page 336)	Only two people (1.3%) were lost to follow-up, both from the pembrolizumab group. Low rate of patient withdrawal across KEYNOTE-177 (12 people [4.1%]), but a larger proportion withdrew from the SoC group (1/153 [0.7%] with pembrolizumab versus 11/154 [7.1%] with SoC). Although there is an imbalance between groups in withdrawal from the study, given the small numbers, the ERG considers that the difference does not affect the internal validity of KEYNOTE-177.
Outcomes assessed	B.2.3 (page 27)	**All clinically relevant outcomes reported.** No evidence to suggest that additional outcomes were assessed and not reported. PFS was the primary outcome for the study and was determined by an independent central imaging vendor based on the first radiologic progressive disease. RECIST 1.1 was followed for treatment decisions on trial site until verification of the site assessment of progressive disease by the blinded independent central imaging vendor. Secondary outcomes were: • OS; • ORR. Exploratory outcomes included: • PFS as assessed by irRECIST; • PFS2;[a] • Duration of response;

		• HRQoL (as assessed by EORTC QLQ-C30 and EORTC QLQ-C29).
ITT analysis carried out	B.2.4 (page 32)	**Yes.** ITT population forms the basis for analyses of efficacy.
Subgroup analyses	B.2.4 (page 39)	As outlined in Section 2.3.1, the ERG considers that the company has not fully explored the subgroup of RAS wild-type, which is specified in the final scope issued by NICE as being of interest. Prespecified subgroup analyses were based on: • Age category (≤70 vs >70 years); • Geographic region (Asia vs Western Europe/North America vs Rest of World); • Hepatic or pulmonary metastases versus other metastases; • Recurrent versus newly diagnosed stage IV CRC; • BRAF V600E (wild type vs mutant); • Surgical vs non-surgical subjects. Data are reported for additional *post hoc* subgroups based on: • KRAS/NRAS status (wild type versus mutant); • Gender; • Site of primary tumour (right versus left); • ECOG score (0 versus 1). Strata were not applied at randomisation and so all subgroup analyses break randomisation.
Statistical analysis plan		
Sample size	B.2.4 (page 38)	Based on sample size calculations to detect a difference between pembrolizumab and SoC in the primary outcome of PFS, the company reported that they planned to enrol about 300 people into KEYNOTE-177. Sample size calculations were based on the following assumptions: • PFS follows an exponential distribution with a median of 10 months in the SoC group; • enrolment period of 30 months from first patient randomised and a minimum of 13 months of follow-up after enrolment is completed; • yearly dropout rate of 5%.

Power	B.2.4 (page 38)	The final PFS analysis is planned to be performed at the time of Interim Analysis 2 when approximately 209 PFS events have occurred or 24 months after last the person has been randomised, whichever occurs first. With 209 PFS events, KEYNOTE-177 has ~98% power to detect an HR (pembrolizumab vs SoC) of 0.55 at the 1.25% (one-sided) significance level. Should fewer than 209 events be observed 24 months after randomisation of the last person enrolled, the power of the study will be reduced. For example, if 192 events were observed, then the study has 97% power for PFS.
Analysis for estimate of effect	B.2.4 (page 37)	The company reports that the overall type I error (false positive – reject null hypothesis when it is true) over the primary endpoints of PFS and OS, and the secondary endpoint of ORR is strongly controlled at 2.5% (one-sided), with initially 1.25% allocated to the PFS hypothesis, 1.25% to the OS hypothesis, and 0% to the ORR hypothesis. To account for multiple statistical tests, the company implemented an extension of the graphical method of Maurer and Bretz to strongly control the overall type I error rate for testing of multiple endpoints at the 2.5% 1-sided level (Anderson et al, unpublished data, 2018).[29] Figure 2 shows the initial 1-sided α-allocation for each hypothesis in the ellipse representing the hypotheses.

[a] PFS2 was defined as the time from randomization to disease progression on the next line of therapy, or death from any cause, whichever occurred first.

Abbreviations: CRC, colorectal cancer; CI, confidence interval; CS, company submission; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ERG, Evidence Review Group; HR, hazard ratio; HRQoL, health-related quality of life; irRECIST, Immune-related Response Evaluation Criteria in Solid Tumors ; ITT, intention to treat; IVRS/IWRS, interactive voice response system/integrated web response system; MSI-H, high microsatellite instability; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; PCR, polymerase chain reaction; RECIST, Response Evaluation Criteria in Solid Tumours; STA, Single Technology Appraisal.

3.2.1 Aspects of trial design

3.2.1.1 Internal validity

The ERG considers KEYNOTE-177 to be a well-designed and well-conducted RCT. As introduced in Table 15, the ERG notes that OS results from KEYNOTE-177 are likely to be severely confounded, as is widespread in studies evaluating treatments for oncological conditions where crossover is allowed. In the SoC group of KEYNOTE-177, 56 (36.4%) participants crossed over to pembrolizumab treatment on stopping initial treatment, and an additional 35 (22.7%) in the SoC group went on to receive subsequent anti-PD-1/anti-PD-L1 therapy (e.g., nivolumab and avelumab). The company presented adjusted analyses of OS to account for confounding (results available in Section 3.3).

3.2.1.2 External validity

The ERG's clinical experts consider the characteristics of the population comprising KEYNOTE-177 to be generalisable to those with MSI-H/dMMR mCRC and likely to be eligible for treatment with pembrolizumab in England. During clarification, the company informed that 20 people were recruited from the UK, with 10 people allocated to each group of pembrolizumab and SoC.

Although testing for MSI-H or dMMR is recommended at time of diagnosis of CRC,[14] at the time of writing, no treatment options are specific to those with untreated MSI-H/dMMR mCRC, with management of the condition following the same recommendations as mCRC. In England, first-line chemotherapy of mCRC is typically one of FOLFOX, FOLFIRI or CAPOX. For those identified as having RAS wild-type, additional options are cetuximab and panitumumab, both of which are administered in combination with FOLFOX or FOLFIRI. In KEYNOTE-177, panitumumab-based regimens were not available to the SoC group, and assessment of RAS status (wild-type versus mutant) was not carried out for all those enrolled. Thus, in the context of external validity to England, some of those randomised to SoC may not have been treated as they would in clinical practice. As noted in the ERG's critique of how the CS aligns with the decision problem (Section 2.3.3), the ERG considers that comparative clinical effectiveness of pembrolizumab versus comparators of interest by RAS status (wild-type versus not wild-type) warrants further analysis. Finally, as highlighted in Section 2.3.3, the availability of bevacizumab-containing regimens as treatment options for SoC does not align with clinical practice in England. To account for the effect of bevacizumab, the company carried out analyses for PFS and OS that excluded those participants receiving bevacizumab-based regimens (results presented in Section 3.3).

In Section 2.3.2, the ERG noted the potential for confusion around the maximum number of cycles of pembrolizumab. As part of the clarification process, the company confirmed that most people (150/153; 98.0%) randomised to pembrolizumab received no more than 35 cycles, with three people receiving between 36 and 52 cycles (Table 16).

Table 16. Summary of number of cycles of pembrolizumab received by those allocated to pembrolizumab group in KEYNOTE-177 (reproduced from company's response to clarification, question B10)

Measure	Cycles of pembrolizumab
Mean (SD)	19.29 (14.39)
Median (range)	16.00 (1.00 – 50.00)
Number of people receiving up to 35 cycles	150
Number of people receiving between 36 and 52 cycles	3

Abbreviations: SD, standard deviation.

Mean duration of follow-up for KEYNOTE-177 at the time of data cut-off was 25.1 months (standard deviation [SD] 13.4 months; Table 17) and 23.5 months (SD 12.5 months) in the pembrolizumab and SoC groups, respectively. At the time of analysis, 195 PFS events have occurred, which is 14 events fewer than the prespecified 209 events to achieve 98% power (Table 15). The ERG appreciates that PFS presented in the CS is not the final analysis (Table 15). Despite the small deficit in required PFS events, the ERG considers duration of follow-up of KEYNOTE-177 at the time of submission to the STA process to be sufficient for shorter-term outcomes in the ITT population, such as PFS, but not for the longer-term outcome of OS, which is immature at the specified data cut-off.

Table 17. Summary of duration of follow-up in KEYNOTE-177 (adapted from CS, Table 17, page 44)

Follow-up duration (months)[a]	Pembrolizumab (N = 153)	SoC (N= 154)
Median (range)	28.4 (0.2 to 48.3)	27.2 (0.8 to 46.6)
Mean (SD)	25.1 (13.4)	23.5 (12.5)

[a] Follow-up duration is defined as the time from randomisation to the date of death or the database cut-off date if the subject is still alive.

Database cut-off date: 19 Feb 2020.

Abbreviations: SD, standard deviation; SoC, standard of care.

3.3 Clinical effectiveness results

Results are reported, where possible, based on the three populations the ERG considers relevant to the decision problem:

- Population A: all participants (ITT population);
- Population B: subgroup of participants with RAS wild-type;
- Population C: subgroup of participants without RAS wild-type.

As described in Section 2.3.3, in KEYNOTE-177, pembrolizumab was evaluated against a SoC group, in which treatment was chosen by the treating clinician from one of:

- mFOLFOX6;
- mFOLFOX6 with bevacizumab;
- FOLFIRI;
- FOLFIRI with bevacizumab;
- Cetuximab with mFOLFOX6;
- Cetuximab with FOLFIRI.

Comparators of interest to the STA not forming part of SoC are CAPOX for all patients, and panitumumab-containing regimens for those with RAS wild-type. For the purposes of their submission, to generate an estimate of effect for pembrolizumab versus CAPOX and panitumumab-based treatment, the company carried out an NMA in all patients. Cetuximab-based therapy was omitted from the NMA, and the company indicated that cetuximab combination regimens formed part of SoC in KEYNOTE-177. The ERG's comments on the company's NMA, together with suggestions as to how to adapt the NMA to more closely align with the NICE final scope, are discussed in Section 3.5.

Here, the ERG focuses on the direct head-to-head evidence available from KEYNOTE-177. At the time of writing, KEYNOTE-177 is the only RCT reporting results for first-line treatment of MSI-H/dMMR mCRC. For reasons outlined earlier, the ERG considers results derived from the ITT population from KEYNOTE-177 to represent the most robust estimate of effectiveness for pembrolizumab in the specified population versus CAPOX, FOLFOX and FOLFIRI.

When reporting results from KEYNOTE-177, the ERG has assumed that CAPOX, FOLFIRI, and FOLFOX are of equal clinical effectiveness. RCTs in the first-line treatment of mCRC report similar median PFS

and OS for CAPOX, FOLFOX and FOLFIRI (Table 18). Additionally, it should be borne in mind that 70% of people in the SoC group of KEYNOTE-177 received a bevacizumab-based regimen, which has been shown to be more clinically effective than FOLFOX or FOLFIRI alone at improving PFS when used as a first-line treatment in mCRC: RCTs reported an improvement in median PFS of 1.2[30, 31] and 1.4[17, 23] months on addition of bevacizumab to FOLFOX, FOLFIRI or CAPOX. Thus, there is bias in the results from the ITT population that favours SoC and as a consequence provides a conservative estimate of the clinical effectiveness of pembrolizumab versus FOLFOX, FOLFIRI or CAPOX in those with untreated MSI-H/dMMR mCRC. The company reported estimates of comparative clinical effectiveness in the subgroup of those not receiving bevacizumab as part of SoC, which the ERG reports for completeness but advises that, as highlighted by the company, results be interpreted with caution as they are derived from *post hoc* subgroup analyses that are informed by small sample size and in which randomisation has been broken.

Table 18. Summary of findings from studies evaluating CAPOX, FOLFIRI and FOLFOX in the first-line treatment of metastatic colorectal cancer

Study	FOLFIRI		FOLFOX		CAPOX	
	Median PFS (months)	Median OS (months)	Median PFS (months)	Median OS (months)	Median PFS (months)	Median OS (months)
Colucci 2005[18] (N = 360)	7.0[a] (range 1 to 47)	14.0 (range 1 to 48)	7.0[a] (range 1 to 32)	15.0 (range 1 to 43)	–	–
Porschen 2007[21] (N = 476)	–	–	8.0	18.8	7.1	16.8
Hochster 2008[20] (N = 97)	–	–	8.7[a]	19.2	5.9[a]	17.2
Cassidy 2011[17] (N = 1,334)	–	–	NR	18.9	NR	19.0
Ducreux 2011[19] (N = 316)			9.3	20.5	8.8	19.9

[a] Study reported time to progression rather than PFS.

Reported studies were identified from a systematic review of RCTs evaluating first-line systemic treatments for metastatic colorectal cancer.[28]

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; OS, overall survival; PFS, progression-free survival.

3.3.1 Progression-free survival

In the ITT population, based on assessment of PFS by central imaging, pembrolizumab was associated with a 40% reduction in the risk of disease progression or death compared with SoC, with the difference between treatment groups reaching statistical significance (HR 0.60, 95% CI: 0.45 to 0.80; p=0.0002). Median PFS was reported to be 16.5 months and 8.2 months in the pembrolizumab and SoC groups, respectively (Table 19). The ERG notes that the median PFS in the SoC group is within the range of median PFS (5.9 to 9.3 months) in the RCTs evaluating CAPOX, FOLFIRI and FOLFOX in untreated mCRC (Table 18). The Kaplan–Meier (KM) plots for PFS for the ITT population from KEYNOTE-177 indicate an initial crossing of the curves at about 6 months with a subsequent separation between the curves for the pembrolizumab and SoC groups (Figure 1).

For the subgroup of people not receiving bevacizumab, estimates of effect for pembrolizumab versus SoC [redacted], pembrolizumab is [redacted] Table 18). The company selected 52 people allocated to pembrolizumab to form the pembrolizumab group not receiving bevacizumab, indicating that those selected were people who would not have received bevacizumab if they had been randomised to SoC (chemotherapy regimen for SoC was specified before randomisation)..

The company indicated that sample size required to give ~98% power to detect an HR (pembrolizumab vs SoC) of 0.55 is 209 PFS events. Reported PFS for the ITT population is based on 195 events. As a statistically significant result for PFS has been generated in the ITT population, with narrow CI and a small p value, the ERG considers the results for this population to be robust. The clinical effect of pembrolizumab on PFS compared with SoC is predominantly consistent across subgroups, although some differences are no longer statistically significant, for example, ECOG score of 1, and in those with left-sided tumours (Figure 16, Appendix 9.2).

In the CS, Figure 1 could be taken to indicate that disease progression was determined by irRECIST in the pembrolizumab arm, but centrally verified by RECIST 1.1 in the SoC group. During clarification, the company expanded on the use of irRECIST, indicating that irRECIST and RECIST 1.1 provide the same response assessment until disease progression, and that irRECIST was used to make treatment decisions beyond progression as determined by RECIST 1.1. PFS per irRECIST by central imaging

vendor is an exploratory objective of KEYNOTE-177, and was not analysed at the second interim analysis. Exploratory analysis of irRECIST will be carried out at the final analysis for KEYNOTE-177.

Data are available for PFS2 in the ITT population in Appendix L of the CS. PFS2 was defined as the time from randomisation to disease progression on the next line of therapy, or death from any cause, whichever occurs first. The ERG considers PFS2 data to be immature. PFS2 does not inform the analysis of cost effectiveness. In brief, median PFS2 was 23.5 months (95% CI: 16.6 to 32.6) for SoC but was not reached in the pembrolizumab group (HR 0.63, 95% CI: 0.45 to 0.88). Bearing in mind the immaturity of PFS2, the ERG notes that PFS and PFS2 for pembrolizumab versus SoC are similar (PFS HR 0.60, 95% CI: 0.45 to 0.80 vs PFS2 HR 0.63, 95% CI: 0.45 to 0.88).

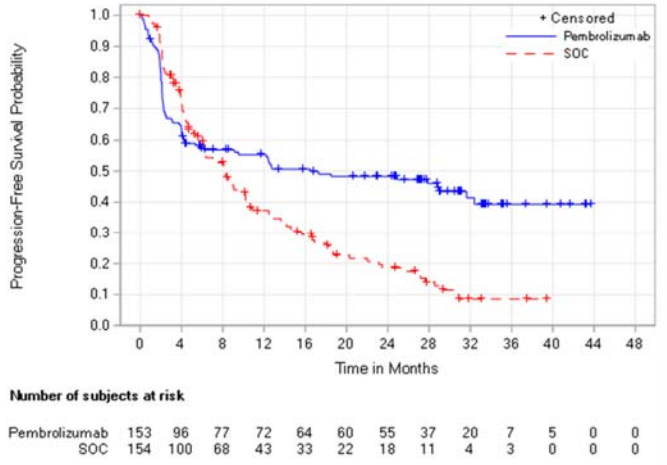
Table 19. Summary of event and censoring description for PFS by central imaging vendor per RECIST 1.1 (ITT population) (reproduced from CS, Tables 25–27, pages 60–62)

Event	ITT population		ITT population excluding those receiving bevacizumab	
	Pembrolizumab (N = 153)	SoC (N = 154)	Pembrolizumab (N =52)	SoC (N = 47)
PFS rate at time point, % (95% CI)				
6 months	57.6 (49.3 to 65.0)	59.7 (51.1 to 67.3)	[redacted]	[redacted]
9 months	56.8 (48.5 to 64.3)	45.5 (36.9 to 53.7)	[redacted]	[redacted]
12 months	55.3 (47.0 to 62.9)	37.3 (29.0 to 45.5)	[redacted]	[redacted]
18 months	49.1 (40.7 to 57.0)	26.7 (19.2 to 34.7)	[redacted]	[redacted]
24 months	48.3 (39.9 to 56.2)	18.6 (12.1 to 26.3)	[redacted]	[redacted]
Number of people with a PFS event, n (%)	82 (53.6)	113 (73.4)	[redacted]	[redacted]
Documented progression	65 (42.5)	86 (55.8)	[redacted]	[redacted]
Death	17 (11.1)	27 (17.5)	[redacted]	[redacted]
Median PFS, months (95% CI)	16.5 (5.4 to 32.4)	8.2 (6.1 to 10.2)	[redacted]	[redacted]
Subjects censored	71 (46.4)	41 (26.6)	[redacted]	[redacted]
Curative-intent surgery	12 (7.8)	12 (7.8)	[redacted]	[redacted]

New anti-cancer therapy	5 (3.3)	15 (9.7)	[redacted]	[redacted]
Last radiologic assessment showing no progression	53 (34.6)	10 (6.5)	[redacted]	[redacted]
No adequate post-baseline imaging assessment	1 (0.7)	4 (2.6)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CS, company submission; ITT, intention to treat; PFS, progression-free survival.

Figure 1. Kaplan–Meier estimates of PFS based on central imaging vendor per RECIST 1.1 (ITT population; database cut-off date: 19 Feb 2020) (reproduced from CS, Figure 9, page 61)



In terms of the two remaining populations that the ERG considers relevant based on RAS status (wild-type versus non wild-type), compared with SoC, the clinical benefit of pembrolizumab is maintained in those with RAS wild-type (HR 0.44, 95% CI: 0.29 to 0.67). CAPOX, FOLFIRI and FOLFOX are treatment options in England for RAS wild-type mCRC, and again the ERG considers that SoC in KEYNOTE-177 provides the most robust estimate of effect for pembrolizumab versus these three regimens. Also, as SoC includes a proportion of people who have received bevacizumab-based regimens, the bias in the analysis favours SoC and the estimate of effect for pembrolizumab is conservative.

Treatment comprising cetuximab, but not panitumumab, was available as an option for the treating clinician for SoC, but only a small proportion of people in the ITT population (11.2%; Table 13) received cetuximab in combination with FOLFOX or FOLFIRI. As with bevacizumab, RCTs have reported that addition of cetuximab to FOLFOX or FOLFIRI in those with RAS wild-type is associated with an improvement in PFS over FOLFOX or FOLFIRI alone, which introduces additional bias in favour of SoC. The CRYSTAL[26] and OPUS[24, 32] RCTs reported an improvement in median PFS of 1.5 months and 6.2 months with cetuximab-combination regimen compared with FOLFIRI or FOLFOX alone, respectively.

RAS status does not seem to have been a determining factor for treatment choice in KEYNOTE-177, as assessment of RAS status was not carried out for all those enrolled in the study. Thus, treatment of participants with RAS wild-type MSI-H/dMMR mCRC in the SoC group is likely not entirely representative of clinical practice in England. To substantiate the observed effect for pembrolizumab on PFS noted in the subgroup from KEYNOTE-177, for those with RAS wild-type MSI-H/dMMR mCRC, the ERG considers it important to provide estimates of effect versus those treatments that have been found to be clinically effective in this group, albeit in mCRC and not MSI-H/dMMR mCRC, that is, cetuximab and panitumumab in combination with FOLFOX or FOLFIRI. The ERG's critique of the company's NMA to generate an estimate of effect for pembrolizumab versus panitumumab combination treatment is provided in Section 3.5.

The subgroup analysis of those without RAS wild-type, that is, those with a RAS mutation, provides a markedly different result for the effect of pembrolizumab on PFS compared with SoC. The direction of effect for PFS no longer favours pembrolizumab, with pembrolizumab potentially associated with a 19% increase in risk of disease progression or death compared with SoC, albeit that the difference between the treatments does not reach statistical significance (HR 1.19, 95% CI: 0.68 to 2.07). The company comments that the results of the analyses should be interpreted with caution, given the small sample size, but does not discuss the potential implications or clinical rationale for the result. During clarification, the ERG asked that the company carry out subgroup analysis for those without RAS wild-type comparing pembrolizumab versus SoC, which the ERG defined as FOLFOX or FOLFIRI with or without bevacizumab. The company declined the ERG's request, commenting that such an analysis would be inappropriate.

Relevant comparators for those with mutations in RAS are CAPOX, FOLFOX and FOLFIRI. As with other analyses, the bias is against pembrolizumab, due to a large proportion of people having

received bevacizumab. However, as also with other analyses, the extent of bias is difficult to quantify. During clarification, the ERG requested that the company carry out an analysis of those without RAS wild-type, focusing on FOLFOX and FOLFIRI, with or without bevacizumab, as the comparator. The company commented that it would be inappropriate to carry out such an analysis as any analysis would be considerably under-powered because of the low number of events, which would likely produce false-negative results. Additionally, randomisation would be broken in the subgroups, and differences in patient baseline characteristics are noted between treatment arms that could confound the results of the analyses, rendering them unreliable. The ERG appreciates that subgroup analyses are less robust and are hypothesis generating, but considers that the difference in results for PFS in the subgroup of those with mutation of KRAS or NRAS is prominent amongst the other subgroup analyses, and the clinical effectiveness of pembrolizumab in this subgroup warrants further investigation. Given that OS data are immature, the ERG considers that additional data could be accrued on PFS in the subgroups of those with RAS mutations during longer-term follow-up.

3.3.2 Overall survival

OS data for KEYNOTE-177 are immature are the time of writing. Analysis of OS is based on 125 events and median OS has yet to be reached in the pembrolizumab group. Additionally, OS is likely to be severely confounded, with 59% of participants allocated to SoC receiving pembrolizumab (36.4%) or a PD-1/PD-L1 inhibitor (22.7%) on cessation of initial treatment, primarily because of disease progression. The ERG appreciates that, due to the potential confounding, the OS advantage of pembrolizumab, if any, will be underestimated but considers the data too immature to draw reliable conclusions.

The company attempted to mitigate against confounding through sensitivity analyses of OS, with adjustment for crossover carried out based on three models recommended by the NICE Decision Support Unit (DSU) in the Technical Support Document (TSD) 16:[33]

- simplified 2-stage model;
- rank preserving structural failure time (RPSFT) model;
- inverse probability of censoring weighting (IPCW) model.

In their analysis of cost-effectiveness, the company supplied a state transition model (STM) as their primary model, and a partitioned survival model (PSM), which was used as a validation tool. Adjusted OS data were implemented only in the PSM. Within the STM, the company assumes no

additional benefit in OS for patients in the post-progression state, which the ERG considers a reasonable assumption that removes the uncertainty associated with the estimation of OS from the trial (assumption is discussed in more detail in Section 4.2.4.1). As adjusted OS data are only applicable to the PSM, the ERG does not discuss further the estimates for adjusted OS.

In the ITT population, there were 56 (36.6%) events in the pembrolizumab group compared with 69 (44.8%) events in the SoC group (Table 20). The direction of effect favours pembrolizumab but the difference between treatments does not reach statistical significance (HR 0.77, 95% CI: 0.54 to 1.09; p = 0.0694). The KM curves for OS for the ITT population depict a crossing of the curves at about 6 months with a subsequent separation between the curves for the pembrolizumab and SoC groups (Figure 2). At the time of analysis, both the pembrolizumab and SoC curve appear to reach a plateau at about 35 months. The ERG considers the plateaus observed in the OS curves for pembrolizumab and SoC to be a common artefact observed in the "tails" of KM curves, and is likely to be due to small patient numbers, few events, and heavy censoring.

Estimates of effect for pembrolizumab were consistent across pre-specified subgroups, [redacted] (Figure 17, Appendix 9.2). The ERG [redacted].

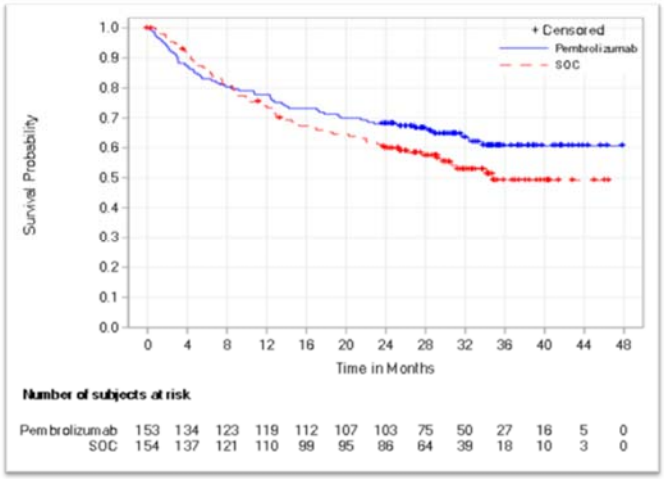
Table 20. Summary of event for OS (ITT population) (reproduced from CS, Tables 20 and 21, pages 46 and 47)

Event	ITT population	
	Pembrolizumab (N = 153)	SoC (N = 154)
OS rate at time point, % (95% CI)		
6 months	83.0 (76.1 to 88.1)	86.0 (79.4 to 90.7)
9 months	79.7 (72.5 to 85.3)	78.7 (71.3 to 84.4)
12 months	77.8 (70.3 to 83.6)	74.0 (66.2 to 80.3)
18 months	71.2 (63.4 to 77.7)	65.9 (57.7 to 72.9)
24 months	68.0 (59.9 to 74.7)	59.8 (51.5 to 67.2)

Number of people with a OS event, n (%)	56 (36.6)	69 (44.8)
Median OS, months (95% CI)	NR (NR to NR)	34.8 (26.3 to NR)

Abbreviations: CI, confidence interval; CS, company submission; ITT, intention to treat; NR, not reached; OS, overall survival.

Figure 2. Kaplan–Meier estimates of OS (ITT population; database cut-off date: 19 Feb 2020) (reproduced from CS, Figure 4, page 47)



3.3.3 *Response outcomes*

Within the ITT population of KEYNOTE-177, a larger proportion of people in the pembrolizumab group achieved a complete response (CR) to treatment as assessed by central imaging vendor per RECIST 1.1 (11.1% with pembrolizumab versus 3.9% with SoC; Table 21). Best overall response rate (ORR), which combines CR and partial response (PR), was also higher in the pembrolizumab group (43.8% with pembrolizumab versus 33.1% with SoC). The absolute difference in ORR between pembrolizumab and SoC was 10.7% higher with pembrolizumab, a difference that approaches statistical significance (95% CI: –0.2% to +21.3%; one sided p value of 0.0275).

Mean and median time to response were similar for pembrolizumab and SoC, but duration of response was considerably longer with pembrolizumab:

- Median time to response: 2.2 (range 1.8 to 18.8) months with pembrolizumab versus 2.1 (range 1.7 to 24.9) months with SoC;
- Mean time to response: 4.0 (SD 3.7) months with pembrolizumab versus 3.6 (SD 4.1) months with SoC;
- Proportion of participants with duration of response at ≥12 months: 85.1% with pembrolizumab versus 43.8% with SoC;
- Proportion of participants with duration of response at ≥24 months: 82.6% with pembrolizumab versus 35.3% with SoC.

Table 21. Summary of best overall response by central imaging vendor per RECIST 1.1 (ITT population; database cut-off date of 19 Feb 2020) (reproduced from CS, Table 29, page 64)

Response evaluation	Pembrolizumab (N = 153)			SoC (N = 154)		
	n	%	95% CI[a]	n	%	95% CI[a]
CR	17	11.1	(6.6 to 17.2)	6	3.9	(1.4 to 8.3)
PR	50	32.7	(25.3 to 40.7)	45	29.2	(22.2 to 37.1)
Stable disease	32	20.9	(14.8 to 28.2)	65	42.2	(34.3 to 50.4)
PD	45	29.4	(22.3 to 37.3)	19	12.3	(7.6 to 18.6)
Objective response (CR+PR)	67	43.8	(35.8 to 52.0)	51	33.1	(25.8 to 41.1)
Disease control (CR+PR+stable disease)	99	64.7	(56.6 to 72.3)	116	75.3	(67.7 to 81.9)
Not evaluable	3	2.0	(0.4 to 5.6)	2	1.3	(0.2 to 4.6)
No assessment[b]	6	3.9	(1.5 to 8.3)	17	11.0	(6.6 to 17.1)

Only confirmed responses are included.

[a] Based on binomial exact confidence interval method.

[b] No Assessment: subject had no post-baseline imaging.

Abbreviations: CI, confidence interval; CR, complete response; CS, company submission; PD, progressive disease; PR, partial response; SoC, standard of care.

3.3.4 *Health-related quality of life*

Health-related quality of life (HRQoL) was assessed using three tools, EQ-5D (3L), EORTC QLQ-C30 and EORTC QLQ-C29. The EQ-5D tool is used to evaluate general health status, whereas EORTC questionnaires are the instruments most frequently used to measure QoL in people with cancer. Assessments were based on responses from the full analysis set rather than the ITT population and captured changes in QoL at 18 weeks of follow-up.

Results from EQ-5D indicate that, compared with SoC, pembrolizumab is associated with improvements in utility score and on the visual analogue scale (Table 22), although the improvement over SoC in utility score is reported by the company not to be clinically meaningful. Responses to EORTC QLQ-C30 identified a small, but reported to be a clinically important, improvement in QoL with pembrolizumab over SoC (Table 22).

Table 22. Summary of results from assessment of health-related quality of life from KEYNOTE-177 (reproduced from CS, Tables 32 and 33, page 69, and from Table 110 from Appendix L, page 537)

Treatment	Baseline		Week 18		Change from baseline at week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)[a]
EQ-5D utility score						
Pembrolizumab	142	0.77 (0.195)	102	0.84 (0.175)	151	0.04 (0.00 to 0.08)
SoC	133	0.75 (0.197)	82	0.77 (0.199)	141	–0.01 (–0.05 to 0.02)
Pembrolizumab versus SoC						Difference in LS means (95% CI): 0.05 (0.00 to 0.10) p = 0.0311
EQ-5D VAS						
Pembrolizumab	142	70.12 (18.862)	102	76.86 (17.916)	151	4.50 (1.16 to 7.83)
SoC	133	70.83 (19.788)	82	70.76 (18.198)	141	–2.88 (–6.46 to 0.69)
Pembrolizumab versus SoC						Difference in LS means (95% CI): 7.38 (2.82 to 11.93) p = 0.0016
EORTC QLQ-C30 Global Health Status/QoL scales						
Pembrolizumab	141	66.19 (21.029)	102	72.14 (20.530)	151	3.33 (–0.05 to 6.72)

SoC	131	66.60 (20.737)	82	62.60 (17.677)	141	–5.63 (–9.32 to –1.94)
Pembrolizumab versus SoC					Difference in LS means (95% CI): 8.96 (4.24 to 13.69) p = 0.0002	

[a] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction as covariates.

Abbreviations: CI, confidence interval; CS, company submission; EORTC, European Organisation for Research and Treatment of Cancer; LS, least squares; QoL, quality of life; SD, standard deviation; SoC, standard of care; VAS, visual analogue scale.

3.3.5 Adverse effects

Adverse events (AEs) in KEYNOTE-177 were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and grouped system organ class, and were graded by investigators using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The All Subjects as Treated (ASaT) population was used for the analyses of safety data in KEYNOTE-177. The ASaT population comprised all randomised patients who received at least one dose of study medication, with patients included in the treatment group corresponding to the study medication they received rather than the randomised treatment group, unless they only received the incorrect study medication for one cycle but received the correct treatment for all other cycles. The company provided a summary of the AEs data from KEYNOTE-177 in the CS with further details in Appendix F of the CS.

The median duration of study drug exposure was longer in the pembrolizumab group (11.1 months) compared with the SoC group (5.7 months), but the proportion of participants with at least one AE in those who received pembrolizumab was slightly smaller (97.4%) than in those allocated to SoC (99.3%). In addition, compared with SoC, pembrolizumab was associated with a lower frequency of Grade 3 to 5 AEs (56.2% vs 77.6%), serious adverse events (SAEs; 40.5% vs 52.4%), and investigator assessed drug-related AEs (79.7% vs 98.6%; Table 23) compared with SoC. Only one person from KEYNOTE-177, who was allocated to the SoC group, was categorised as having died as a result of an AE. The proportion of participants who experienced an AE resulting in treatment discontinuation was slightly larger in the pembrolizumab group compared with the SoC group (13.7% vs 11.9%).

The eleven most frequently experienced treatment-related AEs in the pembrolizumab group were: diarrhoea (24.8%); fatigue (20.9%); pruritis (13.7%); nausea (12.4%); rash (11.1%); increased aspartate aminotransferase (11.1%); arthralgia (10.5%); hypothyroidism (10.5%), increased alanine aminotransferase (9.8%); increased blood alkaline phosphatase (7.8%); and decreased appetite

(7.8%). As already noted, the frequency of drug-related AEs was higher with SoC, and the AE profile in the SoC group differed from that of pembrolizumab, with commonly occurring AEs being: diarrhoea (52.4%); nausea (55.2%); fatigue (44.1%); decreased appetite (34.3%); stomatitis (30.1%); vomiting (28.0%); decreased neutrophil count (23.1%); neutropenia (21.0%); and peripheral sensory neuropathy (20.3%). The ERG's clinical experts reported that the AEs observed in KEYNOTE-177 were as expected, and did not have any concerns relating to the AEs experienced by those randomised to pembrolizumab.

The company also conducted an exposure-adjusted analysis of AEs that showed similar results to the data for unadjusted AEs. The ERG notes that the company used the AE data from KEYNOTE-177 for Grade 3+ AEs that occurred in at least 5% of patients to inform the AEs in the economic model. The AE data and their implementation in the economic model are discussed in Section 4.2.6.

Table 23. Summary of adverse events (ASaT population)

Adverse effect	Pembrolizumab (N = 153)		SoC (N = 143)	
	n	(%)	n	(%)
One or more AE	149	(97.4)	142	(99.3)
No AE	4	(2.6)	1	(0.7)
Drug-related[a] AEs	122	(79.7)	141	(98.6)
Toxicity Grade 3–5 AEs	86	(56.2)	111	(77.6)
Toxicity Grade 3-5 drug-related AEs	33	(21.6)	94	(65.7)
Serious AEs	62	(40.5)	75	(52.4)
Serious drug-related AEs	25	(16.3)	41	(28.7)
Death	6	(3.9)	7	(4.9)
Death due to a drug-related AE	0	(0.0)	1	(0.7)
Discontinued[b] drug due to an AE	21	(13.7)	17	(11.9)

Discontinued[b] drug due to a drug-related AE	15	(9.8)	8	(5.6)
Discontinued[b] drug due to a serious AE	12	(7.8)	13	(9.1)
Discontinued[‡] drug due to a serious drug-related AE	7	(4.6)	5	(3.5)

[a] Determined by the investigator to be related to the drug.

[b] All study medications withdrawn.

Notes: Grades are based on NCI CTCAE version 4.03. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Database Cutoff Date: 19 Feb 2020.

Abbreviations: AE, adverse event; ASaT, All Subjects as Treated; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SoC, standard of care.

3.3.5.1 *Summary of adverse events of special interest*

A higher incidence of AEs of special interest (AEOSIs) was recorded with pembrolizumab than with SoC (47 [30.7%] vs 18 [12.6%]). Serious AEOSIs were experienced by 10.5% of participants allocated to pembrolizumab compared with 0.7% of participants randomised to SoC. However, the number of AEOSIs that led to discontinuation of pembrolizumab treatment was low (6.5 %). The company reported that most AEOSIs were manageable with systemic corticosteroids, supportive care, and dose interruption. No fatal AEOSIs was reported.

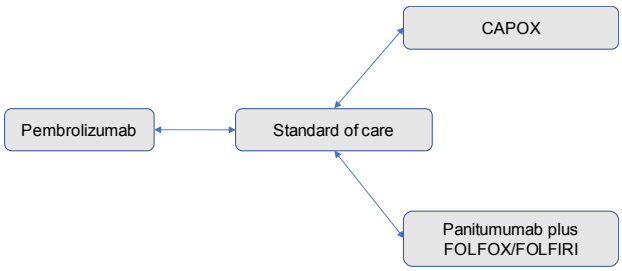
The most common AEOSIs categories, with ≥2% incidence, in the pembrolizumab group were: hypothyroidism; hyperthyroidism; colitis; pneumonitis; adrenal insufficiency; hepatitis; and infusion reactions. Of particular note, the incidence of hypothyroidism was much higher in the pembrolizumab group (19 participants [12.4%]) than in the SoC group (3 participants [2.1%]). However, all hypothyroidism AEOSIs occurring with pembrolizumab group were of Grade 1 or 2 in severity. Colitis AEOSIs were more frequent in the pembrolizumab group than the SoC group (6.5% vs 0%). Colitis AEOSIs experienced with pembrolizumab comprised five participants with Grade 1 or 2 events, three with a Grade 3 event, and two with a Grade 4 event. Five participants had colitis events deemed to be drug-related SAEs, and a colitis AEOSI led to four participants discontinuing treatment, with two events categorised as serious AEs. Of the 65 AEOSIs episodes experienced during treatment with pembrolizumab, 23.1% were initially treated with high-dose corticosteroids. Further details on the breakdown of the AEOSIs are provided in the CS (Table 46 and Appendix F).

3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

NMAs were used to generate estimates of comparative clinical effectiveness for PFS and OS for pembrolizumab versus comparators not included in SoC of KEYNOTE-177 but listed in the final scope issued by NICE, that is, CAPOX and panitumumab in combination with FOLFIRI or FOLFOX. The company decided against including cetuximab in combination with FOLFIRI or FOLFOX as a separate comparator as cetuximab-based therapy was an option in SoC of KEYNTOE-177, a decision with which the ERG does not agree (more detail available in Section 3.5).

Using the same SLR carried out to identify studies providing head-to-head evidence on pembrolizumab in MSI-H/dMMR mCRC, five studies, including KEYNOTE-177, were identified as relevant to the NMA.[2, 17, 20, 21, 25] The company's NMA was informed by a population of "all patients", which, based on RCTs informing the network, encompasses those with mCRC, with RAS wild-type mCRC, and with MSI-H/dMMR mCRC, and, as such with overlap across populations because MSI-H/dMMR status is unknown for studies in mCRC and RAS wild-type. As the population is based on all patients, an approach with the ERG disagrees (more detail in Section 3.5.1.2), only one network of interventions is required (Figure 3). Not all identified studies provided data on PFS or OS in a format that met the requirements of the company and, as a result, not all RCTs inform both networks.

Figure 3. Network diagram for network meta-analyses of PFS and OS



Within the Appendices forming part of the CS, for the five studies included in the NMA, the company provides:

- detailed descriptions of study characteristics (Appendix D1.1, Tables 13 to 19);
- tabulated data (Appendix D1.1, Table 20);
- quality assessments (Appendix D1.3, Tables 23 to 26).

As highlighted by the company, differences are noted across FOLFOX regimens, with RCTs evaluating FOLFOX4, FOLFOX6 and mFOLFOX6. The ERG's clinical experts advised that the various FOLFOX regimens are of similar clinical effectiveness and it is appropriate to combine data from all studies evaluating FOLFOX.

The five RCTs included in the company's networks are:

- Pembrolizumab versus SoC:
    - KEYNOTE-177, contributes to PFS and OS.[2]
- CAPOX versus SoC:
    - NO16966, contributes to OS;[17]
    - Porschen 2007, contributes to PFS and OS;[21]
    - TREE-1, contributes to OS.[20]
- Panitumumab plus FOLFOX/FOLFIRI versus SoC:
    - PRIME, contributes to PFS and OS.[25]

3.4.1 CAPOX

The ERG considers the three identified RCTs evaluating CAPOX to be relevant to the decision problem as set out by the company. The ERG identified an additional RCT comparing CAPOX versus FOLFOX6 that met the company's SLR inclusion criteria and provided data to inform both the PFS and OS networks.[19] However, as discussed in Section 3.3, the ERG has assumed CAPOX to be of similar clinical effectiveness to FOLFIRI and FOLFOX in the first-line treatment of mCRC, and so considers it appropriate to exclude CAPOX from the NMA: in the company's response to clarification, base case results for CAPOX are based on equivalency with SoC, from which the ERG has inferred that the company considers the ERG's assumption of similar clinical effectiveness for CAPOX, FOLFIRI and FOLFOX to be appropriate. Here, the ERG does not describe in full or critique further the four RCTs evaluating CAPOX versus SoC. Should the ERG have considered it necessary to generate estimates of effect for pembrolizumab versus CAPOX, to minimise clinical heterogeneity within the networks, the ERG would have requested that the networks be separated by RAS wild-type (more detail available in Section 3.5).

3.4.2 Panitumumab in combination with FOLFOX or FOLFIRI

For panitumumab-combination treatment, the company identified one RCT — PRIME — that compared panitumumab plus FOLFOX4 versus FOLFOX4 alone.[25] PRIME is an open-label Phase III

study that enrolled adults aged ≥18 years with an ECOG score of ≤2 and first occurrence of mCRC, and had a primary end point of PFS.[25] As noted by the ERG undertaking the assessment that informed TA439, estimates of effectiveness of panitumumab plus FOLFOX4 versus FOLFOX4 alone in RAS wild-type tumours were derived from a subgroup of the full trial population.[13]

During the design and conduct of PRIME, research emerged on the impact of KRAS and NRAS mutations in reducing the clinical effectiveness of EGFR inhibitors, such as panitumumab. In the case of PRIME, extended RAS subgroup analysis was noted alongside a protocol amendment to restrict analysis of the ITT population to compare PFS and OS according to KRAS status.[13] In the first-line setting, panitumumab is indicated for the treatment of adults with RAS wild-type mCRC in combination with FOLFOX or FOLFIRI.[34]

Baseline characteristics of the RAS wild-type subgroup from PRIME are comparable with those of the ITT population of KEYNOTE-177, in terms of age and ECOG score. Median age of participants was 61 years in PRIME compared with 63 years in KEYNOTE-177. A small proportion of participants enrolled in PRIME had ECOG score of 2 at baseline (6%), whereas KEYNOTE-177 specified an ECOG score of 0 or 1 as an inclusion criteria: an ECOG score of 2 indicates a poorer health status than score of 0 or 1. Data on site of primary tumour, in terms of left or right location, are not available for PRIME.

In its critique of the quality assessment of PRIME, the ERG on project TA439 considered that randomisation allocation was adequate for the full population of PRIME but that relevant data based on RAS wild-type were derived from a subgroup. However, the ERG went on to comment that they considered the biological rationale for the re-evaluation by RAS status to support the validity of the estimates of effect. As an open-label study, there is risk of bias in assessment of subjective outcomes, such as PFS. In PRIME, an independent monitoring committee reviewed interim analyses of safety and one descriptive interim analysis of PFS.[13] Uncertainties associated with effect estimates from subgroup analyses potentially arise from ascertainment bias and selection bias, but, in TA439, the ERG's assessment was that the potential for the two types of bias was minimal. Lack of statistical power to identify a true difference in effect between two treatments is also associated with use of subgroup data. In TA439, the ERG considered that the underlying rationale of tumour biology and consistency of effect estimates for panitumumab supported the validity of estimates of effect.[13] The ERG for this STA agrees with the points raised in TA439 and considers estimates of effect for

panitumumab plus FOLFOX4 derived from the subgroup analysis based on RAS wild-type from PRIME to provide the best estimate for panitumumab-based treatment in the population in which panitumumab has been shown to have clinical benefit, and are relevant to the decision problem.

3.4.3 Cetuximab in combination with FOLFIRI or FOLFOX

TA439 described two RCTs evaluating cetuximab in combination with FOLFIRI or FOLFOX – CRYSTAL[26] and OPUS in first-line treatment of mCRC.[24, 32] In contrast to PRIME, research indicating the negative impact of RAS mutations on the clinical effectiveness of EGFR inhibitors was not available at the protocol development stage of CRYSTAL and OPUS. Thus, the re-analyses of the ITT populations of the two studies based on RAS status are retrospective in nature. Nevertheless, the analyses formed the basis for revision of the licensed population for cetuximab.[35] Cetuximab is indicated for the treatment of EGFR-expressing, RAS wild-type mCRC in combination with irinotecan-based chemotherapy (FOLFIRI) and, in first-line, in combination with FOLFOX.

CRYSTAL and OPUS are Phase III randomised, open-label studies.[13] Primary outcome assessed in OPUS was the proportion of participants who had an objective response rate, with tumour response assessed by an independent review committee according to modified World Health Organisation criteria. By contrast, primary endpoint in CRYSTAL was PFS. Baseline characteristics in the ITT populations of the two studies were balanced between treatment groups and were similar. The ERG for project TA439 noted that, because relevant data are derived from retrospective subgroup analyses, and randomisation was not stratified by RAS status, randomisation has been broken in all comparisons, increasing the risk of selection bias.[13] However, the ERG stated that, from the evidence provided during the project (published and unpublished), they were able to verify that the treatment groups in CRYSTAL and OPUS were adequately similar at baseline on a range of prognostic factors for the RAS wild-type population. Characteristics were similar across the ITT and RAS wild-type populations, suggesting a low risk of selection bias in the RAS tested trial population.[13] The internal validity of OPUS and CRYSTAL is affected by the same issues associated with PRIME, in terms of data are derived from *post hoc* subgroup analyses, with the resulting lack of statistical power. However, as with PRIME, the biological rationale for carrying out the retrospective analyses, together with consistency of estimates of effect for cetuximab plus FOLFIRI or FOLFOX, support the validity of the analyses.

Subsequent to the publication of TA439, results from the TAILOR RCT became available.[27] TAILOR is an open-label Phase III randomised study set in China and designed to evaluate prospectively the

efficacy and tolerability cetuximab in combination with FOLFOX4 versus FOLFOX4 alone in the first-line treatment of RAS wild-type mCRC. No strata was applied at randomisation. Baseline characteristics were balanced between treatment groups. However, the study did not stipulate detectable tumour EGFR expression as an inclusion criteria, which is not in line with the marketing authorisation for cetuximab. The primary endpoint in TAILOR is PFS as assessed by RECIST 1.0, with a blinded review of imaging and clinical data carried out by an independent review committee.[27] Analysis was based on a modified ITT population, comprising 393 out of 397 randomised. As a prospective study, the risk of selection bias is minimal compared with PRIME, CRYSTAL, and OPUS.

As with PRIME, baseline characteristics for CRYSTAL, OPUS and TAILOR are not available by MSI-H/dMMR status. The ERG acknowledges that there is likely clinical heterogeneity between the population enrolled in KEYNOTE-177 and those of the three studies evaluating cetuximab-combination treatments, but considers that data from CRYSTAL, OPUS and TAILOR provide the best estimate of effect for cetuximab-based regimens in the population in which cetuximab has been shown to have clinical benefit.

3.5 Critique of the indirect comparison and/or multiple treatment comparison

3.5.1 Methods of indirect comparison

3.5.1.1 *Methods and assumptions*

Section D1.1 of the Appendices component of the CS provides an overview of the methods followed by the company to produce estimates of effect for pembrolizumab versus CAPOX and panitumumab in combination with FOLIRI or FOFOX. The ERG considers the company's approach and rationales for decisions made to be mostly appropriate. Here, the ERG provides a brief summary of the company's methods, together with comments where the ERG has a suggestion for an alternative approach.

Initially, the company assessed assumption of proportional hazards (PHs), which is required for NMA based on constant HRs. KM curves for PFS and OS for included studies, when available, were visually inspected for crossing survival curves, together with more formal assessments of proportionality. Through their analyses, the company identified that the assumption of PHs was violated for some studies for PFS and OS.

Fractional polynomials (FPs) offer an alternative method to generate estimates of effect via NMA when the assumption of PHs is violated.[36] For the FP NMA, to generate estimates for OS and PFS, the

company used the Weibull and Gompertz distributions, which are both first order FPs, and also second order FPs with varying values of the two powers required for second order (Table 24). The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models, with a difference in DIC of about 5 points considered meaningful. Plausibility of the curves produced was also considered. The ERG considers that, based on methods reported in Jansen,[36] that evaluation of a wider range of powers for the first and second order FPs would have been helpful to underscore the company's choice of FP.

Table 24. Models assessed by company in FP NMA

Model
Weibull: First order FP (p = 0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)
Gompertz: First order FP (p = 1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)
Second order FP: p1 = 0, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)
Second order FP: p1 = 0, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)
Second order FP: p1 = 1, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)
Second order FP: p1 = 1, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)

Abbreviations: FP, fractional polynomial; NMA, network meta-analysis.

Within Appendix M, the company presents results for analyses based on constant HR and FPs. Given that assumption of PHs does not hold for PFS for KEYNOTE-177, the ERG considers constant HR NMA to be inappropriate and has a preference for the results derived from the FP NMA. Moreover, results from the FP analysis are implemented in the economic model. Given the ERG's preference for the FP analysis, the ERG does not discuss the results from the constant HR NMA further.

During the clarification process, the company provided the code and digitised data used in the FP NMA. Using the company's data set, and following the company's methodology, the ERG was able to validate the company's choice of FP model for PFS in all patients. The ERG focused on PFS as OS data are immature. Using the preferred model, the ERG was able to replicate the company's estimates of effect of PFS at the time points reported for CAPOX and pembrolizumab versus SoC, but notes deviations from the company's results for panitumumab plus FOLFOX versus SoC (provided in Section 3.5.2.1).

Given that the RCTs included in the FP NMA involve different patient populations in mCRC, with KEYNOTE-177 enrolling only those with MSI-H/dMMR mCRC and PRIME focusing on RAS wild-type mCRC, clinical heterogeneity is present and introduces bias into the analyses, the impact of which on estimates of effect is difficult to quantify. For the NMA of all patients, given that MSI-H/dMMR mCRC is associated with a poor prognosis and SoC in KEYNOTE-177 included bevacizumab treatment, it is likely that bias in the analysis is against pembrolizumab and generated estimates of effect might underestimate the true effect of pembrolizumab.

Differences are noted across studies in the FOLFOX and FOLFIRI regimens administered. However, the ERG's clinical experts have advised that the variations in schedule are unlikely to have an impact on clinical effectiveness.

In summary, the ERG considers the company's use of FP NMA to derive estimates of effect to be appropriate, but notes that evaluation of further powers would be valuable.

3.5.1.2 *Network structure*

As highlighted in Section 2.3.3, the final scope issued by NICE specifies that panitumumab-combination regimens are a first-line treatment option for those with RAS wild-type mCRC, together with cetuximab plus FOLRIRI or FOLFOX for EGFR-expressing RAS wild-type, and CAPOX is an option for all mCRC. The network of treatments created by the company (Figure 3) omits cetuximab-combination treatment and is based on all patients. The rationale for not including cetuximab plus FOLFIRI or FOLFOX in the NMA was that cetuximab-based treatment formed part of SoC, and the six regimens comprising SoC were considered as a single group for the purposes of the NMA. The ERG notes that only 11.2% (16/143) of people allocated to SoC received a cetuximab-containing treatment, and thus removing those who received cetuximab from the SoC group for purposes of NMA would leave a relatively large sample size.

Given that cetuximab-combination treatment is considered in the cost effectiveness analysis, the ERG considers it appropriate to generate an estimate of effect for pembrolizumab versus cetuximab-based treatment via FP NMA that is based on available RCTs, as was done for panitumumab plus FOLFOX. To align more closely with the final scope issued by NICE, during clarification, the ERG requested that the company carry out FP NMA for the subgroup of people from KEYNOTE-177 with RAS wild-type tumours as depicted in Figure 4. The RCTs included in the network are based on studies identified by two systematic reviews.[13, 28] For the FP NMA, the ERG defined SoC as FOLFOX or

FOLFIRI, with or without bevacizumab, and assumed equivalence of FOLFOX and FOLFIRI regimens. The company declined to carry out the requested FP NMA, citing that It would be inappropriate to perform the analyses as:

- the analyses would be considerably under-powered and likely to produce false-negative results.
- randomisation would be broken for treatment comparisons in the subgroups.

The company also commented that, "*subgroup analyses for the subgroup of patients with RAS-wildtype colorectal cancer are not necessary for the purposes of this appraisal, as the results from the analyses in the overall population would be reasonable and appropriate proxies for what would be observed in RAS-wildtype patients*". The ERG agrees with the company's points around the limitations associated with *post hoc* subgroup analyses. However, the ERG counters that the network suggested by the ERG is more relevant to the decision problem than that carried out by the company, minimising clinical heterogeneity through exclusion of studies evaluating CAPOX in mCRC with no analysis of biomarker status and by focusing on RAS wild-type. Subgroup analysis by RAS wild-type in KEYNOTE-177 shows a clear benefit for pembrolizumab versus SoC (HR 0.44, 95% CI: 0.29 to 0.67; Figure 16), a benefit that is also likely underestimated because of the inclusion of cetuximab- and bevacizumab-based treatment. To provide the best available estimate of effect to inform the cost effectiveness analysis that is derived from available evidence, the ERG considers it important to evaluate the effectiveness of pembrolizumab in RAS wild-type versus all relevant comparators, albeit that MSI-H/dMMR status is not known for comparator studies.

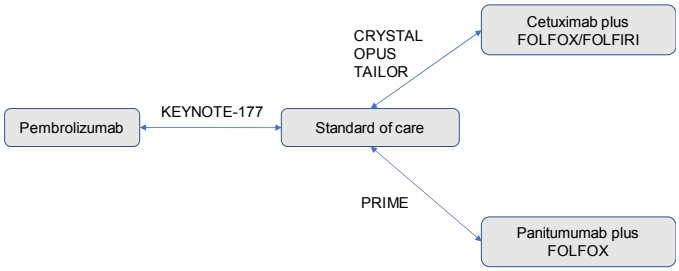
Given that estimates of effect are not available for the ERG's preferred network, and the company's network is informing estimates of effect for CAPOX, the ERG reiterates that the network for all patients omits an RCT that could inform the comparison of CAPOX versus SoC (discussed in Section 3.1).[19] As the ERG is assuming equivalent clinical effectiveness for CAPOX, FOLFIRI and FOLFOX in the first-line treatment of mCRC, the ERG did not request that the company reanalyse the data to include the RCT in their network as part of the clarification process. Additionally, within KEYNOTE-177, because RAS status was not necessarily a factor in choice of treatment in SoC, some allocated to SoC might not have received the optimum intervention according to clinical practice in England.

No estimate of effect for pembrolizumab versus cetuximab-combination treatment in the first-line setting is available from the FP NMA, thus, based on results from NMA presented in TA439,[13] for

economic analyses the ERG has assumed that panitumumab and cetuximab-combination regimens have equivalent clinical effectiveness in RAS wild-type mCRC. TA439 presented results from NMA based on separate networks for FOLFIRI and FOLFOX-based treatments. [13] As noted by the company, and TA439, no study is available that evaluates panitumumab plus FOLFIRI, and so indirect evidence on cetuximab and panitumumab was reported for FOLFOX combinations. TA439 reports that NMA provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was more effective than panitumumab plus FOLFOX at increasing PFS or OS, with HRs reported as:

- PFS: cetuximab plus FOLFOX versus panitumumab plus FOLFOX: HR 0.74, 95% credible interval (CrI): 0.36 to 1.49;
- OS: cetuximab plus FOLFOX versus panitumumab plus FOLFOX: HR 1.22, 95% CrI: 0.71 to 2.11.

Figure 4. ERG's suggested network for generation of estimates of effect for pembrolizumab versus cetuximab and panitumumab combination treatments in RAS wild-type mCRC



3.5.2 *Results of indirect comparison*

3.5.2.1 *Progression-free survival*

A second order FP was deemed to be the model with the best fit to the PFS data available from the RCTs informing the network for the ITT population (Table 26). By the company's FP NMA, compared with SoC, CAPOX and panitumumab plus FOLFOX, the clinical benefit for pembrolizumab noted in KEYNOTE-177 for PFS [redacted] (Table 25; [redacted]). At follow-up of 8 months and beyond, [redacted].

Using the data set and code supplied by the company, and applying the same number of burn-in, chains, iterations as the company, the ERG generated the [redacted]

[redacted] (Table 25). [redacted]. The ERG also validated the company's FP NMA for comparisons versus SoC. [redacted]: results for company's and ERG's FP NMA using SoC as the baseline treatment are presented in Appendix 1.1 (Table 68, Figure 18, Figure 19).

Table 25. Time-varying hazard ratios for PFS at selected follow-up times for competing interventions versus pembrolizumab (second order FP model [p1 = 0, p2 = 0]) (adapted from CS, Table 42, page 80)

Month	HR versus pembrolizumab (95% CrI)[a]					
	CAPOX Company	CAPOX ERG	Panitumumab + FOLFOX Company	Panitumumab + FOLFOX ERG	SoC Company	SoC ERG
4	[redacted]					
8						
12						
16						
20						
24						
28						
32						

36	[redacted]					
40	[redacted]					

[a] HR >1 favours pembrolizumab, HR <1 favours comparator.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CS, company submission; CrI, credible interval; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; HR, hazard ratio; PFS, progression-free survival; SoC, standard of care.

Table 26. Model fit estimates for fixed-effects network meta-analysis with parametric survival models for PFS (reproduced from CS, Table 41, page 79)

Model	Dbar	pD	DIC
Weibull: First order FP (p = 0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		
Gompertz: First order FP (p = 1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		
Second order FP: p1 = 0, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		
Second order FP: p1 = 0, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		
Second order FP: p1 = 1, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		
Second order FP: p1 = 1, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]		

Abbreviations: CS, company submission; DIC, deviance information criterion; FP, fractional polynomial; NMA, network meta-analysis; PFS, progression-free survival.

3.5.2.2 *Overall survival*

For analysis of OS, the ERG cautions that OS data from KEYNOTE-177 are immature and OS data are likely to be confounded due to crossover from SoC to pembrolizumab on progression of disease. A second order FP was deemed to be the model with the best fit to the OS data available from the RCTs informing the network for the ITT population (Table 27).

By FP NMA, pembrolizumab [redacted] (Table 28; [redacted]).

Table 27. Time-varying hazard ratios for OS at select follow-up times for competing interventions versus pembrolizumab (second order FP model [p1 = 0, p2 = 0]) (reproduced from CS, Table 36, page 75)

Month	HR versus pembrolizumab (95% CrI)[a]		
	CAPOX	Panitumumab + FOLFOX	SoC
4	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]

[a] HR >1 favours pembrolizumab, HR <1 favours comparator.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CS, company submission; CrI, credible interval; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; HR, hazard ratio; OS, overall survival; SoC, standard of care.

Table 28. Model fit estimates for fixed-effects network meta-analysis with parametric survival models for OS (reproduced from CS, Table 35, page 74)

Model	Dbar	pD	DIC
Weibull: First order FP (p = 0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
Gompertz: First order FP (p = 1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
Second order FP: p1 = 0, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
Second order FP: p1 = 0, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]
Second order FP: p1 = 1, p2 = 0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]

Second order FP: p1 = 1, p2 = 1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company submission; DIC, deviance information criterion; FP, fractional polynomial; NMA, network meta-analysis; OS, overall survival.

3.6 Conclusions of the clinical effectiveness section

The ERG considers the company's SLR to be of reasonable quality and likely to have retrieved all studies relevant to pembrolizumab, despite limiting inclusion to English-language publications. In the context of the FP NMA for all patients, the ERG notes that there is an RCT, which was identified but excluded by the company, that meets the SLR inclusion criteria and provides data relevant to the company's NMA.

The ERG considers KEYNOTE-177 to be a well-designed and well-conducted RCT, with an overall low risk of bias and high internal validity. KEYNOTE-177 is the only RCT, at the time of writing, reporting clinical effectiveness of first-line treatments of those specifically with MSI-H/dMMR mCRC. For the primary outcome of PFS, the ERG considers that the evidence derived from the ITT population of KEYNOTE-177 supports the company's proposal that pembrolizumab markedly improves PFS compared with SoC. Pembrolizumab was associated with a median PFS of 16.5 months compared with a median of 8.2 months for SoC, a difference that was statistically significant (HR 0.60, 95% CI: 0.45 to 0.80; p=0.0002).

SoC in KEYNOTE-177 comprised FOLFOX and FOLFIRI given either alone or in combination with bevacizumab or cetuximab. Evidence from RCTs indicates that bevacizumab- and cetuximab-based regimens are more clinically effective at improving PFS and OS than FOLFIRI or FOLFOX alone. In KEYNOTE-177, 70% of those in the SoC group received FOLFOX or FOLFIRI with bevacizumab, and 10% cetuximab with FOLFOX or FOLFIRI. Additionally, bevacizumab is not available as a treatment option for clinicians in England. Given that bevacizumab-based treatment is associated with improved PFS and OS, the ERG considers that bias in the comparison of pembrolizumab versus SoC is likely to be against pembrolizumab, resulting in a conservative estimate of treatment effectiveness. For comparison with CAPOX, FOLFIRI and FOLFOX, the ERG considers the SoC group in totality provides the most robust estimate of comparative treatment effectiveness for pembrolizumab versus CAPOX, FOLFIRI and FOLFOX in the specified group of all patients with MSI-H/dMMR mCRC.

In the first-line setting for treatment of mCRC in England, cetuximab and panitumumab in combination with either FOLFIRI or FOLFOX are additional options if a person is identified as having

RAS wild-type mCRC. *Post hoc* subgroup analyses from KEYNOTE-177 indicate that, in those with RAS wild-type, pembrolizumab is associated with a statistically significant improvement in PFS compared with SoC (HR 0.44, 95% CI: 0.29 to 0.67). In KEYNOTE-177, panitumumab-based regimens were not available to the SoC group, and assessment of RAS status (wild-type versus mutant) was not carried out for all those enrolled. Thus, in the context of external validity to England, some of those randomised to SoC might not have received treatment as they would in clinical practice.

Direct head-to head data for pembrolizumab versus cetuximab- and panitumumab-combination regimens in RAS wild-type mCRC are not available, and to generate estimates of effect required that the company carry out an NMA. In the CS, the company presented an NMA for all patients that included panitumumab-containing regimens as a comparator, but not cetuximab-based treatment, with the rationale that cetuximab combination treatment was an option in the SoC group of KEYNOTE-177. The ERG considers the subgroup analysis based on RAS wild-type from KEYNOTE-177 provides the best estimate for PFS for pembrolizumab versus CAPOX, FOLFOX and FOLFIRI in that subgroup. However, given that RCTs are available evaluating panitumumab and cetuximab-based therapies as first-line treatments in RAS wild-type mCRC, and clinical effectiveness informs the economic analyses, the ERG considers more robust estimates for pembrolizumab versus comparators relevant to the decision problem could be derived from an NMA based on IPD for those with RAS wild-type from KEYNOTE-177. The ERG appreciates that the evidence from KEYNOTE-177 on the benefit of pembrolizumab in improving PFS is strong, but considers that the requested NMA could substantiate the estimate of effect for pembrolizumab noted in KEYNOTE-177. The ERG acknowledges that, as with the company's original NMA in all patients, because the impact of MSI-H or dMMR is not accounted for in trials other than KEYNOTE-177, there will be bias in an NMA evaluating treatments in RAS wild-type subgroup.

Considering the company's NMA, the ERG agrees with the company's rationale for choice of FP NMA, but considers evaluation of a wider range of powers than those reported by the company would be valuable. Using the data and code supplied by the company during the clarification process, the ERG found similar results to the company for pembrolizumab versus interventions of interest to the decision problem, and also for CAPOX and pembrolizumab versus SoC. Considering panitumumab + FOLFOX versus SoC, the ERG's results were similar up to 16 months, but diverged thereafter. The ERG has no explanation for the discrepancy in the results.

Post hoc subgroup analyses of PFS based on those identified as having RAS mutations generated a markedly different result from other subgroups, with a change in direction of effect to favour SoC, albeit that the difference between pembrolizumab and SoC was not statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). However, the ERG notes that the 95% CIs for estimates of PFS for RAS wild-type and non-RAS wild-type do not overlap and, as such, considers the results in the two subgroups unlikely to have arisen due to random chance.

OS data for KEYNOTE-177 are immature are the time of writing. Analysis of OS is based on 125 events and median OS has yet to be reached in the pembrolizumab group. Additionally, OS is likely to be severely confounded as crossover from SoC to pembrolizumab was allowed: 59% of participants allocated to SoC received pembrolizumab (36.4%) or a PD-1/PD-L1 inhibitor (22.7%) on cessation of initial treatment, primarily because of disease progression. The ERG appreciates that, due to the potential confounding, the OS advantage of pembrolizumab, if any, will be underestimated but considers the data too immature to draw reliable conclusions. Additionally, OS data are not implemented in the cost effectiveness analysis, with the company assuming that post progression survival is the same for pembrolizumab as for SoC.

4 Cost effectiveness

A summary of the company's deterministic and probabilistic cost-effectiveness results for the pembrolizumab versus standard of care (SoC), CAPOX and panitumumab + mFOLFOX6 are presented in Table 29 to Table 31.

Table 29. Company's base case results versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	13,497	3.145	1.862	7,250
Probabilistic results							
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	18,199	3.133	1.858	9,795

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 30. Company's base case results versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,968	3.145	1.855	27,474
Probabilistic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	55,820	3.133	1.852	30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 31. Company's base case results versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,317	3.145	1.688	Dominant
Probabilistic results							
Panitumumab + mFOLFOX6	167,456	4.212	2.590	-	-	-	-
Pembrolizumab	[redacted]	7.022	4.274	-43,910	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed two systematic literature reviews (SLRs) to identify published studies that could inform the cost-effectiveness evaluation of pembrolizumab for adult patients with untreated metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). The first search attempted to identify resource use, costs and cost-effectiveness studies, while the second search was designed to identify health-related quality of life (HRQoL) estimates.

The searches focused on identifying cost-effectiveness evidence for the MSI-H and dMMR mCRC patient cohort. A summary of the Evidence Review Group's (ERG) critique of the company's SLR is given in Table 32.

Table 32. Systematic review summary

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix H	Appendix I	Appropriate
Inclusion/exclusion criteria	Appendix G	Appendix H	Appendix I	Appropriate

Screening	Appendix G	Appendix H	Appendix I	Appropriate
Data extraction	Appendix G	Appendix H	Appendix I	Appropriate
Quality assessment of included studies	Appendix G	Appendix H	Appendix I	Appropriate

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health-related quality of life.

The cost-effectiveness SLR identified one study, Chu 2019[37], that fulfilled the inclusion criteria. A further nine studies were listed in the PRISMA chart that covered first-line mCRC cancer treatment, however these were not included in the final evidence table. The HRQoL literature review included 38 studies. The company states that there were 21 included studies, but only included details for the 2 in the MSI-H/dMMR subpopulation.

None of the studies identified in in the SLR were used for parameterising the model. Instead, the data sources used in the model came from the KEYNOTE-177 trial, a multiple technology assessment of cetuximab and panitumumab (TA439), the company's clinical experts, the NHS Reference Cost Schedule and the PSSRU Unit Costs of Health and Social Care. The ERG considers the data sources used by the company to be reasonable.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 33 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the National Institute for Health and Care Excellence (NICE) reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 33. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects for adult patients with untreated unresectable or mCRC with MSI-H or dMMR have been included.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.

Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis with fully incremental analysis has been provided by the company.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (40 years).
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs based on EQ-5D-3L data from KEYNOTE-177 used in the base case analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-3L data obtained directly from patients in KEYNOTE-177.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in KEYNOTE-177 are representative of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs included in the analysis have been sourced using NHS reference costs,[38] MIMS,[39] eMIT[40] and published literature and are reported in pounds sterling for the price year 2019.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: dMMR, mismatched repair deficiency; ERG, evidence review group; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year, UK, United Kingdom.

4.2.2 Population

The population considered by the company for this Single Technology Appraisal (STA) is based on the proposed marketing authorisation, which includes adult patients with untreated unresectable or metastatic colorectal with MSI-H or dMMR. The population can be further divided by RAS mutation status (RAS wild-type or non-RAS wild-type). The population included in the company's base case

analysis is the intention-to-treat (ITT) population of KEYNOTE-177, which includes all MSI-H or dMMR patients irrespective of RAS mutation status. In addition, in their response to clarification questions, the company confirmed that no patients in KEYNOTE-177 had unresectable disease at baseline.

In KEYNOTE-177, approximately 70% of standard of care (SoC) patients received bevacizumab combination treatments, but NICE guidance does not recommend its use for treating mCRC.[41, 42] The company presented subgroup analyses for the ITT population excluding patients treated with bevacizumab, but note that the analyses are not robust due to small sample size and imbalances in baseline characteristics. The ERG agrees that the analyses for the "ITT population minus bevacizumab" patients are likely to be subject to substantial uncertainty and that including patients receiving treatment with bevacizumab is likely to be biased against pembrolizumab, resulting conservative estimates of treatment effectiveness. Please see Section 2.3 for further detail on the population of KEYNOTE-177.

The ERG's primary concern with the population of the model is that in addition to the analysis using the ITT population, the company should have presented subgroup analyses by RAS mutation status. The NICE final scope specifies that, "If the evidence allows the subgroup of people with RAS wild-type colorectal cancer will be considered".[1] Treatment options in the UK differ if a patient has RAS wild-type mCRC (see Section 4.2.3 for further details). According to the NICE pathway for managing mCRC, first-line biological therapy (cetuximab or panitumumab combination treatments) are only recommended for patients with RAS wild-type mCRC.[42] Furthermore and as mentioned in Section 2.3.1, subgroup analyses reported within the company submission (CS) indicate that, in those with RAS wild-type, pembrolizumab is associated with a statistically significant improvement in progression-free survival (PFS) compared with SoC (hazard ratio [HR] 0.44, 95% confidence interval [CI]: 0.29 to 0.67). However, in the non-RAS wild-type subgroup, the direction of effect favours SoC, albeit that the benefit with SoC would not be considered statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). The ERG notes that the 95% CIs for the two subgroups do not overlap and, as such, considers the difference in the two subgroups unlikely to be due to random chance.

Given the importance of RAS mutation status, not only in terms of relative treatment effectiveness but also for directing treatment choice for patients in the NHS, during the clarification stage the ERG requested the company to provide cost-effectiveness analyses for RAS wild-type and non RAS wild-type subgroups from KEYNOTE-177 and update the fractional polynomial (FP) network meta-analysis

(NMA) to generate relative estimates of treatment effect for pembrolizumab versus the listed comparators in the NICE final scope for the relevant subgroups.

The company declined to provide subgroup analyses based on RAS mutation status, stating that the requested analyses were inappropriate because the results would be underpowered and likely to produce false-negative results due to small numbers of events, randomisation would be broken and that RAS mutation status was unknown for 27% of the trial population. However, the ERG notes that the issues highlighted by the company for the subgroup analyses apply to the ITT minus bevacizumab subgroup analyses the company provided within their submission.

In addition, the company stated that analyses for the RAS wild-type subgroup are unnecessary as the results for the ITT population (used for the company base case analyses) would be appropriate proxies for what would be observed in this patient group. For the ITT population, pembrolizumab is associated with a statistically significant improvement in PFS compared with SoC (HR 0.60, 95% CI: 0.45 to 0.80), which the ERG considers is more conservative compared with the results for the RAS wild-type subgroup. However, there are several issues with the company's assertation that the ITT analysis can be used as a proxy for the RAS wild-type subgroup. Cetuximab combination treatment is included within the SoC comparison, but only approximately 10% of patients in KEYNOTE-177 received this treatment. However, it is not clear whether all RAS wild-type patients in KEYNOTE received cetuximab combination treatment, as this was not routinely tested for, as would happen in the NHS. Furthermore, cetuximab combination treatment costs are used as a proxy for the patients who received bevacizumab combination treatment and as such the analysis implicitly assumes that approximately 80% of the model population in the SoC arm have RAS wild-type mCRC.

The ERG is also concerned that the direction of effect for the non-RAS wild-type subgroup in KEYNOTE-177 favours SoC. If cost-effectiveness estimates were provided for the non-RAS wild-type subgroup by the company, the ERG predicts it would have demonstrated that pembrolizumab is less effective and more costly that SoC and as such would be dominated by the comparator. However, it should be noted that as mentioned earlier in this section, SoC in KEYNOTE-177 is made up of approximately 70% of patients who have received bevacizumab combination treatment and thus may not be reflective of what would be seen in UK clinical practice. While the use of bevacizumab containing treatments may be inflating the effectiveness of SoC in the non-RAS wild-type subgroup to infer that SoC is potentially more effective than pembrolizumab, the ERG still considers that it is likely that if this bias was corrected for that SoC and pembrolizumab may well have similar

effectiveness in this subgroup. This is illustrated by the HR of 0.90 (95% CI: 0.24 to 3.39) for the non-RAS wild-type subgroup analyses for the ITT minus bevacizumab subgroup, though caution should be applied when interpreting these results due to small sample sizes.

Section 4.2.3 discusses the issue of comparators and Section 4.2.5.1 discusses the issues around treatment effectiveness for the subgroup analyses based on RAS mutation status and within each section outlines the ERG's preferred approach to the subgroup analyses. The ERG highlights that clinical data provided within the CS and used in the model from KEYNOTE-177 are based on the second interim analysis (database cut-off date: 19 February 2020). Thus, the ERG considers that longer term data from KEYNOTE-177 will be crucial to determine whether the direction of effect for the non-RAS wild-type subgroup will be substantiated in the longer term and also to reduce the overall uncertainty in the cost-effectiveness analysis.

4.2.3 Interventions and comparators

The intervention considered for the economic analysis is pembrolizumab. The primary comparator considered by the company is SoC and is based on the comparators included in KEYNOTE-177, which are mFOLFOX6 (folinic acid plus fluorouracil plus oxaliplatin), FOLFIRI (folinic acid plus fluorouracil plus irinotecan), cetuximab in combination with mFOLFOX6 or FOLFIRI, and bevacizumab in combination with mFOLFOX6 or FOLFIRI. Over 70% of SoC patients in KEYNOTE-177 received bevacizumab combination treatments, but NICE guidance does not recommend its use for treating mCRC.[41, 42] Thus, the company adjusted the drug acquisition costs in the model so that the proportion of patients who received bevacizumab combination treatments in KEYNOTE-177 were costed as receiving cetuximab combination treatments. Table 34 outlines the distribution of patients across each of the SoC regimens in KEYNOTE-177.

Table 34. Distribution of patients across each of the SoC regimens in KEYNOTE-177 (Table 49 of CS)

Treatment regimen	Percentage of patients (n=154)*
mFOLFOX6 – 9.1%	9.1%
FOLFIRI – 11.0%	11.0%
Cetuximab + mFOLFOX6 or FOLFIRI	10.4%
Bevacizumab + mFOLFOX6 or FOLFIRI[a]	69.5%

[a] Assumed in the model to be cetuximab + mFOLFOX6 or FOLFIRI.
Abbreviations: FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin.
* based on all randomized subjects in treatment arm whether or not treatment was administered

In line with the NICE final scope, the company has also presented cost-effectiveness analyses for CAPOX (capecitabine plus oxaliplatin) and panitumumab in combination with mFOLFOX6. Table 35 presents the treatment regimens included in the economic analysis. All treatments are delivered by intravenous (IV) infusion, except capecitabine, which is given orally.

The company expects that the pembrolizumab monotherapy licence will include an option to administer pembrolizumab at a 400mg dose once every six weeks. The ERG clinical experts advised that in clinical practice, they would prefer to administer pembrolizumab using the 400mg dose once every six weeks for patient convenience and also to reduce NHS resource use and as such, the ERG considers this regimen to be appropriate to include in its preferred analysis, presented in Section 6.4.

Table 35. Treatment regimens included in the model (adapted from Table 9 and Table 66 of the CS)

Treatment	Dose	Treatment cycle
Pembrolizumab	200 mg IV over 30 minutes	Once every three weeks
mFOLFOX6	Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion	Once every two weeks

FOLFIRI	Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 Leucovorin 400 mg/m2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion	Once every two weeks
Cetuximab + FOLFIRI	Cetuximab: 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour weekly FOLFIRI: Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion	Once every two weeks
Cetuximab + mFOLFOX6	Cetuximab: 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour, **weekly** mFOLFOX6: Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion	Once every two weeks
Panitumumab + mFOLFOX6	Panitumumab: 6mg/kg IV via an infusion pump over 30 – 90 minutes, day 1 mFOLFOX6: Leucovorin 300 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion	Once every two weeks
CAPOX	Oxaliplatin 130mg/m^2 over 2 hours, day 1 Capecitabine 1000mg/m^2 orally twice daily for first two weeks and then one week off	Once every three weeks

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; IV, intravenous; m2, metre squared; mg, milligram;

In the NICE final scope, panitumumab in combination with FOLFIRI was listed as a relevant comparator, but the company stated that no studies were found for this combination that could be included in the NMA and based on clinical expert opinion in TA439, the company considered FOLFOX and FOLFIRI to be clinically equivalent.[13] Furthermore, the NICE final scope also listed tegafur with uracil (in combination with folinic acid), capecitabine and raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) as comparators, but the company excluded these from the analysis.[1] The company stated that tegafur with uracil (in combination with folinic acid) is no longer available in the UK, capecitabine is only used in the elderly and frail (most often with an ECOG status of >1), and that raltitrexed is rarely used in UK clinical practice. Based on advice from the ERG's clinical experts, the company's rationale to exclude tegafur with uracil (in combination with folinic acid), capecitabine, and raltitrexed is considered reasonable by the ERG. With regards to assuming clinical equivalence for FOLFOX and FOLFIRI for the panitumumab combination treatment comparison, the ERG agrees with the assumption of clinical equivalence based on a study evaluating FOLFOX versus FOLFIRI which was supported by the ERG's clinical experts.[18] Please refer to Section 3.3 for further detail on the FOLFOX and FOLFIRI trials.

As mentioned in Section 4.2.2, a key issue with the company's approach to the cost-effectiveness analysis is the lack of analyses of relevant comparators based on the different indicated populations, as outlined by the NICE final scope. The company used the ITT population of KEYNOTE-177 for all comparators even though, in the UK, treatment regimens that are combined with panitumumab are indicated for the treatment of patients with RAS wild-type mCRC and cetuximab combination treatments are further specified for patients with epidermal growth factor receptor (EGFR) expressing RAS wild-type mCRC. The ERG notes the company's rationale for their approach, as RAS wild-type is not a consideration in the proposed marketing authorisation for pembrolizumab. Nonetheless, to enable appropriate cost-effectiveness estimates of pembrolizumab compared with cetuximab and panitumumab combination regimens, the appropriate population for the analysis should be the RAS wild-type subgroup of the ITT population in KEYNOTE-177. Table 36 presents the relevant comparators by population, which the ERG considers more appropriately reflects the NICE final scope compared with the approach adopted by the company for its base case analysis.

Table 36. Comparators by population based on the NICE final scope

Population from KEYNOTE-177	Comparator
A – ITT	• mFOLFOX6/ FOLFIRI • CAPOX
B – RAS wild-type	• Cetuximab in combination with FOLFOX or FOLFIRI • Panitumumab in combination with FOLFOX or FOLFIRI • mFOLFOX6/ FOLFIRI • CAPOX
C – non-RAS wild-type	• mFOLFOX6/ FOLFIRI • CAPOX

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; ITT, intention-to-treat.

As mentioned in Section 4.2.2, at the clarification stage the ERG requested the company to produce cost-effectiveness analyses based on the populations and associated comparators listed in Table 36. The company declined to provide the subgroup analyses by RAS-mutation status as they considered them to be inappropriate because the results would be underpowered and likely to produce false-negative results due to small numbers of events, randomisation would be broken and that RAS mutation status was unknown for 27% of the trial population. Furthermore, the company considered that the ITT analysis serves as an appropriate proxy for the RAS wild-type subgroup. However, as mentioned previously, the ERG considers the company's reasoning to exclude subgroup analysis by RAS mutation status to be inconsistent as the company provided subgroup cost-effectiveness analyses for the ITT minus bevacizumab subgroup analyses within their submission.

For population B (RAS wild-type), the ITT cost-effectiveness analysis presented by the company may provide conservative approximations for the comparisons against mFOLFOX6/FOLFIRI, CAPOX and panitumumab combination treatment, based on a comparison of HRs from KEYNOTE-177 for pembrolizumab versus SoC for each population (ITT HR = 0.60 versus RAS wildtype HR = 0.44). However, currently there is no explicit comparison of pembrolizumab versus cetuximab combination treatment as it is blended with the SoC analysis. As presented in Table 34, approximately 10% of patients were randomised to receive cetuximab combination treatment, whereas in UK clinical practice this figure could be higher as patients are routinely tested for gene mutations when

diagnosed with mCRC.[1] However, as the company has assumed the costs of cetuximab combination treatment for the proportion of patients who received bevacizumab combination treatment, SoC is assumed to be made up of 80% of patients receiving cetuximab combination treatment and implicitly assumes that these patients have RAS wild-type mCRC (based on the NICE pathway[1]).

As mentioned in Section 3.5.1.2, TA439 reports that NMA provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was more effective than panitumumab plus FOLFOX at increasing PFS or OS.[13] To provide an estimation of the cost effectiveness of pembrolizumab versus cetuximab combination treatment in lieu of the ERG analysis requested at the clarification stage, the ERG considers that a simplified analysis assuming clinical equivalence between cetuximab combination treatment and panitumumab combination treatment may not be unreasonable. Please refer to Section 4.2.5.1 for the ERG's critique on treatment effectiveness and Section 6.3 for the results of the scenario assuming clinical equivalence between panitumumab and cetuximab combination treatment. However, the ERG reiterates that its preferred approached is that outlined in Table 17 and detailed in the ERG's clarification questions, as that would provide a more robust estimation of the relative treatment effects of pembrolizumab compared with the listed comparators.

As a secondary issue, the ERG's clinical experts advised that those patients in KEYNOTE-177 who received bevacizumab combination treatments would have likely been given FOLFOX or FOLFIRI in UK clinical practice as cetuximab is only indicated for EGFR expressing RAS wild-type mCRC patients, whereas bevacizumab is indicated for all mCRC patients. Please refer to Section 4.2.8 for more details on the issue of comparator costs used in the economic model.

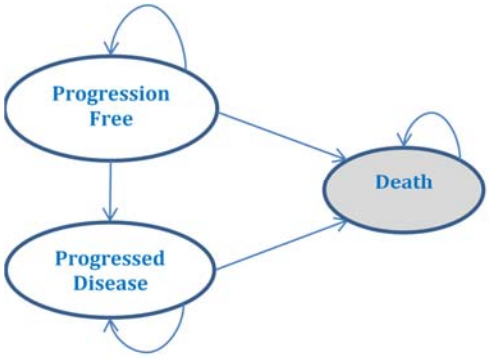
4.2.4 Modelling approach and model structure

Two *de novo* economic models were developed by the company to assess the cost-effectiveness of pembrolizumab for adult patients with untreated unresectable or mCRC with MSI-H or dMMR using Microsoft© Excel. The company base-case model was a five health state-transition model (STM) and the second model was a three health state partitioned survival model (PSM), which the company used as a validation tool.

The STM included two health states (progression-free and progressive disease) for patients who underwent surgery with curative intent (Figure 20 of the company submission). The proportion of surgery patients in each arm of the model was below 10% and the company assumed that clinical

outcomes for these patients (PFS and overall survival [OS]) would be equal. However, the difference in surgery rates between pembrolizumab and the comparators was less than 1%. As surgery rates are similar between treatment arms in KEYNOTE-177 and the clinical outcomes of surgery are the same for all patients, the ERG requested the company during the clarification stage to amend the STM to exclude surgery health states as it is unlikely to be a primary driver of cost-effectiveness and it can be considered an appropriate simplification of the model. In addition, by excluding the surgery health states from the STM, the structure of the model aligns with the structure of the PSM, allowing the PSM to better validate the STM. Figure 5 presents the company's revised base-case structure for the STM and the original structure of the PSM.

Figure 5. Model schematic for the state-transition and partitioned survival models (Figure 19 of the company submission)



As mentioned in Section 3.3.2, OS data from KEYNOTE-177 are immature and are likely to be confounded for SoC due to crossover to pembrolizumab. The PSM relies on immature OS data (adjusted for crossover using the two-stage method) from KEYNOTE-177. In KEYNOTE-177, 36.4% of SoC patients switched over to pembrolizumab monotherapy after discontinuation of the protocol treatment and a further 22.7% switched over to another anti-PD1 or PD-L1 treatment. Given the large amount of crossover in the SoC arm and the immaturity of the OS data, PSM is subject to a substantial amount of uncertainty. As such, for the remainder of the report, the ERG focuses its description and critique around the company's revised three health state STM.

All patients enter the model in the progression-free health state. During each model cycle, patients in the progression-free health state can be either on-treatment or off-treatment, with different treatment discontinuation rules applied depending on treatment regimen (see Section 4.2.8 for

more details). Furthermore, from the progression-free health state, patients can transition to either the progressed disease health state when they experience disease progression or die (thus transitioning to the death health state). When patients transition to the progressed disease health state, they remain there until death. Table 37 presents an overview of clinical data informing the health state transition probabilities. Please refer to Section 4.2.5 for more detail on the clinical data informing the economic model.

Table 37. Overview of clinical data informing the health state transitions in the economic model

Health state transition	Clinical data informing the transition probability
Progression-free to progression-free	PFS data from KEYNOTE-177. For non-trial comparators, time-varying hazard ratios obtained from the fractional polynomial network meta-analysis applied to SoC PFS data from KEYNOTE-177.
Progression-free to progressed disease	Time to progression (TTP) data from KEYNOTE-177. For non-trial comparators, time-varying hazard ratios obtained from the fractional polynomial network meta-analysis applied to SoC TTP data from KEYNOTE-177.
Progression-free to death	PFS minus TTP.
Progressed disease to death	Post-progression survival (PPS) data from KEYNOTE-177. For SoC, PPS is assumed to be equal to PPS for pembrolizumab to mitigate the issue of crossover. For non-trial comparators, PPS is also equal to PPS for pembrolizumab.

Abbreviations: PFS, progression-free survival; PPS. Post-progression survival SoC, standard of care; TTP, time to progression;

A model cycle length of one week with half-cycle correction applied was implemented in the model and the model time horizon was set to 40 years (lifetime), as the mean age in KEYNOTE-177 at baseline was 61 years. The perspective of the analysis was based on the UK NHS, with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.[43]

4.2.4.1 *ERG critique*

The ERG considers the revised structure of the company's STM to be appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other oncology models submitted for NICE appraisal. The one-week cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has

been appropriately applied in the model to prevent over or under-estimation of costs and quality-adjusted life-years (QALYs).

With regards to the clinical transitions between the health states in the model, the ERG notes that as post-progression survival (PPS) is used in lieu of mature OS data from KEYNOTE-177, any gain in PFS directly equates to a gain in the estimated OS, which becomes more significant as the company has assumed that PPS for all comparators is equal to PPS for pembrolizumab. Please refer to Section 4.2.5 for further detail on how PFS and PPS are used in the model.

4.2.5 Treatment effectiveness

Clinical data included in the economic model for pembrolizumab and SoC are based on individual patient level data from KEYNOTE-177 and include time to progression (TTP), PFS, PPS, adverse events (AEs) and time on treatment (ToT) outcomes. Please refer to Sections 4.2.6 and 4.2.8 for further details of AEs and ToT included in the model. For panitumumab combination treatment, "per cycle" HRs derived from the FP NMA described in Section 3.5 are used and the application of the estimates is described later in this section. During the clarification stage, the ERG outlined its preferred assumption that, based on studies evaluating FOLFOX versus FOLFIRI[18] and CAPOX versus FOLFIRI,[17, 19-21] the treatments can be considered clinically equivalent, which the company accepted and implemented in its revised base case analysis.

Overview of the company's approach to survival analysis

To extrapolate the KEYNOTE-177 Kaplan-Meier (KM) data, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[44] The company first tested whether the assumption of proportional hazards (PH) held for TTP, PFS and PPS outcomes for the ITT population (excluding surgery patients) by producing log-cumulative hazard and Schoenfeld residual plots. The company used the outcomes of the PH assessment to decide to either jointly or independently fit survival distributions. Extrapolations of the KM data were then explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) and piecewise models with different time-point cut-offs. To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian

information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the model.

During the clarification stage, the ERG requested the company exclude post-surgery health states from the economic model and as such, the company updated the data used for TTP, PFS and PPS to include outcomes for patients who received surgery. However, as the original curve selection process indicated proportional hazards didn't hold, the company did not present updated tests for proportional hazards in their clarification response and modelled curves independently as per the original base case approach.

Time to progression

The company fit standard parametric distributions as well as two-piece models (KM data and standard parametric distribution after cut-off point) with 10- and 20-week cut-off points to the TTP KM data from KEYNOTE-177 for pembrolizumab and SoC. Based on statistical fit (Table 11 of the company's clarification response) and visual inspection of the curves, the company selected the two-piece exponential model with a cut-off point of 20 weeks to model TTP. Based on the ERG's preferred approach, the company assumed that TTP for SoC and CAPOX are clinically equivalent. For panitumumab combination treatment, the company applied time-varying "per cycle" hazard ratios estimated from the FP NMA for PFS to the SoC TTP extrapolation. General population mortality was applied to TTP estimates as a minimum, such that the probability of a patient being alive and progression-free could never be below background mortality.

Figure 6 presents the company's base case TTP extrapolations for pembrolizumab, SoC (CAPOX) and panitumumab combination treatment.

Figure 6. Company base case extrapolation of time to progression outcomes from KEYNOTE-177 (taken from the economic model)

Abbreviations: FP, fractional polynomial; KM, Kaplan-Meier; KN177, KEYNOTE-177; NMA, network meta-analysis; SoC, standard of care; TTP, time to progression; XELOX, CAPOX.

Progression-free survival

As with TTP, the company fit standard parametric distributions as well as two-piece models with 10- and 20-week cut-off points to the PFS KM data from KEYNOTE-177 for pembrolizumab and SoC. Based on statistical fit (Table 12 of the company's clarification response) and visual inspection of the curves, the company selected the two-piece exponential model with a cut-off point of 20 weeks to model PFS. Based on the ERG's preferred approach, the company assumed that PFS for SoC and CAPOX are clinically equivalent. For panitumumab combination treatment, the company applied time-varying "per cycle" hazard ratios estimated from the FP NMA for PFS to the SoC PFS extrapolation. General population mortality was applied to PFS estimates as a minimum, such that the probability of a patient being alive and progression-free could never be below background mortality.

Figure 7 presents the company's base case PFS extrapolations for pembrolizumab, SoC (CAPOX) and panitumumab combination treatment.

Figure 7. Company base case extrapolation of progression-free survival outcomes from KEYNOTE-177 (taken from the economic model)

Abbreviations: FP, fractional polynomial; KM, Kaplan-Meier; KN177, KEYNOTE-177; NMA, network meta-analysis; PFS, progression-free survival; SoC, standard of care; XELOX, CAPOX.

Post-progression survival

As mentioned in Section 3.3.2, in KEYNOTE-177 patients in the SoC arm were allowed to crossover to pembrolizumab upon disease progression. To mitigate the issue of crossover, the company assumed that PPS for all comparators was the same as PPS for pembrolizumab. As such, the company fit standard parametric distributions to PPS KM data from KEYNOTE-177 for pembrolizumab. Based on statistical fit (Table 13 of the company's clarification response), visual inspection of the curves and external validation against real world data, the company selected the Weibull distribution to extrapolate PPS.

Figure 8. Company base case extrapolation of post-progression survival outcomes from KEYNOTE-177 (taken from the economic model)

Abbreviations: FP, fractional polynomial; KM, Kaplan-Meier; KN177, KEYNOTE-177; NMA, network meta-analysis; PPS, post-progression survival; SoC, standard of care; XELOX, CAPOX.

As mentioned in Section 4.2.4, as PPS is used in lieu of mature OS data from KEYNOTE-177, any gain in PFS directly equates to a gain in the estimated OS. Table 38 presents the mean life years estimated for each treatment by population based on the company's extrapolation of the KEYNOTE-177 data, application of the time-varying "per cycle" HRs and subsequent calculation of transition probabilities for the health states in the model.

Table 38. Estimated life years by health state for each population

Health state	Pembrolizumab	SoC	CAPOX	Panitumumab + mFOLFOX6
PFS	4.56	1.21	1.21	1.55
PPS	2.37	2.57	2.57	2.55
Total	**6.93**	**3.78**	**3.78**	**4.10**

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; PFS, progression-free survival; PPS, post-progression survival; SoC, standard of care.

4.2.5.1 *ERG critique*

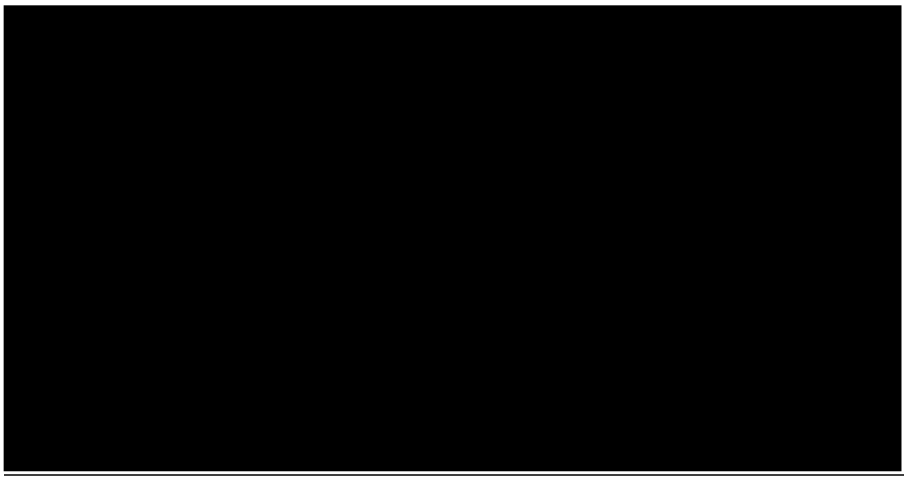
Overall, the ERG considers the company's general approach to extrapolating outcomes for TTP, PFS and PPS to be appropriate. The use of piecewise models, with a cut-off point of 20 weeks for TTP and PFS appropriately captures the change in the hazard observed in log-cumulative hazard plots presented in Figure 22 and Figure 27 of the CS. Use of the exponential model after the cut-off point of 20 weeks can be considered appropriate for the pembrolizumab arm based on the log-cumulative hazards plots, but for the SoC arm hazards are increasing. Therefore, use of the Weibull model for both pembrolizumab and SoC may be more appropriate as the hazard function can increase monotonically, but also reduces down to the exponential function if the hazard rate is constant over time (i.e. $\gamma = 1$).[44] However, the ERG notes that diagnostic plots were only provided for the company's original analysis which excluded surgery patients from the clinical outcomes data, whereas the revised base case analysis includes these patients and as such there may be a some change to the hazards over time for pembrolizumab and SoC, but the ERG anticipates it is not likely to be significantly different based on a comparison of the KM curves for TTP and PFS with and without surgery patients included.

The ERG ran a scenario using a piecewise model with a cut-off point of 20 weeks and the Weibull model implemented as the second piece and found this did not have a substantial impact on the incremental cost-effectiveness ratio (ICER). Please refer to Section 6.3 for results of the Weibull scenario.

In KEYNOTE-177, 36.4% of SoC patients switched over to pembrolizumab monotherapy after discontinuation of the protocol treatment and a further 22.7% switched over to another anti-PD1 or PD-L1 treatment. To mitigate the impact of crossover on OS outcomes (and as such PPS outcomes) for the SoC arm, the company assumed that PPS outcomes for SoC would be equal to PPS for the pembrolizumab arm. The company also extended the PPS assumption for the comparison with CAPOX and panitumumab. The ERG notes that the company did explore crossover adjustment methods using OS data from KEYNOTE-177 and this analysis was implemented in the company's PSM. However, the company state that due to the substantial amount of crossover in the SoC arm and the immaturity of OS data in KEYNOTE-177, the OS analyses are subject to a substantial amount of uncertainty. The ERG considers that adjustment of OS using crossover adjustment methods is more robust, but as OS data are immature, the company's simplified assumption of equal PPS for all arms of the model may be acceptable even though it bypasses the issue altogether.

The company's PPS assumption implies that the treatment effect with pembrolizumab is not extended beyond the progression-free health state. The ERG considers that it is not unreasonable that the treatment effect of pembrolizumab is assumed to only be in the progression-free health state as long-term overall survival data are immature, therefore estimating the duration of treatment effect beyond progression is currently problematic. Furthermore, in KEYNOTE-177 pembrolizumab is given for 35 cycles, with a mean treatment duration of 13.3 months, median 16.5 months and the median duration of follow-up was 28.4 months, but beyond discontinuation of treatment there continues to be an ongoing separation of the PFS curves (See Figure 9), though the data for PFS are still immature. Thus, longer term data from KEYNOTE-177 will determine the duration of the treatment effect for pembrolizumab.

Figure 9. Comparison of time on treatment and progression-free survival for pembrolizumab in KEYNOTE-177



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; ToT, time on treatment; yrs, years.

The ERG notes that the use of PPS for all arms of the model directly impacts OS, as any gain in PFS directly equates to a gain in the estimated OS. There is uncertainty around whether the PFS to OS relationship holds or whether patients on pembrolizumab are likely to have an accelerated mortality rate upon progression compared to patients on other treatments, particularly for RAS wild-type patients treated with biological therapies (panitumumab and cetuximab). However, in KEYNOTE-177 median PFS2 was [redacted] months (95% CI: [redacted]) for SoC [redacted] pembrolizumab group (HR [redacted], 95% CI: [redacted]). Bearing in mind the immaturity of PFS2,

the ERG notes that [redacted] for pembrolizumab versus SoC [redacted] (PFS HR 0.60, 95% CI: 0.45 to 0.80 vs PFS2 [redacted]). As such, the ERG considers it may not be unreasonable that [redacted], thus providing initial support for the assumption that there isn't an accelerated mortality rate for pembrolizumab upon progression compared with SoC. However, mature OS data from KEYNOTE-177 is required to mitigate the uncertainty around long term survival outcomes.

As mentioned throughout this report, the ERG's primary issue with the cost-effectiveness analysis is that subgroup analysis by RAS mutation status has not been explored by the company. All the clinical data in the model relates to the ITT population of KEYNOTE-177 and thus, estimates of relative treatment effect for non-trial comparators are also for all mCRC patients, irrespective of RAS mutation status. Moreover, for non-trial comparators, there is no evidence in the MSI-H/dMMR population, however this is an unresolvable issue. The company's analysis of PFS by subgroup factors (Figure 10 of the company submission) indicates that, in those with RAS wild-type, pembrolizumab is associated with a statistically significant improvement in PFS compared with SoC (HR 0.44, 95% CI: 0.29 to 0.67). However, in those with a RAS mutation (assumed to be reflective of the non-RAS wild-type subgroup), the direction of effect favours SoC, albeit that the benefit for SoC would not be considered statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). Furthermore, the ERG notes that the 95% CIs for the two subgroups do not overlap and, as such, considers the difference in the two subgroups unlikely to be due to random chance. For the ITT population, the estimate PFS HR is 0.60 (95% CI: 0.45 to 0.80).

At the clarification stage, the ERG requested subgroup analyses by RAS mutation status, but the company stated that the ITT analysis is preferred as it reflects the marketing authorisation for pembrolizumab, and it can also be considered a reasonable proxy for the RAS wild-type subgroup as it is more conservative. However, the company made no mention of estimates of treatment effect for the non-RAS wild-type subgroup. As such, to align the analysis with NICE final scope and provide the committee with estimates of cost-effectiveness for subgroups by RAS mutation status, the ERG outlines its assumptions of treatment effectiveness for the subgroups by RAS mutation status in Table 20. In particular, as the company has not provided separate analysis comparing pembrolizumab versus cetuximab combination treatment, the ERG has made a simplified assumption that cetuximab combination treatment is clinically equivalent to panitumumab combination treatment. As mentioned in Section 3.5.1.2, TA439 reports that NMA provided no

statistically significant evidence to suggest that cetuximab plus FOLFOX was more effective than panitumumab plus FOLFOX at increasing PFS or OS.[13]

The ERG considers the approach outlined in Table 39 only provides illustrative estimates of cost-effectiveness for populations B and C and reiterates that the preferred approach is for the company to:

- Produce relative estimates of treatment effectiveness for patients with and without RAS wildtype mCRC from KEYNOTE-177 using the recommended ERG FP NMA outlined in the ERG's clarification questions;
- Implement the results of the subgroup treatment effectiveness analyses in the economic model to produce cost-effectiveness estimates by relevant comparator for population B and C, as presented in Table 39.

New estimates of cost-effectiveness relate to the cetuximab combination treatment comparison for the RAS wild-type subgroup and the results of this scenario can be found in Section 6.3.

Table 39. ERG approach to treatment effectiveness by population

Population from KEYNOTE	Comparator	Treatment effectiveness approach/ assumptions
A – ITT	mFOLFOX6/ FOLFIRI	Company base case - based on ITT SoC clinical data from KEYNOTE-177.
	CAPOX	Company base case - assumed to be clinically equivalent to mFOLFOX6/ FOLFIRI.
B – RAS wild-type	mFOLFOX6/ FOLFIRI	Company suggested proxy - ITT analysis assumed as proxy for subgroup.
	Panitumumab in combination with FOLFOX or FOLFIRI	Company suggested proxy - ITT analysis assumed as proxy for subgroup.
	Cetuximab in combination with FOLFOX or FOLFIRI	Assumed to be clinically equivalent to panitumumab in combination with FOLFOX or FOLFIRI.
	CAPOX	ITT analysis assumed as proxy for subgroup.

C – non-RAS wild-type	mFOLFOX6/ FOLFIRI	Subgroup analysis based on data from KEYNOTE-177 suggest that relative treatment effect favours SoC (HR 1.19, 95% CI: 0.68 to 2.07). It can be reasonably assumed that because pembrolizumab is more expensive and less effective than SoC, it is dominated by the comparator.
	CAPOX	Assumed to be clinically equivalent to mFOLFOX6/ FOLFIRI. As such, it can be reasonably assumed that because pembrolizumab is more expensive and less effective than SoC, it is dominated by the comparator.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; ERG, evidence review group; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; HR, hazard ratio; ITT, intention to treat; SoC, standard of care.

4.2.6 Adverse events

For the base case analysis, the company included grade 3 or higher treatment-emergent adverse events (TEAEs) that were reported by at least 5% of patients in the safety population in either treatment arm of KEYNOTE-177, presented in Table 40.

Table 40. Grade 3 or higher AEs with ≥ 5% incidence implemented in the model (Table 54 of the CS)

Adverse events	Pembrolizumab (%)	SoC (%)
Anaemia	5.2	10.5
Neutropenia	0.0	15.4
Diarrhoea	5.9	11.2
Abdominal pain	5.2	5.6
Fatigue	3.9	9.1
Neutrophil count decreased	0.0	16.8
Hyponatraemia	5.2	2.8
Hypokalaemia	1.3	6.3
Hypertension	7.2	4.9

Abbreviations: SoC, standard of care.

The company estimated weekly adverse event rates for each adverse event by treatment arm by multiplying the number of patients experiencing a particular adverse event by mean number of episodes of the adverse event per patient and the averaging over the total time on treatment for all patients in a treatment arm. For CAPOX and panitumumab in combination with mFOLFOX6, the company performed an NMA of grade 3 or higher TEAEs in the ITT population, to generate odds ratios (ORs). The estimated ORs are presented in Table 55 of the CS. The ORs were applied to the SoC weekly AE rates for SoC. Table 41 presents the weekly AE rate by treatment.

Table 41. Weekly adverse event rates by treatment arm (adapted from Table 54 and Table 55 of the CS)

Adverse event	Pembrolizumab (%)	SoC (%)	CAPOX (%)	Panitumumab + mFOLFOX6 (%)
Anaemia	0.0009	0.0033	0.0026	0.0075
Neutropenia	0.0000	0.0058	0.0045	0.0131
Diarrhoea	0.0010	0.0039	0.0031	0.0089
Abdominal pain	0.0012	0.0019	0.0015	0.0043
Fatigue	0.0007	0.0029	0.0023	0.0066
Neutrophil count decreased	0.0000	0.0070	0.0055	0.0159
Hyponatraemia	0.0009	0.0010	0.0008	0.0024
Hypokalaemia	0.0002	0.0025	0.0019	0.0056
Hypertension	0.0014	0.0027	0.0021	0.0061

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; SoC, standard of care.

The impact of AEs on patients' quality of life is considered in the model and is described further in Section 4.2.7, while the costs of managing AEs are discussed in Section 4.2.8.

4.2.6.1 *ERG critique*

The ERG considers that there are no major issues with the company's approach to estimating AEs for inclusion in the economic model.

4.2.7 Health-related quality of life

4.2.7.1 Health state utility values

In KEYNOTE-177, HRQoL data for the ITT population were collected at treatment cycles one, two, three, four, five and seven and at end of treatment, or at one year, depending on which occurred first, and at the 30-day post-treatment follow up. Measurement of HRQoL was based on the EQ-5D-3L instrument and UK preference scores.

The company explored two approaches to estimate utility values from the EQ-5D-3L data: time-to-death utilities and utilities based on progression status. The time-to-death approach captures the time-based decline in HRQoL cancer patients experience as they progress through the disease and as a result it provides more health states than progression-based approaches.

For the time to death approach, the company split the utility data from KEYNOTE-177 into four time point categories: >360 days; 180-360 days; 30-180 days and <30 days. Utility values were estimated by treatment (pembrolizumab and SoC) and the company also provided pooled utility values.

The company states that while the preference is to use time-to-death utilities in the economic model, due to the low number of patients in each group, even after pooling the results, the sample sizes were small, particularly in the <30 days to death group, with wide confidence intervals. (See Table 59 of the CS).

The company instead preferred the standard approach used in NICE appraisals, using a binary pre-progression/progression disease approach to the utility valuation for the model. The progression status approach allowed for more robust estimates with narrower confidence intervals (see Table 60 of the CS). Again, the utility data were split by treatment arm, with a pooled estimate also provided. Patient data from KEYNOTE-177 was used for all patients, including those who received surgery with curative intent.

The company used treatment specific utility values in the progression-free health state for the base case, with the justification that the confidence intervals for the utility estimates between the intervention and SoC arms did not overlap. For the progressed disease health state, the company used a pooled utility value based on all patients, regardless of treatment arm. An overview of the utility values used in the model is presented in Table 42.

Table 42. Health state utility values (adapted from Table 60 in CS)

Health state	Pembrolizumab	SoC
Progression free	0.843	0.787
Progressed disease	0.730	0.730

Abbreviations: SoC, standard of care.

The company also included age-related utility decrements in the economic model using a published algorithm by Ara and Brazier 2010[45].

4.2.7.2 *Adverse event utility values*

For adverse events, rather than an event-specific rate, utility decrements were estimated based on the difference between progression-free utility values with and without status any serious adverse events (grade 3+) present. The adverse event utility data came from the KEYNOTE-177 trial. Adverse event disutility values for each treatment included in the model are presented in Table 43.

Table 43. Adverse event disutility values (taken from the economic model)

Treatment	Disutility value
Pembrolizumab	0.031
SoC	0.031
CAPOX	0.025
Panitumumab + mFOLFOX6	0.065

Abbreviations: AE, Adverse event; QALY, Quality Adjusted Life Year; SoC, Standard of Care.

4.2.7.3 *ERG Critique*

The company generated the utility values from the KEYNOTE-177 trial, which the ERG agrees is preferable to estimates derived from the literature, even with the uncertainty around the estimates used in the model.

The use of progression-based utility values is appropriate for the base case. However, the ERG considers that the company did not sufficiently explore plausible scenarios for alternative utility values in the CS. Furthermore, the ERG queried the use of treatment specific utilities for the progression-free health state, as the difference between pembrolizumab and SoC was substantial

(0.056). In the CS, the company stated that use of treatment specific utility values was based on statistical tests and during the clarification stage, explained that the confidence intervals for the utility estimates between the intervention and SoC arms did not overlap rather than statistical tests directly comparing the differences in the utility estimates.

The ERG confirmed the use of treatment specific utilities with its clinical experts, who supported the use of treatment specific values as pembrolizumab might result in improved quality of life compared with SoC in the progression free state, as it is a monotherapy and as such would require shorter duration and less frequent hospital visits. Nonetheless, at the clarification stage, the ERG requested that the company explore scenario analyses using pooled utility estimates rather than the treatment specific estimates and also where the pooled progression-free utility value was applied only in the first cycle, after which the progression-free no AE utility value was implemented. The utility values for the requested scenarios are presented in Table 44.

Table 44. Alternative utility values for scenario analysis (Table 60 in the CS)

Health state	Utility value
Progression-free - pooled	0.819
Progressed disease - pooled	0.730
Progression-free – no AE	0.833

Abbreviations: SoC, standard of care.

The results of the ERG requested scenarios are presented in Table 45 and show that changes had minimal impact on the ICERs.

Table 45. Results of the utility value scenario analyses

Pembrolizumab vs.	Company base case	Pooled utility value scenario	Pooled progression-free AE utility value in first cycle
Standard of Care	7,250	7,762	7,615
CAPOX	27,474	29,432	28,869
Panitumumab + mFOLFOX6	Panitumumab + mFOLFOX6 is dominated	Panitumumab + mFOLFOX6 is dominated	Panitumumab + mFOLFOX6 is dominated

Abbreviations: AE, adverse event; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin

The ERG considers that because the company's used utility values that do not distinguish between patients with and without an AE, that the impact of AEs is inherently included in the overall utility value. As such, it is the ERG's preference to exclude disutility associated with AEs and has used this assumption for its base case analysis presented in Section 6.4.

The ERG also requested a scenario where the time to death estimates reported in the company submission were used for the QALY calculations in the model; however, the company did not provide the scenario. Thus, the ERG implemented the time-to-death scenario using the pooled utility estimates from the company's submission for each arm of the model, presented in Table 46. The ERG's scenario is based on estimating the proportion of patients in each cycle who die and utilities for the model cycle are applied based on which time-to-death category it falls within. The results of the scenario using time-to-death utility values can be found in Section 6.3 and show that the scenario had minimal impact on the ICER. However, as mentioned earlier in this section, the time-to-death utility estimates are immature, with small sample sizes and large confidence intervals, particularly for the categories closest to death.

Table 46. Pooled time to death utility values (adapted from Table 59 of the company submission)

Time to death	Pooled estimate
<30 days to death	0.781
30-180 days to death	0.762
180-360 days to death	0.701
>360 days to death	0.499

As mentioned throughout this report, the ERG requested subgroup analysis for the RAS wild-type population and at the clarification stage requested that utilities values for patients with RAS wild-type mCRC were explored in a scenario. However, the company declined to provide the analyses by RAS mutation status. The company's SLR identified studies which contained utility values for patients with RAS wild-type mCRC as well as estimates for total metastatic disease utilities. The ERG examined the SLR results and found that most of the studies that included utility values for RAS wild-type mCRC relied on estimates from four papers, of which only one provided utility values based on RAS wild-type mutation status (Bennett *et al*. 2011[46]). The baseline utility score in the study by Bennett *et al*. 2011 for KRAS wildtype colorectal cancer was 0.778, which is similar to the SoC PFS

utility value from KEYNOTE-177.[46] As such, the ERG considers the available evidence doesn't support a difference in HRQoL if a patient has RAS wild-type mCRC.

4.2.8 Resource use and costs

The company included the following costs in the economic model: drug acquisition costs, administration costs, disease management costs, adverse reaction costs, subsequent treatment costs and terminal care costs. The details for each of these are given in the following subsections.

Unit costs used in the model were inflated to 2018/2019 prices using the PSSRU hospital and community health services pay and prices index.[47]

4.2.8.1 Drug acquisition costs

Pembrolizumab is a fixed dose drug given as a 200mg infusion in two 100ml vials every three weeks. The list price per vial is £2,630, and the total cost of a dose is £5,260. There is currently a patient access scheme (PAS) discount in place for pembrolizumab of [redacted], therefore the price per dose of the intervention drug is [redacted]. Pembrolizumab can also be given as a 400mg infusion every 6 weeks and assuming the same discount and usage of 100mg vials, the drug cost of the 400mg dosage is [redacted].

The comparator drugs are dosed according to the patients' body surface area or body mass, depending on the drug. The company details eight standard of care drug dosing schedules as options (please refer to Section 4.2.3 for the dosing regimens). Details of the costs and frequencies are presented in Table 47.

Table 47. Drug acquisition costs (taken from the economic model)

Drug treatment	Total cost	Frequency
mFOLFOX6	£35.51	Cost per 2 weeks
FOLFIRI	£39.85	Cost per 2 weeks
CAPOX	£15.15	Cost per week (applied ever 3 weeks)
	£0.66	Cost per week (applied 2 weeks on 1 week off)
Cetuximab + mFOLFOX6	£35.51	Cost per 2 weeks

Cetuximab + FOLFIRI	£39.85	Cost per 2 weeks
	£1289.44	One-off cost
	£805.90	Cost per 1 week
Panitumumab + FOLFOX6	£1643.31	Cost per week, applied every 2 weeks

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin

Drug acquisition costs are taken from eMIT (electronic market information tool)[40] and MIMS (Monthly Index of Medical Specialities)[39] databases.

4.2.8.2 *Relative dose intensity*

The company accounted for the relative dose intensity (RDI) of each of the treatment regimens to factor in doses that were not received and therefore did not incur costs. The RDIs were calculated as the percentage of planned doses that were administered and these were then multiplied by the drug acquisition costs per cycle. Details of the RDI are shown in Table 64 of the CS. The RDI for pembrolizumab was higher than for SoC (96.5% vs 88.6%) and reflects the more intensive and toxic nature of SoC treatments. For instance, in KEYNOTE-177 the adverse event profile of SoC was higher than pembrolizumab both in percentage of patients affected (56.2% for pembrolizumab vs 77.6% for SoC) and by mean number of episodes (2.64 for pembrolizumab vs 3.42 for SoC). Vial sharing was assumed in the SoC arm. It was not considered for pembrolizumab as it is a flat dose for all patients.

4.2.8.3 *Time on treatment*

Time on treatment (ToT) was modelled for pembrolizumab and SoC separately using data from KEYNOTE-177. For the pembrolizumab arm, the company used ToT KM data from the trial and included a 35-cycle stopping rule (reflective of the stopping rule in KEYNOTE-177), while for the SoC arm, KM ToT data were extrapolated using an exponential distribution (Figure 39 of the CS). Details of the company's methods for survival analysis and model selection can be found in Section 4.2.5. For non-trial comparators (CAPOX and panitumumab combination treatment), the company assumed that ToT was equal to PFS. Mean time on treatment for each arm of the model is shown in Table 48.

Table 48. Mean time on treatment (taken from the economic model)

Arm	Mean time on treatment (weeks)
Pembrolizumab	[redacted]
SoC	[redacted]
CAPOX	63.1
Panitumumab + mFOLFOX6	80.3

Abbreviation: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin SoC, Standard of Care

In KEYNOTE-177, >90% of pembrolizumab patients discontinued treatment at around 2 years (see Figure 38 in CS and in Figure 6). Only around 10% of patients were still on pembrolizumab after 2 years, and all had discontinued by 3 years. Based on the extrapolation, most patients on SoC are estimated to discontinue treatment after 4 years.

A scenario exploring the cost of retreatment with pembrolizumab was provided by the company at the clarification stage to capture the small proportion of patients (2.6%) who had treatment for longer than 35 cycles (presented in Section 5.1.2.2). The cost of treatment for pembrolizumab increased by [redacted] under this scenario.

4.2.8.4 *Administration costs*

Administration costs for the infusion of pembrolizumab were based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS reference costs 2018-19, as has been used for previous submissions to NICE.[13, 38] The unit cost of SB12Z is given as £254.14.

The company assumed the number of treatment days for SoC and panitumumab combination treatment as three days and for CAPOX was one day. Table 49 presents a summary of the comparator administration costs included in the economic model. The ERG notes that administration costs for oral capecitabine were only applied in the first model cycle.

Table 49. Comparator administration costs

Treatment	Number of days of treatment per cycle	Unit cost	Cost description
Pembrolizumab	1	£254.14	NHS reference cost code SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance, Daycase and Reg Day/Night.[38]
SoC	3	£385.25	Day 1. NHS reference cost code SB14Z - Deliver complex chemotherapy, including prolonged infusion treatment at first attendance, Daycase and Reg Day/Night.[38]
		£362.35	Day 2 & 3. NHS reference cost code SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, Daycase and Reg Day/Night.[38]
CAPOX	1	£385.25	Oxaliplatin IV infusion. NHS reference cost code SB14Z - Deliver complex chemotherapy, including prolonged infusion treatment at first attendance, Daycase and Reg Day/Night.[38]
		£216.08	Oral capecitabine. NHS reference cost code SB11Z - Deliver Exclusively Oral Chemotherapy, Daycase and Reg Day/Night.[38]
Panitumumab +mFOLFOX6	3	£385.25	Day 1. NHS reference cost code SB14Z - Deliver complex chemotherapy, including prolonged infusion treatment at first attendance, Daycase and Reg Day/Night.[38]
		£362.35	Day 2 & 3. NHS reference cost code SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, Daycase and Reg Day/Night.[38]

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; IV, intravenous; NHS, National Health Service; SoC, standard of care

4.2.8.5 *Disease management costs*

A SLR was undertaken to identify resource use evidence for the dMMR/MSI-H population (see Section 4.1); however, most of the resource use assumptions were obtained from TA439.[13] The unit costs are summarised in Table 50.

Table 50. Disease management costs (adapted from Table 68 of the company submission)

Resource	Unit Cost	Pre-progression monthly units	Post-progression monthly units	Total monthly cost
Consultant outpatient cost	£187	2.17	0	£405.79
Tumour marker test	£14	0.25	0	£3.50
Liver function test	£29	1.25	0	£36.25
CT scan	£116	0.33	0	£38.28
MRI scan	£206	0.25	0	£51.50
Best supportive care	£1600	0	1	£1600

Abbreviations: CT, Computer Tomography; MRI, Magnetic Resonance Imaging.

The company submission does not include the cost of testing for dMMR and MSI-H status as these are routinely performed in UK clinical practice, as per NICE guidance DG27.[14]

4.2.8.6 *Adverse events costs*

The unit costs of treating AEs are given in Table 70 of the company submission. Unit costs were derived from the NHS Reference Costs schedule 2018-19.[38] The company stated that guidance on appropriate AE unit costs was informed by previous submissions for pembrolizumab. In the model these costs are calculated first as a weekly cost for each of the 22 subtypes of adverse event, multiplied by the normalised weekly risk of each adverse event (please refer to Section 4.6.2), and then multiplied by the average length of treatment to get a total cost of adverse events that is then applied as a one-off cost to the first cycle of the model. Table 51 presents the total costs of AEs for each comparator considered in the economic model.

Table 51. Adverse event costs

Treatment	Weekly adverse event cost	Mean treatment duration in months	Total adverse event cost (as one-off cost)
Pembrolizumab	£5.85	13.3	£337.74
SoC	£21.38	8	£743.77
CAPOX	£16.69	8	£580.55

Panitumumab + mFOLFOX6	£48.76	8	£1696.30

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin SoC, Standard of Care

4.2.8.7 *Subsequent treatment costs*

Upon progression, patients in the model are assigned second-line treatment costs. The base case model assumes that there is no difference in subsequent treatment distribution between the arms of the model after patients experience disease progression. Based on data from KEYNOTE-177, 53.7% of pembrolizumab patients received second-line therapy compared to 83.2% of SoC. The treatment distribution used in the model is based on either estimate from the company's experts of clinical practice in the UK. The proportion from the KEYNOTE-177 trial was explored in scenario analysis requested by the ERG during the clarification stage (presented in Section 5.1.2.2). Details of the second-line treatment scenarios are shown in Table 52.

Table 52. Proportion of patients on subsequent treatment costs (adapted from Table 57 and 58 of the company submission)

Second line treatment	Company's clinical experts estimate (both arms)	KEYNOTE-177	
		Pembrolizumab	SoC
No second line treatment	46.3%	46.3%	16.8%
mFOLFOX6	0.0%	13.2%	6.9%
FOLFIRI	37.6%	10.0%	8.2%
Cetuximab + mFOLFOX6	0.0%	1.6%	0.0%
Cetuximab + FOLFIRI	16.1%	1.3%	0.0%
Bevacizumab + FOLFOX6	0.0%	15.6%	30.9%
Bevacizumab + FOLFIRI	0.0%	11.9%	37.1%
Pembrolizumab	0.0%	0.0%	0.0%

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin

The unit cost of second-line treatment is assumed to be the same for patients in both the pembrolizumab and the standard of care arms at £8,449. This is split between drug acquisition costs of £2,577 and administration costs of £5,872 across 20 weeks.

The total subsequent treatment costs for pembrolizumab and standard of care in the two different approaches is given in Table 53.

Table 53. Subsequent therapy costs

Subsequent therapy scenario	KEYNOTE-177 estimate	Clinical expert estimate
Pembrolizumab costs	£7,913	£8,305
SoC costs	£12,941	£8,086

Abbreviations: SoC, standard of care.

4.2.8.8 *Terminal care costs*

The company did not assume a separate cost for terminal care in their base case, instead choosing to base post-progression resource on 'Best Supportive Care' costs from estimated from Färkkilä *et al.* 2015[48]. However, the company did include an option in the model to include a terminal care cost based on Round *et al.* 2015.[49] The terminal care cost option is £5,156.50, a proportion of which is allocated to each cycle the patient is in the progressed health state. This is compared to the £1,600 monthly cost for best supportive care, which is the direct health costs of being in a 'palliative' health state from Färkkilä *et al.* 2015 made up of outpatient, inpatient and travel costs.[48] Best Supportive Care costs are applied for the whole time the patient is in the progressed health state within the model.

4.2.8.9 *ERG Critique*

The ERG considers the company's methods regarding the estimation of unit costs and resource use to be generally reasonable. The ERG considers the administration costs presented in the model to be acceptable. In the CS, the administration cost for the intervention reflects an outpatient simple cost and the comparator a complex day case, based on the treatment days in a cycle of between 1 and 3 days for the comparator and half a day for pembrolizumab. The company's approach reflects the time and complexity required to administer each treatment and the difference in intensity between the intervention and compactor regimens. Furthermore, the ERG considers the decision to not include testing for dMMR or MSI-H status to be correct, as these tests are routinely performed in the NHS.

In KEYNOTE-177, the treatment regimen for pembrolizumab was 200mg once every three weeks, but the company stated that it can also be administered at a 400mg dose once every six weeks. The ERG

clinical experts advised that in clinical practice, they would prefer to administer pembrolizumab using the 400mg dose once every six weeks for patient convenience and also to reduce NHS resource use. The ERG requested that the company to provide a scenario exploring the less frequent dosing regimen for pembrolizumab at the clarification stage. The company provided the results of the ERG requested scenario (presented in Section 5.1.2.2), which improved the ICERs, but not substantially. The company expects that the monotherapy licence will include an option to administer pembrolizumab at a 400mg dose once every six weeks. As such, the ERG considers includes the use of the less frequent treatment regimen for pembrolizumab in its preferred analysis, as that is likely to be how it is used in UK clinical practice.

Related to the less frequent treatment regimen for pembrolizumab is the frequency of consultant oncologist appointments, which is a primary driver of cost-effectiveness. In the company's base case, consultant oncologist appointments occurred according to the SoC treatment cycle (every 2 weeks), even when the treatment was given less frequently (once every three weeks), as was the case for pembrolizumab and CAPOX. The ERG asked at the clarification stage for a scenario analysis where consultant oncologist appointments and liver function tests were included once per cycle of treatment and this was implemented by the company. The ERG made a minor correction to the company's resource use scenario as its implementation affected costs for comparators with regimens that were once every two weeks. For the scenario a formula was used to derive the number of appointments per month, resulting in a slightly higher estimation (~2.174). However, in the company's base case, consultant oncologist appointment per month were hardcoded in the economic model as 2.17, which is just a rounded figure of the calculation, which the ERG used to correct the company's scenario.

The results of the ERG corrected one-way sensitivity analysis show that the model is sensitive to the assumption around the frequency of consultant oncologist appointments in particular, with the ICER changing from £7,250 to £4,043 for the comparison with SoC and from £27,474 to £25,275 for the comparison with CAPOX, but pembrolizumab still dominates panitumumab combination treatment under this scenario. Further details of the resource use scenario are presented in Section 5.1.2.2. The ERG also ran another scenario to align consultant oncologist appointments to be used in conjunction with the scenario exploring the pembrolizumab treatment regimen of 400mg once every six weeks, which reduce the ICER further to £535 for the comparison with SoC, £20,736 for CAPOX, with pembrolizumab still dominant against panitumumab combination treatment. The ERG believes that oncologist appointments and liver function tests aligned to treatment cycle is more reflective of

clinical practice in the UK, but only consultant oncologist appointments had a substantial impact on the ICER and as such has included in its base case, further details of which can be found in Section 6.4.

As mentioned previously, in KEYNOTE-177 approximately 70% of patients received bevacizumab combination treatment, which is not recommend in the NHS.[41] The company assumed that costs for patients who received bevacizumab combination treatment would be reflective of cetuximab combination treatment. However, cetuximab combination treatment is only recommend in the NHS for patients with RAS-wildtype mCRC. As such, for the ERG's preferred ITT and RAS wildtype analysis (population A and B),which focuses only on the comparison with FOLFOX and FOLFIRI (SoC), the ERG ran a scenario where treatment costs for standard of care are based only on FOLFOX and FOLFIRI treatments – this increased the ICER from £7,250 to £21,636 (See Section 6.3 for further details). The ERG notes that the results of this scenario should be interpreted with caution as the clinical efficacy of SoC includes the efficacy of bevacizumab and as such breaks the alignment of costs with observed efficacy in KEYNOTE-177. The ERG considers it is important to highlight that SoC treatment costs for the company base case are higher than may be incurred in UK clinical practice and as such, the scenario can be considered conservative.

Another key issue with the costs used in the model, is the assumption of ToT used for the non-trial comparators, CAPOX and panitumumab combination treatment. In the base case analysis, the company assumed ToT to be equal to estimated PFS for CAPOX and panitumumab combination treatment, in the absence of alternative data. As presented in Table 48, mean ToT for CAPOX and panitumumab is substantially longer compared with pembrolizumab and SoC, which results in inflated treatment costs. In TA439, mean treatment duration for panitumumab combination treatment was estimated to be approximately nine months, which is shorter than the company's estimated mean treatment duration of 18.5 months based on ToT equal to PFS.[13] As such, the ERG considers that a more appropriate assumption for ToT for non-trial comparators is to assume it is equal to KEYNOTE-177 ToT for SoC. Mean ToT for SoC was estimated to be approximately [redacted] months, which is closer to the estimates in TA439 for panitumumab combination treatment. Furthermore, given the company are assuming clinical outcomes for CAPOX are equal to SoC, it is not unreasonable to assume ToT is equal to ToT for SoC. The ERG performed a scenario for the non-trial comparators, where ToT is equal to ToT for SoC and this had a negligible impact on the ICER for CAPOX, but changed the ICER for panitumumab combination treatment from being dominant to

£3,158 and as such is included in the ERG's preferred analysis. Further details of this scenario can be found in Section 6.3 and 6.4.

The ERG notes that the estimation of treatment costs for pembrolizumab is based on KM data from KEYNOTE-177 and the company has also included a 35-cycle stopping rule to reflect the maximum number of cycles of treatment patients could receive in the trial. The ERG is satisfied with the approach taken in the pembrolizumab arm of the model, but highlights that as per the draft SmPC, [redacted]. As such, the ERG has run an illustrative scenario, which assumes ToT is equal to PFS for pembrolizumab and removed the 35-cycle stopping rule, presented in Section 6.3.

Subsequent treatment costs for patients with progressed disease were calculated as a single 20-week post-progression treatment cost applied as a one-off cost upon progression. The ERG considers this assumption is appropriate as the ERG's clinical experts advised that post-progression survival for patients with mCRC is limited. However, the distribution of subsequent treatment costs was split between FOLFIRI and cetuximab + FOLFIRI treatments. NICE guidance does not recommend cetuximab for use as a monotherapy or in combination therapies as second line treatment for mCRC, thus the ERG has run a scenario where cetuximab + FOLFIRI has been removed from the subsequent treatment costs.[50] The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%). The ERG's subsequent treatment scenario reduces the total cost of the subsequent treatment cost to £5,509 from £8,449, but has limited impact on all ICERs, as presented in Section 6.3.

The ERG is satisfied with the company's approach for relative dose intensity, adverse event costs and terminal care costs. Best supportive care costs were tested as part of the model validation process and the model was not found to be sensitive to extremes in these values.

5 Cost effectiveness results

5.1.1 *Company's cost effectiveness results*

The results of the company's base-case analysis are given in Table 54, showing an incremental cost-effectiveness ratio (ICER) of £7,250 per QALY gained for pembrolizumab versus standard of care (SoC). For the comparison with CAPOX, the cost per QALY was £27,474 (Table 55), and pembrolizumab dominates panitumumab + mFOLFOX6 (Table 56). The results include the company's agreed patient access scheme (PAS) discount for pembrolizumab of [redacted] on the list price. The company's fully incremental cost-effectiveness analysis is presented in Table 57.

The ERG notes that the ICERs for CAPOX presented in the company's clarification responses were incorrect when compared with the economic model submitted with the response. The company confirmed that on the day of submission of the clarification response, an amendment was made to the economic model. Therefore, the ICERs for CAPOX presented in the ERG report are obtained from the company's economic model submitted with the clarification response.

Table 54. Company's base case deterministic results: pembrolizumab versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	13,497	3.145	1.862	7,250

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 55. Company's base case deterministic results: pembrolizumab versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,968	3.145	1.855	27,474

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 56. Company's base case deterministic results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-48,317	2.825	1.688	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 57. Company's base case deterministic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	37,472	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,968	1.86	27,379
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	48,317	-1.68	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.1.2 Company's sensitivity analyses

The company conducted a probabilistic sensitivity analysis (PSA) based on 5,000 samples. The results for pembrolizumab against SoC, CAPOX and mFOLFOX6 + panitumumab are shown in Table 58 to Table 60. Table 62 presents the company's probabilistic fully incremental analysis. The cost-effectiveness planes for these results are given in Figure 10 to Figure 12. It should be noted that the company only explored variation around clinical efficacy for the estimates derived from the proportional hazards network meta-analysis, which is not used for the base case, resulting in similar estimates of life years between the deterministic and PSA results. As such, the ERG considers that the uncertainty around clinical efficacy has not been fully explored in the PSA.

Table 58. Company's PSA results: pembrolizumab versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	18,199	3.133	1.858	9,795

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 59. Company's PSA results: pembrolizumab versus vs CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	55,820	3.133	1.852	30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 60. Company's PSA results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-43,910	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 61. Company's base case probabilistic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	37,620	-0.006	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	18,199	1.858	9,795
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	43,910	-1.684	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 10. Cost-effectiveness plane: pembrolizumab versus standard of care

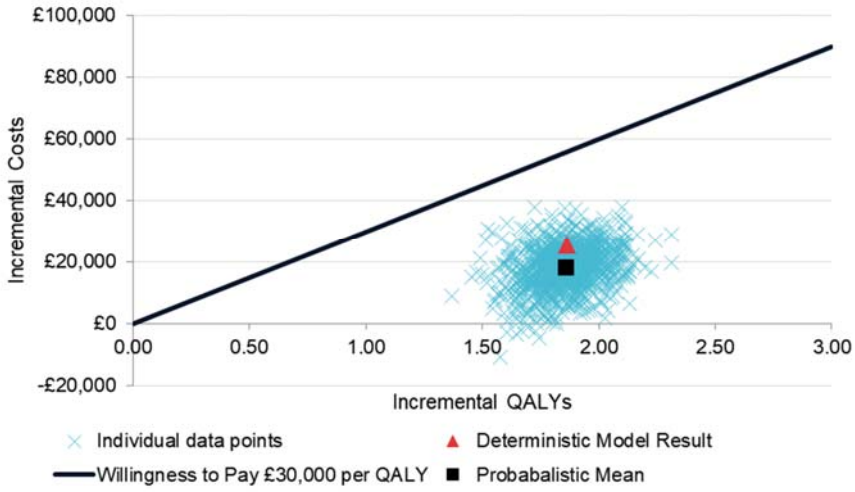


Figure 11. Cost-effectiveness plane: pembrolizumab versus CAPOX

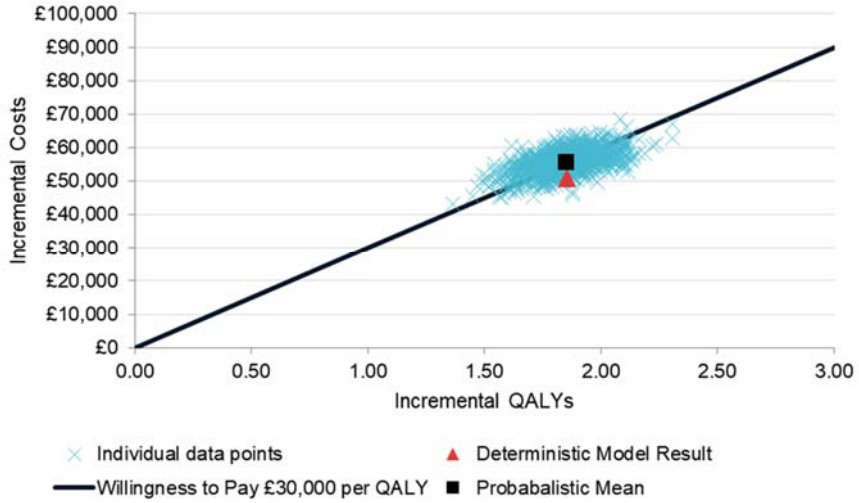
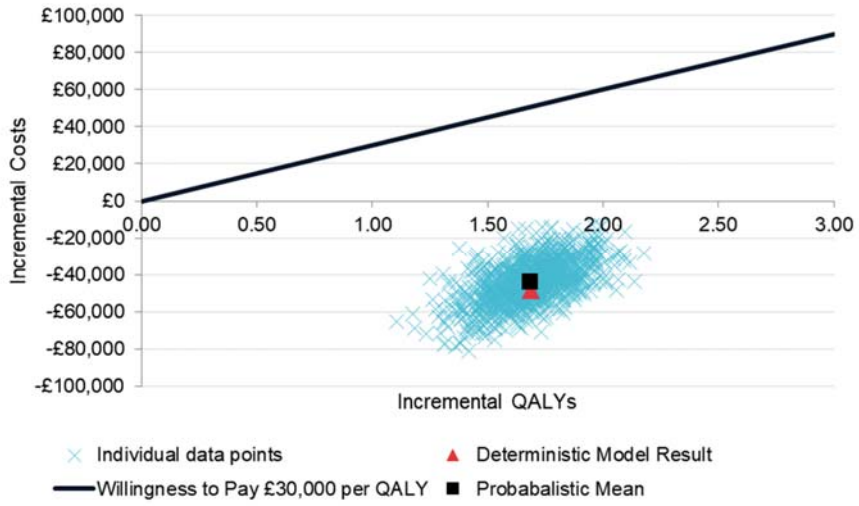


Figure 12. Cost-effectiveness plane: pembrolizumab versus panitumumab + mFOLFOX6



5.1.2.1 *One-way sensitivity analysis*

The company conducted a range of one-way sensitivity analyses (OWSAs) to test the impact that plausible changes on parameters have on the overall results. The tornado plot in Figure 13 shows the parameters that had the greatest impact, with the Best Supportive Care (BSC) costs having the largest impact with ICERs ranging between £3,575 and £10,925.

Consultant treatment had the biggest impact on the ICERs for the CAPOX comparator, with values between £26,176 and £28,772 (Figure 14). For the mFOLFOX6 + panitumumab comparator the main driver of the difference in costs is best supportive care, with ICERs remaining dominated (Figure 15).

Figure 13. OWSA tornado diagram: pembrolizumab versus standard of care

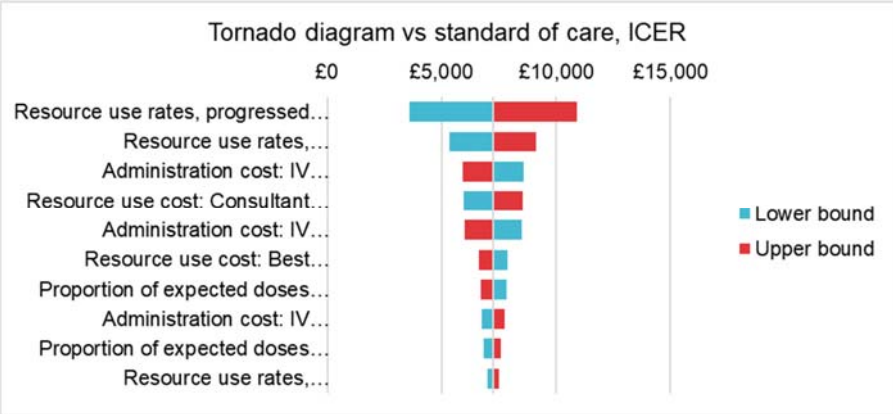


Figure 14. OWSA tornado diagram pembrolizumab vs CAPOX

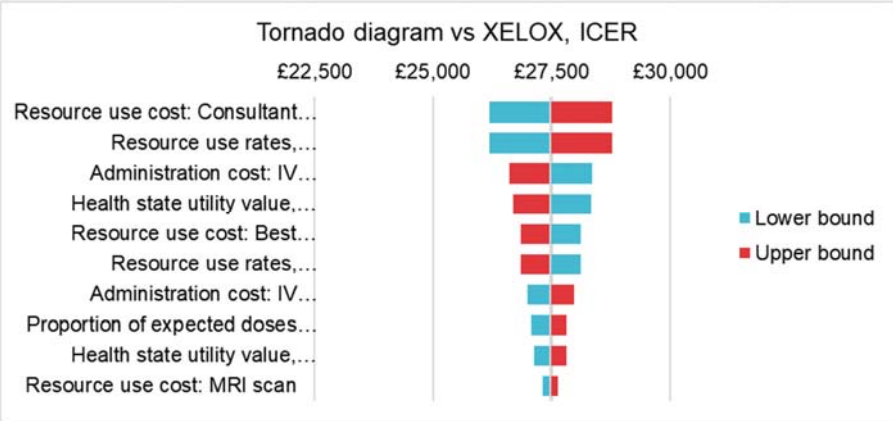
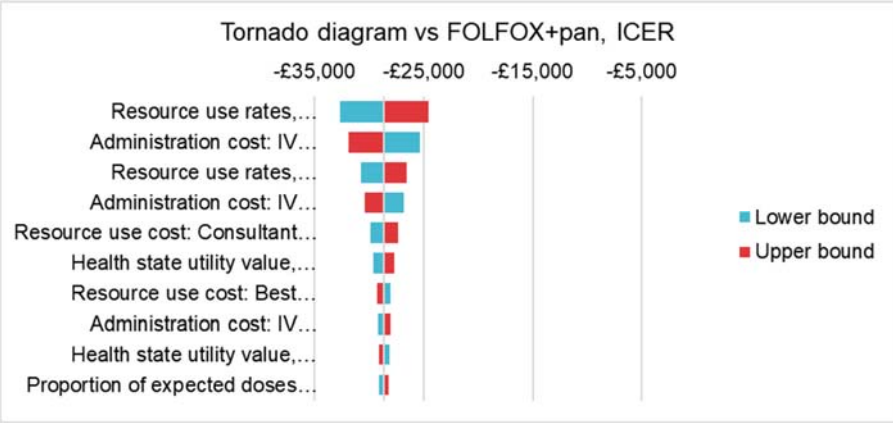


Figure 15. OWSA tornado diagram pembrolizumab vs panitumumab + mFOLFOX6



5.1.2.2 *Scenario analysis*

The company provided a range of scenario analyses around their base case, which are detailed in full in Table 79 of the CS. The impact of the scenario analyses on the ICER for pembrolizumab versus SoC, CAPOX and panitumumab combination treatment is shown in Table 62.

Table 62. Scenario analysis results

Scenario	ICER (£) – pembrolizumab versus.		
	SoC	CAPOX	Panitumumab + mFOLFOX6
Base case	**7,250**	**27,474**	**Dominant**
Company scenarios provided in the company submission			
Time horizon- 30 years	7,115	27,484	Dominant
PH NMA results used	7,250	27,474	Dominant
Time to progression and Progression free survival (pembrolizumab & SoC) -Two-piece Weibull with 10- week cut-off point	6,548	20,971	Dominant
Post progression survival (pembrolizumab & SoC) - Lognormal	6,046	27,419	Dominant
Vial sharing assumed	5,961	27,455	Dominant

Scenarios requested by the ERG at the clarification stage			
Pooled utility values for the progression-free health state from KEYNOTE-177	7,762	29,422	Dominant
Pooled progression-free AE utility value is applied only in the first cycle, after which the progression-free no AE utility value is implemented	7,615	28,860	Dominant
Second phase retreatment with pembrolizumab (as per KEYNOTE-177)	7,976	28,203	Dominant
Subsequent treatment proportions based on KEYNOTE-177	4,467	24,681	Dominant
Pembrolizumab treatment regimen – 400mg once every 6 weeks	6,967	27,190	Dominant
Oncologist outpatient appointment and liver function test aligned to treatment cycle (**ERG corrected scenario**)	4,043	25,275	Dominant

Abbreviations: NMA, network meta-analysis; PH, proportional hazard; SoC, standard of care.

5.1.3 Model validation and face validity check

For the model validation, the company stated that quality control checks were performed by model developers to ensure calculations were correct and consistent with the model specification. In addition, health economists not involved with model development performed quality assurance of the model for coding errors, inconsistencies and plausibility of model parameters and results. The company performed external validation of the model by comparing estimated clinical outcomes from the model against the observed data in KEYNOTE-177 as well as using real world data to validate extrapolations of post-progression survival used in the model.[51] The ERG considers the company's model validation and face validity check to be robust and as such has not identified any errors in the model.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The Evidence Review Group (ERG) did not identify any model errors.

6.2 Exploratory and sensitivity analyses undertaken by the ERG

In Section 4 of this report, the ERG has described several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The deterministic scenarios the ERG has produced are applied to the company's revised base case analysis for the ITT population, with the underlying assumption that the ITT analyses are a proxy for the RAS wild-type subgroup for FOLFOX, FOLFIRI, CAPOX and panitumumab combination treatment. A separate scenario, estimating the cost-effectiveness of pembrolizumab versus cetuximab combination treatment is provided in Table 64. The scenarios that the ERG has performed are as follows:

1. Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of time to progression (TTP) and progression-free survival (PFS) – Section 4.2.5.1
2. Time to death utility values – Section 4.2.7.3
3. Removal of AE disutility – Section 4.2.7.3
4. Using only mFOLFOX6 (50%) and FOLFIRI (50%) costs for SoC treatment costs – Section 4.2.8.9
5. Assuming time on treatment (ToT) for panitumumab and CAPOX is equal to ToT for standard of care (SoC) – Section 4.2.8.9
6. Exploring ToT for pembrolizumab equal to PFS and removing the 35-cycle stopping rule. The draft SmPC states pembrolizumab [redacted], but was restricted to 35 cycles in KEYNOTE-177 – Section 4.2.8.9
7. Removal of subsequent cetuximab combination treatment – Section 4.2.8.9
8. Less frequent treatment regimen and consultant oncologist appointments for pembrolizumab (400mg once every six weeks) based on advice from ERG's clinical experts – Section 4.2.8.9

9. RAS wild-type subgroup analysis – cetuximab combination treatment is clinical equivalent to panitumumab combination treatment– Sections 4.2.2, 4.2.3 and 4.2.5.1.

6.3 ERG scenario analysis

Table 63 presents the results of the ERG exploratory analyses described in Section 6.2. Results reported include the company's proposed patient access scheme (PAS) of [redacted].

Table 63. Results of the ERG's scenario analyses – ITT/RAS wild-type population

	Results per patient	Pembrolizumab (1)	SoC (2)	CAPOX (3)	Panitumumab +mFOLFOX6 (RAS wild-type only) (4)	Incremental value (1-2)	Incremental value (1-3)	Incremental value (1-4)
0	**Company base case**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,250	27,474	Dominant
1	**Weibull distribution applied after 20-week cut-off point for TTP and PFS**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,171	50,307	-56,167
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.89	1.88	1.68
	ICER (£/QALY)					6,966	26,698	Dominant
2	**Implementation of time-to-death utility values from KEYNOTE-177**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.71	1.71	1.50
	ICER (£/QALY)					7,896	29,819	Dominant

3	**Removal of AE disutility**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.65
	ICER (£/QALY)					7,251	27,383	Dominant
4	**FOLFOX and FOLFIRI costs used for SoC**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	40,278	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					21,636	27,474	Dominant
5	**ToT for CAPOX and panitumumab + mFOLFOX6 equal to ToT for SoC**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	54,180	5,330
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,250	29,205	3,158
6	**ToT for pembrolizumab equal to PFS and removal of 35-cycle stopping rule**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	137,400	17,4871	75,586
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					73,809	94,262	44,777

7	**Removal of second-line cetuximab combination treatment**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,911	51,383	-47,946
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,473	27,697	Dominant
8	**Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	996	38,468	-60,817
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					535	20,736	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality adjusted life year; TTP, time to progression

Table 64. Scenario 9 - pembrolizumab versus cetuximab combination treatment - RAS wild-type only.

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cetuximab + mFOLFOX6/FOLFIRI	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-49,510	2.83	1.69	Dominant

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

6.4 ERG preferred assumptions

In this section, the ERG presents its base-case ICER for ITT/ RAS wild-type proxy analyses. For the ERG base case, the assumption of cetuximab combination treatment is clinically equivalent to panitumumab combination treatment in the RAS wild-type subgroup has been included and all relevant assumptions applied. Deterministic results and fully incremental analyses are presented in Table 65 and Table 66 and incorporates the company's patient access scheme (PAS) simple discount of [redacted]. The ERG could not produce PSA ICERs for its base case as the PSA takes several hours to run and due to paucity of time and complexity of the model, some scenarios could not be integrated with the PSA.

Table 65. ERG's preferred model assumptions – ITT/ RAS wild-type population

Preferred assumption	Section in ERG report	Pembrolizumab vs Standard of Care		Pembrolizumab vs CAPOX		Pembrolizumab vs Panitumumab + mFOLFOX6 (RAS wild-type only)		Pembrolizumab vs Cetuximab + FOLFIRI/ mFOLFOX6 (RAS wild-type only)	
		ICER (£/QALY)	Cumulative ICER (£/QALY)	ICER (£/QALY)	Cumulative ICER (£/QALY)	ICER (£/QALY)	Cumulative ICER (£/QALY)	ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	-	7,250	-	27,474	-	Dominant	-	-	-
Cetuximab combination treatment is clinical equivalent to panitumumab combination treatment	*4.2.2, 4.2.3 and 4.2.5.1*	-	-	-	-	-	-	Dominant	-
Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks	*4.2.3 and 4.2.8.9*	535	535	20,736	20,736	Dominant	Dominant	Dominant	Dominant
Implementing the Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS	*4.2.5.1*	6,966	164	26,698	19,872	Dominant	Dominant	Dominant	Dominant
Removal of AE disutility	*4.2.7.3*	7,251	164	27,383	19,808	Dominant	Dominant	Dominant	Dominant

ToT for comparator is equal to ToT for standard of care	*4.2.8.9*	-	164	29,205	21,684	3,158	Dominant	2,852	Dominant
FOLFOX/FOLFIRI costs for SoC	*4.2.8.9*	21,636	14,330	-	21,684	-	Dominant	-	Dominant
Removal of second-line cetuximab combination treatment	*4.2.8.9*	7,473	14,569	27,697	21,923	Dominant	Dominant	Dominant	Dominant
ERG preferred ICER	**-**	**-**	**14,569**	**-**	**21,923**	**-**	**Dominant**	**-**	**Dominant**

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 66. ERG's base case deterministic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Standard of care	[redacted]	[redacted]	[redacted]	13,902	0.00	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	41,443	1.89	21,923
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	7,675	-1.65	Dominated
Cetuximab + mFOLFOX6/FOLFIRI	[redacted]	[redacted]	[redacted]	8,191	-1.65	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

6.5 Conclusions of the cost effectiveness sections

Overall, the case made by the company to demonstrate the cost-effectiveness of pembrolizumab compared with relevant comparators based on the intention-to-treat (ITT) population of the primary trial, KEYNOTE-177, is considered by the ERG to be generally robust. In KEYNOTE-177, progression-free survival (PFS) outcomes for pembrolizumab demonstrate a statistically significant improvement compared with standard of care (SoC) in the trial. The ERG notes that standard of care in KEYNOTE-177 comprised mFOLFOX6 (folinic acid plus fluorouracil plus oxaliplatin), FOLFIRI (folinic acid plus fluorouracil plus irinotecan), cetuximab in combination with mFOLFOX6 or FOLFIRI, and bevacizumab in combination with mFOLFOX6 or FOLFIRI. Over 70% of SoC patients in KEYNOTE-177 received bevacizumab combination treatments, but NICE guidance does not recommend its use for treating mCRC.[41, 42] However, bevacizumab combination regimens are likely to be more effective than FOLFOX and FOLFIRI alone. As such, the ERG considers that receiving treatment with bevacizumab is likely to be biased against pembrolizumab, resulting conservative estimates of treatment effectiveness.

One of the ERG's primary concerns with the company's approach to the cost-effectiveness analysis is with the population of the economic model. The ERG considers that in addition to the analysis using the ITT population, the company should have presented subgroup analyses by RAS mutation status. The NICE final scope specifies that, "If the evidence allows the subgroup of people with RAS wild-type colorectal cancer will be considered".[1] Treatment options in the UK differ if a patient has RAS wild-type mCRC. According to the NICE pathway for managing mCRC, first-line biological therapy (cetuximab or panitumumab combination treatments) are only recommended for patients with RAS wild-type mCRC.[42] Furthermore, subgroup analyses reported within the company submission (CS) indicate that, in those with RAS wild-type, pembrolizumab is associated with a statistically significant improvement in PFS compared with SoC (hazard ratio [HR] 0.44, 95% confidence interval [CI]: 0.29 to 0.67). However, in the non-RAS wild-type subgroup, the direction of effect favours SoC, albeit that the benefit with SoC would not be considered statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). The ERG notes that the 95% CIs for the two subgroups do not overlap and, as such, considers the difference in the two subgroups unlikely to be due to random chance. The ERG concludes that the company should have presented cost-effectiveness analyses by RAS mutation status.

In lieu of the RAS mutation subgroup analyses, the ERG considers that using the ITT analyses as a proxy for the RAS wild-type population may provide a conservative estimate of the cost-

effectiveness of pembrolizumab, but for the non-RAS wild-type subgroup, the ERG predicts that pembrolizumab is less effective and more costly that SoC and as such would be dominated by the comparator. With regards to cetuximab combination treatment, in the company's current analysis, it is blended with SoC, but approximately 10% of SoC patients in KEYNOTE-177 received this treatment. As such, the ERG considers that a separate analysis for cetuximab combination treatment is appropriate, as it is only recommended for patients with RAS wild-type mCRC. TA439 reports an NMA that provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was more effective than panitumumab plus FOLFOX at increasing PFS or OS and as such, the ERG implemented a scenario assuming cetuximab and panitumumab combination treatment are clinically equivalent to provide an illustrative estimate of cost-effectiveness. However, the ERG reiterates that its preferred approach for the subgroup analyses by RAS mutation status is for the company to:

- Produce relative estimates of treatment effectiveness for patients with and without RAS wildtype mCRC from KEYNOTE-177 using the recommended ERG FP NMA outlined in the ERG's clarification questions;
- Implement the results of the subgroup treatment effectiveness analyses in the economic model to produce cost-effectiveness estimates by relevant comparator for RAS wild-type and non-RAS wild-type subgroups.

Setting aside the issue of the subgroup analyses by RAS-mutation status and appropriate comparators, the ERG interrogated the company's ITT state-transition model (STM). The structure of model was considered appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other oncology models submitted for NICE appraisal. With regards to the clinical transitions between the health states in the model, the ERG notes that as post-progression survival (PPS) is used in lieu of mature OS data from KEYNOTE-177, any gain in PFS directly equates to a gain in the estimated OS, which becomes more significant as the company has assumed that PPS for all comparators is equal to PPS for pembrolizumab.

The ERG considers the company's general approach to extrapolating outcomes for TTP, PFS and PPS to be appropriate. The use of piecewise models, with a cut-off point of 20 weeks for TTP and PFS appropriately captures the change in the hazard observed in log-cumulative hazard plots presented in the CS. However, the ERG questioned the use of an exponential model after the 20-week cut-off point for the TTP and PFS extrapolations for SoC, as the log-cumulative hazard plots indicate

increasing hazards. As such, use of the Weibull model after the 20-week cut-off point was considered more appropriate.

For their base case, the company assumed that PPS for all comparators was equal to PPS for pembrolizumab. The company's PPS assumption implies that the treatment effect with pembrolizumab is not extended beyond the progression-free health state. The ERG considers that it is not unreasonable that the treatment effect of pembrolizumab is assumed to only be in the progression-free health state as long-term overall survival data are immature, therefore estimating the duration of treatment effect beyond progression is currently problematic.

The ERG notes that the use of PPS for all arms of the model directly impacts OS, as any gain in PFS directly equates to a gain in the estimated OS. There is uncertainty around whether the PFS to OS relationship holds or whether patients on pembrolizumab are likely to have an accelerated mortality rate upon progression compared to patients on other treatments, particularly for RAS wild-type patients treated with biological therapies (panitumumab and cetuximab). However, the ERG notes that PFS and PFS2 for pembrolizumab versus SoC are similar (PFS HR 0.60, 95% CI: 0.45 to 0.80 vs PFS2 HR 0.63, 95% CI: 0.45 to 0.88), though this data are not mature. As such, the ERG considers it may not be unreasonable that gains in PFS are maintained in PFS2, thus providing initial support for the assumption that there isn't an accelerated mortality rate for pembrolizumab upon progression compared with SoC. However, mature OS data from KEYNOTE-177 is required to mitigate the uncertainty around long term survival outcomes.

Health-related quality of life (HRQoL) in the model was based on utility values obtained from the KEYNOTE-177 trial, which the ERG agrees is preferable to estimates derived from the literature. The use of progression-based utility values is appropriate for the base case. However, the ERG considers that the company did not sufficiently explore plausible scenarios for alternative utility values in the CS. Furthermore, the ERG queried the use of treatment specific utilities for the progression-free health state, as the difference between pembrolizumab and SoC was substantial (0.056). However, the ERG's clinical experts supported the use of treatment specific values as pembrolizumab might result in improved quality of life compared with SoC in the progression free state, as it is a monotherapy and as such would require shorter duration and less frequent hospital visits.

The ERG considers the company's methods regarding the estimation of unit costs and resource use to be generally reasonable. However, a key driver of the cost-effectiveness analysis is the frequency

of pembrolizumab treatment and in turn the resource use associated with different regimens. In KEYNOTE-177, the treatment regimen for pembrolizumab was 200mg once every three weeks, but the company stated that it can also be administered at a 400mg dose once every six weeks. The ERG's clinical experts advised that in clinical practice, they would prefer to administer pembrolizumab using the 400mg dose once every six weeks for patient convenience and also to reduce NHS resource use. The company expects that the monotherapy marketing authorisation will include an option to administer pembrolizumab at a 400mg dose once every six weeks. As such, the ERG considers includes the use of the less frequent treatment regimen for pembrolizumab in its preferred analysis, as that is likely to be how it is used in UK clinical practice. Furthermore, the ERG's clinical experts also advised that consultant oncologist appointments would be aligned to treatment cycle. The ERG ran a scenario which combined the pembrolizumab treatment regimen of 400mg once every six weeks with consultant oncologist appointments once every six weeks, which resulted in a substantial reduction in the ICER. The ERG considers that a key benefit of pembrolizumab is around the reduction in the need for frequent treatment resulting in decreased patient burden and NHS resource use savings. However, the ERG considers that the strength of the evidence for pembrolizumab remains around the comparison with SoC/CAPOX, as uncertainties still remain for the comparison with panitumumab and cetuximab combination treatments.

As mentioned previously, in KEYNOTE-177 approximately 70% of patients received bevacizumab combination treatment, which is not recommend in the NHS.[41] The company assumed that costs for patients who received bevacizumab combination treatment would be reflective of cetuximab combination treatment. However, cetuximab combination treatment is only recommend in the NHS for patients with RAS-wildtype mCRC. As such, for the ERG's preferred ITT and RAS wildtype analysis (population A and B),which focuses only on the comparison with FOLFOX and FOLFIRI (SoC), considers that a scenario exploring only including FOLFOX and FOLFIRI costs is important to highlight that SoC treatment costs for the company base case are higher than may be incurred in UK clinical practice. Using only FOLFOX and FOLFIRI costs in a scenario analysis substantially reduced the costs of SoC and as such increased the ICER, resulting in a conservative estimate of the cost effectiveness of pembrolizumab.

Another key issue with the costs used in the model, is the assumption of time on treatment (ToT) equal to PFS for the non-trial comparators, CAPOX and panitumumab combination treatment. Mean ToT for CAPOX and panitumumab is substantially longer compared with pembrolizumab and SoC, which results in inflated treatment costs. In TA439, mean treatment duration for panitumumab

combination treatment was estimated to be approximately nine months, which is shorter than the company's estimated mean treatment duration of 18.5 months based on ToT equal to PFS.[13] As such, the ERG considers that a more appropriate assumption for ToT for non-trial comparators is to assume it is equal to KEYNOTE-177 ToT for SoC (estimated to be approximately [redacted] months), which is closer to the estimates in TA439 for panitumumab combination treatment.

Subsequent treatment costs for patients with progressed disease in the company's base case was split between FOLFIRI and cetuximab + FOLFIRI treatments. NICE guidance does not recommend cetuximab for use as a monotherapy or in combination therapies as second line treatment for mCRC, thus the ERG considers that second line treatment should only reflect FOLFOX and FOLFIRI, but changing this assumption has minimal impact on the ICERs.

7 End of Life

The company has not made a case for pembrolizumab to be considered as an end-of-life treatment, which the ERG considers is appropriate.

8 References

1. NICE. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency - Final scope. 2020. Available from: https://www.nice.org.uk/guidance/gid-ta10420/documents/final-scope. Date accessed: 20 Oct 2020.
2. Merck Sharp & Dohme Limited. KEYNOTE-177 Clinical Study Report. 2020.
3. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. *Gastroenterology Res* 2018; **11**: 264-73.
4. Tidy C. Colorectal cancer. 2020. Available from: https://patient.info/doctor/colorectal-cancer. Date accessed: 21 Oct 2020.
5. Cancer.org. What is colorectal cancer? 2020. Available from: https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html. Date accessed: 5 Nov 2020.
6. Zlobec I, Lugli A. Prognostic and predictive factors in colorectal cancer. *Postgrad Med J* 2008; **84**: 403-11.
7. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. *Curr Treat Options Oncol* 2015; **16**: 30.
8. Nojadeh JN, Behrouz Sharif S, Sakhinia E. Microsatellite instability in colorectal cancer. *EXCLI J* 2018; **17**: 159-68.
9. Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2014; **20**: 5322-30.
10. Clarke CN, Kopetz ES. BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies. *J Gastrointest Oncol* 2015; **6**: 660-7.
11. Garcia-Foncillas J, Sunakawa Y, Aderka D, Wainberg Z, Ronga P, Witzler P, et al. Distinguishing Features of Cetuximab and Panitumumab in Colorectal Cancer and Other Solid Tumors. *Front Oncol* 2019; **9**: 849.
12. NICE. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer [TA61]. 2003. Available from: https://www.nice.org.uk/Guidance/TA61. Date accessed: 19 Oct 2020.
13. NICE. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer ID794 - Committee papers. 2015. Available from: https://www.nice.org.uk/guidance/ta439/documents/committee-papers. Date accessed: 19 Oct 2020.
14. NICE. Molecular testing strategies for Lynch syndrome in people with colorectal cancer [DG27]. 2017. Available from: https://www.nice.org.uk/guidance/dg27. Date accessed: 30 Oct 2020.
15. European Medicine Agency (EMA). Keytruda. 2020. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-1#:~:text=Opinion-,Opinion,is%20Merck%20Sharp%20%26%20Dohme%20B.V. Date accessed: 4 January 2021.
16. Merck Sharp & Dohme Limited. KEYTRUDA 25 mg/mL concentrate for solution for infusion. Draft Summary of Product Characteristics. 2020.
17. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011; **105**: 58-64.

18. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; **23**: 4866-75.
19. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. *Int J Cancer* 2011; **128**: 682-90.
20. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008; **26**: 3523-9.
21. Porschen R, Arkenau HT, Kubicka S, Greil R, Seufferlein T, Freier W, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin Oncol* 2007; **25**: 4217-23.
22. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-42.
23. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013-9.
24. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2008; **27**: 663-71.
25. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; **28**: 4697-705.
26. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-17.
27. Qin S, Li J, Wang L, Xu J, Cheng Y, Bai Y, et al. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. *J Clin Oncol* 2018; **36**: 3031-9.
28. Xu S, Sak A, Erol YB. Systemic therapy as first-Line treatment for patients with metastatic colorectal cancer: a systematic review and network meta-analysis of randomized clinical trials. 2020. Available from: https://www.researchsquare.com/article/rs-12790/v1. Date accessed: 3 Nov 2020.
29. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. *Stat Biopharm Res* 2013; **5**: 311-20.
30. Passardi A, Nanni O, Tassinari D, Turci D, Cavanna L, Fontana A, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. *Ann Oncol* 2015; **26**: 1201-7.
31. Passardi A, Scarpi E, Cavanna L, Fontana A, Vertogen B, Ruscelli S, et al. Effectiveness of bevacizumab added to gold standard chemotherapy in metastatic colorectal cancer (mCRC): Final results from the Itaca randomized clinical trial. *J Clin Oncol.* 2013; **31**: 3517.
32. Bokemeyer C, Kohne CH, Ciardiello F, Lenz HJ, Heinemann V, Klinkhardt U, et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. *European journal of cancer* 2015; **51**: 1243-52.
33. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. 2014. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf. Date accessed: 13 Nov 2020.

34. Electronic Medicines Compendium (eMC). Vectibix 20 mg/mL concentrate for solution for infusion. 2020. Available from: https://www.medicines.org.uk/emc/product/6178. Date accessed: 21 Nov 2020.
35. Electronic Medicines Compendium (eMC). Erbitux 5 mg/mL solution for infusion. 2020. Available from: https://www.medicines.org.uk/emc/product/317. Date accessed: 21 Nov 2020.
36. Jansen JP. Network meta-analysis of survival data with fractional polynomials. *BMC Med Res Methodol* 2011; **11**: 61.
37. J.N C, J C, S O, J.A T, K.L R, A T, et al. Cost-effectiveness of immune checkpoint inhibitors for microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer. *Cancer* 2019; **15**: 278-89.
38. NHS. 2018/19 National Cost Collection data. 2019. Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819. Date accessed.
39. MIMS. Monthly Index of Medical Specialties (MIMS). Available at: https://www.mims.co.uk/.
40. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. 2018.
41. NICE. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer [TA212]. 2010. Available from: https://www.nice.org.uk/guidance/TA212. Date accessed.
42. NICE. NICE Pathways - Managing metastatic colorectal cancer - First-line biological therapy. 2020. Available from: https://pathways.nice.org.uk/pathways/colorectal-cancer/managing-metastatic-colorectal-cancer#content=view-node%3Anodes-first-line-biological-therapy. Date accessed.
43. NICE. Guide to the methods of technology appraisal [PMG9]. 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. Date accessed.
44. (DSU) DSU. NICE DSU Technical Support Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. 2013. Available from: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/. Date accessed.
45. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**: 509-18.
46. Bennett L, Zhao Z, Barber B, Zhou X, Peeters M, Zhang J, et al. Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. *Br J Cancer* 2011; **105**: 1495-502.
47. Curtis LAaB, Amanda. Unit Costs of Health and Social Care 2019. 2019.
48. Farkkila N, Torvinen S, Sintonen H, Saarto T, Jarvinen H, Hanninen J, et al. Costs of colorectal cancer in different states of the disease. *Acta Oncol* 2015; **54**: 454-62.
49. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med* 2015; **29**: 899-907.
50. NICE. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy[TA242]. 2012. Available from: https://www.nice.org.uk/guidance/ta242. Date accessed.
51. Tougeron D, Sueur B, Zaanan A, de la Fouchardiere C, Sefrioui D, Lecomte T, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: An AGEO retrospective multicenter study. *Int J Cancer* 2020; **147**: 285-96.

9 Appendices

9.1 Baseline characteristics

Table 67. Summary of population baseline characteristics for KEYNOTE-177 (adapted from CS, Table 10, page 29)

Characteristic	Pembrolizumab (N = 153) n (%)	SoC (N = 154) n (%)	Total (N = 307) n (%)
Gender			
Male	71 (46.4)	82 (53.2)	153 (49.8)
Female	82 (53.6)	72 (46.8)	154 (50.2)
Age			
<65	80 (52.3)	83 (53.9)	163 (53.1)
≥65	73 (47.7)	71 (46.1)	144 (46.9)
<70	105 (68.6)	112 (72.7)	217 (70.7)
≥70	48 (31.4)	42 (27.3)	90 (29.3)
Mean (SD)	61.9 (14.9)	60.6 (14.8)	61.2 (14.8)
Median (range)	63.0 (24 to 93)	62.5 (26 to 90)	63.0 (24 to 93)
Race			
Asian	24 (15.7)	26 (16.9)	50 (16.3)
Black or African American	9 (5.9)	5 (3.2)	14 (4.6)
White	113 (73.9)	116 (75.3)	229 (74.6)
Missing	7 (4.6)	7 (4.5)	14 (4.6)
Ethnicity			
Hispanic or Latino	11 (7.2)	10 (6.5)	21 (6.8)
Not Hispanic or Latino	128 (83.7)	131 (85.1)	259 (84.4)
Not reported	10 (6.5)	10 (6.5)	20 (6.5)
Unknown	2 (1.3)	2 (1.3)	4 (1.3)

Missing	2 (1.3)	1 (0.6)	3 (1.0)
Geographic region			
Asia	22 (14.4)	26 (16.9)	48 (15.6)
Western Europe/North America	109 (71.2)	113 (73.4)	222 (72.3)
Rest of World	22 (14.4)	15 (9.7)	37 (12.1)
ECOG			
0	75 (49.0)	84 (54.5)	159 (51.8)
1	78 (51.0)	70 (45.5)	148 (48.2)
Site of primary tumour[a]			
Right	102 (66.7)	107 (69.5)	209 (68.1)
Left	46 (30.1)	42 (27.3)	88 (28.7)
Other	4 (2.6)	5 (3.2)	9 (2.9)
Missing	1 (0.7)	0 (0.0)	1 (0.3)
Metastases location			
Hepatic or pulmonary	86 (56.2)	73 (47.4)	159 (51.8)
Other metastases	67 (43.8)	81 (52.6)	148 (48.2)
Diagnosed stage			
Recurrent	80 (52.3)	74 (48.1)	154 (50.2)
Newly diagnosed stage	73 (47.7)	80 (51.9)	153 (49.8)
Prior systemic therapy			
Adjuvant only	33 (21.6)	37 (24.0)	70 (22.8)
Neoadjuvant only	2 (1.3)	3 (1.9)	5 (1.6)
Neoadjuvant and adjuvant	3 (2.0)	5 (3.2)	8 (2.6)
None	115 (75.2)	109 (70.8)	224 (73.0)
Mutation status[b]			
BRAF/KRAS/NRAS all wild type	34 (22.2)	35 (22.7)	69 (22.5)

KRAS/NRAS mutant and BRAF V600E not mutant	33 (21.6)	38 (24.7)	71 (23.1)
BRAF V600E mutant and KRAS/NRAS not mutant	34 (22.2)	40 (26.0)	74 (24.1)
BRAF V600E and KRAS/NRAS mutant	0 (0.0)	3 (1.9)	3 (1.0)
Other	52 (34.0)	38 (24.7)	90 (29.3)
MSI-High status[c]			
Positive	153 (100.0)	153 (99.4)	306 (99.7)
Negative	0 (0.0)	1 (0.6)	1 (0.
Oncologic surgery with curative intent[d]			
Received surgery	14 (9.2)	13 (8.4)	27 (8.8)
Did not receive surgery	139 (90.8)	141 (91.6)	280 (91.2)

[a] If there were primary tumours in both left side and right side, the subject would be categorized into Other.

[b] When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other.

[c] MSI status by PCR test or IHC test at local site laboratory.

[d] Oncologic surgery that was with curative intent and occurred after subject randomisation and before initiation of new anti-cancer therapy, crossover treatment and second course treatment.

Database Cutoff Date: 19FEB2020.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; MSI, microsatellite instability; PCR, polymerase chain reaction; SD, standard deviation; SoC, standard of care.

9.2 Pre-specified subgroup analyses

Figure 16. Analysis of progression-free survival by subgroup factors by central imaging vendor per RECIST 1.1 (ITT population), based on Cox regression model with Efron's method of tie handling with treatment as a covariate (database cut-off 19 Feb 2020; reproduced from CS, Figure 10, page 63)

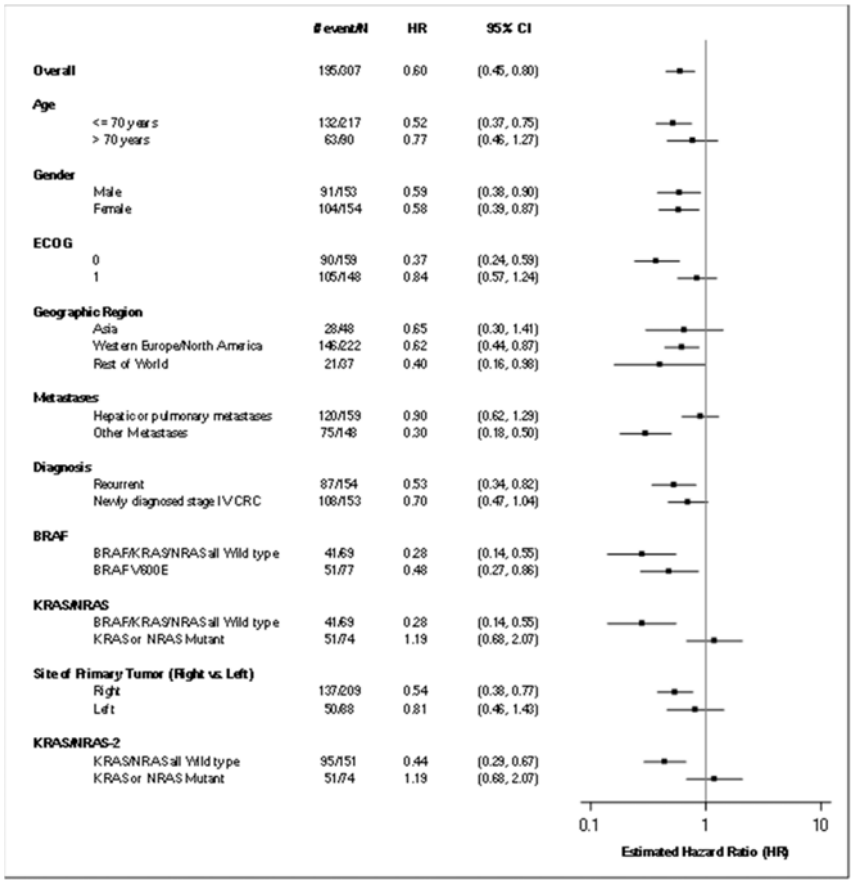
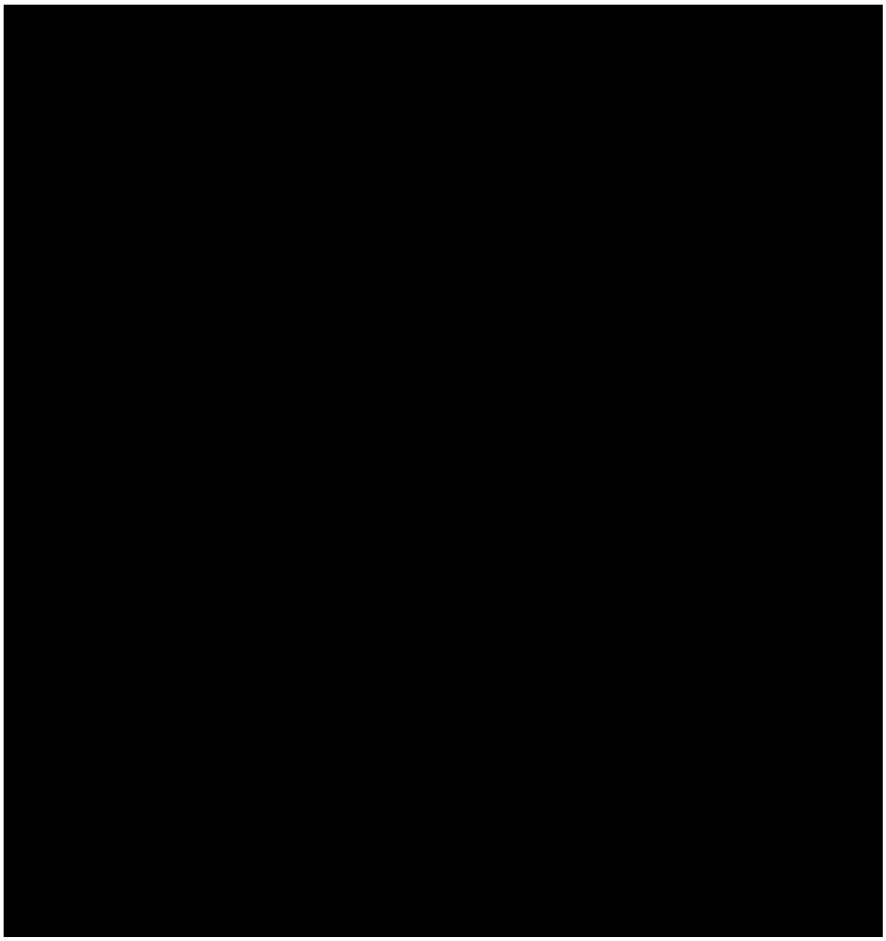


Figure 17. Analysis of overall survival by subgroup factors (ITT population), based on Cox regression model with Efron's method of tie handling with treatment as a covariate, database cut-off date 19 Feb 2020 (reproduced from CS, Figure 5, page 48)



9.3 Fractional polynomial NMA: ERG validation for comparators versus standard of care

Table 68. Time-varying hazard ratios for PFS at selected follow-up times using standard of care as the baseline treatment (second order FP model [p1 = 0, p2 = 0]) (adapted from CS, Appendix M, Table 191, page 627)

Month	HR versus SoC (95% CrI)[a]					
	CAPOX Company	CAPOX ERG	Panitumumab + FOLFOX Company	Panitumumab + FOLFOX ERG	Pembrolizumab Company	Pembrolizumab ERG
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] HR >1 favours SoC, HR <1 favours comparator.

Abbreviations: CAPOX, capecitabine plus oxaliplatin; CS, company submission; CrI, credible interval; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; HR, hazard ratio; PFS, progression-free survival; SoC, standard of care.

Figure 18. Estimated treatment hazard ratio over time for PFS and treatments relative to SoC (second order FP model; p1=0, p2=0)) based on the ITT population (reproduced from CS, Appendix M, Figure 97, page 626)

Figure 19. ERG's validation of estimated treatment hazard ratio over time for PFS and treatments relative to SoC (second order FP model; p1=0, p2=0)) based on the ITT population

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.'* (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 17 December** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Rationale for MSD not providing the requested subgroup analyses for RAS wild-type and non RAS wild-type subgroups from KEYNOTE-177

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 22, section 1.4, Table 3, second -to-last row, second column: The text states that "The company declined to provide the requested analyses." with regard to provision of cost-effectiveness analyses for RAS wild-type and non RAS wild-type subgroups from KEYNOTE-177 and update the FP NMA to generate relative estimates of treatment effect for pembrolizumab versus the listed comparators in the NICE final scope for the relevant subgroups.	The text should be amended to: "The company declined to provide the requested analyses and provided statistical rationale for why conducting these analyses would be inappropriate."	The text as it currently is implies MSD did not provide rationale for not providing the requested analyses, while in fact MSD provided rationale for why doing these analyses would not be appropriate.	Not a factual inaccuracy – no change required. The ERG considers that the company's rationale for not carrying out the requested NMA is reported in full in the main body of the Evidence Review Group's (ERG's) report (Section 3.5.1.2). In Section 3.5.1.2, the ERG agrees with the company's comments around the limitations of *post hoc* subgroup analyses but comments that the ERG's proposed network would be more relevant to the decision problem than that presented in the CS.
Page 112 after Table 46 lines 91 – 94, the ERG states "the ERG requested subgroup analysis for the RAS wild-type population and at the clarification stage requested that utilities values for patients with RAS wild-type mCRC were explored in a scenario. However, the company declined to provide the analyses by RAS mutation status".			

Issue 2 Marketing authorisation for pembrolizumab for the treatment of colorectal cancer.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 38, section 2.3.2: The text states that "The expected date of the opinion from the Committee for Human Medicinal Products is February 2021. The company anticipates the marketing authorisation for the UK to be the first-line treatment of unresectable or metastatic MSI-H or dMMR CRC in adults."	The text should be amended to: "On 10-DEC-2020 the Committee for Medicinal Products for Human Use adopted a positive opinion recommending a change to the terms of the marketing authorisation for pembrolizumab to include treatment or mCRC. The company anticipates the marketing authorisation for the UK to be the first-line treatment of metastatic MSI-H or dMMR colorectal cancer in adults."	Positive CHMP opinion for pembrolizumab in this indication was published on 11-DEC-2020. The CHMP adopted the new indication as follows: • Keytruda 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. As this indication wording has now been published by the CHMP, it also does not need to marked as confidential.	The ERG has updated the text and reference as suggested by the company. The text now reads: In December 2020, the Committee for Medicinal Products for Human Use adopted a positive opinion on the use of pembrolizumab as a monotherapy for the first-line treatment of unresectable or metastatic MSI-H or dMMR CRC in adults.

Issue 3 Publication of the KEYNOTE-177 study results in a peer-review journal.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 47, section 3.2: The text states that "The ERG notes that the results for KEYNOTE-177 have been made public through conference abstracts but are yet to be published in full in a peer-	The text should be amended to: "The results for KEYNOTE-177 have been made public through conference abstracts and have been published in full in a peer-reviewed journal."	The results for the KEYNOTE-177 study have been very recently published in the New England Journal of Medicine.	The ERG thanks the company for highlighting the recent publication in the NEJM. The ERG does not have access to the article, which has not been supplied by the company, and is therefore unable to validate that the data presented in the

reviewed journal."			paper are the same as those reported in the CS. The ERG has updated the text to read: The ERG notes that the results for KEYNOTE-177 have been made public through conference abstracts but, at the time of writing, are yet to be published in full in a peer-reviewed journal

Issue 4 KEYNOTE-177 patient withdrawal numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 49, section 3.2, Table 15, Dropouts: The text states that "Low rate of patient withdrawal across KEYNOTE-177 (11 people [3.6%]), but a larger proportion withdrew from the SoC group (1/153 [0.7%] with pembrolizumab versus 10/154 [6.5%] with SoC)."	The text should be amended to: "Low rate of patient withdrawal across KEYNOTE-177 (12 people [4.1%]), but a larger proportion withdrew from the SoC group (1/153 [0.7%] with pembrolizumab versus 11/154 [7.1%] with SoC)."	These are the corrected numbers as provided in B.2.4, Table 15, page 43, and Appendix D.1.2 (Figure 37, page 336).	The ERG has updated the text as suggested by the company.

Issue 5 KEYNOTE-177 subgroup of people not receiving bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 57: "The company selected 52 people	The text should be amended to: "The subgroup consisted of 52 people who	The current wording implies that selection of these patients was done post-hoc and could potentially	The ERG has amended the text to read:

allocated to pembrolizumab to form the pembrolizumab group not receiving bevacizumab, citing that they chose those participants they deemed would be most likely to have received bevacizumab."	were randomised to the pembrolizumab treatment arm, and who would not have received bevacizumab if they had been randomised to the SoC arm (the chemotherapy to be used [should the patient be randomised to the SoC arm] was chosen before randomisation).	be biased, whereas the most appropriate therapy in the SoC arm for these patients to receive was determined immediately prior to randomisation to the treatment or experimental arm (see section B.2.3 page 18 of the company submission for details).	The company selected 52 people allocated to pembrolizumab to form the pembrolizumab group not receiving bevacizumab, indicating that those selected were people who would not have received bevacizumab if they had been randomised to SoC (chemotherapy regimen for SoC was specified before randomisation).

Issue 6 KEYNOTE-177 most frequent treatment-related AEs

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 66, section 3.3.5: List following "The 10 most frequently experienced treatment-related AEs in the pembrolizumab group were:"	The following has been omitted as the 5th/6th most frequent treatment-related AE: "increased aspartate aminotransferase (11.1%)"	This has been omitted as one of the 10 most frequently experienced treatment-related AEs in the pembrolizumab group of KEYNOTE-177, as shown in Appendix F Table 30 of the submission.	The ERG has updated the text as suggested by the company.
Page 67, section 3.3.5: List following "the AE profile in the SoC group differed from that of pembrolizumab, with the 10 most commonly occurring AEs being:"	The following item should be removed from the list: "increased aspartate aminotransferase (55.2%)"	The proportion of patients who experienced this as a treatment-related AE is 4.9%, as shown in Appendix F Table 30 of the company submission.	The ERG has updated the text as suggested by the company.

Issue 7 Provision of baseline characteristics for the RAS wild-type subgroup from KEYNOTE-177

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 71: The text states that "baseline characteristics for the RAS wild-type subgroup from KEYNOTE-177 are not available at this time"	This text should be deleted.	Baseline characteristics for the RAS wild-type subgroup from KEYNOTE-177 study were provided in MSD's responses to the ERG's clarification questions, in Table 5 in response to question A8.	The ERG thanks the company for highlighting the factual error and has removed the text suggested by the company.

Issue 8 Exploratory Analysis beyond Maximum 35 cycles

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 23 Table 5, the ERG states "in KEYNOTE-177, treatment with pembrolizumab was restricted to 35-cycles, which has been implemented in the cost-effectiveness analysis. However, the draft SmPC states that it can be given until disease progression or unacceptable toxicity". As a result the ERG performed a scenario analysis looking at the cost effectiveness of pembrolizumab beyond 35 cycles.	Please note, in KEYNOTE-177, patients were to continue pembrolizumab until progressive disease, unacceptable adverse events or intercurrent illness preventing further administration of treatment, the subject has a confirmed positive serum pregnancy test or a maximum of 35 cycles of uninterrupted treatment with pembrolizumab. As is the case of all pembrolizumab indications, Pembrolizumab should be stopped at 2 years of uninterrupted treatment or earlier if disease progresses because the clinical- and cost-effectiveness evidence was limited to 2 years of treatment. An example of this in previous TAs can be seen in TA557 here.	Clarification; although SmPC states until disease progression, there is a maximum cycle length to be adhered to based on the trial.	Not a factual inaccuracy – no change required.

Issue 9 Adverse events disutilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG states "the company's used utility values that do not distinguish between patients with and without an AE, that the impact of AEs is inherently included in the overall utility value".	This statement is incorrect, as stated in the submission separate utility values were estimated for pre-progression patients not experiencing a Grade 3+ AE, pre-progression patients experiencing a Grade 3+ AE and progressed patients for the pembrolizumab and SoC arm. Also, the ERG report states from line 47 for adverse events, decrements were estimated based on the difference between progression-free utility values with and without status any serious adverse events (grade 3+) present.	The report states from line 47 for adverse events, decrements were estimated based on the difference between progression-free utility values with and without status any serious adverse events (grade 3+) present.	Not a factual inaccuracy – no change required. The company did present separate utility values with and without the impact of AEs on pre-progression utility, but the company's base case analysis used the overall progression free utility value for each treatment arm (please refer to Table 60 of the company submission).

Issue 10 ICER terminology

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 111, Table 45	The text dominant in the table implies panitumumab + FOLFOX is dominant versus pembrolizumab. The text should read Dominated as it is in reference to the comparator.	The term 'Dominant' implies the comparator dominates pembrolizumab due to the way the table is formatted. It should read panitumumab + FOLFOX is dominated.	The ERG thanks the company for highlighting the factual error. This has been corrected in the ERG report.

Pembrolizumab vs.	Company base case	Pooled utility value scenario	Pooled progression-free AE utility value in first cycle
Standard of Care	7,250	7,762	7,615
CAPOX	27,474	29,432	28,869

Panitumumab + mFOLFOX6	Dominant	Dominant	Dominant		
Abbreviations: AE, adverse event; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid plus fluorouracil plus irinotecan; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin					

Issue 11 Incorrect ICER Values

ERG response – The ERG thanks the company for highlighting the factual errors, these have been corrected in the ERG report.

Description of problem	**Description of proposed amendment**	**Justification for amendment**
Page 120 line 239, the statement "the ICER changing from £7,250 to £4,043 for the comparison with SoC and from £27,474 to £25,275 for the comparison with CAPOX".	The values stated are incorrect, the statement should read, the ICER changing from £7,250 to £4,037 for the comparison with SoC and from £27,474 to £25,275 for the comparison with CAPOX	ICER values have been incorrectly stated. Amended figures have been highlighted in red font.

Page 125 Tables 60

Table 1. Company's PSA results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	£167,456	4.212	2.590	-	-	-	-
Pembrolizumab	[redacted]	7.022	4.274	£18,199	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table should read as below as incremental costs for panitumumab + FOLFOX incorrect

Table 2. Company's PSA results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-£43,910	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Pages 84-85, tables 29 – 31. Figures within the table are incorrect.

Table 3. Company's base case results versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Standard of Care	104,368	3.782	2.389	-	-	-	-
Pembrolizumab	[redacted]	6.927	4.250	£13,497	3.145	1.862	£7,250
Probabilistic results							
Standard of Care	£105,346	3.889	2.416	-	-	-	-
Pembrolizumab	[redacted]	7.022	4.274	£18,199	3.133	1.858	£9,795
Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio							

Table should read

Table 4. Company's base case results versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£13,497	3.145	1.862	£7,250
Probabilistic results							
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£18,199	3.133	1.858	£9,795
Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio							

Table 5. Company's base case results versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CAPOX	66,885	3.782	2.395	-	-	-	-
Pembrolizumab	[redacted]	6.927	4.250	£50,968	3.145	1.855	£27,474
Probabilistic results							
CAPOX	£67,726	3.889	2.423	-	-	-	-
Pembrolizumab	[redacted]	7.022	4.274	£55,820	3.133	1.852	£30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 6. Company's base case results versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£50,968	3.145	1.855	£27,474
Probabilistic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£55,820	3.133	1.852	£30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 7. Company's base case results versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
mFOLFOX6 + panitumumab	166,171	4.102	2.562	-	-	-	-
Pembrolizumab	[redacted]	6.927	4.250	-£48,317	3.145	1.688	Dominant
Probabilistic results							
Panitumumab + mFOLFOX6	£167,456	4.212	2.590	-	-	-	-
Pembrolizumab	[redacted]	7.022	4.274	£18,199	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 8. Company's base case results versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-£48,317	2.825	1.688	Dominant
Probabilistic results							
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-£43,910	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

ERG response – The ERG thanks the company for clarifying the CIC marking for the cost-effectiveness results, as this is different to the marking presented in the company submission and clarification documents. The ERG report has been amended to reflect the CIC marking advised by the company in the below tables.

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th></tr>
<tr><td>Tables 29-31</td><td>Total Costs for comparators, Total LYG and QALYs should be marked commercial in confidence. Only increments to be shown as the discount can be back-calculated.</td><td>
Table 9. Company's base case results versus standard of care
<table>
<tr><th>Interventions</th><th>Total Costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="8">Deterministic results</td></tr>
<tr><td>Standard of Care</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Pembrolizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£13,497</td><td>3.145</td><td>1.862</td><td>£7,250</td></tr>
<tr><td colspan="8">Probabilistic results</td></tr>
<tr><td>Standard of Care</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Pembrolizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£18,199</td><td>3.133</td><td>1.858</td><td>£9,795</td></tr>
</table>
</td></tr>
</table>

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 10. Company's base case results versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£50,968	3.145	1.855	£27,474
Probabilistic results							
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£55,820	3.133	1.852	£30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 11. Company's base case results versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
mFOLFOX6 + panitumumab	[redacted]	[redacted]	[redacted]	-	-	-	-

Pembrolizumab	[redacted]	[redacted]	[redacted]	-£48,317	3.145	1.688	Dominant
Probabilistic results							
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£18,199	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Tables 54 - 57

Table 12. Company's base case deterministic results: pembrolizumab versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£13,497	3.145	1.862	£7,250

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 13. Company's base case deterministic results: pembrolizumab versus CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£50,968	3.145	1.855	£27,474

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER,

incremental cost effectiveness ratio

Table 14. Company's base case deterministic results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-£48,317	2.825	1.688	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 15. Company's base case deterministic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	37,472	-0.01	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	50,968	1.86	27,379
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	48,317	-1.68	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Tables 58-61

Table 16. Company's PSA results: pembrolizumab versus standard of care

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£18,199	3.133	1.858	£9,795

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 17. Company's PSA results: pembrolizumab versus vs CAPOX

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	£55,820	3.133	1.852	£30,143

Abbreviations: CAPOX, capecitabine plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 18. Company's PSA results: pembrolizumab versus panitumumab + mFOLFOX6

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	-	-	-	-

Pembrolizumab	[redacted]	[redacted]	[redacted]	£18,199	2.81	1.684	Dominant

Abbreviations: mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin; LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 19. Company's base case probabilistic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	37,620	-0.006	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	18,199	1.858	9,795
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	43,910	-1.684	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 20. Results of the ERG's scenario analyses – ITT/RAS wild-type population

	Results per patient	Pembrolizumab (1)	SoC (2)	CAPOX (3)	Panitumumab +mFOLFOX6 (RAS wild-type only) (4)	Incremental value (1-2)	(1-3)	(1-4)
0	**Company base case**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317

	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,250	27,474	Dominant
1	**Weibull distribution applied after 20-week cut-off point for TTP and PFS**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,171	50,307	-56,167
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.89	1.88	1.68
	ICER (£/QALY)					6,966	26,698	Dominant
2	**Implementation of time-to-death utility values from KEYNOTE-177**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.71	1.71	1.50
	ICER (£/QALY)					7,896	29,819	Dominant
3	**Removal of AE disutility**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.65

	ICER (£/QALY)					7,251	27,383	Dominant
4	**FOLFOX and FOLFIRI costs used for SoC**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	40,278	50,968	-48,317
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					21,636	27,474	Dominant
5	**ToT for CAPOX and panitumumab + mFOLFOX6 equal to ToT for SoC**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,497	54,180	5,330
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,250	29,205	3,158
6	**ToT for pembrolizumab equal to PFS and removal of 35-cycle stopping rule**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	137,400	17,4871	75,586
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					73,809	94,262	44,777

7	**Removal of second-line cetuximab combination treatment**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	13,911	51,383	-47,946
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					7,473	27,697	Dominant
8	**Treatment regimen and consultant outpatient appointments for pembrolizumab – 400mg once every six weeks**							
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	996	38,468	-60,817
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	1.86	1.86	1.69
	ICER (£/QALY)					535	20,736	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality adjusted life year; TTP, time to progression

Table 64

Table 21. Scenario 9 - pembrolizumab versus cetuximab combination treatment - RAS wild-type only.

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cetuximab + mFOLFOX6/FOLFIRI	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	-49,510	2.83	1.69	Dominant

Abbreviations: LYG, Life Years Gained; QALYs, Quality Adjusted Life Years; ICER, incremental cost effectiveness ratio

Table 66

Table 22. ERG's base case deterministic fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Total LYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
CAPOX	[redacted]	[redacted]	[redacted]	-	-	-
Standard of care	[redacted]	[redacted]	[redacted]	13,902	0.00	Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	41,443	1.89	21,923
Panitumumab + mFOLFOX6	[redacted]	[redacted]	[redacted]	7,675	-1.65	Dominated
Cetuximab + mFOLFOX6/FOLFIRI	[redacted]	[redacted]	[redacted]	8,191	-1.65	Dominated

Abbreviations: CAPOX, capecitabine plus oxaliplatin; mFOLFOX6, folinic acid plus fluorouracil plus oxaliplatin ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, Monday 15 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Younan Zhang
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Merck Sharp & Dohme (UK) Limited - Respondent
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: KEYNOTE-177 is the only RCT reporting data for first-line treatment of MSI-H/dMMR mCRC and includes a comparator of physician's choice	No	MSD agrees with the ERG that for the comparison with CAPOX, FOLFIRI and FOLFOX, the standard of care (SoC) group in totality from KEYNOTE-177 provides an appropriate estimate of comparative treatment effectiveness for pembrolizumab, and likely underestimates the true effect of pembrolizumab, because SoC included bevacizumab and cetuximab-combination regimens. With regard to the ERG's proposal to provide more robust estimates of progression-free survival (PFS) for pembrolizumab versus cetuximab- and panitumumab-combination treatments in those patients with RAS wild-type metastatic colorectal cancer (mCRC) by carrying out a fractional polynomial network meta-analysis (FP NMA) in the subgroup of patients with RAS wild-type mCRC, MSD do not agree that this would be more appropriate than the original NMA in all patients as this analysis will be considerably under-powered due to the low number of events in the subgroup of patients with RAS wild-type mCRC in the KEYNOTE-177 study. As described in the submission in Section B.2.4, *Sample size and power calculations*, 209 PFS events are required for the KEYNOTE-177 study to be appropriately powered for the analysis of PFS however there were only 95 PFS events in the RAS wild-type subgroup of the KEYNOTE-177 study at the time of the second interim analysis (the latest available analysis). Additionally, randomisation would be broken for treatment comparisons in these subgroups, as described in the submission in Section B.2.3, *Trial design*, no stratification of randomisation based on age, sex, or other characteristics were used in the KEYNOTE-177 study.

		It should also be noted that the PFS hazard ratio for pembrolizumab versus SoC in the RAS wild-type subgroup of the KEYNOTE-177 study (HR: 0.44) favours pembrolizumab even more than in the full ITT population (HR: 0.60). Therefore, the results of the NMA proposed by the ERG informed by the RAS wild-type subgroup of the KEYNOTE-177 study would most likely yield results that would favour pembrolizumab more strongly than the results based on the NMA presented in the company submission.
Key issue 2: Subgroup analyses based on RAS mutation status	No	The ERG has noted that: "Post hoc subgroup analyses of PFS based on those identified as having RAS mutations generated a markedly different result from other subgroups, with a change in direction of effect to favour SoC, albeit that the difference between pembrolizumab and SoC was not statistically significant (HR 1.19, 95% CI: 0.68 to 2.07). However, the ERG notes that the 95% CIs for estimates of PFS for RAS wild-type and non-RAS wild-type do not overlap and, as such, considers the results in the two subgroups unlikely to have arisen due to random chance." This issue was explored by the European Medicines Agency (EMA) in their regulatory assessment of pembrolizumab in this indication (https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0091-epar-assessment-report-variation_en.pdf) via multivariate Cox regression analysis of PFS to investigate potential covariates of prognostic interest in CRC. Two-sided p-values of <0.05 were observed for treatment by ECOG interaction and treatment by KRAS/NRAS status interaction. Multivariate Cox regression analysis was adjusted for ECOG, KRAS/NRAS status, treatment by ECOG interaction, and treatment by KRAS/NRAS status interaction. While the EMA considered that results of this analysis may suggest evidence of an interaction effect, it was recognised that this analysis was not prespecified or adjusted for multiplicity and is underpowered due to the small sample size among participants with known KRAS/NRAS mutations (N = 74), as well as the fraction of the study population (29% of participants) whose KRAS/NRAS results were either undetermined or missing, and accordingly the EMA

		approved pembrolizumab for the indication under assessment without restriction by RAS status. It is also worth noting that cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). RAS genes code for small g-proteins downstream of EGFR that are an essential component of the EGFR signalling cascade, which can acquire activating mutations in exon 2 (i.e. becoming RAS-mutant), thus isolating the pathway from the effect of EGFR and rendering EGFR inhibitors such as cetuximab and panitumumab ineffective. Pembrolizumab, however, targets the PD-1/PD-L1 signalling pathway that acts independently of the RAS pathway and so should not be affected by whether RAS is wildtype or mutated in the patient. With regard to the ERG's suggestion to carry out an FP NMA based on individual patient data (IPD) for those patients from KEYNOTE-177 identified as RAS wild-type, MSD do not agree that this would be an appropriate approach, for the reasons as described in the response to the previous key issue.
Key issue 3: Treatment regimen and resource use for pembrolizumab	No	MSD agrees with the ERG that the treatment regimen of pembrolizumab administered at a 400mg dose once every six weeks would be preferred by clinicians in clinical practice given the added convenience for patients and the reduced burden on NHS resources. MSD further agrees that aligning consultant outpatient visits to the six-weekly treatment cycle is appropriate.
Key issue 4: Duration of treatment with pembrolizumab	No	MSD appreciates that the removal of the 35-cycle stopping rule to reflect a strategy of treatment until progression or unacceptable toxicity proposed by the ERG is an illustrative scenario intended to highlight the impact of this assumption on the base-case cost-effectiveness results. However, MSD does not consider this scenario to be plausible, as it expects a 35-cycle / 2-year stopping rule to be included as part of a potential NICE recommendation, consistent with the company base case reflecting treatment

		duration in the KEYNOTE-177 study. Previous NICE recommendations of pembrolizumab across multiple oncology indications have consistently reflected similar protocol-driven stopping rules featured in the clinical trials that have provided clinical evidence base.
Key issue 5: Treatment costs for standard of care	No	The ERG notes that 70% of patients [in the SoC arm] in KEYNOTE-177 received bevacizumab-combination therapy, and they provide an alternative to the company base assumption of estimating these patients' treatment costs using the cost of cetuximab. The ERG posits that a like-for-like costing of bevacizumab as cetuximab inflates treatment costs in the SoC arm given that eligibility for cetuximab in UK clinical practice requires RAS WT mutation status, and the proportion of these patients in UK practice is estimated to be lower than 70%. In the ERG's alternative scenario, the estimation of treatment costs for patients who received bevacizumab in KEYNOTE-177 is done by replacing the cost of bevacizumab with the treatment costs of FOLFOX/FOLIRI, rather than using cetuximab. As treatment costs of FOLFOX/FOLFIRI are substantially lower cost than cetuximab, which is a branded targeted therapy, this alternative assumption increases the base-case ICER. As the ERG has noted, however, this alternative scenario does not adjust the efficacy of the SoC arm downwards to account for the less favourable efficacy of FOLFOX/FOLFIRI versus bevacizumab reported in clinical trials. MSD notes that the base-case assumption of costing bevacizumab using cetuximab treatment costs is conservative, in that it does not adjust SoC efficacy downwards in light of the significantly better OS reported for patients treated with bevacizumab versus cetuximab [1]. MSD agrees with the ERG that the net effect of the base case assumption costing bevacizumab using cetuximab costs with no associated reduction in efficacy leads to a bias that, on net, favours the SoC arm.

		[1] Innocenti F, Ou FS, Qu X, Zemla TJ, Niedzwiecki D, Tam R, et al. Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome. J Clin Oncol. 2019;37(14):1217-27.
Key issue 6: Time on treatment for non-KEYNOTE-177 comparators	No	The ERG considers that a more appropriate assumption for time on treatment for non-KEYNOTE-177 comparators is to assume it is equal to KEYNOTE-177 time on treatment for the SoC arm, whereas the base-case assumption estimated non-KEYNOTE-177 comparators' treatment costs based on an assumption of treatment to progression. MSD agrees with the ERG that its scenario sufficiently explores the uncertainty around time on treatment for comparators not evaluated in KEYNOTE-177.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
[*Not addressed in ERG report*]: Revised pembrolizumab PAS	N/A	No	MSD have recently agreed a revised PAS discount for pembrolizumab with PASLU and which is effective from February 2021 to all NHSE providers. The updated PAS discount has been changed to [redacted]%. The cost-effectiveness estimates reflecting the updated company base case following technical engagement presented below report ICERs at both the previous and revised PAS discount levels.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Revised company base case – pembrolizumab vs SoC

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost associated treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: £535 • Change from base case ICER: -£6,715
ERG preferred scenario	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment, as follows: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: £7,473 • Change from base case ICER: +£223
ERG preferred scenario	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: £6,996 • Change from base case ICER: -£284

Company's preferred base case following technical engagement	Incremental QALY's: 1.891	Incremental costs: £1,368 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: £402 • Change from base case ICER: -£6,848 ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A

Revised company base case – pembrolizumab vs CAPOX

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost of treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: £21,755 • Change from base case ICER: -£5,719
ERG preferred assumption	Comparator ToT equal to Comparator PFS	Comparator ToT equal to SoC ToT	• ICER vs SoC resulting from change: £29,205 • Change from base case ICER: +£1,731
ERG preferred assumption	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: £27,697 • Change from base case ICER: +£223
ERG preferred assumption	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: £26,698 • Change from base case ICER: -£776

Company's preferred base case following technical engagement	Incremental QALY's: 1.884	Incremental costs: £43,409 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: £23,038 • Change from base case ICER: -£4,436 ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from change: £20,360 • Change from base case ICER: -£7,114

Revised company base case – pembrolizumab vs panitumumab

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost of treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A
ERG preferred assumption	Comparator ToT equal to Comparator PFS	Comparator ToT equal to SoC ToT	• ICER vs SoC resulting from change: £3,158 • Change from base case ICER: N/A
ERG preferred assumption	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A
ERG preferred assumption	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A

Company's preferred base case following technical engagement	Incremental QALY's: 1.679	Incremental costs: -£7,674 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: Dominating • Change from base case ICER: N/A --- ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from combined changes: Dominating • Change from base case ICER: N/A

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Monday 15 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and current treatment options	
About you	
1. Your name	**Dr Kai-Keen Shiu PhD FRCP**
2. Name of organisation	**UCLH NHS Foundation Trust**
3. Job title or position	**Consultant Medical Oncologist, Gastrointestinal Oncology Service**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency? **X** a specialist in the clinical evidence base for metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency or technology? **X** other (please specify): UK Chief Investigator for the KEYNOTE 177 trial
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links**
The aim of treatment for metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To control, shrink, prevent progression of MSI-H/MMR-deficient advanced/metastatic bowel cancer and improve survival.
9. What do you consider a clinically significant treatment response? (For example, a	Tumour shrinkage of more than 30%, prolonged stabilisation of disease/non progression for more than 6 months, complete radiological responses, no relapse for more than 6 months off treatment

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?	Yes
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Standard of care 5FU based chemotherapy (including oral capecitabine) with or without Oxaliplatin, Irinotecan, Cetuximab or Panitumumab for RAS wild type mCRC, Cetuximab and Encorafenib for BRAF mutated mCRC in 2nd or 3rd line, Lonsurf for chemorefractory mCRC.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Immunotherapy not licensed/funded for MSI-H/MMR-deficient CRC in any line of therapy. There are however ASCO, ESMO and NCCN guidelines to help clinicians who have access to immunotherapy for CRC.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not yet. However I would expect all patients to be discussed at local or regional CRC MDTs.

• What impact would the technology have on the current pathway of care?	The response rate, duration of response and complete responses seen on immunotherapy will change the pathway of care/sequence of systemic therapy as well as surgical and ablative options. It represents a paradigm shift in how we look after patients with MSI-H CRC.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• No as not used in NHS unless part of named patient access programs or as compassionate use access. However current NHSE-COVID guidelines allow used of nivolumab monotherapy 'as first- line immunotherapy instead of chemotherapy for the treatment of metastatic colorectal cancer with high levels of micro-satellite instability and/or deficient mis-match repair to reduce the number of admissions and reduce the risk of neutropenia' a
• How does healthcare resource use differ between the technology and current care?	Yes
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, GI oncologists/as part of best practice via a Colorectal MDT
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None extra. Biomarker test of MMR IHC or PCR for MSI status is now standard of care test for all CRC patients – there is some heterogeneity of reflex testing and also length of time it takes to get a result which may impact patient care. However if Pembrolizumab is approved to be in first line setting I am sure all hospitals/histopathologists will do it as reflex test on all CRC patients – it would be negligent to deny a patient immunotherapy because these tests were not done.
13. Do you expect the technology to provide clinically meaningful benefits compared with current	Yes and in some patients life changing as some patient may have a durable response/remission for many years like we have seen in for example melanoma patient whom have immunotherapy. I have patients now who have achieved complete responses, long term stable disease (ie more than 2 years) and in some pathological complete response when metastatic or primary sites of disease are resected after immunotherapy.

care?	
• Do you expect the technology to increase length of life more than current care?	Yes, significantly more
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, significantly better
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only indicated in MSI-High/MMR-deficient cancer patients (currently). There is a very rare subgroup of CRC patients who are POLE mutated (<1%) who display high somatic/tumour mutation burden (higher than some MSI-H patients) so are even more likely to respond to immunotherapy but the mechanism of generating these mutations are different so is not detected using MMR or MSI-H testing. I expect very few patients to fit this category and would expect an individual application to CDF/NHSE in this scenario.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	Easier. Treatment given as a monotherapy every 3 weeks over 30mins intravenously.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Based on KEYNOTE 177 trial in first line, patients had up to 2 years/ 35 cycles of pembrolizumab then stopped. If they relapsed they could have a rechallenge of 1 year/17 cycles of Pembrolizumab. I know of no additional testing beyond confirming MSI-H/MMR-deficient status at this time to inform stop rules.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not that I know of – see ESMO Virtual 2020 presentation by Thierry Andre et al and there is an upcoming publication of the HRQoL benefits of Pembrolizumab from the KEYNOTE 177 trial – Lancet Oncology – in press.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need	Yes – the responses, duration of response and possibility to offer patients chemo free treatment and possibly chemo-free life with far less side effects than SOC chemotherapy is innovative. In addition, as some patients may go into long term remission/never relapse so will never need further lines of systemic therapy, palliative surgery or radiotherapy.

is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, as above
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as above.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are side effects which are autoimmune related that need to be recognised and treated appropriately with a cross silo multidisciplinary approach with medical specialities as we have now in melanoma and lung cancer. However, the KEYNOTE 177 trials showed immune related side effects were few with only 3% of patients getting Grade 3 Colitis or hepatitis and there were no immune suppression/neutropenic adverse events related to Pembrolizumab. Therefore overall, I think the patient's quality of life on immunotherapy is significantly better than on SOC SACT and surgery/radiotherapy. In addition, some patients will have durable responses once immunotherapy stops and may not need any further treatment for their cancer for many years or the rest of their lives.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No as we do not have access to immunotherapy for MSI-H CRC outside of clinical trials or compassionate /named patient access programs. As mentioned above the COVID NHSE 1st line Nivolumab option remains at this time. The SOC chemotherapy arm of the KEYNOTE 177 trial does reflect NHS practice except they allowed the use of Bevacizumab, and did not allow a CAPOX chemo backbone.
• If not, how could the results	This is difficult as there have been no MSI-H specific trials and little MSI-H specific RWE analyses of outcomes on

be extrapolated to the UK setting?	SOC treatment as MSI-H/MMR-d is only seen in around 5% of patients with mCRC. However, the response and survival results so far on the KEYNOTE 177 trial are so superior to trial outcomes for any other biomarker/driven subgroup in mCRC. Of note, due to COVID pandemic, NHSE is currently funding nivolumab monotherapy in treating MSI-H mCRC so there will be emerging data on RWE if there is a plan to collect patient outcomes.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate including complete responses, progression free survival, duration of response are already reported. Final Overall Survival is yet to be reported but will be collected and reported in the next few months. I also believe that more complete radiological responses will be reported as more first line Pembrolizumab patients get past 1-2 years on treatment. Of note EMA has approved 1st line Pembrolizumab for these patients based on the latest interim OS. FDA have already approved it based on PFS data. I would hope NICE would also approve this treatment, so we do not fall behind international standards of clinical practice.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, as it is clear that patient who respond/ do not progress on 1st line immunotherapy after the first 6-8 months are much less likely to progress subsequently compared to patient who had chemotherapy – see the DoR curve. We await OS, but as the PFS curve does seem to flatten out beyond 18 months I predict some patients – currently more than a third will not progress at all.
• Are there any adverse effects that were not	Not that I am aware of and would be updated in any SPC

apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As before, no prior phase 3 randomised trial in this MSI-H mCRC looking only at outcomes of SOC chemotherapy +/- Bevacizumab/Cetuximab/Panitumumab
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA439?	No
23. How do data on real-world experience compare with the trial data?	Limited as not licensed until recently in 1st line – first country is USA last year.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	I am concerned that some patients will not get MMR or MSI testing a part of their standard diagnostic work up for colorectal cancer – both in early and late stage settings, or that the results are not available in a timely manner. I would propose that if a patient's MMR status is confirmed MMR-Def/MSI-H and the clinician decides not to give immunotherapy after discussion with a patient, that is a very different scenario where the test was not done at

	all/tissue quality was not good enough/safe enough for a repeat biopsy and emergency chemotherapy had to be given. If subsequently the patient was found to have MMR-D/MSI-H cancer I do believe the patient should have access to Pembrolizumab on the NHS as the response rates and QOL benefits in last line are already demonstrated to be superior to 2nd line chemotherapy (KEYNOTE 16 and 164). This may be a moot point if 2nd line Nivolumab-Ipilimumab is approved by NICE in the future.
24b. Consider whether these issues are different from issues with current care and why.	It is different because the potential life changing benefits are so superior for patient on immunotherapy compared to SOC chemotherapy +/- Bevacizumab/Cetuximab/Panitumumab. If you get the biomarker wrong but give immunotherapy but also if you get the biomarker right but do not give (or at least not offer) immunotherapy I think this would be poor/bad practice and at worse negligent.
Topic-specific questions	
25. Are the following treatments (excluded in the company submission) relevant comparators for this population in the NHS: • Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil	Tegafur – no – rarely used Raltitrexed – no rarely used and only in very specific indication e.g. angina/MI on 5FU based chemo Capecitabine – yes relevant but efficacy of 5FU and CAP are felt by clinicians and prior trials to be generally equivalent. Only used as monotherapy if frailer patients

are not tolerated or unsuitable) • Capecitabine	
26. In NHS clinical practice, would pembrolizumab be more likely to be given as 200mg every three weeks or 400mg every six weeks?	I would recommend that we should follow the trial protocol of giving Pembrolizumab 3 weekly for at least the first 3-6 months as this ensure patient safety in terms of bloods/immune related toxicities, and that they are achieving a clinical and radiological response. However once scans confirm response/stability and bloods are ok/no significant toxicities, I would be supportive of using 6 weekly Pembrolizumab but final decision of 3 versus 6 weekly dosing should be clinically driven and/or patient preference.
27. What proportion of people with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency would you expect to also have RAS mutations?	Very difficult to gauge this as no large trial has looked at this in the MSI-High only patients. We generally expect 40-50% of patients to be RAS WT, 40% to be RAS mutant and 10% BRAF mutant in the MSS population. We do know that MSI-H CRC patients are more likely to have BRAF mutations approx. 25-30%+ which means that the proportion of RAS WT and RAS Mutant patients will be less in the MSI-H population. Of note, the KEYNOTE 177 trial did collect these KRAS/NRAS/BRAF data but is incomplete for around 25-30% of patients in both arms of the trial. Of note, the reason why this was a high percentage is the trial protocol was strict and if the site did not give the status of all 3 mutations and only one e.g. KRAS mutation then it was labelled as unknown/other.
28a. What factors would determine the choice of standard care treatment for a patient,	28a) RAS/RAF/MMR status, tumour site and burden and operability of primary and metastatic disease Patient fitness, organ function, quality of life, convenience of therapy

where multiple different treatments are an option? 28b. Would this differ based on RAS status?	Financial constraints 28b) Yes, as NICE now approve EGFR antibodies in first line for RAS WT mCRC patients we would generally offer that to patients especially for left sided primary cancers. In my clinical practice I have noted a significant proportion of MSI-H RAS WT patients are younger and have Lynch Syndrome which has a bearing on how at the MDT we discuss the treatment them both surgically and with systemic/multimodality therapy. In addition now that BRAF targeted therapy of Cetuximab and Encorafenib is now NICE approved in 2nd or 3rd line for patients with BRAF mutated MSI-H or MSS mCRC and prior cetuximab is an exclusion criteria so most clinicians would (should) not give EGFR inhibitors in first line to BRAF mutant patients – though it is allowed on the Cetuximab SPC and NICE. This must be considered as relevant in MSI-H/BRAF mutant CRC patients which form a higher percentage of MSI-H patients due to the different biology of MSI-H CRC to MSS CRC. Also, if a BRAF mutant/MSI-H patient does not receive immunotherapy their survival outcomes would revert to similar outcome to a BRAF mutant/MSS mCRC patient ie. usually less than 12-16 months.
29a. What percentage of people with mCRC in the NHS would receive a checkpoint inhibitor as a second line therapy? 29b. Are there any differences in the treatment pathway for people	29a) Currently not funded in the NHS outside of clinical trials or compassionate/named patient access programmes. I am aware that NICE are considering a company's application for use of Nivolumab and Ipilimumab in second line for MSI-H/MMR-d mCRC. 29b)This can only be narrative based on the patients I treated at UCLH on the KEYNOTE 177 trial but yes the treatment pathway has been markedly different either because patient achieve a complete response and remain in remission, or had a good enough response to go ahead with curative intent surgery. Patients who progressed on

who had pembrolizumab at first-line?	pembrolizumab did have SOC treatment but also I referred them for clinical trial of combination immunotherapies to see if that would over resistance. I would expect these pathways to continue to evolve and mature if more patients do get access to 1st line or indeed 2nd line+ immunotherapy
30. After progression on first-line treatment, would you expect a worse prognosis (i.e. quicker progression on second line treatment or death) for people: a) who received pembrolizumab at first-line b) dependant on RAS mutation status	30a: In my patients on the trial I saw no evidence of that and based on PFS2 data presented at ASCO GI Jan 2021 there does not seem to be any signal that would be the case. I also have treated patients off trial on COVID-NHSE Nivolumab and have not seen any worse treatment outcomes or prognosis after progression on Nivolumab. 30b) No evidence of any difference based on RAS mutation status. One has to be aware though that in KEYNOTE 177 patients could/would have access to 1st, second and 3rd line Bevacizumab as well as Cetuximab/Panitumumab dependant their countries where there is funding/regulatory approve. We do know that these antibodies increase response rates, extend PFS and OS. As the RAS mutant group do not benefit from EGFR antibodies and NHS do not fund Bevacizumab, immunotherapy may be the only antibody therapy which will offer them a non-chemotherapy/targeted therapeutic option. I also strongly oppose denying a RAS WT patient access to chemotherapy + Cetuximab or Panitumumab if they progressed on Pembrolizumab. There is no evidence that MSI-H status is detrimental or that prior immunotherapy as any detrimental effect on chemotherapy or EGFR antibodies. I have had patients on the trial who had Chemo + Cetuximab as first line treatment with durable benefit then crossed over to Pembrolizumab to complete response. I have also had patients who progressed on Pembrolizumab and had complete radiological/PET/CEA responses to Chemo + EGFRi.
31. Would you expect to give pembrolizumab until progression or for a limited cycle duration?	Based on KEYNOTE 177 data so far, the new standard of care would be for 2 years of Pembrolizumab then stop. I have been comfortable in counselling my patients why there is the stop for a number of reasons. Firstly I generally believe that if they have managed to get to 2 years of treatment with no progression, they are much less likely to progress (or at all). Secondly there are immune toxicities that can occur at any time during and in the long term after

	cessation of immunotherapy. For patients with Lynch Syndrome who are usually diagnosed at a much earlier age I am not sure I want them to be on lifelong immunotherapy. In summary would prefer patients are given up to two year of pembrolizumab then have a break + option of rechallenge of 1 year as per trial, rather than treat to progression and not have a rechallenge – that would save the NHS money.
30a. Would you expect treatment effect to continue after stopping treatment with pembrolizumab? 30b. Would you expect a proportion of patients to receive a lifelong benefit with pembrolizumab? Please provide an estimate of this proportion if possible.	30a) Yes I would based on significantly better ORR (including complete responses) PFS/DoR and PFS2 results compared to SOC chemotherapy from KEYNOTE 177 trial. I have seen that in my trial and non-trial patients too. 30b) Yes I would – as above, based on PFS2 data presented at ASCO GI Jan 2021, median PFS2 has not been reached in patients who had pembrolizumab first compared to 23.5 months for patients who had chemotherapy first – even though 59% of patients crossed over to some form of immunotherapy on or off the trial. Although we don't have mature OS data, as the PFS2 curves are flattening out beyond 2-3 years I would expect around 30-50% of patients will have lifelong benefit from having pembrolizumab as first line therapy.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: KEYNOTE-177 is the only RCT reporting data for first-line treatment of MSI-H/dMMR mCRC and includes a comparator of physician's choice	Correct. Note, there is an ongoing phase 3 trial in the USA of Atezolizumab immunotherapy versus Atezolizumab + FOLFOX + Bevacizumab in first line in the same patient population as KEYNOTE 177 but mature results will only be available in 3-4 years' time (NRG-GI004/SWOG-1610 trial).
Key issue 2: Subgroup analyses based on RAS mutation status	I note the ERG are keen to get extra data and analyses from the company re any variation in outcomes based on RAS status based on the PFS of subgroups/Forest Plots. I can understand their interest and I am as a clinician and scientist also very keen to know these data too but for different reasons. As there is as yet no proven biological rationale why a RAS mutant CRC would respond differently to immunotherapy, and all prior trials showed the only biomarker for response was MSI-H/MMR-def; this trial cannot answer the ERG's question to my satisfaction.

	I also do not believe that we can or should deny the potential survival and quality of life benefits of Pembrolizumab based on retrospective subgroup analyses. For example, PFS in the KRAS or NRAS mutant group is based on only 51 events out of 74 patients (out of a total of 195/307) This number of this subgroup of patients is for the size of a small phase 2 trial at best; explaining why the whiskers are long. In addition the confidence intervals cross 1 on the PFS Forest Plot so clearly some patients do benefit from Pembrolizumab more than chemotherapy arm in the trial. In addition, I do not have access to patient level data, but suspect/expect that the majority of the chemotherapy trial patients who were RAS or NRAS mutant had chemotherapy + Bevacizumab which we know from prior trials improve response rates by around 10% and PFS by 2-3 months. As NHS patients do not have access to Bevacizumab this would have to be considered, as the PFS curves would then more likely further favour Pembrolizumab over chemotherapy alone. This is an assumption of mine but again demonstrates why decisions cannot be made only small subgroups when the overall benefit for all MSI-H mCRC patients in a randomised phase 3 trial which clearly favours Pembrolizumab as 1st line therapy. The reasons I personally want to know these data is to help us inform how to design future trials where we can build in pre-specified analyses so we can power trials with sufficient statistical power to determine any differences based on molecular or clinically relevant subgroups. If pembrolizumab is approved and used in first line in the UK and globally, RWE/Phase 4 data may reveal nuances which will change clinical practice for clinical or molecular subgroups of patients but thus far all trial data from earlier studies of immunotherapy (albeit non-randomised and in pre chemotherapy treated patients) do not support this.
Key issue 3: Treatment	A major advantage of giving Pembrolizumab is that is given 3 weekly and only over 30mins iv compared

regimen and resource use for pembrolizumab	to FOLFOX/FOLFIRI/CAPOX so there will be less hospital visits and time spent on chemo day units. As the treatment is less toxic and patient more likely to respond to treatment there will be less treatment or cancer related admissions on immunotherapy. Lastly if some of these patients have durable responses/remissions they may not need any subsequent lines of treatment for mCRC or need end of life care for mCRC.
Key issue 4: Duration of treatment with pembrolizumab	Patient should be treated up to 2 years as per trial protocol and only stop if there is disease progression, unacceptable toxicity or patient choice.
Key issue 5: Treatment costs for standard of care	Answered I think in my answer to Key Issue 3
Key issue 6: Time on treatment for non-KEYNOTE-177 comparators	DoR for patients who respond to Pembrolizumab is superior to any prior trials of chemotherapy based treatment for mCRC regardless of MSI/RAS/RAF status
Are there any important issues that have been missed in ERG report?	As above but I repeat this here as I am concerned/would like clarification that RAS WT patients who receive Pembrolizumab first are not denied NHS funded Chemotherapy + Cetuximab or Panitumumab if they progressed? This came up I believe in the cost comparators. My own personal experience of patients on KEYNOTE 177 trial and for patients off trial is they do benefit from EGFR inhibitors, there is no biological rationale to explain why immunotherapy would make EGFR inhibitors work less well (or indeed chemotherapy) – which is reflected so far in the PFS2 trial data.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- The results of the KEYNOTE 177 trial show the importance of biomarker driven trials and represent a new standard care for these patients with MSI-High/MMR-deficient mCRC whose outcomes are otherwise poor on chemotherapy/surgically based treatment and who will die from their disease.
- I do not support stratification or potential denial of access to 1st line Pembrolizumab based on RAS status as the trial was not designed or powered that way; nor are there statistically significantly worse PFS outcomes in any of the clinical or molecular subgroups reported by the trial.
- I predict a proportion of patients – at least 30-50% will achieve lifelong benefit from Pembrolizumab with significantly better quality and productive lives when on it as well as off/after completion of immunotherapy; we await final OS results in the next few months.
- I believe the biomarker for selection, survival and quality of life benefits of Pembrolizumab in 1st line treatment for MSI-H mCRC are superior to approved PD-1 inhibitor (monotherapy or combination) for biomarker or non- biomarker selected treated cancers e.g. PDL1 +ve lung cancer or melanoma/HCC respectively, and that should be a consideration when deciding whether NICE will fund this treatment.
- It is critical that if Pembrolizumab/immunotherapy is approved in the UK that patients must have their MMR/MSI test done if diagnosed with bowel cancer – testing must be made mandatory - so they are not denied such potentially life changing treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

14

+

Clinical expert statement & technical engagement response form

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that

cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 15 February 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and current treatment options	
About you	
1. Your name	**Mark Saunders**
2. Name of organisation	**The Christie, Manchester, UK**
3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency? ☐ a specialist in the clinical evidence base for metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it

encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
The aim of treatment for metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve a patient's progression free and overall survival with the best quality of life during and after treatment. If the response is profound and a cCR is achieved, then the patient may be cured.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	I would say a significant treatment response is one that improves a patient's symptoms and may allow inoperable disease to become operable. The degree of response is less important compared to PFS/OS.
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?	Yes. These patients represent a small cohort of all patients with MCRC (<5%) and they have a worse prognosis than those with pMMR/MSS. Results from the drug under consideration (and other checkpoint inhibitors) provide a novel therapy for these patients to improve their outcome.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Conventional 1st line chemotherapy with FOLFOX/FOLFIRI/FOLFOXIRI Patients with wt RAS / BRAF / left-sided colon tumours may also have an EGFR inhibitor
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE give general guidelines but until this evaluation, none are available specifically for MSI-H patients in the UK.
• Is the pathway of care well defined? Does it vary or are there differences of opinion	It is well defined. You either do or don't have MSI-H/dMMR

between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Massive. The survival benefits are significantly greater and the toxicity of the treatment considerably lower. A step-change with large and increasing divergence of the survival curves over at least a two-year period.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Presently due to COVID, we can give nivolumab for these patients. I understand this is a temporary arrangement and this funding is likely to cease in the coming months. If NICE give positive guidance to allow funding of pembrolizumab, then this drug will be used for these patients. We then have the problem that now we can use a CPI for any line of treatment. This NICE guidance is assessing only 1st line therapy. So, we could lose out and patients will be disadvantaged. KEYNOTE177 allowed cross-over and these patients gained advantage from the CPI. So pembrolizumab is active 2nd line and this must be taken into consideration now.
• How does healthcare resource use differ between the technology and current care?	Clinicians are likely to opt for pembrolizumab rather than conventional chemotherapy due to the better survival benefits and also reduced toxicity profile. If it is given 6 weekly, then clinic and treatment time will be reduced which will be beneficial to all parties (hospitals / patients / clinicians)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Within units that already specialise in the administration of chemotherapy for colorectal cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Less facilities since the treatment is likely to be given less frequently than conventional treatment (6 v 2/3 weekly). Shorter infusion time compared to SOC Likely to be given for longer period due to the better response and survival.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitely. The survival benefits are significantly greater and the toxicity of the treatment considerably lower. A step-change with large and increasing divergence of the survival curves over at least a two-year period.
• Do you expect the technology to increase length of life more than current care?	Considerably, as is high-lighted in the ERG report and the KEYNOTE177 publication.
• Do you expect the technology to increase health-related quality of life more than current care?	Definitely, as is high-lighted in the ERG report and the KEYNOTE177 publication.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. The inclusion criteria for the KEYNOTE177 trial included all patients who were MSI-H and I cannot see good evidence to show that some of these patients won't benefit.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	It is likely to be given 6 weekly. If so, the clinic and treatment time will be reduced which will be beneficial to all parties (hospitals / patients / clinicians). There is no need for a central venous line and therefore there will also be reduced risks of line infections and clots. Reduced toxicity will mean less OP visits, supportive medications and also

practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	less admissions compared to conventional chemotherapy.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would say treatment should be stopped if it isn't working or causes unacceptable toxicity. If the treatment is tolerated and the response is continued, I would say it should be stopped at 2 years. However, if this is the case and the disease recurs, then this treatment must be available to be used again.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is likely to be given 6 weekly. If so, the clinic and treatment time will be reduced which will be beneficial to all parties (hospitals / patients / clinicians). There is no need for a central venous line and therefore there will also be reduced risks of line infections and clots. Reduced toxicity will mean less OP visits, supportive medications and also less admissions compared to conventional chemotherapy.
18. Do you consider the technology to be innovative in its potential to make a significant and	Definitely. A step-change. – please see my previous answers.

substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is no need for a central venous line and therefore there will also be reduced risks of line infections and clots. Reduced toxicity compared to SOC will mean less OP visits, supportive medications and also less admissions compared to conventional chemotherapy.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The SOC in the KEYNOTE177 trial include bevacizumab. However, the addition of this drug dose not reduce the impact of the results seen in the KEYNOTE177 trial. This is shown clearly in Table 19 on p58 of the ERG.

• If not, how could the results be extrapolated to the UK setting?	See above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved PFS / OS, reduced toxicity, improved QoL
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	OS not reached yet in KEYNOTE177 but it looks as though the prolonged PFS will lead to a prolonged OS. I understand the OS results may be available to NICE soon.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance TA439?	
23. How do data on real-world experience compare with the trial data?	N/A
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
25. Are the following treatments (excluded in the company submission) relevant comparators for this population in the NHS:	No to all 3 T/U – not available now in UK R – Only used if angina related to 5FU / Capecitabine

• Tegafur with uracil (in combination with folinic acid) • Raltitrexed (only when folinic acid and fluorouracil are not tolerated or unsuitable) • Capecitabine	C – Only given as a single agent to more elderly / frail patients.
26. In NHS clinical practice, would pembrolizumab be more likely to be given as 200mg every three weeks or 400mg every six weeks?	May be 3 weekly at start to more closely monitor patient. But 6 weekly more likely for long-term use.
27. What proportion of people with metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency would you expect to also have RAS mutations?	This isn't relevant since subgroup analysis is not possible due to the small numbers and therefore considerably reduced power of any subsequent stats. Only 33 pts had mRAS (22%). From the evidence I can see, pembrolizumab should be made available to all patients whatever their RAS status. Also, the mechanism of action of this drug does not involve the RAS pathway and so I cannot see why RAS is relevant. I do not think KEYNOTE177 subgroup analysis can answer this question due to the small number of patients. Also, another CPI inhibitor (Nivolumab and Ipilimumab) did **not** show a link with RAS status – "Investigator-

	assessed responses were observed irrespective of tumor BRAF or KRAS mutation status, tumor PD-L1 expression" (Overmann et al, JCO 2018). This further supports not limiting immunotherapy to pts with wtRAS.
28a. What factors would determine the choice of standard care treatment for a patient, where multiple different treatments are an option? 28b. Would this differ based on RAS status?	Improved PFS / OS, reduced toxicity, improved QoL. These are all better with pembrolizumab compared to the present SOC. RAS status: It must be remembered that science has evolved since the previous NICE guidance on cetuximab and panitumumab. Clinicians now do NOT give either of these agents with mBRAF due to the lack of benefit, increased toxicity and increased cost. There is also compelling emerging evidence that these agents should NOT be used in patients with right sided colon tumours due to the lack of benefit, increased toxicity and increased cost. So even though there is NICE funding for the use of cetuximab and panitumumab, clinicians would not or very rarely give these agents to patients with mBRAF or right-sided colonic tumours.
29a. What percentage of people with mCRC in the NHS would receive a checkpoint inhibitor as a second line therapy? 29b. Are there any differences in the treatment pathway for people who had pembrolizumab at first-line?	If we assume 5% of patients with MCRC are MSI-H and most get a CPI 1st line, then very few would need it 1st line. But, the real world may not be so precise. If a clinician does not check MSI status and gives conventional chemo before finding out their patient is MSI-H, then there may be some who require a CPI 2nd line. It would be a travesty if the faults of the system or treating clinician disadvantaged patient care. I would hope that NICE guidance would show compassion and would allow a CPI in such a scenario. Presently due to COVID, we can give nivolumab for these patients. I understand this is a temporary arrangement and this funding is likely to cease in the coming months. If NICE give positive guidance to allow funding of pembrolizumab, then this drug will be used for these patients. We then have the problem that now we can use a CPI for any line of treatment. This NICE guidance is assessing only 1st line therapy. So, we could lose out and patients

	will be disadvantaged. KEYNOTE177 allowed cross-over and these patients gained advantage from the CPI. So pembrolizumab is active 2nd line and this must be taken into consideration now. Re-treatment with a CPI should also be considered. I would say 1st line CPI treatment should be stopped if it isn't working or causes unacceptable toxicity. If the treatment is tolerated and the response is continued, I would say it should be stopped at 2 years. However, if this is the case and the disease recurs, then this treatment must be available to be used again.
30. After progression on first-line treatment, would you expect a worse prognosis (i.e. quicker progression on second line treatment or death) for people: a) who received pembrolizumab at first-line b) dependant on RAS mutation status	I am afraid I cannot answer this question with authority based on the evidence available to me. Accepting this, I would say no, I wouldn't expect a worse prognosis. The overall prognosis of patients with MSI-H MCRC is worse than MSS patients and if they have failed CPI treatment, then I would say their outlook is poor (but no worse by having received a CPI)
31. Would you expect to give pembrolizumab until progression or for a limited cycle duration?	I would say 1st line CPI treatment should be stopped if it isn't working or causes unacceptable toxicity. If the treatment is tolerated and the response is continued, I would say it should be stopped at 2 years. However, if this is the case and the disease recurs, then this treatment must be available to be used again. Re-treatment with a CPI should also be considered if they have initially responded to a CPI and had stopped simply due to a time factor and

	not due to progression / toxicity.
30a. Would you expect treatment effect to continue after stopping treatment with pembrolizumab? 30b. Would you expect a proportion of patients to receive a lifelong benefit with pembrolizumab? Please provide an estimate of this proportion if possible.	Yes. If a patient has had a cCR with a CPI, or 2 years of treatment, then I would expect the benefits to be maintained and possibly be life-long (estimate a third). So a dramatic benefit compared to SOC which only very rarely achieves this sort of advantage.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: KEYNOTE-177 is the only RCT reporting data for first-line treatment of MSI-H/dMMR mCRC and includes a comparator of physician's choice	MSI-H pts represent on 4-5% of pts with MCRC. Therefore, further large studies or supporting evidence is unlikely to be available soon. The compelling and significant results of the KEYNOTE177 trial must be taken into consideration now (as NICE are doing) so that appropriate pts gain benefit from this treatment now rather than waiting for more data to become available. If we do wait, then present patients will almost certainly suffer and die earlier.
Key issue 2: Subgroup analyses based on RAS mutation status	I think this is irrelevant based on the data available for a small number of patients. It is also seems odd to me to include a lot of mBRAF pts (34) who are wtRAS in with the rest of the wtRAS patients ("All wild type RAS" in the paper). Also, the mechanism of action of this drug does not involve the RAS pathway and so I cannot see why RAS is relevant. I see the RAS data came from the forest plot in the NEJM paper. The figures are: All wtRAS 0.44 (0.29–0.67) and KRAS or NRAS mutant. 1.19 (0.68–2.07). This latter group was only 74 patients and 51 events.

	It crosses 1.0 and the two "bars" for wtRAS and mutRAS virtually touch. I don't think this data can be used to justify excluding the mutRAS patients from having pembrolizumab. To exclude them, I think there needs to be greater justification or more evidence from elsewhere. Also, another CPI inhibitor (Nivolumab and Ipilimumab) did **not** show a link with RAS status – "Investigator-assessed responses were observed irrespective of tumor BRAF or KRAS mutation status, tumor PD-L1 expression" (Overmann et al, JCO 2018). This further supports **not** limiting immunotherapy to pts with wtRAS.
Key issue 3: Treatment regimen and resource use for pembrolizumab	It is likely to be given 6 weekly. If so, the clinic and treatment time will be reduced which will be beneficial to all parties (hospitals / patients / clinicians). There is no need for a central venous line and therefore there will also be reduced risks of line infections and clots. Reduced toxicity will mean less OP visits, supportive medications and also less admissions compared to conventional chemotherapy.
Key issue 4: Duration of treatment with pembrolizumab	I would say 1st line CPI treatment should be stopped if it isn't working or causes unacceptable toxicity. If the treatment is tolerated and the response is continued, I would say it should be stopped at 2 years. However, if this is the case and the disease recurs, then this treatment must be available to be used again. Re-treatment with a CPI should also be considered if they have initially responded to a CPI and had stopped simply due to a time factor and not due to progression / toxicity.
Key issue 5: Treatment costs for standard of care	SOC will be cheaper but the benefits of the CPI in terms of outcome / toxicity and QoL are greater.
Key issue 6: Time on treatment for non-KEYNOTE-177 comparators	I would agree 8-9 months as is discussed in ERG. But if they stop 1st line therapy at this point, they will then probably start 2nd line treatment immediately or after a short time off of treatment. Then 3rd line. So it is likely that SOC patients will be on chemo most of their life and it shouldn't be assumed they have 8-9 months of treatment and then nothing.
Are there any important issues that have been missed in ERG	EGFR inhibitors are not given as SOC to mBRAF tumours and many right sided colon cancers

report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Pembrolizumab is a **step-change** for all patients (all RAS) with MSI-H MCRC and should be considered as the **new SOC** for these patients
- The **reduced toxicity and improved QoL** is much better with pembrolizumab compared with SOC
- If we give a patient with wtRAS pembrolizumab 1st line, can we give an EGFRi 2nd line? The present EGFRi guidance only allows 1st line and this guidance may need up-dating based on the outcome of this review. Asking clinicians to choose one or the other (CPI or EGFRi) is **morally wrong,** when both treatments are likely to benefit a patient. Both are needed, 1st and 2nd line in some patients.
- **Re-treatment** on progression with CPIs must be considered for those who have stopped at 2 years (not PD or toxicity) if NICE guidance states this time-frame.
- If a clinician does not check MSI status and gives conventional chemo before finding out their patient is MSI-H, then there may be some who require a **CPI 2nd line**. It would be a travesty if the faults of the system or treating clinician disadvantaged patient care. I would hope that **NICE guidance would show compassion** and would allow a CPI in such a scenario.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Hayley Crawley**
2. Are you (please tick all that apply):	a patient with the condition? YES a carer of a patient with the condition? NO a patient organisation employee or volunteer? NO other (please specify): NO
3. Name of your nominating organisation	Bowel Cancer UK
4. Did your nominating organisation submit a submission?	yes, they did Yes

5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it Yes
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	NA
7. How did you gather the information included in your statement? (please tick all that apply)	I have personal experience of the condition - YES I have personal experience of the technology being appraised - YES I have other relevant personal experience. Please specify what other: EX-NURSE I am drawing on others' experiences. Please specify how this information was gathered: NA

Living with the condition

8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with advance colorectal cancer in 2014 at 46 years old with an eight year old son. Following numerous treatments, including self funded immunotherapy, I have had no evidence of disease since February 2018. Commencing pre-operative adjuvant therapy of chemo and radiotherapy, I rapidly deteriorated from being an independent mother, Working full time, and managing a high profile NHS commissioning nursing service, to becoming completely dependent on my husband. During this time I was frequently hospitalised due to dehydrating from diarrhoea and vomiting. Furthermore, I suffered severe rectal pain, resulting in a diamorphine infusion for six weeks. Prior to bowel surgery, a review CT scan identified liver metastasis which require a resection. Following my bowel surgery, I had a PET scan in preparation for the liver resection. This unfortunately identified metastasis throughout my lymph system. I was, therefore, unable to have the liver surgery and assessed as being palliative. Discussions became centred around place of death, making a will and preparing our son for what looked to be my impending death. This was 2014, which meant that there were no other options other than fortnightly chemotherapy for the rest of my life or until it stopped working. The stress and anxiety of living with a life limiting illness is very difficult to put into words that do it justice. The heightened level of anxiety affects your whole life and those closest to you. It constantly bears down on you. My condition was also robbing me of living an active life and contributing to society. Demoralising and degrading is an understatement. I was stripped of my identity. My family's whole lives were turned upside down during that palliative conversation. My fortnightly chemotherapy rapid 'poisonings' and slow recoveries dominated our lives. During some weeks, I would need to visit the hospital on four different occasions. My husband tried initially to continue working but he was overwhelmed with the fear he would return home one night to find me dead. I also debilitated rapidly during the chemotherapy and therefore he had to give up his management NHS job to be able to care for me. We lost 75% of our income from our combined jobs, but at least had pensions to fall back on. The impact of this spills into all aspects of life. We had to financially plan very carefully what we could prioritise, including my sons education. In order for me to remain living in our family home, we also needed to make some major alterations to enable me to be able to live on one level during my sickest times. Depleting savings added further to our stress levels. One of the chemotherapies was a targeted drug, Oxaliplatin, and whilst it stabilised tumour growth, it caused me severe peripheral neuropathy. Affecting my mobility, fine dexterity and balance. At my worse, for

	several months, I became wheelchair dependent, needing assistance with all activities of daily living including; washing, dressing, cutting up my food and mobility. Our home became a hive of activity of community services staff. District nurses, physiotherapists and occupational therapists were frequently invading our private space to provide care. Personally, it was a grieving process for the life I had lived simply and treasured. I mourned for my past. I was alive but not really living. Being unable to create happy memories for my son and husband. I missed so many of my son' childhood activities too, due to the debilitating side effects. I was too weak to stand on a rugby touchline cheering his team on. The cold wind affected my speech and swallowing, so watching his rugby matches became a distant memory. Sports days, school plays and parents evenings became significant risks, given I was immuno-suppressed. I became the 'absent parent'. Slowly deteriorating during the relentless chemotherapy cycles. Nausea was a real challenge, but through my husband's research we found that fasting around the time of the chemotherapy cycles helped mitigate this. However, due to the chemotherapy infusion lasting 48 hours, it meant that I had to fast for four days every fortnight. This was an enormous undertaking, but I coped with it and felt better able to go on. Our whole lives revolved the chemo cycles. It was an existence. My husband had to become a single parent to our son. Chemotherapy robbed our son of his young childhood and my husband of his wife. I promised my husband and son that I would never give up while treatments showed promise, but to carry on was a huge daunting daily burden. In my darkest moments, all I wanted was my end to come quickly and cleanly, but I knew I couldn't break my promise to those I loved. We clung together as a family, cast adrift and waiting for the next storm which might be the one to finish me. Some of the conversations I had to have with our young son in preparing him for a life without his mum were heart wrenching and something no child should have to experience. The chemotherapy regime was only holding off the inevitable and allowing little normality or hope for at least some good times. Living through over three years of fortnightly chemotherapy is an immense roller coaster of emotions. Together with the three months surveillance scans, it rendered our lives into constant vigils looking for the next signs of my doom We were unable to plan more than a few days ahead. Holiday insurance was an impossibility and left us no choice but to travel somewhere accessible risking no insurance. In July 2017, the inevitable happened. The chemotherapy had finally become less effective. My metastasis were growing/spreading. There are various chemotherapy combinations available on the NHS. Unfortunately not all are tolerated and all stop being effected at some point as the cancer mutates. Tolerating the

	fortnightly chemotherapy regime is very debilitating both physically and mentally. The risk of permanent peripheral neuropathic damage is high, resulting in a disability. It has also resulted in portal hypertension, which is life limiting. By 2017, through our personal research, I knew I was MSI High and that Pembrolizumab had been proven effective against this rare sub-type of colorectal cancer. Cruelly, this lifeline was not however available on the NHS and we could not afford the significant cost of a full course of treatment. My oncologist had previously considered applying on my behalf for one of the few a Pembrolizumab trials, but I could not meet all the strict criteria. Therefore, we approached our local NHS commission group and my oncologist applied for an Individual Funding Request (IFR). When this was declined, we wrote to NHS England and NICE. Further rejection replies resulted in us convincing our local MP to raise my funding request refusal at Prime Ministers Questions (PMQ's). These increasingly desperate attempts to secure funding were some of the most depressing and anxious times, when I was already weak from fighting the disease. It felt that no one above the hospital level was prepared to help me. Time was fast running out for me and the remaining option was for me to try and raise the money through crowd funding. We had never asked anyone for financial help, so this did not initially sit easy with us. For the fundraising to be a successful campaign, my husband put in countless of hours into publicity, creating a website, attracting media attention, leaflet drops and numerous fundraising opportunities. It took a toll on us, but the payback in support, love and hope was immense. It offset how a price had been put on my life, which I estimated at £260 a day for the immunotherapy. The cost of giving me the opportunity to extend my life, so I could continue being a mum, a wife, a daughter and sister. Physically and emotionally the fundraising was almost as hard on us as my treatments.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There are various chemotherapy combinations available on the NHS. Unfortunately not all are tolerated and all stop being effected at some point as the cancer mutates. Tolerating the fortnightly chemotherapy regime is very debilitating both physically and mentally. The risk of permanent peripheral neuropathic damage is high, resulting in a disability.
10. Is there an unmet need for patients with this condition?	Yes as there is no real access to immunotherapy and no other potentially curative treatments.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Immunotherapy is a big step towards a better and kinder future for treatments. It is potentially curative and much kinder on the patients body, with less debilitating side effects, avoiding further treatment burdens. Giving the opportunity of being able to live a relatively normal life, thereby also able to continue contributing to the economy and not become a burden on society and the NHS.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Cost and access to allow the treatment to become a standard of care.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those with MSI-high. I was also at an advanced deteriorating stage with my cancer and immunotherapy was my last best chance and proved to be still effective.
Equality	
14. Are there any potential equality issues that should be taken into account when	As this treatment is not currently available on the NHS there is an inequality in access. People who can afford to pay are able to receive the treatment whilst those who cannot are not.

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	Could the clinical evidence not also include patient case studies, given the relatively few patients in the cohort? Who would be best placed to undertake such studies? Also, How will this work will lead on to combination therapies with even greater impacts.
Key messages	

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Potentially curative (I have had no evidence of disease since February 2018)
- Much less debilitating than chemotherapy (chemo side effects included neuropathy and life limiting portal hypertension)
- Access and cost
- Effective even in very late stage 4 progressed disease
- Should become a standard of care

NICE National Institute for Health and Care Excellence

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency ID1498

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	Momenul Haque
2. Are you (please tick all that apply):	a patient with the condition
3. Name of your nominating organisation	Bowel Cancer UK
4. Did your nominating organisation submit a submission?	yes, they did

5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	I have personal experience of the condition I have personal experience of the technology being appraised I have other relevant personal experience. Please specify what other experience: I am drawing on others' experiences. Please specify how this information was gathered: All of the above. In addition to having the condition, and experiencing the technology. I have met other patients who have also had experience of the technology. I've also met and spoken with a number of oncologists who have experience with administering the treatment.

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with stage 4 bowel cancer is devastating and instantaneously life changing. The current first line treatment, chemotherapy, has brutal side effects each compounding upon the other. The instant lifestyle changes meant not being able to go into work, losing my independence, dependence on others for the very basics, my everyday routine completely overhauled. It was all about hospitals, appointments, procedures, whilst feeling sick, fatigued, and in pain- physical, psychological, emotional. It was shock after shock. The diagnosis, the chemo, the side-effects, the blood transfusions, the blood clot, surgery. After two lines of chemo failed over the course of a year, there was nothing else the NHS could offer. This has an unbearable emotional impact, especially so because a treatment such as Pembrolizumab shows an incredible response rate for people with this condition. Carers and family members are left helpless.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The NHS is currently letting down a number of patients by not making proven breakthrough drugs available, to those who would benefit based on their genetic markers. There are a number of breakthroughs in medicine and science, through personalised treatments, which show amazing results in trials and private practice, yet are unavailable for many who would see a good response.

10. Is there an unmet need for patients with this condition?	Metastatic Bowel cancer patients vary in nature (lynch syndrome, MSI high etc), yet they are all treated the same, and are given the same treatment lines as they were from decades ago. This being so regardless of the advancements in drug development such as immunotherapy. Therefore those with genetic certain genetic bowel cancers are at a disadvantage, whereby the chemo offered most likely wont work. With information readily available about those receieving immunotherapy doing well, this adds to damaging a person's mental and emotional health, in addition to the physical suffering.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Pembro works very differently to chemotherapy. The first benefit is the speed and duration of the treatment. The doses/ infusion are very quick. A pembro infusion can be over within 30 minutes. The cycles are every 3 weeks. This is very significant, as chemo includes a 48 hour pump in addition to a few hours in the hospital, which takes place every 2 weeks. The implications to this mean fewer visits exerting less energy, reduction in travel time and cost, better use of resources e.g. hospital bed space and nurse time etc. Secondly, there isn't the toxicity associated with chemo, such as sickness, diarrhoea, fatigue. Thirdly and most importantly, the response to the treatment is incredible. I had one year of Pembro treatment, 16 cycles from June 2016, to May 2017, and have seen a complete response with no evidence of disease. Writing this in Feb 2021, almost 4 years since stopping the drug, is miraculous. In comparison to chemo, I had 2 lines, 18 cycles between December 2014 and December 2015, whereby the cancer continued to spread, into the lymph nodes, spleen and liver. The NHS could not offer me any other treatment. Without crowdfunding to gain access to the pembro, I would not have had this extra life. This extra life has allowed me to spend quality and meaningful time with my friends and family, see my 5 school aged nephews grow older, make several new friends. I have been able to publish my book Choosing To Stay, have been invited to speak at events and medical conferences (including MD Anderson in Texas), have helped other patients with their care, am on a number of cancer related advisory/working group.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The side effects are very different from chemotherapy. The ones I experience include rheumatoid arthritis and ulcerative colitis. I manage the arthritis with naproxen, which helps, and allows me to be mobile. The ulcerative colitis is manageable day to day without treatment. What both these conditions suggest is that the immune response stimulated from the pembro is still active within my body, even though I stopped taking the drug almost 4 years ago. The reason for stopping pembro was the cost per dose, which is very restrictive. The price is extremely high/unaffordable. Not being on the NHS is heartbreaking, especially if a certain treatment has a very high response rate. Not all doctors are knowledgable of these newer technologies, and how to manage side effects.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have lynch syndrome and MSI high bowel cancers are most likely to benefit, due to the nature of the technology. Pembrolizumab is made up of antibodies and anti gens which are designed to activate T cells and stimulate the immune system, which is compromised within this patient population. Therefore the targeted and personalised approach this drug has offers so much hope.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	This drug is very costly outside the NHS. Only the very richest in society will be able to pay for it privately. The poorest in society are most likely to belong to the 9 protected characteristics under the Equality Act, and hence excluded from having a life saving drug
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • Current provisions for this bowel cancer population is inadequate • Pembrolizumab works incredibly well in targeting the cancer, by reducing and even eliminating the disease. • The toxicity of the drug is less impactful than current NHS provisions • The administration and efficiency of the drug is patient friendly, with fewer hospital visits, and duration of each cycle • This is a life saving and enhancing drug that offers so much hope, yet its heartbreaking to not have access with fatal consequences.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, Monday 15 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Promega**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: [insert issue as described in ERG report, e.g. 'appropriateness of methotrexate as a comparator']	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 7: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 11: [insert issue as described in ERG report]	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue N: [insert issue as described in ERG report]	**YES/NO**	[INSERT / DELETE ROWS AS REQUIRED]

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: M**SI/dMMR testing method**	Background Section 2.2.2, pg30	**Yes**	The ERG report notes that "on occasion, a person could be identified as microsatellite stable but dMMR, and, therefore, evaluating MMR proteins could be the preferred technique." This statement infers that only MSI testing can result in a false negative result. In rare instances, IHC may retain MMR protein staining but the protein is non-functional, leading to discordant pMMR/MSI-H results [1, 2]. Studies have consistently shown that MSI and IHC have similar sensitivity in colorectal cancer and each assay may result in false positive or false negative results in rare instances. Retrospective results from studies of clinical trial patients receiving immunotherapy have shown that both assays are susceptible to misinterpretation and for this reason, the European Society of Medical Oncology has recommended testing using both approaches for maximal sensitivity in determining immunotherapy eligibility for MSI/dMMR tumors. This distinction is important to include as the entire pathway for this appraisal are predicated on an accurate diagnostic assessment of CRC tumor MSI/dMMR status.[3, 4]
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

[1] Raevaara TE, Korhonen MK, Lohi H, Hampel H, Lynch E, Lonnqvist KE, et al. Functional significance and clinical phenotype of nontruncating mismatch repair variants of MLH1. Gastroenterology. 2005;129:537-49.

[2] Zighelboim I, Powell MA, Babb SA, Whelan AJ, Schmidt AP, Clendenning M, et al. Epitope-positive truncating MLH1 mutation and loss of PMS2: implications for IHC-directed genetic testing for Lynch syndrome. Familial cancer. 2009;8:501-4.
[3] Cohen R, Hain E, Buhard O, Guilloux A, Bardier A, Kaci R, et al. Association of Primary Resistance to Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer With Misdiagnosis of Microsatellite Instability or Mismatch Repair Deficiency Status. JAMA oncology. 2019;5:551-5.
[4] Luchini C, Bibeau F, Ligtenberg MJL, Singh N, Nottegar A, Bosse T, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30:1232-43.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, Monday 15 February 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Younan Zhang
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Merck Sharp & Dohme (UK) Limited - Respondent
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 1: KEYNOTE-177 is the only RCT reporting data for first-line treatment of MSI-H/dMMR mCRC and includes a comparator of physician's choice	No	MSD agrees with the ERG that for the comparison with CAPOX, FOLFIRI and FOLFOX, the standard of care (SoC) group in totality from KEYNOTE-177 provides an appropriate estimate of comparative treatment effectiveness for pembrolizumab, and likely underestimates the true effect of pembrolizumab, because SoC included bevacizumab and cetuximab-combination regimens. With regard to the ERG's proposal to provide more robust estimates of progression-free survival (PFS) for pembrolizumab versus cetuximab- and panitumumab- combination treatments in those patients with RAS wild-type metastatic colorectal cancer (mCRC) by carrying out a fractional polynomial network meta-analysis (FP NMA) in the subgroup of patients with RAS wild-type mCRC, MSD do not agree that this would be more appropriate than the original NMA in all patients as this analysis will be considerably under-powered due to the low number of events in the subgroup of patients with RAS wild-type mCRC in the KEYNOTE-177 study. As described in the submission in Section B.2.4, *Sample*	The ERG recognises that there are limitations with the NMA requested in the RAS wild-type subgroup and, as noted in the ERG report, considers that the analysis is likely to favour pembrolizumab. However, the ERG maintains that the analysis would provide more accurate estimates of effect than those currently available for pembrolizumab versus panitumumab and cetuximab combination therapies in those with RAS wild-type. The NMA was also requested to align with the decision problem as set out in the NICE final scope, and with clinical practice in England. An estimate of effect for pembrolizumab versus cetuximab plus FOLFOX or FOLFIRI is based on assumption and is not derived

		size and power calculations, 209 PFS events are required for the KEYNOTE-177 study to be appropriately powered for the analysis of PFS however there were only 95 PFS events in the RAS wild-type subgroup of the KEYNOTE-177 study at the time of the second interim analysis (the latest available analysis). Additionally, randomisation would be broken for treatment comparisons in these subgroups, as described in the submission in Section B.2.3, *Trial design*, no stratification of randomisation based on age, sex, or other characteristics were used in the KEYNOTE-177 study. It should also be noted that the PFS hazard ratio for pembrolizumab versus SoC in the RAS wild-type subgroup of the KEYNOTE-177 study (HR: 0.44) favours pembrolizumab even more than in the full ITT population (HR: 0.60). Therefore, the results of the NMA proposed by the ERG informed by the RAS wild-type subgroup of the KEYNOTE-177 study would most likely yield results that would favour pembrolizumab more strongly than the results based on the NMA presented in the company submission.	from a direct or indirect comparison.
Key issue 2: Subgroup analyses based on RAS mutation status	No	The ERG has noted that: "Post hoc subgroup analyses of PFS based on those identified as having RAS mutations generated a markedly different result from other subgroups, with a change in direction of effect to favour SoC, albeit that the difference between pembrolizumab and SoC was not statistically significant (HR 1.19, 95% CI: 0.68	The ERG acknowledges that the subgroup analyses in those with RAS mutations is post hoc and, therefore, hypothesis generating, and that the EMA has approved pembrolizumab for the indication under assessment without restriction by RAS status. The ERG

		to 2.07). However, the ERG notes that the 95% CIs for estimates of PFS for RAS wild-type and non-RAS wild-type do not overlap and, as such, considers the results in the two subgroups unlikely to have arisen due to random chance." This issue was explored by the European Medicines Agency (EMA) in their regulatory assessment of pembrolizumab in this indication (https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0091-epar-assessment-report-variation_en.pdf) via multivariate Cox regression analysis of PFS to investigate potential covariates of prognostic interest in CRC. Two-sided p-values of <0.05 were observed for treatment by ECOG interaction and treatment by KRAS/NRAS status interaction. Multivariate Cox regression analysis was adjusted for ECOG, KRAS/NRAS status, treatment by ECOG interaction, and treatment by KRAS/NRAS status interaction. While the EMA considered that results of this analysis may suggest evidence of an interaction effect, it was recognised that this analysis was not prespecified or adjusted for multiplicity and is underpowered due to the small sample size among participants with known KRAS/NRAS mutations (N = 74), as well as the fraction of the study population (29% of participants) whose KRAS/NRAS results were either undetermined or missing, and accordingly the EMA approved pembrolizumab for the indication under assessment without restriction by RAS status.	maintains that the result for PFS for pembrolizumab versus SoC for those with RAS mutation is markedly different from all other subgroup analyses and warrants further research in an appropriately powered study.

		It is also worth noting that cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). RAS genes code for small g-proteins downstream of EGFR that are an essential component of the EGFR signalling cascade, which can acquire activating mutations in exon 2 (i.e. becoming RAS-mutant), thus isolating the pathway from the effect of EGFR and rendering EGFR inhibitors such as cetuximab and panitumumab ineffective. Pembrolizumab, however, targets the PD-1/PD-L1 signalling pathway that acts independently of the RAS pathway and so should not be affected by whether RAS is wildtype or mutated in the patient. With regard to the ERG's suggestion to carry out an FP NMA based on individual patient data (IPD) for those patients from KEYNOTE-177 identified as RAS wild-type, MSD do not agree that this would be an appropriate approach, for the reasons as described in the response to the previous key issue.	
Key issue 3: Treatment regimen and resource use for pembrolizumab	No	MSD agrees with the ERG that the treatment regimen of pembrolizumab administered at a 400mg dose once every six weeks would be preferred by clinicians in clinical practice given the added convenience for patients and the reduced burden on NHS resources. MSD further agrees that aligning consultant outpatient visits to the six-weekly treatment cycle is appropriate.	The ERG is satisfied that the company has incorporated the ERG's preferred assumption in their revised base case.

Key issue 4: Duration of treatment with pembrolizumab	No	MSD appreciates that the removal of the 35-cycle stopping rule to reflect a strategy of treatment until progression or unacceptable toxicity proposed by the ERG is an illustrative scenario intended to highlight the impact of this assumption on the base-case cost-effectiveness results. However, MSD does not consider this scenario to be plausible, as it expects a 35-cycle / 2-year stopping rule to be included as part of a potential NICE recommendation, consistent with the company base case reflecting treatment duration in the KEYNOTE-177 study. Previous NICE recommendations of pembrolizumab across multiple oncology indications have consistently reflected similar protocol-driven stopping rules featured in the clinical trials that have provided clinical evidence base.	The ERG agrees with the company that because the trial data has a 35 cycle/ 2-year stopping rule this may form part of the committee's considerations about treatment duration and that the ERG's scenario removing the stopping rule is only illustrative.
Key issue 5: Treatment costs for standard of care	No	The ERG notes that 70% of patients [in the SoC arm] in KEYNOTE-177 received bevacizumab-combination therapy, and they provide an alternative to the company base assumption of estimating these patients' treatment costs using the cost of cetuximab. The ERG posits that a like-for-like costing of bevacizumab as cetuximab inflates treatment costs in the SoC arm given that eligibility for cetuximab in UK clinical practice requires RAS WT mutation status, and the proportion of these patients in UK practice is estimated to be lower than 70%.	The ERG considers that there is agreement between the company and itself regarding the direction of bias when FOLFOX/FOLFIRI costs are assumed for SoC. However, for its revised base case, the company did not include the ERG's preferred assumption, as it is biased against pembrolizumab. Nonetheless, the ERG's preferred approach remains unchanged and thus considers that using

		In the ERG's alternative scenario, the estimation of treatment costs for patients who received bevacizumab in KEYNOTE-177 is done by replacing the cost of bevacizumab with the treatment costs of FOLFOX/FOLIRI, rather than using cetuximab. As treatment costs of FOLFOX/FOLFIRI are substantially lower cost than cetuximab, which is a branded targeted therapy, this alternative assumption increases the base-case ICER. As the ERG has noted, however, this alternative scenario does not adjust the efficacy of the SoC arm downwards to account for the less favourable efficacy of FOLFOX/FOLFIRI versus bevacizumab reported in clinical trials. MSD notes that the base-case assumption of costing bevacizumab using cetuximab treatment costs is conservative, in that it does not adjust SoC efficacy downwards in light of the significantly better OS reported for patients treated with bevacizumab versus cetuximab [1]. MSD agrees with the ERG that the net effect of the base case assumption costing bevacizumab using cetuximab costs with no associated reduction in efficacy leads to a bias that, on net, favours the SoC arm. [1] Innocenti F, Ou FS, Qu X, Zemla TJ, Niedzwiecki D, Tam R, et al. Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome. J Clin Oncol. 2019;37(14):1217-27.	FOLFOX/FOLFIRI costs for SoC provides a conservative estimate of the ICER.

Key issue 6: Time on treatment for non-KEYNOTE-177 comparators	No	The ERG considers that a more appropriate assumption for time on treatment for non-KEYNOTE-177 comparators is to assume it is equal to KEYNOTE-177 time on treatment for the SoC arm, whereas the base-case assumption estimated non-KEYNOTE-177 comparators' treatment costs based on an assumption of treatment to progression. MSD agrees with the ERG that its scenario sufficiently explores the uncertainty around time on treatment for comparators not evaluated in KEYNOTE-177.	The ERG is satisfied that the company has incorporated the ERG's preferred assumption in their revised base case.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
[*Not addressed in ERG report*]: Revised pembrolizumab PAS	N/A	No	MSD have recently agreed a revised PAS discount for pembrolizumab with PASLU and which is effective from February 2021 to all NHSE providers. The updated PAS discount has been changed to [redacted]%. The cost-effectiveness estimates reflecting the updated company base case following technical engagement presented below report ICERs at both the previous and revised PAS discount levels.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Revised company base case – pembrolizumab vs SoC

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost associated treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: £535 • Change from base case ICER: -£6,715	The ERG has been able to validate the ICER.
ERG preferred scenario	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment, as follows: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: £7,473 • Change from base case ICER: +£223	The ERG has been able to validate the ICER.
ERG preferred scenario	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: £6,996 • Change from base case ICER: -£284	The ERG has been able to validate the ICER.

Company's preferred base case following technical engagement	Incremental QALY's: 1.891	Incremental costs: £1,368 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: £402 • Change from base case ICER: -£6,848 ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A	The ERG has been able to validate the ICER of £402. However, the ERG estimates the incremental costs as £768, not £1,368 The ERG has been able to validate the ICER using the revised PAS

Revised company base case – pembrolizumab vs CAPOX

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost of treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: £21,755 • Change from base case ICER: -£5,719	The ERG cannot validate the company's ICER. Instead, the ERG estimates the ICER to be £20,736
ERG preferred assumption	Comparator ToT equal to Comparator PFS	Comparator ToT equal to SoC ToT	• ICER vs SoC resulting from change: £29,205 • Change from base case ICER: +£1,731	The ERG has been able to validate the ICER
ERG preferred assumption	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: £27,697 • Change from base case ICER: +£223	The ERG has been able to validate the ICER

ERG preferred assumption	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: £26,698 • Change from base case ICER: -£776	The ERG has been able to validate the ICER

Company's preferred base case following technical engagement	Incremental QALY's: 1.884	Incremental costs: £43,409 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: £23,038 • Change from base case ICER: -£4,436 ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from change: £20,360 • Change from base case ICER: -£7,114	The ERG could not validate the ICER and considers that the difference in ERG and company results for the scenario around treatment regimen and resource use for pembrolizumab is causing the difference in the overall ICER. The ERG estimates that the incremental costs using the company's original PAS is £41,443 and the ICER is £21,994. The ERG estimates the ICER using the revised PAS is £19,316.

Revised company base case – pembrolizumab vs panitumumab

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG response

Key issue 3: Treatment regimen and resource use for pembrolizumab	Outpatient consultant visits and the cost of treatment administration were aligned with the Q3W dosing of pembrolizumab	Treatment regimen of 400mg once every six weeks is assumed and consultant oncologist appointments for the pembrolizumab arm is aligned to 6-week treatment cycle	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A	The ERG has been able to validate the ICER
ERG preferred assumption	Comparator ToT equal to Comparator PFS	Comparator ToT equal to SoC ToT	• ICER vs SoC resulting from change: £3,158 • Change from base case ICER: N/A	The ERG has been able to validate the ICER
ERG preferred assumption	Removal of second-line cetuximab combination treatment	Implementation of ERG assumption of 0% use of cetuximab-based therapy as subsequent treatment: "The ERG removed the proportion of patients receiving second-line cetuximab + FOLFIRI (16.1%) and added this to the proportion of patients assumed to receive FOLFIRI (37.6%+16.1%)."	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A	The ERG has been able to validate the ICER

ERG preferred assumption	Exponential distributed used to extrapolate TTP and PFS beyond 20-weeks for both pembrolizumab and SoC	Weibull distribution after the 20-week cut-off point for the extrapolation of TTP and PFS for both pembrolizumab and SoC as per ERG preferred scenario. MSD accepts this assumption as a conservative scenario.	• ICER vs SoC resulting from change: Dominating • Change from base case ICER: N/A	The ERG has been able to validate the ICER
Company's preferred base case following technical engagement	Incremental QALY's: 1.679	Incremental costs: -£7,674 (Not reflecting revised PAS)	• ICER vs SoC resulting from combined changes: Dominating • Change from base case ICER: N/A ICER using revised Pembrolizumab PAS • ICER vs SoC resulting from combined changes: Dominating • Change from base case ICER: N/A	The ERG has a minor discrepancy with the incremental cost and estimates it to be -£7,675, so the difference may be due to a rounding error. The ERG has been able to validate the ICERs.